REVIEW® of Ophthalmology
December 2019
reviewofophthalmology.com

Burned Out No More:

How to Relight the Fire

Physician burnout has become an epidemic. Here's what you can do to keep it at bay. **P. 26**

ALSO INSIDE:

Review of Ophthalmology Vol. XXVI, No. 12 • December 2019 • Managing Physician Burnout • Bridging the Generation Gap • Trifocal and EDOF Lenses

DEXYCU®
(dexamethasone intraocular suspension) 9%

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

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

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

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

INDICATION AND USAGE

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

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

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

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

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

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

ADVERSE REACTIONS

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

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

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

EyePoint™ PHARMACEUTICALS

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10/2019
US-DEX-1900208

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

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

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

4 CONTRAINDICATIONS
None.

5 WARNINGS AND PRECAUTIONS

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

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

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

Employment of a corticosteroid medication in the treatment of patients with a history of herpes simplex requires caution. Use of ocular steroids may prolong the course and may exacerbate the severity of many viral infections of the eye (including herpes simplex). Fungal infections of the cornea are particularly prone to develop coincidentally with long-term local steroid application. Fungus invasion must be considered in any persistent corneal ulceration where a steroid has been used or is in use. Fungal culture should be taken when appropriate.

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

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

6 ADVERSE REACTIONS
The following adverse reactions are described elsewhere in the labeling:
- Increase in Intraocular Pressure *[see Warning and Precautions (5.1)]*
- Delayed Healing *[see Warnings and Precautions (5.2)]*
- Infection Exacerbation *[see Warnings and Precautions (5.3)]*
- Cataract Progression *[see Warnings and Precautions (5.4)]*

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

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

8 USE IN SPECIFIC POPULATIONS

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

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

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

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

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

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

DEX0019

REVIEW NEWS
Volume XXVI • No. 12 • December 2019

Predicting DME's Response to Bevacizumab Therapy

In a retrospective, noncomparative, consecutive case series, researchers sought to investigate the effects of systemic and local co-factors on the therapeutic response of intravitreal bevacizumab in diabetic macular edema, in order to assess how these co-factors could help in the management of DME, as well as help prognosticate the therapeutic response to anti-VEGF. While OCT has greatly improved our ability to diagnose and quantify the severity of DME, Alastair D. Bezzina, MD, ChM (Clin Ophth), FEBO, one of the study's co-authors, says he believes that in addition to OCT, profiling DME and recognizing clues such as cystoid changes, subretinal fluid and the newly-coined DRIL (disorganization of the retinal inner layers) will help in gauging treatment success and planning therapy. He hopes to expand the current repertoire of biomarkers related to DME treatment.

The study included baseline imaging data and clinical records of 65 eyes (58 patients) with DME, secondary to type II diabetes mellitus. All eyes were anti-VEGF treatment-naïve as of January 2016. After three loading doses, central macular thickness, macular volume and BCVA were measured to explore correlations between risk factors and anatomical and functional outcomes.

"Macular volume mirrored the fluctuations seen in central macular thickness in many cases," notes Dr. Bezzina. He says that one advantage of macular volume as an anatomical measure is that it considers the status of the parafoveal subfields, which play an important role in day-to-day activities such as reading, thanks to their influence on the psychophysical aspect of vision.

Participants in the study ranged between 46 and 84 years of age, with 41 males and 24 females. At baseline, mean CMT was 443.21 ±121.04 µm. Following the loading phase, mean CMT measured 390.86 ±125.92 µm, demonstrating a mean reduction of 52.35 µm (-11.23 percent, $p<0.0005$), which was highly significant and showed an overall positive therapeutic response. Highly significant changes were also observed in macular volume readings, with a mean reduction of -6.83 percent from baseline. An overall improvement in BCVA was also noted, with a mean reduction of 0.07, or a gain of three Snellen letters. No statistically significant correlations were noted between sex and secondary outcome measures such as glycemic control, raised cholesterol and lipoprotein levels, or baseline functional and anatomical parameters.

Females responded better to bevacizumab therapy, with a significantly greater reduction in CMT after the loading phase (-16.66 percent) than males (-8.04 percent), $p<0.05$. "As demonstrated in other studies, the possibility of sex-hormone-induced neurovascular protection may help in the resolution of [DME] when the effect of VEGF is mitigated with agents such as bevacizumab," says Dr. Bezzina. "Not surprisingly, patients with PDR fared the worst anatomically, a finding which may be explained by increased VEGF levels in such patients."

One interesting finding in the study was a reduced influence of systemic co-factors, including diabetic control, on therapeutic benefit. While the study doesn't contraindicate the control of systemic factors as a means of limiting disease progression, Dr. Bezzina says it raises the question of whether tight blood pressure, glycemic and lipidemic control have any weight once the blood-retinal barrier is impaired and the vasogenic and inflammatory responses are triggered. He adds that larger, ideally prospective, studies are required to support this notion.

Patients with cystoid macular edema, a DME phenotype, demonstrated a poor result. Dr. Bezzina says this outcome may be explained by CME's more pronounced inflammatory profile, which is less-responsive to anti-VEGF compared to a phenotype such as diffuse retinal thickening, which is thought to be more vasogenic. "Our hypothesis is that a vasogenic [DME] profile may demonstrate a better therapeutic response to anti-VEGF agents when compared to one which is predominantly inflammatory with more cystoid changes and the presence of subretinal fluid." He says the latter may be more amenable to primary steroid treatment, but further studies are required to support this, espe-

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cially considering the adverse effect profile of intraocular steroids and the fact that DRT and CME may, and generally do, co-exist. "Tackling both vasogenic and inflammatory aspects is the key to successful, long-term therapy of [DME] patients," he says.

It's important that clinicians keep in mind these systemic and ocular co-factors when managing DME patients so they can begin to think of alternative treatments if the response to anti-VEGF is poor, says Dr. Bezzina. He believes that DME may at times be either more inflammatory or more vasogenic. "This brings up the question of whether one class of agent may be more appropriate than another as a first-line treatment, depending on the [DME] profile," he notes. "More comparative studies need to be performed in order to further affirm this notion."

RGX-314 Back on Track

RGX-314, the subretinal gene therapy for neovascular AMD that has been progressing through FDA trials since 2017, is expected to begin a Phase IIb study during the first quarter of 2020, following a clinical hold order that the FDA had placed on the development of the therapy on October 18. The Phase IIb trial was rescheduled from the end of 2019 until early in 2020 after the developer of RGX-314, RegenxBio (Rockville, Maryland), filed a lawsuit against the FDA in federal court on November 7, challenging the agency's clinical hold order.

Before the clinical hold order was issued, RegenxBio had submitted two investigational new drug applications for RGX-314: one for nAMD and one for diabetic retinopathy.

Tricia Truehart, vice-president, investor relations and communications at RegenxBio, says in a written statement that RGX-314 is being developed as a potential one-time subretinal treatment—not only for nAMD and DR, but for other chronic retinal conditions for which anti-vascular endothelial growth factor treatment is the standard of care. She says the treatment includes the "NAV AAV8 vector containing a gene encoding for a monoclonal antibody fragment. The expressed protein is designed to neutralize VEGF activity, modifying the pathway for formation of new leaky blood vessels and retinal fluid accumulation."

In its complaint, the company said the FDA hadn't offered "a reasoned explanation for issuing a clinical hold without advance warning." In the interest of patient safety, the FDA had ordered the company to stop administering RGX-314 to existing and new study subjects (unless permitted by the agency) and to halt recruitment of study subjects, according to RegenxBio's complaint. The lawsuit noted that the FDA said it was placing both INDs on hold because of unspecified "issues associated with their delivery systems" and that the FDA said it was "working on addressing" unspecified "device concerns."

Though RegenxBio officials wouldn't confirm if the FDA had lifted the clinical hold, they released this statement: "RegenxBio has received a letter from the FDA which provides us with information about their concerns around the third-party commercially-available devices that are used to deliver RGX-314 in our Phase I/IIa trial for the treatment of wet AMD. We will continue to work with FDA to address the concerns that they have raised regarding the devices, and support plans to initiate the RGX-314 Phase IIb study in subjects with wet AMD and file the IND for DR in Q1 2020."

The FDA declined to comment for this article.

(Continued on p. 43)

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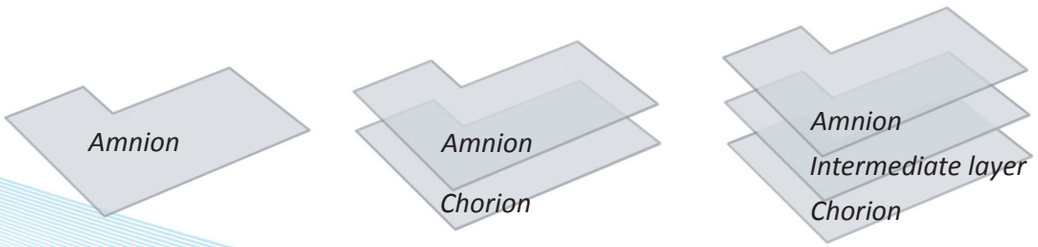

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BRIEF SUMMARY OF PRESCRIBING INFORMATION

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

LOTEMAX® SM (loteprednol etabonate ophthalmic gel) 0.38%

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

INDICATIONS AND USAGE

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

DOSAGE AND ADMINISTRATION

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

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

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

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

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

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

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

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

ADVERSE REACTIONS

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

USE IN SPECIAL POPULATIONS

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

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

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

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

NONCLINICAL TOXICOLOGY

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

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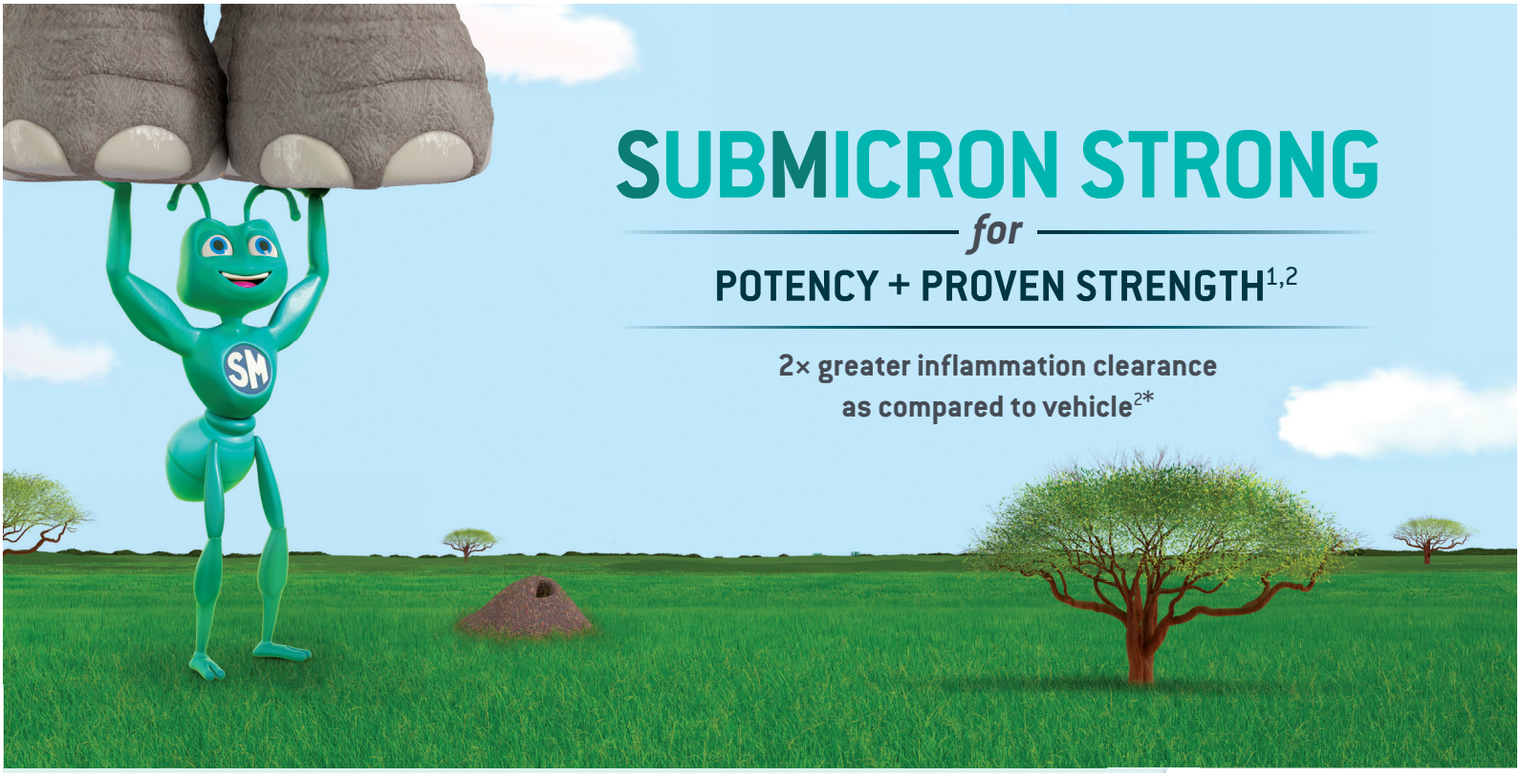

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for

POTENCY + PROVEN STRENGTH[1,2]

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

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

Clinical significance of these preclinical data has not been established.

LOTEMAX® SM
(loteprednol etabonate ophthalmic gel) 0.38%

SMALL & MIGHTY
SUBMICRON PARTICLES

*PROVEN STRENGTH

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

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

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

Indication

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

Important Safety Information

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

Important Safety Information (cont.)

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

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

Please see brief summary of Prescribing Information on adjacent page.

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

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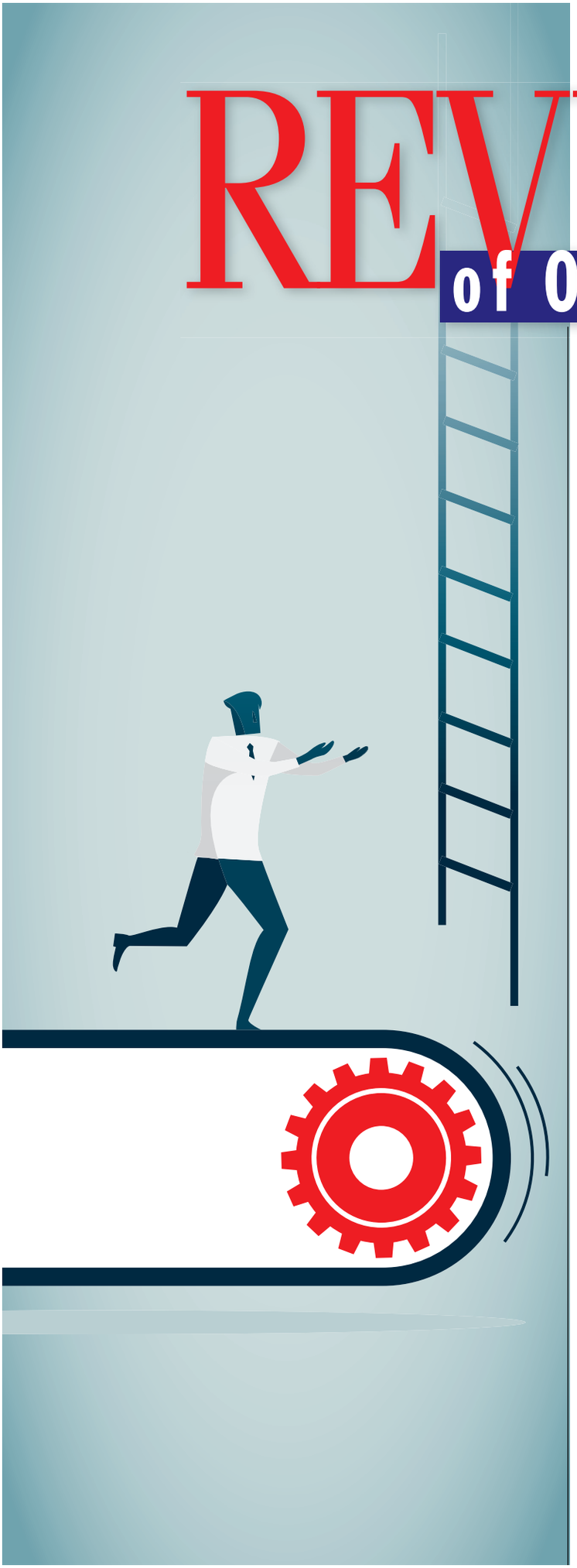

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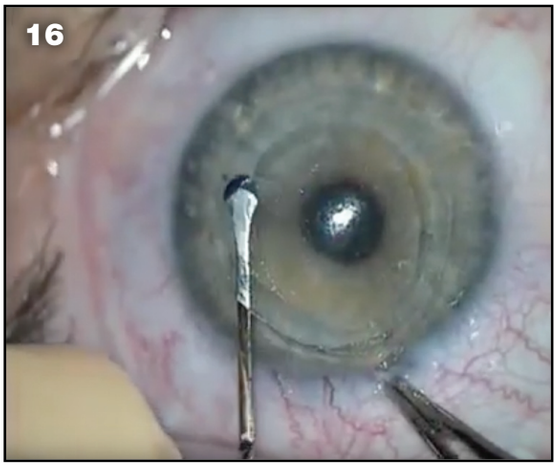

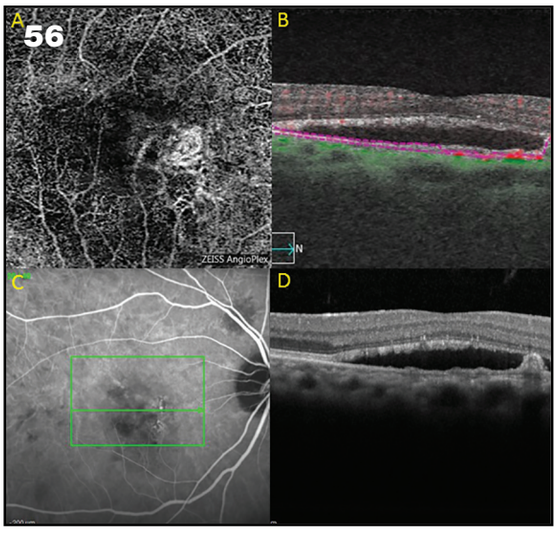

TED'S LONG-TERM DAMAGE IS SOMETHING SHE CAN'T COME BACK FROM.

Since there's a limited window for Active Thyroid Eye Disease, every moment counts.[1,2]
To fight back against the impact of this disease, focus on early diagnosis, active monitoring, and prompt medical intervention.[1,3-5]

To learn more about what to look for, visit **TEDimpact.com**

References: 1. McAlinden C. An overview of thyroid eye disease. *Eye Vis.* 2014;1:9. doi:10.1186/s40662-014-0009-8. **2.** Weiler DL. Thyroid eye disease: a review. *Clin Exp Optom.* 2017;100:20-25. **3.** Verity DH, Rose GE. Acute thyroid eye disease (TED): principles of medical and surgical management. *Eye (Lond).* 2013;27:308-319. doi:10.1038/eye.2012.284. **4.** Barrio-Barrio J, Sabater AL, Bonet-Farriol E, Velázquez-Villoria Á, Galofré JC. Graves' ophthalmopathy: VISA versus EUGOGO classification, assessment, and management. *J Ophthalmol.* 2015;2015:249125. doi:10.1155/2015/249125. **5.** Bartalena L, Baldeschi L, Boboridis K, et al. The 2016 European Thyroid Association/European Group on Graves' Orbitopathy Guidelines for the Management of Graves' Orbitopathy. *Eur Thyroid J.* 2016;5:9-26. doi:10.1159/000443828.

HORIZON

Managing the Challenges of SMILE

This flapless refractive procedure may be safe. But you'll need to prevent and respond to untoward events.

By Majid Moshirfar, MD, and Yasmyne C. Ronquillo, MD
Draper, Utah

Most of us believe small-incision lenticule extraction is a safe alternative to LASIK. The flapless procedure spares you and your patient the challenge of flap-related issues, maintains the ocular surface, preserves corneal sensitivity, causes less dry eye and reduces the incidence of injury to the sub-basal plexus.[1] Despite these benefits, however, rare intraoperative complications can occur, especially when inexperienced refractive surgeons confront the steep learning curve associated with this procedure.[2]

In this article, we'll help you avoid and manage common and rare complications.

Select the Right Patients

SMILE, performed exclusively with the VisuMax femtosecond laser (Carl Zeiss Meditec), is indicated for the reduction or elimination of myopia ranging from -1 to -8 D of nearsightedness and -0.5 D or less of astigmatism in patients 22 years of age or older.[3] When evaluating potential surgical candidates, you'll need to perform a complete ocular exam, including a thorough history and analysis of appropriate corneal parameters. Identify common contraindications—many of which also rule out LASIK—as well as conditions that require treatment before you proceed with SMILE.

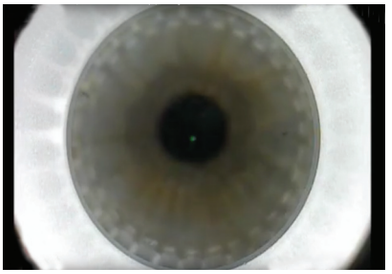

Figure 1. Successfully mastering suction with a femtosecond laser can be a challenge for surgeons learning SMILE, especially if they have no experience creating LASIK flaps.

Contraindications include uncontrolled glaucoma and underlying corneal pathologies, such as membrane dystrophies, corneal degeneration or keratoconus. Even a history of keratoconus in a sibling, mother or father should be carefully evaluated. A thorough initial eye examination and close follow-up with testing are necessary.

With keratometry, evaluate and analyze any findings of astigmatism and asymmetry. If the posterior and anterior elevations don't match, don't perform SMILE. You should also investigate pachymetry readings below 500 µm, as well as abnormally thin corneal tissue within a radius of 0.5 mm to determine if SMILE is appropriate. Altering tissue by more than 40 percent may be associated with an increased risk of ectasia.[4]

Although no guideline exists for evaluating PTA percentage in SMILE, we refuse to perform SMILE or LASIK if the patient's pachymetry is below 500 µm and the residual stromal bed is less than 250 µm. We also won't give the green light if we see a pupil diameter that's more than 8 mm in dim light. Naturally, any sign of keratoconus rules out the surgery.[1]

Treatable Conditions

As would be the case for any refractive procedure, patients with treatable corneal conditions that would rule out SMILE can still undergo the procedure if the conditions are treated and controlled before you perform the procedure.

Using conventional approaches, you

can diagnose and treat dry eye, blepharitis and meibomian gland dysfunction. You can then follow this therapy with the SMILE procedure, and continue to treat the patients postop to keep their conditions under control. We treat patients with herpes simplex keratitis preoperatively with acyclovir or an acyclovir-derived medication, allowing for 12 to 18 months of pre-treatment quiescence. After SMILE has been successfully performed, the same medication is used for seven weeks of postop treatment. Without any actual guidelines governing treatment of herpes simplex keratitis for these patients, we treat and monitor them based on our experience and anecdotal information, varying the dosages according to patient responses.

A critical side point: If your patient takes isotretinoin for treatment of severe recalcitrant nodular acne, keep in mind that the treatment can increase the risk of dry eye and abnormal postop wound healing. Work with the patient's dermatologist or primary care physician, as needed, to confirm that the isotretinoin can be withheld during the perioperative period.

It's important to consider that uncontrolled diabetes, autoimmune disorders and even allergies may increase the risk of delayed wound healing after SMILE. You'll need to coordinate closely with patients' endocrinologists, rheumatologists, allergists and primary care physicians. For autoimmune disorders, proceed with surgery only if the rheumatologist can assure you that the patient's condition has been consistently controlled without relapses for at least one year. Even after SMILE, the patient should follow up closely with the rheumatologist or internist.

Ensuring a Smooth Start

As we mentioned, inexperience can lead to intraoperative complications because SMILE can be a challenge to learn. The standard SMILE technique involves focused patterns of femtosecond pulses, applying a laser wavelength of 1,043 nm at a 500-kHz frequency. SMILE involves docking, femtosecond laser delivery, lenticule dissection and extraction.[2,5] If you want to add this procedure to your refractive surgery arsenal, concentrate initially on mastering the suction phase. To do so, Zeiss recommends that you create LASIK flaps with the VisuMax before turning your attention to SMILE. That's because lenticule creation and dissection are particularly challenging in the hands of an inexperienced surgeon.[2]

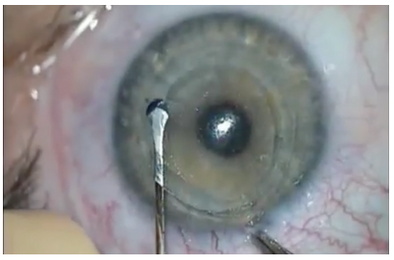

Figure 2. Dissect with care. An untimely dissection into the posterior plane causes the lenticule to adhere anteriorly to the cap.

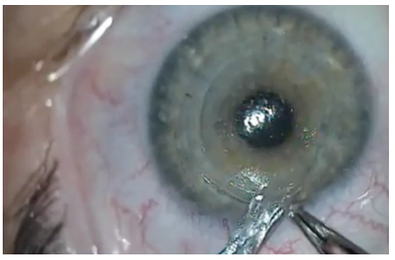

Figure 3. Be careful to completely remove the lenticule, leaving no portion behind in the pocket.

When creating a lenticule as a beginner, you may experience suction loss, especially when contending with a small palpebral aperture and poor patient fixation.[6] To avoid suction loss, ask your patients to fixate correctly, especially at crucial points during the procedure. Advise them not to clench their jaws, tighten their shoulders or squeeze their eyes as if to close them. Also tell your patients to not move their heads or feet. Communication with your patients at every stage is essential. Continually explaining what will happen next helps keep them calm.

Responding to Suction Loss

Depending on when suction is lost, you'll need to decide whether to continue with the procedure or convert to LASIK or PRK.[7] Another option we use is restarting SMILE, which we recommend if suction loss occurs when you've cut less than 10 percent of the lenticule. You can repeat the lenticule side cut after decreasing the lenticule diameter if suction loss occurs during the side cut. If suction loss occurs during the cap side cut, repeat the cap side cut after decreasing the cap diameter.[2] For additional insights, the manufacturer's guidelines will help determine what to do after suction loss occurs.

Potential Complications

Here are potential complications that are important to keep in mind:

- Centration is more critical in SMILE than in LASIK. The procedure involves no auto-centration on the machine. Docking must be done over the corneal vertex, which usually corresponds to the pupil center.
- If gas bubbles produced by photodisruption don't dissipate, an opaque bubble layer forms. The main risk factors are low refractive errors (thin lenticule) and a thick cornea. Because of poor visibility in the presence of an opaque bubble layer, the dissection may enter the subepithelial plane instead of the anterior plane. You can avoid significant problems by gently massaging out the opaque bubble layer.
- Debris or air entrapped between the ocular surface and the interface can cause black spots.[2] The black spots cause adhesions and difficulty with dissection. To avoid this complication, use adequate wetting of the cornea before docking, and clean debris off the ocular surface and contact lens.

• Suction can lead to a SMILE subconjunctival hemorrhage, but it resolves spontaneously. We don't recommend vasoconstrictors preop because this pretreatment may affect the pupil size. Avoiding multiple re-applications of suction helps prevent subconjunctival hemorrhage.

Postop Follow-Up

After SMILE, your patient should adhere to a strict follow-up treatment schedule. Our postop regimen consists of topical steroids and a fourth-generation fluoroquinolone, both q.i.d., for a week. We taper the steroids during the following three weeks. We see patients after one day, one week, one month, three months and at one year.

Besides testing our patients' vision to identify potential overcorrection or undercorrection, we're careful to assess for signs and symptoms of dry eye. We routinely ask if they have any complaints of halos, glare, starbursts, hazy vision, blurred vision, distorted vision, double or multiple images, fluctuating vision, difficulty focusing, difficulty with night driving, eye pain or soreness, grittiness, foreign body sensation or light sensitivity. Determining if any symptoms are improving or getting worse is important.

The incidence of dry eye is reportedly lower after SMILE than after LASIK. Nevertheless, you need to inform patients about this potential complication before the procedure.

Below are additional potential postop complications:

• ***Transient light sensitivity syndrome.*** Photophobia may occur, but only transiently right after SMILE. Transient light sensitivity syndrome is a rare complication seen in some patients about seven weeks after SMILE. They'll experience severe bilateral photophobia but should recover after a month-long tapering dose of prednisolone acetate 1%. These patients typically have normal corneal topography results and no other eye pathology.[8]

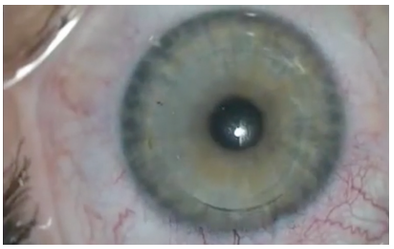

Figure 4. Strict follow-up after SMILE is critical to avoid complications. The authors prescribe topical steroids and a fourth-generation fluoroquinolone, both q.i.d., for a week, followed by a three-week taper of steroids. The patient is seen after one day, one week, one month, three months and at one year.

• ***Infectious keratitis.*** SMILE poses a risk of infectious keratitis. Careful antisepsis is paramount. Prompt interface irrigation and an antibiotic solution will avoid further vision-threatening progression.

• ***Diffuse lamellar keratitis.*** The incidence of DLK is lower after SMILE than after LASIK. An increased DLK incidence is found in patients with a thin and wide-diameter lenticule. Early diagnosis and treatment with topical steroids leads to a good prognosis.

• ***Epithelial ingrowth.*** Epithelial ingrowth, which has occurred in only one patient in an early report on SMILE, is less likely in SMILE because of the small incision involved.[9] To reduce the risk of this complication, avoid excessive manipulation during the extraction and dissection phase to spare the patient epithelial denudation and inadvertent pushing of epithelial cells into the cap. You can also avoid this complication by heeding previously mentioned contraindications, including recurrent corneal erosions, corneal basement membrane dystrophy and uncontrolled type 1 diabetes.

Irregular Astigmatism, Ectasia

A recent report noted that SMILE, when compared to FS-LASIK, led to a reduced magnitude of minute amounts of regular astigmatism and irregularities and less flattening of the midperiphery of the anterior and total cornea. (One of the authors is a consultant to Carl Zeiss.) The posterior cornea remains unaffected after SMILE.[10] Residual lenticule fragments that contribute to irregular astigmatism can be safely removed during a second surgery, if necessary, and avoided altogether with careful dissection and extraction of the complete lenticule.

The key to preventing post-SMILE ectasia is meticulous attention to the preoperative data found in the corneal topography, keratometry and pachymetry, as well as a careful and complete eye examination. A family history of keratoconus and some systemic diseases are risk factors. Fortunately, a 2017 literature review found postop ectasia was reported in only four patients out of 750,000 SMILE procedures. Three of the patients had subclinical keratoconus and were at high risk based on the Randleman Ectasia Risk Score System. In closing, we must remind all surgeons of the good news: Most complications after SMILE don't affect the final visual outcome.[8] REVIEW

1. Moshirfar M, Albarracin JC, Desautels JD, et al. Ectasia following small-incision lenticule extraction (SMiLe): A review of the literature. Clin Ophthalmol (Auckland, NZ). 2017;11:1683.
2. Titiyal JS, Kaur M, Rathi A, et al. Learning curve of small incision lenticule extraction: Challenges and complications. Cornea 2017;36:11:1377-1382.
3. Facts you need to know about the visuMax SMILE procedure for the correction of myopia. ttps://www.accessdata.fda.gov/cdrh_docs/pdf15/P150040C.pdf (Accessed Nov. 8, 2019)
4. Santhiago MR. Percent tissue altered and corneal ectasia. Curr Opin Ophthalmol 2016;27:4.
5. Sekundo W, Kunert KS, Blum M. Small incision corneal refractive surgery using the small incision lenticule extraction (SMILE) procedure for the correction of myopia and myopic astigmatism: Results of a 6 month prospective study. Br J Ophthalmol 2011;95:3:335-339.
6. Hamed AM, Heikal MA, Soliman TT, et al. SMILE intraoperative complications: Incidence and management. Int J Ophthalmol 2019;12:2:280-283.
7. Ivarsen A, Asp S, Hjortdal J. Safety and complications of more than 1500 small-incision lenticule extraction procedures. Ophthalmology 2014;121:4:822-828.
8. Desautels JD, Moshirfar M, Quist TS, et al. Case of presumed transient light-sensitivity syndrome after small-incision lenticule extraction. Cornea 2017;36:9:1139-1140.
9. Sekundo W, Gertnere J, Bertelmann T, Solomatin I. One-year refractive results, contrast sensitivity, high-order aberrations and complications after myopic small-incision lenticule extraction (ReLEx SMILE). Graefe's Arch Clin Exp Ophthalmol 2014;252:5:837-843.
10. Sideroudi H, Sekundo W, Kozobolis V, et al. Fourier analysis of corneal irregular astigmatism after small incision lenticule extraction and comparison to femtosecond laser-assisted laser in situ keratomileusis. Cornea. 2019 Dec;38:12:1536-1542. Cornea June 2019.
11. Krueger RR, Meister CS. A review of small incision lenticule extraction complications. Curr Opin Ophthalmol 2018;29:4:292-298.

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Accommodating IOLs: Two More Possibilities

More entries in the race to create a device that will truly let patients see near, far and everywhere in between.

Christopher Kent, Senior Editor

The race to create a working accommodative intraocular lens—one that can give patients something resembling the visual range most of us had in our youth—continues. In the June issue of *Review* we profiled three accommodating lenses in the pipeline (the Juvene, the Lumina and the FluidVision lens). This month we add two more to the list of aspiring contenders.

The Atia Vision Lens

The Atia Vision modular presbyopia-correcting intraocular lens (Atia Vision, Campbell, California) features a modular, two-part design. The back part of the device is a shape-changing "accommodating engine" that works using what the company calls a "hydraulic multiplier," intended to mimic the mechanism used in natural accommodation. This part of the device maintains direct contact with the capsular bag to maximize energy transfer between the ciliary muscle and the optic. The front section of the device is an exchangeable optic that's used to address the specific refractive needs of the individual patient. This part will be available in multiple powers and degrees of toricity, and should allow for future upgrades as refractive technology advances.

In preliminary (not-in-human) testing of the Atia Vision lens, both subjective and objective measurements confirm that accommodation is taking place inside the eye. No significant product-related adverse events have been seen to date.

P. Dee G. Stephenson, MD, FACS, president of the American Board of Eye Surgery, is familiar with the lens. "The goal of the Atia Vision lens design is to restore a full range of functional vision to patients," she explains. "Previous accommodative lens designs have produced limited accommodative response, difficult surgical procedures and unpredictable refractive outcomes.

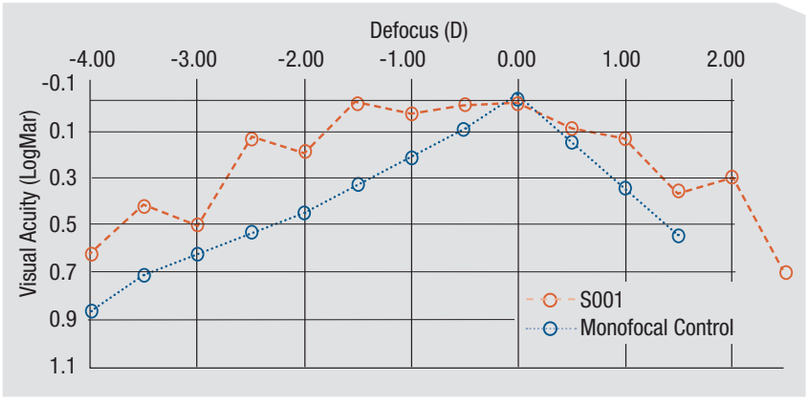
"The Atia features a modular design that should prevent visual disturbances and artifacts," she continues. "The shape-changing engine maintains direct contact with the open capsular bag to allow efficient energy transfer from the ciliary muscle, while the front optic is designed for refractive predictability and astigmatism control. It's easily exchangeable.

"Because of the modular design,

The Atia Vision modular presbyopia-correcting intraocular lens features a posterior section that changes shape to produce accommodation and an anterior exchangeable optic that addresses a patient's specific refractive needs.

This article has no commercial sponsorship.

Atia Vision Lens: Defocus Test



After ultrasound biomicroscopy showed accomodative movement in the lens, subjective testing corroborated that accomodation was occurring. (Monofocal control data used for comparison from Alio JL et al, 2016.[1])

implantation is a two-step procedure," she adds. "Otherwise, the surgeon follows normal cataract surgical procedures. Currently, first-in-human studies are under way in Europe. The results of those studies will inform future modifications of the lens."

For more information, visit atiavision.com/#company.

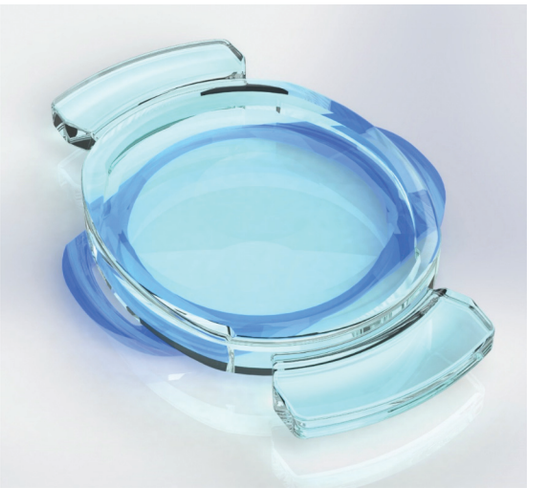
The Opira Lens

Another accommodative IOL in the pipeline is the Opira AIOL, from ForSight Vision6 (Menlo Park, California). The Opira is a dynamic, shape-changing lens, designed for placement in the sulcus (haptic-fixated within the capsulorhexis). The company says this placement allows direct ciliary body engagement without zonular or capsular bag intermediaries. (The company acknowledges that placing a lens inside the capsular bag may seem more intuitive, but that differences in capsular bag dimensions, elasticity, and healing/fibrosis factors between patients are problematic.)

The anterior surface of the Opira lens is dynamic; a static posterior lens can be used to correct regular astigmatism or for postoperative refractive adjustment. The company says the lens is easy to implant, requiring less than three minutes to position. An early clinical study involving 16 patients with a nine-month follow-up compared contralateral eyes, one implanted with a monofocal, the other with an Opira lens. The study found that when the eyes were corrected for distance, both lenses were 20/20 at distance, but at near the monofocal was 20/60, while the Opira lens was 20/25.

"The primary characteristic that distinguishes the Opira AIOL from many others is that it employs direct ciliary body engagement," explains Ayman Naseri, MD, president and CMO at ForSight Vision6. (Dr. Naseri is also a professor of ophthalmology at the University of California San Francisco.) "It doesn't rely on the elasticity of the capsular bag as an intermediary for dynamic shape change. Although the Opira lens is haptic-fixated within the capsule, direct engagement of the ciliary body allows robust accommodative function without relying on an important variable in pseudophakic accommodation—capsular bag elasticity and size differences between patients and over time."

Dr. Naseri says the data from the clinical studies conducted so far have been very promising. "They've demonstrated excellent safety and visual acuity, including monocular distance-corrected vision of 20/20 at intermediate and 20/25 at near," he notes. "Also, the Opira defocus curves are flat at



The Opira accomodating IOL features a dynamic anterior surface and a static posterior lens that's used to correct refractive errors, including astigmatism. A study with nine-month follow-up comparing the Opira to a monofocal lens found better vision at both intermediate and near (see table below).

Opira: Distance-corrected Contralateral Eye Study

Monocular visual acuity	Monofocal	Opira
Distance	20/20	20/20
Intermediate	20/30	20/20
Near	20/60	20/25

START WITH
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INDICATIONS AND IMPORTANT SAFETY INFORMATION

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

CONTRAINDICATIONS

- EYLEA® (aflibercept) Injection 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.

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*IBM Truven MarketScan data: Number of injections administered from Q4 2017 through Q3 2018; data on file.

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ADVERSE REACTIONS

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

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

anti-VEGF = anti–vascular endothelial growth factor; AMD = Age-related Macular Degeneration; DME = Diabetic Macular Edema; MEfRVO = Macular Edema following Retinal Vein Occlusion.

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

EYLEA®
(aflibercept) Injection
For Intravitreal Injection

09/2019
EYL.19.09.0044

EYLEA®
(aflibercept) Injection
For Intravitreal Injection

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

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

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

4 CONTRAINDICATIONS

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

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

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

5 WARNINGS AND PRECAUTIONS

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

8 USE IN SPECIFIC POPULATIONS.

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

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

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

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

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

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

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

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

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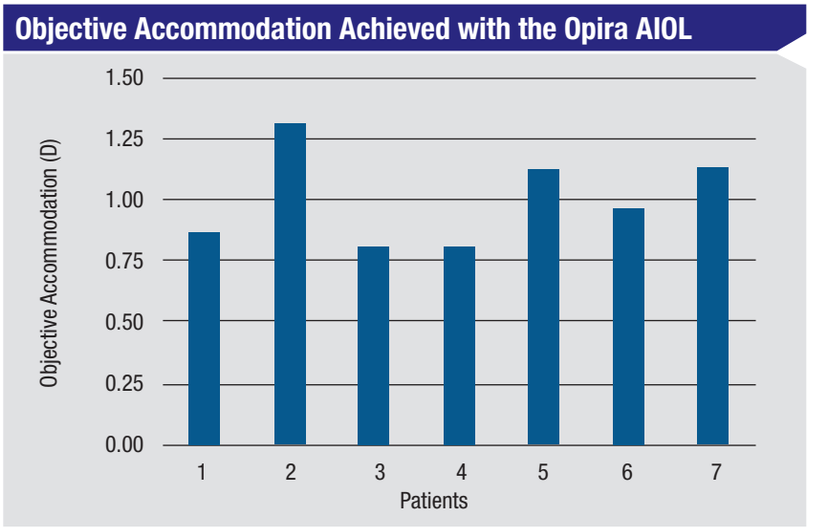
Manufactured by:
Regeneron Pharmaceuticals, Inc.
777 Old Saw Mill River Road
Tarrytown, NY 10591

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

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

EYL.19.07.0306



Early testing indicates that subjects implanted with the Opira accommodative lens are indeed showing accommodation.

the top. That's consistent with true accommodation."

Dr. Naseri says the Opira is implanted using an injector via a temporal clear corneal incision. "The insertion is straightforward and intuitive," he says. "It takes about one minute longer than the time required to insert a monofocal IOL."

The company is currently recruiting new patients for a proof-of-concept trial to demonstrate 1 D of objective accommodation with the lens. "In terms of what's next, we'll continue fine-tuning certain aspects of the Opira lens as we conduct additional clinical studies," Dr. Naseri says. "It's availability in the U.S. marketplace will depend largely on the FDA regulatory approval process, which we're preparing for now." REVIEW

1. Alio JL, Simonov A, Plaza-Puche AB, et al. Visual outcomes and accommodative response of the Lumina accommodative intraocular lens. Am J Ophthalmol 2016;164:37-48.

Burned Out No More: Relighting the Fire

Christopher Kent, Senior Editor

Physician burnout has become an epidemic. Here's what you can do to keep burnout at bay.

No matter how you look at it, physician burnout has become an epidemic—and one with serious consequences. Not only does it rob doctors of the pleasure they might expect to derive from being a physician, it undercuts patient care; it's contributing to doctors abandoning the profession, while the number of patients keeps increasing; and it's contributing to an alarming increase in physician suicide. Leaving matters as they are isn't an option; physician burnout is becoming more widespread every year.

To help get a handle on this epidemic, three professionals who have devoted significant time and effort to dealing with this crisis share what they've learned about 1) the causes of burnout—which may extend beyond the obvious culprits; 2) recognizing that you're not simply tired—you're in trouble; and 3) specific steps you can take to prevent burnout from derailing your life and career.

The Root of the Problem

Susan E. Connolly, MD, who practices at the Palo Alto Foundation Medical Group, a large multispecialty medical group in northern California that employs more than 1,500 physicians, says she became interested in the subject of physician burnout when she realized that the phenomenon was becoming an epidemic—both across the country and in her own organization. (Dr. Connolly is an active member of the organization's physician wellbeing committee, and she's spoken on the topic of physician burnout at the past two meetings of the American Academy of Ophthalmology.)

"Over the past five to seven years, more and more physicians in our organization started showing symptoms of burnout," she explains. "Doctors were complaining about the changing nature of the job and cutting back

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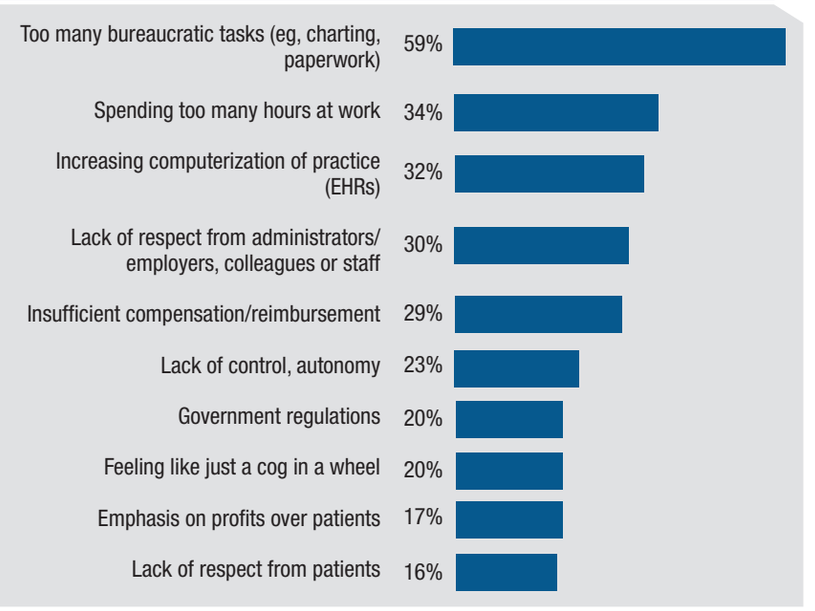
their hours. Physicians who used to talk enthusiastically about their work stopped doing so. Doctors began retiring early or leaving medicine. Never in my career had I seen such a mass exodus from the profession.

"It's no secret that a big part of why we're all burned out is because of the way American medicine and technology have evolved," she says. "Technology in medicine, for example, has been sort of an evil rather than a benefit. Our medical records are now computerized, so we wind up typing the whole time we're with a patient instead of making eye contact the way we would have in the past.

"That's piled on top of other stresses," she continues. "We have to fulfill countless requirements just to be reimbursed. We spend a lot of time trying to convince insurance companies that medicines or other treatments we recommend are truly best for our patients, even though they may be more expensive than what the insurance company wants to cover. Essentially, we're doing the opposite of what we intended to do when we entered the profession. I think that's why physicians are more burned out than most other professions."

Dr. Connolly says she decided to join her organization's wellbeing committee because she had some ideas she thought might help alleviate the situation. "One of the first things we did was to formally study physician burnout in our organization," she says. "We created a one-page survey that we distributed to about 1,000 of our physicians. We discovered many factors that are associated with increased levels of burnout, including having less control over your work schedule and work environment; spending more hours documenting data on the computer; and feeling undervalued and underappreciated. We also found higher levels of burnout associated with female gender, and with holding leadership positions within the organization."

What Contributes Most to Your Burnout?



The Medscape National Physician Burnout, Depression & Suicide Report 2019 surveyed 15,069 physicians in more than 29 specialties practicing in the United States about their experiences with burnout. Some of the survey results are shown here and on the upcoming pages. (For more information and additional survey results, visit medscape.com.)

Dr. Connolly says the next question they asked was how their survey results compared to the rest of the nation. "Medscape has surveyed more than 15,000 physicians across the country in the past several years," she says. "Their data is very similar to ours. For example, the specialties with the highest levels of burnout are the primary care specialties, such as internal medicine and family medicine. Ophthalmologists are about the third lowest among all physicians in terms of burnout, but we still have more than 30-percent burnout. This is no small problem."

Delving Deeper

Robert Pearl, MD, the former CEO of The Permanente Medical Group, who now writes and lectures about how to improve health care in America, agrees that the obvious systemic problems physicians face contribute to burnout. However, he believes there may be more to this than meets the eye. "If you survey physicians about the problem of burnout, they all point to practical day-to-day issues," he says. *(For example, see the chart above.)* "Those factors are real, of course, but they don't fully explain the problem of physician burnout. There's a second aspect to this that doctors often fail to recognize. Why do some specialties have a lot more burnout than others? It's not about money, because some specialties, like pediatrics, make very little money but have a relatively low rate of burnout. I believe the answer has to do with the issue of mission and purpose.

"There's a clash between the rapidly changing world around us and a very slowly changing health-care culture," he says. "Physicians pursue medicine partly to make a good living, but also for mission and purpose. Right now, mission and purpose are being eroded. The culture of medicine and the

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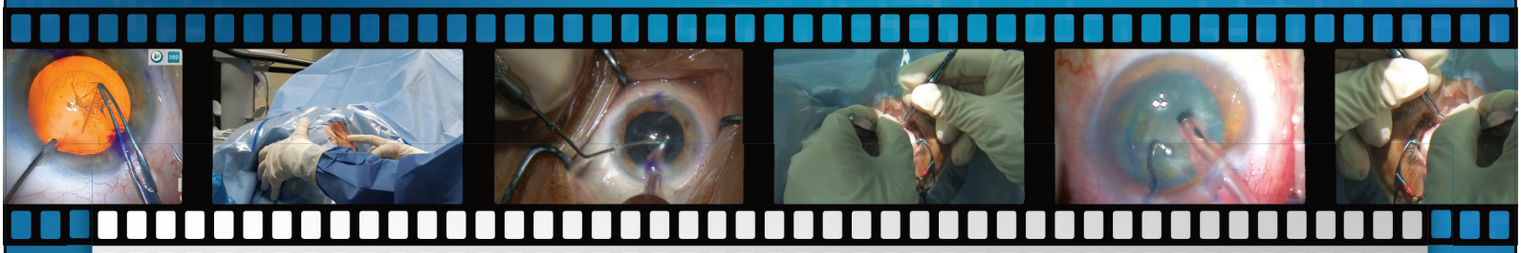

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Richard J. Mackool, MD

We are excited to continue into our fourth year of Mackool Online CME. With the generous support of several ophthalmic companies, I am honored to have our viewers join me in the operating room as I demonstrate the technology and techniques that I have found to be most valuable, and that I hope are helpful to many of my colleagues. We continue to edit the videos only to either change camera perspective or to reduce down time – allowing you to observe every step of the procedure.

As before, one new surgical video will be released monthly, and physicians may earn CME credits or just observe the case. New viewers are able to obtain additional CME credit by reviewing previous videos that are located in our archives.

I thank the many surgeons who have told us that they have found our CME program to be interesting and instructive; I appreciate your comments, suggestions and questions. Thanks again for joining us on Mackool Online CME.

CME Accredited Surgical Training Videos Now Available Online: www.MackoolOnlineCME.com

Richard Mackool, MD, a world renowned anterior segment ophthalmic microsurgeon, has assembled a web-based video collection of surgical cases that encompass both routine and challenging cases, demonstrating both familiar and potentially unfamiliar surgical techniques using a variety of instrumentation and settings.

This educational activity aims to present a series of Dr. Mackool's surgical videos, carefully selected to address the specific learning objectives of this activity, with the goal of making surgical training available as needed online for surgeons motivated to improve or expand their surgical repertoire.

Learning Objective:
After completion of this educational activity, participants should be able to:

- Understand the ability to vary nuclear segment removal by adjustment of the maximum vacuum level.

Satisfactory Completion - Learners must pass a post-test and complete an evaluation form to receive a certificate of completion. You must listen to/view the entire video as partial credit is not available. If you are seeking continuing education credit for a specialty not listed below, it is your responsibility to contact your licensing/certification board to determine course eligibility for your licensing/certification requirement.

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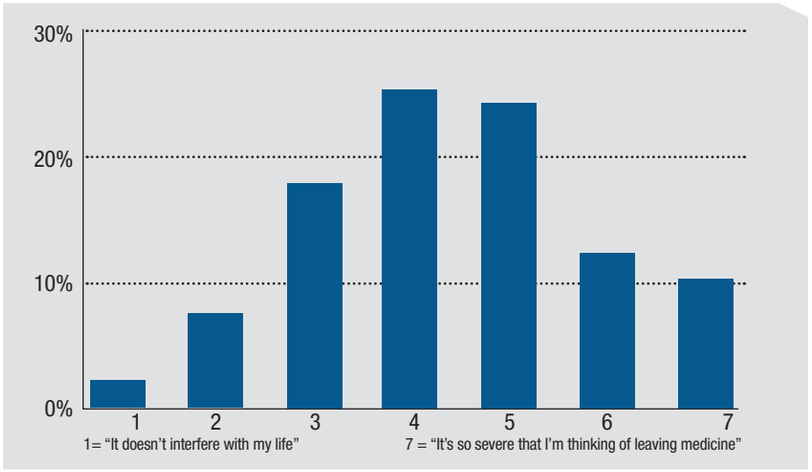
How Severe Is Your Burnout?



world around us don't connect the way they used to. As a result, medicine has become a far less fulfilling profession than it used to be. This change is easy to overlook, because we don't usually notice the culture we're enmeshed in. We just accept it. It's only when it starts to clash with what's happening around us that we start to notice it."

Dr. Pearl says a key to dealing with this culture clash is to stop resisting change; instead, find ways to make it work to your advantage. "For example, one development that could help reduce cost and improve patient care is using artificial intelligence to evaluate the retina," he says. "This could be far more efficient than the system we have today. Are ophthalmologists going to help that change occur, or resist it? My prediction is they'll resist it, simply because it's so different from their historical culture, and there are economic consequences. This is the clash between the old culture and the new science.

"Doctors need to lead the process of change, not be a brake on it," he says. "We have to be the ones coming up with solutions, because we'll come up with better answers than administrators or elected officials. The insurance companies and drug companies aren't going to get this right. Physicians have to lead the way. If we don't, the problem of burnout will just continue to grow."

Realizing That You're in Trouble

One reason the epidemic is growing is that physicians aren't always good at recognizing when they've gone beyond just being tired to being in danger. Craig N. Piso, PhD, a psychologist and organizational development consultant with a focus in ophthalmology, offers some perspective on how burnout affects an individual.

"I like to think of human beings as having a reservoir of mental energy," says Dr. Piso. "This is a concept I first encountered in the work of C. Nathan DeWall, PhD, a professor of psychology at the University of Kentucky. We need a full reservoir of psychological, emotional and cognitive energy to do all the things we normally do. When our reservoir of energy gets low, we start to get into trouble, not the least of which is—as Dr. DeWall describes it—a gradual erosion of our ability to control ourselves, physically, mentally and emotionally. That's a key symptom of burnout.

"I like to take it to the next level," Dr. Piso continues. "During burnout we start to lose what's called 'emotional intelligence,' a concept championed by Dan Goleman in his book of the same name. Emotional intelligence refers to our ability to recognize and manage our emotions, as well as recognizing emotions in others and being able to influence them.

"Empathy is a big part of this—being able to put yourself in another person's place and understand that person's perspective," he explains. "This is a cornerstone of building and maintaining great relationships, and lack of it is a sure sign of burnout. We become self-absorbed, distancing ourselves from others and cutting off relationships—including those close to us. We become more cold, uncaring and disconnected, and others notice it.

"A second aspect of this is what might be called emotional self-regulation—the ability to manage our own emotions," he says. "When we're healthy, emotions don't overwhelm us. We can maintain an even keel, emotionally speaking. When we get burned out we start to lose control, and our emotions can get the best of us. We become more impulsive, irritable and agitated, and we lose patience more quickly."

Dr. Piso notes that the signs and symptoms of burnout can be similar to those of clinical depression. "For example, people getting burned out start to feel exhausted," he says. "They don't have physical or emotional energy. They stop taking pleasure in things they previously might have enjoyed. They lose interest in what they're doing. They start asking themselves: Why bother? Who cares? What's the use?"

Dr. Pearl points out that recognizing burnout in yourself isn't rocket science; he believes the danger lies in not realizing when it's become a threat. "Most doctors who are burned out are well aware of it," he says. "If you're unhappy and depressed, you know it. If your work is less and less fulfilling, you know it. If you're having increasing difficulty integrating your

Changing Behavior to Change Your Thoughts

"Everybody understands that how we think affects how we behave," says Craig N. Piso, PhD, a psychologist and organizational development consultant with a focus in ophthalmology. "What not everybody realizes is that it also works the other way around: Repeated positive actions will eventually reshape your thinking. The saying, 'Fake it 'til you make it,' that's repeated at support groups reflects this reality. Cognitive behavioral therapy has shown that if you behave in a way that differs from your thinking, eventually your thinking will change to align with your behavior.

"What our brains don't tolerate well is cognitive dissonance," he explains. "A person might not think of himself as competent, but if he continues to act as if he's competent, eventually his brain will decide that he is, in fact, competent. This also applies to feelings of self-worth. Part of staying out of trouble is having a healthy amount of self-love. I know it sounds corny, but if you don't love yourself, you won't deem yourself worthy of putting in the time and energy to nurture or protect yourself from things like burnout. You have to know that it's worth it to go to the trouble to buy good food and eat right, get enough sleep, and take whatever steps will keep you healthy and happy.

"Many people would address a lack of self-esteem by seeing a therapist or pastoral counselor," he continues. "However, you don't have to focus on changing your emotions first. You can act as if you're worthy of self love, even if you believe you aren't. After a while, your brain will decide that you really are worthy."

Dr. Piso notes that this is counterintuitive. "Nevertheless, this approach is a bona fide part of treatment," he says. "If you take the action that you want to be able to take, as if you're already there—as if you already have self-esteem, or confidence, or energy—the act of role-playing, pretending that this is real, contributes to making it real for you. You just have to give it a little time to kick in. It's a paradox, but it works."

Dr. Piso admits that changing your thinking and/or behavior may take some effort. "When we have ingrained thoughts borne out of habit, it's like trails in the desert carved out by wagon wheels from people taking the same route year after year," he says. "Those wagon wheels have made deep ruts that you're likely to fall into. The neuroscience corollary of that is: Neurons that fire together eventually wire together. So if you repeat thoughts or behaviors for a long period of time, they become—literally—a part of your brain wiring. That, in turn, makes it hard to change.

"Nevertheless, making changes may be the key to ending your suffering," he adds. "It's worth making the effort."

—CK

personal and professional lives, you know it. That's why doctors report being burned out in those surveys. They clearly know what they're experiencing.

"On the other hand, it can be a lot harder to realize that you've reached a point at which you're in serious trouble because of the burnout," he says. "Burnout can have negative consequences, all the way to suicide. Four hundred doctors a year commit suicide—more than one a day. So the problem isn't so much knowing that you're experiencing burnout; it's knowing that you've reached a point at which you need to get help before things get out of hand."

Addressing the Problem

Dr. Connolly says that to help come up with effective ways to combat burnout, her wellbeing committee has borrowed a model of professional fulfillment created at Stanford University. "The Stanford model lays out three things that are required in order to have professional fulfillment—or in this case, to prevent physician burnout," she explains. "The three components are: a culture of wellness; personal resilience; and efficiency of practice. You need all three in order to prevent physician burnout. We're working on improving them at our organization, and we've had good results so far.

"The first component is a culture of wellness," she says. "Basically, physician wellness has to be a priority in your practice. You can't make changes for the better if the problem of burnout isn't taken seriously. Fortunately, our CEO—who is an MD—has made it a goal to bring joy back to the workplace. He created the Joy of Work Initiative, and it's part of our budget. That means we have funding to work on alleviating physician burnout.

"The second thing is personal resilience," she continues. "Through the wellbeing committee we've implemented a number of programs to help physicians with this. For one thing, our research showed that physicians who attended more physician meetings had lower levels of burnout, so we realized that socializing with colleagues might be helpful. With that in mind we've sponsored a number of social events, involving things such as eating together, visits to art museums and attending concerts. We also have a wellbeing retreat weekend every year-and-a-half for physicians and their families. These events have been popular and well-attended.

"Putting money towards social events might sound frivolous, but it turns out that we can't afford to not do it," she notes. "Keeping people from feeling isolated is very important. Paying for a happy hour, for example, isn't that expensive. On the other hand, it's

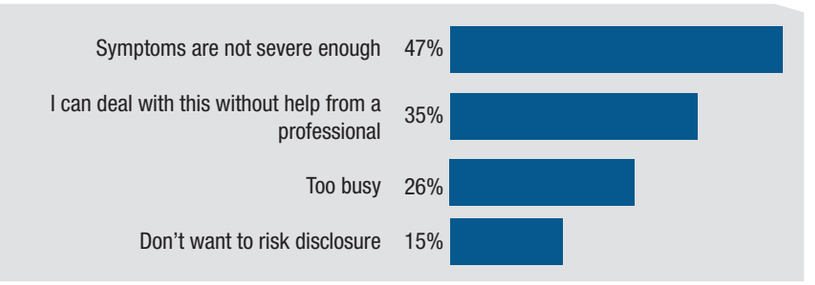
been shown that it can cost a medical organization as much as $500,000 per year to lose a physician. Holding social events increases the sense of community in a practice and increases the happiness set point. The return on investment is high.

"Another way to increase personal resilience is through mindfulness training," Dr. Connolly continues. "The original Mindfulness Based Stress Reduction course was designed by Jon Kabat-Zinn at the University of Massachusetts Medical School more than 40 years ago; the techniques taught in the course have been shown to reduce depression, stress and anxiety. His course is now offered all over the country. In fact, our organization has been offering it to patients and the community for about 20 years.

"Five or six years ago I took the course myself, and it was great," she says. "However, I realized it would have been even more worthwhile for me if the other people in the class were also physicians experiencing things similar to what I was going through. So I suggested to the wellbeing committee that we offer a modified version of the course to our physicians, free of charge. We got approval and funding and then worked with the mindfulness teachers we already employed to create a modified version of the course designed specifically for our physicians. We've been offering it for the past two years, and it's been very popular. It really does help our doctors avoid burnout."

Dr. Connolly notes that the third aspect of the professional fulfillment triad—efficiency of practice—is probably the hardest to accomplish. "It's hard to make the system more efficient," she admits. "Many changes that can increase efficiency require an investment of time and money. However, in our organization, a few simple things have been helpful. For example, we've found that having the same support staff every day, a consistent 'health-care team,' improves efficiency and wellbeing for providers and patients alike." *(For more suggestions, see the pearls below.)*

Why Have You Not Gotten Help?



Keeping Burnout at Bay

As noted earlier, a little burnout may be hard to avoid for many physicians. The key is making sure you address the problem head-on and do everything possible to reignite joy in your work and prevent further decline. The following strategies can help keep burnout from getting out of hand.

• ***Watch out for all-or-nothing negativity.*** Dr. Piso says this is a sign of a more serious level of burnout. "At this stage people start seeing everything as awful," he explains. "A healthy person can tease out the good and separate it from the not-so-good, but a person with advanced burnout just lumps it all together: 'Life sucks and then you die.' 'I can't succeed at anything and I never will.'

"That type of depressive thinking should be a huge red flag that you're in trouble," he notes. "The worst part about this type of thinking is that it becomes a self-fulfilling prophecy and contributes to a more intensive downward spiral. It can culminate in serious depression—or worse."

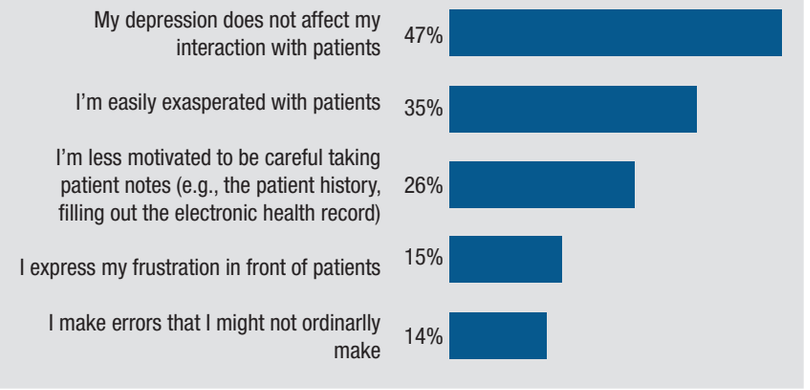
• ***Don't take on the role of victim.*** Dr. Piso says this is one of the most important parts of preventing or recovering from burnout. "It's crucial to take personal responsibility for being the steward of your own heath and wellbeing," he says. "The biggest mistake people make is externalizing, blaming, making excuses and feeling like a victim. You have to stop buying into the idea that the circumstances stressing you out are somebody else's fault. If you take on the role of victim, you're abdicating the power to improve things. The mindset that will put you back in control is: I'm responsible; I'm the steward. The buck stops here. It's up to me to make things better."

• ***If you find you're turning inward, do the opposite.*** "When we get stressed out, we turn inward," Dr. Piso notes. "We make it all about ourselves. We don't necessarily do it consciously, and it's usually not malicious. It's just dysfunctional. It's like a form of self-preservation when we're feeling attacked, in danger and depleted.

"The solution is to do the opposite," he says. "When you're getting tired and thinking 'What's the use? Why bother?' do the opposite of what you're tempted to do: Turn outward. Become altruistic. Decide to get even more focused on taking great care of your patients and your staff, even if you don't feel like you have it in you. Because something miraculous happens when you put your heart back into your work—what I call 'working wholeheartedly.' We know from neuroscience that being of service to others, unselfishly and unconditionally activates a part of the brain that makes us feel joy, fulfillment and satisfaction, and increases our energy."

Dr. Piso acknowledges that doing

Does Your Depression Affect Patient Care?



this may seem like a huge leap when you're already feeling burned out. "You have to prime that pump," he says. "You prime it by saying, I'm going back to the reason I went to medical school in the first place. Most likely, before you thought about money, you thought it would be really cool to heal people, ease their suffering, or perhaps do surgery and correct problems. Go back to focusing on that! Work wholeheartedly.

"It's not necessarily logical, but after 40 years as a psychologist working with thousands of people, I can tell you that this secret sauce is real," he adds. "Focus on the idea of helping others rather than the obstacles you face, and you can come back from burnout. This is something you can do every day. You don't have to wait for a trip to Italy."

• ***Remember that difficult life circumstances can increase the risk of depression and burnout.*** Dr. Connolly says that one of the things her group does to combat burnout is take note when a physician is at higher risk because of challenging life circumstances, such as dealing with a death in the family, having a serious illness or going through a divorce. "Doctors in these situations are at risk of falling way below the curve," she points out.

"We've set up a system to address this type of circumstance discreetly," she continues. "When someone on our wellbeing committee realizes that a doctor is under unusual stress, we reach out and let the doctor know that we're here if he or she needs someone to lean on. We've received additional training in this area, and we're available to provide emotional support. We can also direct the individual to additional resources when necessary.

"It might be even easier to manage this in a small practice where everyone knows everyone else," she says. "One person could be assigned to stay alert for doctors or staff dealing with tough life circumstances, or a committee of two or three people could get together once a month to talk about issues like this."

In the Office

Here are a few steps you can take to improve things and lower stress in your workplace:

• ***Set up your exam rooms to make your job as easy as possible.*** Dr. Connolly describes two changes her organization made to exam rooms that have helped to eliminate a little bit of stress. "First, we make sure every exam room is set up exactly the same," she says. "That allows us to standardize where everything is kept, so we're not wasting our time looking for things.

"Second, we aim to have a printer in every exam room so there's no disruption if we want to give a handout to the patient or print out a prescription," she continues. "If we have to leave the room to go to the printer, we've already broken eye contact with the patient. If there's a printer in every exam room, we can continue to have eye contact with the patient and we don't disrupt the flow. This is helpful, and it doesn't cost much."

• ***Look for additional ways to offload tasks.*** "As part of our effort to make things more efficient, we've tried to figure out which tasks don't really need to be done by an MD," Dr. Connolly says. "For example, we physicians receive numerous emails from patients every day, and patients expect an immediate response. We're now aiming to have our support staff weed through the emails and handle whatever they can on their own, such as helping a patient schedule an appointment, or forwarding medical records or DMV forms. It's worth stepping back for a minute and considering if there are tasks you're doing that could be done just as well by another staff member."

• ***Remember that your team takes their cue from you, creating a feedback loop.*** "In American culture, people see doctors as powerful individuals," notes Dr. Piso. "They'll follow your lead, so your mood and attitude sets the tone for your team. What most people forget is the counterintuitive part: The mood of your team then affects you in return.

"So, if you want your team to be more energized, have more fun, work harder and be more productive, you need to model that behavior," he says, "even if you have to 'fake it until you make it.' If you do this—even when you're not feeling 100 percent—the people around you will follow your lead, and you'll find yourself surrounded by positive people. That, in turn,

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will make it easier for you to avoid becoming tired and negative."

• ***Even if you feel down, don't complain to your team or patients.*** "Complaining will always backfire, because people almost always see a doctor's life situation as more privileged than theirs," notes Dr. Piso. "They won't understand that you're dealing with burnout. They'll say, 'What gives this doctor the right to complain? This is a successful, powerful person who owns three Porches and four houses and has more money than God.' You'll never get sympathy, and it will lower people's estimation of your character. So save your complaints for people who understand that you're struggling with burnout—especially those who may be in a position to help you deal with the problem."

• ***Keep your focus on improving patient care.*** "Many of the problems that lead to burnout are tied to the problems patients are having getting help in the current system," notes Dr. Pearl. "We need to be proactively looking for ways to provide more high-quality care at a lower cost. If we succeed, we'll end up addressing many of the factors that have helped create burnout in the medical profession."

Make the Most of Resources

There are plenty of things you can do to mitigate the challenges of being a physician today:

• ***Take the time to do things that add purpose to your life.*** "Many ophthalmologists travel to other countries and do intraocular lens replacements for patients with cataracts," notes Dr. Pearl. "They come back energized.

"Of course," he adds, "many physicians will say, 'I have no time for that.' If you're experiencing burnout, taking the time to do something like this will not only help save the sight of the people you reach, it might save your life."

• ***Reinstate socializing with your peers.*** Dr. Pearl notes that in large medical systems physicians sometimes have a physician dining room where doctors of many specialties and backgrounds interact during meals. "Meeting with your peers does two things," he says. "First, it minimizes a sense of isolation. You can see that your peers are dealing with challenges similar to yours and find out how they're dealing with them. Second, it makes it possible for our medical culture to evolve. That evolution is necessary for our culture to keep up with the rapidly changing world around us."

Dr. Connolly says that perhaps the most important way to avoid burnout is to take a moment each day and remember why you became a doctor—and why you chose ophthalmology in particular.

Dr. Pearl acknowledges that there's plenty of interaction taking place via social media, but says that's not sufficient. "There's a huge amount of discourse taking place online," he notes. "However, it's mostly people with the same beliefs talking to each other about their unhappiness with the current situation. They're not asking what we can do differently, so it's not helping medicine to evolve."

• ***Give those close to you permission to let you know how you're doing.*** "There are many things you can ask family, friends and coworkers to do to help you deal with burnout, but one of the most helpful is to ask a few people close to you to be your accountability partner," says Dr. Piso. "Of course, you have to select the individuals judiciously. But let them be your social mirror and tell you if your behavior is headed in a bad direction.

"Think of someone who tells you you have parsley in your teeth at a cocktail party," he continues. "You may feel a little embarrassed, but you're grateful that they told you, because they could see what you couldn't see. So, ask people you feel close to to do that for you. When you're starting to be irritable or selfish, insensitive, short-tempered, impatient, lackluster, they'll bring it to your attention so you can take action."

Dr. Piso points out that those close to you are more likely to do this if you give them full consent. "You have to expressly give them permission to upset you," he says. "Ask them not to do it in public, or in a malicious way, but tell them you want to know if you're starting to exhibit signs of burnout. This is far better than having them be silently worried or annoyed while you get deeper in trouble."

• ***Check out Yale University's "happiness class."*** "A very interesting set of conversations is being held right now by Laurie Santos, PhD, a professor from Yale," says Dr. Pearl. "Her 20-hour class, 'The Science of Wellbeing,' delves into what does and doesn't actually make people happy. It's become the most popular course in the history of Yale University. One out of every four students takes it. Best of all, anyone outside of Yale can now take it, for free: It's available online at no cost.

"Dr. Santos shows how and why the things we expect to bring us happiness—and I would add the word 'fulfillment'—often fail to do so," he continues. "For example, many people believe that having more money will make them happier. The data says that's not true, once you've reached a certain basic level of income. (That

income level, by the way, is well below the average ophthalmologist's salary.) She also spells out many specific things you can do that will help to make you happier.

"Taking her course is a good investment of your time, even if you're not burned out," he concludes. *(For more information, visit coursera.org/learn/the-science-of-well-being#)*

• ***Learn some of the "mindfulness" techniques.*** "I realize that a small practice may not be in a position to duplicate some of the things we've done, such as creating a special version of the popular mindfulness course, tailored to physicians," says Dr. Connolly. "However, there are many other things anyone can do for free or very little cost. There's plenty of free information about mindfulness and the course online. Also, some of the techniques it teaches are very simple, such as learning to do mindful breathing. You don't have to attend a formal program to pick up some of those techniques."

Dr. Connolly offers another example. "It may sound overly simple, but one thing I've learned to do is keep a small, smooth stone in my pocket," she says. "When I find myself feeling stressed, I put my hand in my pocket and feel the smoothness. It reminds me to breathe in and out and pay attention to my breath. I may take one minute to just meditate, even in the hallway between patients. It's amazing how much difference small things like this can make."

• ***Take advantage of free online meditation apps.*** "The practice of 'sitting meditation'—even if you only do three minutes a day, ideally in the morning—sets the tone for the day," says Dr. Piso. "It's like calibrating your mind and body and emotions to be in a more helpful mindset. There's a lot of free material online to help guide you through doing this, and it can make a big difference.

"I know some doctors will say, 'I don't have three minutes in the morning.' Well, think about it," he says. "If you don't have three minutes a day to invest in yourself by doing something simple and easy that might really help you, that's an early warning sign that you're already a long way down the wrong road. That's diagnostic. You're living in denial and putting yourself at greater risk."

Don't Wait to Ask for Help

The greatest danger when experiencing burnout is that you'll simply treat it as an unhappy fact of life and do nothing about it. Everyone with expertise in this area agrees: If you're experiencing burnout, don't wait to take corrective action.

"If you're hiking and you're not sure you read the path signs correctly, it's better to stop and retrace your steps when you're only 50 yards down the wrong path than to wait until you've gone five miles," says Dr. Piso. "Similarly, it's easier to do something to counteract your burnout when you're just starting to get exhausted and noticing your negativity and lack of empathy and lack of emotional self-regulation. If you choose to ignore it or pretend it will go away on its own, you'll find yourself getting deeper and deeper into burnout—and potentially in the throes of depression. As in any type of health care, early detection and treatment is the best medicine."

Dr. Pearl notes that seeking help for psychological stress is sometimes seen as a personal failing. "We use the term 'mental health' as a pejorative in this country, as if being overwhelmed by stress is a failure of the individual," he says. "Burnout is not a personal failing. If you're in this situation, it's not your fault. You shouldn't blame yourself—but you SHOULD take action. The symptoms can be debilitating, and they can lead to suicide. So don't blame yourself for needing help dealing with this. Instead, take action."

(Continued on page 53)

Bridging the Generation Gap

By Sean Mckinney, Senior Editor

Myths, hard realities and solutions for millennials and older ophthalmologists to consider in these sometimes divisive times.

The young ophthalmologist had just signed a junior partnership agreement … then discovered the next day that her new practice was going to be sold to a private equity firm. Prospects of a long and prosperous career seemed to be swallowed in one gulp by the takeover, prompting her to abandon her new agreement ASAP. Elsewhere, an aging ophthalmologist worked hard for more than 40 years to build a robust practice … but he couldn't find a younger doctor eager enough to take on the extra hours and weekend calls needed to eventually take over the lucrative concern.

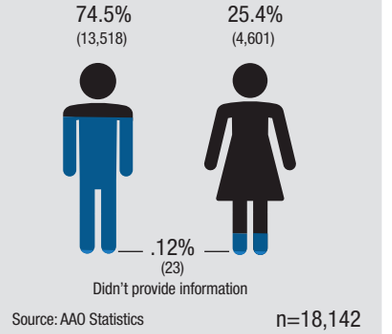
Between these two extreme scenarios lies a gap between millennials and older practitioners created by myriad factors, including decreasing reimbursements, increasing regulations, future practice environment uncertainty and practice consolidation, as well as distinctly different lifestyles, work philosophies, networking behavior and methods of sharing clinical cases.

Although the gap is a reality, it's also part myth and part misunderstanding. In this report, thought leaders lay out some key drivers of generational conflicts and suggest ideas that both sides may use to bridge the gap with new ways of working together.

Private Equity at the Gate

Possibly the deepest divide between millennials (practitioners ages 23 to 38 years old) and older ophthalmologists pertains to the growing private equity movement, driven by firms that purchase medical practices with capital from pension funds, sovereign wealth funds, high-net-worth investors and university endowments. The firms, anticipating average annual returns of 20 percent or more, typically acquire a platform practice, paying 8 to 12 times earnings before interest, taxes, depreciation and amortization (EBITA); then they expand by buying smaller

Practicing U.S. Ophthalmologists by Gender



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Thomas A. Oetting, MD, MS

Thomas A. Oetting, MD, MS, residency program director at the University of Iowa, (left) strives to clear up myths that can blur the views millennials and older ophthalmologists have of each other. Here he is caught via a mobile phone discussing intraocular lens power calculations after cataract surgery with third-year resident Caroline Wilson, MD, (middle) and second-year resident Karam Alawam, MD (right).

practices at two to four times EBITA or less.[1] The second phase of the purchase and development plan for the private equity firms is to streamline practice expenses, add revenue streams and resell the enlarged practices within three to seven years.[2]

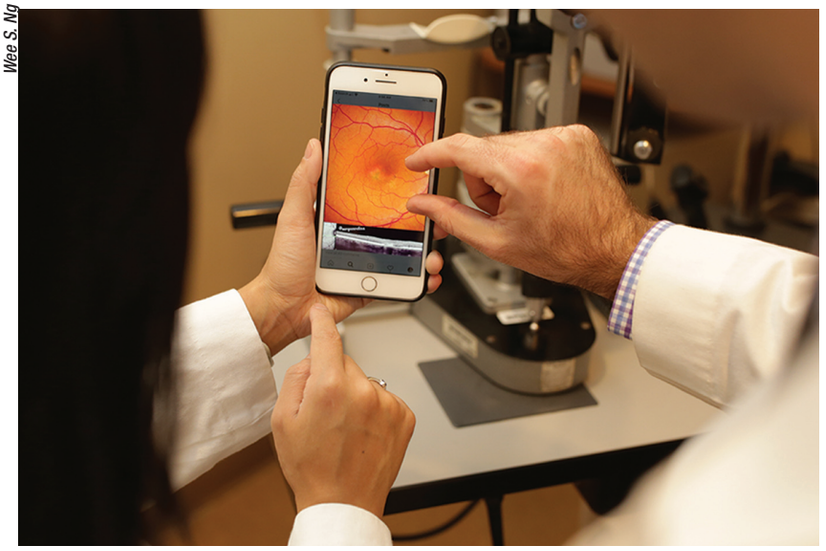
Private equity firms, which focus on specialties that offer higher-income elective procedures, have concentrated primarily on dermatology, but their interest is now turning to ophthalmology, urology and gastroenterology.[2] Some suggest that many firms are now exploring opportunities in ophthalmology, having become more active during the past couple of years. George Williams, MD, president of the American Academy of Ophthalmology, says an estimated 10 percent of ophthalmologists are now working in a private equity model.

Although private equity firms are described by experts as diverse and motivated, in some cases, to use incentives to attract the interest of younger ophthalmologists, millennials are short on enthusiasm for the current offerings. This vocal group of young ophthalmologists now makes up 14 percent of the AAO's membership.

"Private equity is the least favorable option for young ophthalmologists," says Tom Harbin, MD, MBA, a published expert on the business side of medicine. "Under private equity, young ophthalmologists who aren't partners will experience a lifetime of practice with reduced freedom and probably reduced income. As a young ophthalmologist, you typically won't receive a payoff from the private equity group that is taking over your practice, nor will you share in the future growth of the equity or overall earnings of the practice. The young person who is not a partner will earn less money if he or she practices with a group that's been purchased by a private equity group.

"Meanwhile, the physicians who are partners and sell their practice to a private equity firm receive a large upfront payment for the sale of their practice," he says. "That large payoff

Wee S. Ng



Janice C. Law, MD, retinal specialist, assistant professor at Vanderbilt University and chair of the AAO Young Ophthalmologist Committee, uses her iPhone to review fundus photographs, autofluoresence and OCT to demonstrate a challenging case of central serous retinopathy to a first-year resident. The resident's fingers estimate an area of extensive fluid reduction from an epleronone treatment. "Young ophthalmologists constantly use mobile devices to exchange cases and images—with identity masking to protect patient privacy, of course," Dr. Law says. "It's how we learn. It's how we teach."

is taxed as long-term capital gains, at a much lower rate than ordinary income tax. The partners usually give up income generated by practice profits forever and they earn much lower income as practitioners. The benefit for them, however, is that they pay an ordinary tax rate on their reduced income for their remaining years in practice. In this scenario, they usually come out way ahead because it takes years before you can be affected by a financial disadvantage from giving up that yearly revenue from your practice."

Janice Law, MD, a retinal specialist at Vanderbilt and chair of the AAO Young Ophthalmologist (YO) Committee, says her peers worry about practice equity taking away future freedoms and opportunities. One of her friends, the millennial mentioned at the beginning of this article, had to hire an attorney to get out of her partnership agreement with the practice that was positioned for sale into private equity the day after she signed a partnership agreement with the group.

"The young ophthalmologist is very concerned about private equity," she says. "At our YO meetings, any time that we talk about practice management and jobs in the context of contract negotiation, we always get a fellow or a graduating resident who has a very concerned look on his or her face. They come up to me or some of our other committee members asking for advice. 'What should I do? The practice is talking to private equity. What should I put in my contract to protect myself?' "

Dr. Law offers this advice to the young doctors:

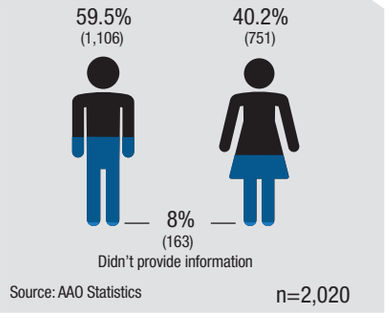
• ***Don't be afraid to advocate for yourself.*** "Young ophthalmologists today are very transparent with each other about each other's contracts," she notes. "Young professionals today want to know the compensation for everyone in the organization, as much as possible. So ophthalmologists are asking each other, what did you get offered? What's your buy-in? What's this other person's buy-in? They're coming in more knowledgeable about what's in their contracts. Of course, when you advocate for yourself, you need to prepare for resistance from the older generation. I've heard a lot of them say, 'well, that's how we've been doing it for 20 years. That contract's not going to change.' But it's going to have to change."

• ***Insist on a partnership agreement that will protect you.*** Dr. Law recommends language that will void the young ophthalmologist's partnership contract in the event of a private equity purchase or other transaction that could end a young partner's equity interest or restrict full revenue-earning potential once becoming a general partner.

"More young ophthalmologists—sometimes with the assistance of attorneys—are asking for clauses in their contracts that will free them from five- to 10-year commitments to a practice if these events occur," she says. "They are also asking for non-compete clauses that will let them continue to practice in the same community if the contractual relationship should end for these reasons."

• ***Consider an employment contract.*** If you're not certain whether a practice will remain independent long into your future, you may want to start out as an employed ophthal-

Ophthalmologists in Training



mologist. "I don't know exactly how many practices offer an employee track, but I do believe this would be an appealing option for someone who wants to learn the ropes without risk," says Dr. Law.

What About the "Old Guys"?

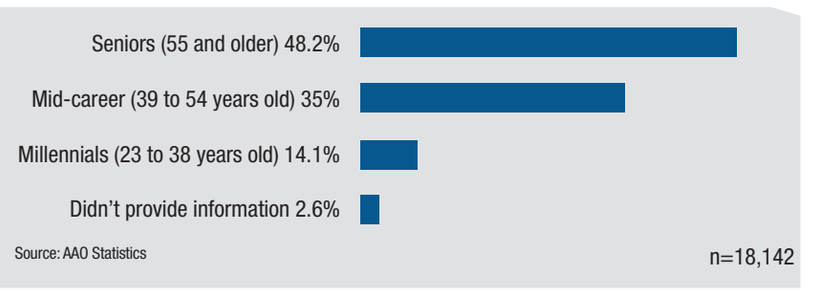
As much as young ophthalmologists fear getting cut off from the future opportunities and independence that their predecessors have always enjoyed, some older solo ophthalmologists are dealing with quite a different experience—an inability to sell their practices that didn't afflict their retiring predecessors. This problem is only expected to get worse, now that the proportion of AAO members who are solo practitioners has dipped below 20 percent (3,543 out of 18,142 members).

"It's happening because everybody is getting old," says Dr. Harbin. More than 48 percent of AAO members are 55 and older, comprising the profession's largest demographic by a significant margin. "They want to retire on their own terms and get a payoff for the many years of developing their practices," he says.

While participating in a breakfast event on giving up surgery at the recent American Academy of Ophthalmology meeting, Dr. Harbin says a lot of older ophthalmologists were focused on retirement. "I can only speak in gross generalities—not based on any scientific example—but what I was hearing was that many millennials don't want to assume the responsibility of running and managing a practice," he says. "A lot of the older ophthalmologists in this category are in smaller towns. Twenty years ago, a younger ophthalmologist would come in and slowly but surely buy out the older ophthalmologists. Now, these older physicians can't sell their offices."

When millennial doctors visit their offices, the older physicians often learn that their practices don't meet the younger doctors' expectations. "What some of them hear is, 'What's my salary? How much vacation do I get? And I don't want to do call.' This is exactly what you don't want to hear from a prospective junior partner. You want to hear somebody say, 'I want to work hard and develop my practice, I'll take call because that's the way to get patients. How can I help?' If your practice is part of a hospital system and you're expected to take call, the call has to be covered. Saying you can't cover call is not real world."

Ophthalmologists by Age



Source: AAO Statistics

n=18,142

Building Generational Bridges

The increasing trend toward consolidation explains why many of these older physicians feel left out. Group practices continue to grow in ophthalmology, accounting for 39.5 percent of AAO members. "I have an old-guy perspective, but I have the data to back me up," says Dr. Willliams, the current president of the AAO, with a polite tone. He is also chair of the department of ophthalmology and director of the Beaumont Eye Institute at Beaumont Health in Royal Oak, Michigan. "My old-guy perspective is also based on my perspective that the residents I train are less likely to go into independent solo practice. The Academy is now seeing a steady decline in members who describe themselves as solo practitioners and I fully expect that trend to continue. As far as the preferred model, that is going to depend on the individual. But increasingly the younger ophthalmologists we're seeing have a proclivity to select the employment option in which they're working for a larger entity, rather than going out and building their own practices."

Young and old ophthalmologists alike agree that they need to build generational bridges to ensure a harmonious future, for both small and large practices.

Thomas A. Oetting, MD, ophthalmology residency program director at the University of Iowa for the past 13 years, is described by residents and practicing physicians as one of those bridge-builders. More than anything, the 60-year-old preaches a practice-focused gospel of mutual respect. His advice to young ophthalmologists?

"Be useful and collegial," he says. "Try to draw upon the great experience and wisdom of your senior partner. Some of a senior partner's wisdom might be subtle or difficult to extract at first, and some of the skills millennials have may be difficult for the senior person to understand or appreciate. But the potential for a great marriage is there. I think the more useful the new person is, the more generous the older people will be. The more appreciative, encouraging and attentive the younger person is, the freer the senior person

Peter Roberts

George Williams, MD, chair of ophthalmology and director of the Beaumont Eye Institute at Beaumont Health in Royal Oak, Michigan, offers a spontaneous traditional didactic teaching session to second-year retina fellow Christianne Wa, MD, reviewing with her a fundus photo next to a fundus autofluorescence image of atrophic AMD. "The millennials get a lot of bad press these days," says Dr. Williams, the 2019 President of the American Academy of Ophthalmology. "I'm struck by the fact that the millennials are not any different than my generation was."

will be with the younger person."

Ruth Williams, MD, a glaucoma specialist at Wheaton Eye Clinic in suburban Chicago, says she thinks many mid-career and older ophthalmologists have misconceptions about millennials. "They're inheriting a different world than we inherited when we were their ages," says Dr. Williams, a mother of three grown children who once served as president of her practice, which attracts 160,000 visits per year and involves the work of 33 ophthalmologists and 13 optometrists. She notes that baby boomer ophthalmologists, such as herself, complain that millennials don't want to work as hard as the boomers have always worked. "That's not so," she observes. "They want to work. One thing that has changed is how we use time. We went home with pagers, but our hours were prescribed. Now, because of digital technologies, we're available around the clock."

Dr. Williams remembers one afternoon when she was managing a patient with orbital cellulitis. She called the cell phone of her young partner who specialized in oculoplastics and orbital surgery. "We worked through the complicated case on the phone," recalls Dr. Williams. "When we were done, he informed me that he was on a ski slope in Utah. That's one example of what happens all the time. I find that most young ophthalmologists are guided by a moral imperative to provide quality patient care and to help their colleagues when help is needed. They don't regard it as an imposition. They are available."

Dr. Williams, who also served as president of the AAO in 2012, notes that the needs of young ophthalmologists are changing. With the number of female ophthalmologists increasing (25.4 percent currently in practice and 40.2 percent in training), she observes that many of these women work extra hard to meet all of their responsibilities. "The young mom in ophthalmology is a serious professional," she says. "She deals with the pull of meeting the objectives of the practice and the needs of her family. This is not just a gender issue, however. What I love about these younger people is that the men are also meeting the responsibilities at home—picking up the kids, going to the kids' games. I think it's wonderful. Workplaces that were once rigid are evolving."

One suggestion she has for busy ophthalmologist parents is to allow them to work from 7 a.m. until 2 p.m. "This is perfect for picking the kids up after school," she observes. "You can work a full day and be home by mid-afternoon. The baby boomer can work 10 a.m. to 7 p.m. And by the way, this schedule accommodates patients who need early morning or early evening appointments." The challenge with this approach, she admits, is providing qualified staff to cover the expanded hours. "Innovative thinking will be needed," she says. "The idea is to be flexible and for us boomers to respect diversity in the workplace. What worked for the baby boomer generation is not going to work for today's young people."

Purnima Patel, MD, associate professor of ophthalmology at Emory Eye Center and a former chair of the AAO YO Committee, agrees. She says potential friction points between new and older ophthalmologists are "deeply individual," adding that "this is something we should be talking about and discussed openly, including an open commitment to physician wellness at all ages. Unfortunately, these issues are just not talked about. That was the culture until now. More conversation is needed—even in journals or publications. Everyone in ophthalmology, young or old, has a stake in this."

Accepting Differences

Conversations with millennial, mid-career and older ophthalmologists yield other perceived and real

Measuring the Impact of Private Equity

Along with value-based payments, mandated electronic health records that have proved burdensome for many ophthalmologists, shrinking reimbursements, increasing regulations and other pressures, private equity appears—at least to some physicians—to be just one more force chasing physicians out of private practice.[1,2,3,4] In fact, according to the American Medical Association's Physician Practice 2018 Benchmark Survey, 2018 marked the first time in which there were fewer physician owners (45.9 percent) than employees (47.4 percent).

Statistics show that at this point private practice in ophthalmology is hardly folding, however. Not at this point. The Medscape Ophthalmologist Compensation Report of 2019 found that 80 percent of ophthalmologists practice in three domains that typically thrive under the direction of entrepreneural self-employed private practitioners: office-based single-specialty group practices (44 percent); office-based solo practices (19 percent); and office-based multispecialty group practices (17 percent). (Note that some employed ophthalmologists, including some in private equity, also work in these settings, although numbers quantifying their presence weren't immediately available. George Williams, MD, president of the AAO, says an estimated 10 percent of all ophthalmologists are in a private equity model.)

Far from documenting the disillusionment that typically characterizes disenfranchised medical professionals, the survey found that 82 percent of ophthalmologists would choose medicine if given a second chance and, within this group of affirming ophthalmologists, 96 percent of them would choose the same specialty, a top rating among 29 reported specialties. Average expected income for ophthalmologists in 2019 is $366,000, a 2.5-percent increase over 2018 and a 19-percent hike over their average income in 2013. In 2019, self-employed ophthalmologists expect to earn an average of $398,000, which is 21 percent higher than an expected income of $329,000 for employed ophthalmologists in 2019.

The Medscape Ophthalmology Compensation Report 2018 found that 58 percent of ophthalmologists were self-employed and 40 percent were employed. Among those employed are new ophthalmologists aspiring to enter private practice as self-employed partners some day.

Source: The Medscape Ophthalmology Compensation Reports (2019-2018) are based on a sample size of 19,328 respondents across 30-plus specialties. The margin of error is ± 0.70. percent at a 95 percent confidence level using a point estimate of 50 percent.

1. Casalino LP. Health Aff (Millwood). The Medicare access and CHIP Reauthorization Act and the corporate transformation of American medicine. 2017 May;36:5:865-869.
2. Murphy DR, Satterly T, Giardina TD, et al. Practicing clinicians' recommendations to reduce burden from the electronic health record inbox: A mixed-methods study. J Gen Intern Med. 2019;34:9;1825-1832.
3. Michele C. Lim MC, Boland, MV, Colin A. McCannel CA, et al. Adoption of electronic health records and perceptions of financial and clinical outcomes among ophthalmologists in the United States. JAMA Ophthalmol. 2018;136:2:164-170.
4. 2020 Medicare physician fee schedule (MPFS) proposed rule released. ASCRS. August 2019. http://ascrs.org/about-ascrs/news-about/2020-medicare-physician-fee-schedule-mpfs-proposed-rule-released. Vewed Nov. 15, 2019.

differences among them, such as ideas about life/work balance, commitment to practice and the use of mobile-based crowdsourcing to share clinical challenges, negotiating strategies and advice for young parents on the go, such as favorite recipes. Meanwhile, the generation that was once known for shaking fists and shouting in protest against "the establishment" now finds itself at the head of another old-world order, contending with the quiet revolution of a fast-moving, digital-savvy generation that thinks and communicates differently. But many of the baby boomers, perhaps reminiscing on the deep changes they left in their wake, are learning to accept the new ways of this generation.

Dr. Oetting articulates an empathic message when describing the residents he's mentored through the years at the University of Iowa: The difference between today's young generation of ophthalmologists and those in the past is that, to some extent, today's practice environment is less hopeful than when Dr. Oetting was a newly-minted practitioner. "For example," he says, "practices are being bought by venture capital organizations, and we have uncertainty in future Medicare payment systems. There's a sense that future revenue streams could be potentially harder to predict. Given that situation, you may be less able to commit to a big buy-in or to commit to some long-term relationship. Forty years ago in ophthalmology all you had to do was put up a shingle and you could make a fortune. It was really easy to start a career."

Tamara Fountain, MD, professor of ophthalmology at Rush University Medical Center in Chicago and the 2020 president-elect of the AAO, expresses gratitude for the opportunity to lead these future leaders, as well all other colleagues in her profession, when she begins her tenure as president in 2021. "Thank goodness there are some [millennials] who go into medicine, because they want to effect a change in health care," she says. "And we should applaud them. We're getting young people who are coming through and wanting to be physicians in a climate in which the nature of how health care is delivered and paid for is very much uncertain."

Dr. Williams, AAO's current president, says millennials "get a lot of bad press these days. I'm particularly struck by the fact that millennials are not any different than my generation was. In ophthalmology, we attract a lot of bright people—I'd like to say the best of the best. I think millennials reflect this level of talent and

Jennifer Taylor

Ruth Williams, MD, a baby boomer glaucoma specialist who rose to the rank of president at Wheaton Eye Clinic in suburban Chicago (160,000 visits per year) and 2012 president of the AAO while raising three children, now in their 20s, is known for counseling patients and millennial ophthalmologists alike with legendary calmness and wisdom. Her words of caution to millennial ophthalmologists, especially those just starting out: "It's a lot harder than it looks."

enthusiasm. Perhaps they bring a little different perspective than some of the older folks had. But I'm not sure I can detect any significant difference."

Strength Through Diversity

Repeating a point that both young and old ophthalmologists have made in interviews, Dr. Oetting observes that the millennials' long-time familiarity with technology and social media differentiates them and makes them an asset to the profession. "They are much savvier and more knowledgeable about what's going on in the world," he says. "They're more connected on issues such as what other practices are paying and what other people are doing than maybe I was when I came out. I might have had a few phone-call contacts, but the virtual network of mentors that our graduates have now is massive."

Dr. Law also sees great potential for senior and millennial ophthalmologists to work together. "Young ophthalmologists are looking for mentors and people to share cases openly with—without judgment—so they can learn," she says. "Senior ophthalmologists can mentor us on coding/billing/practice management—which we may be able to enhance with our technical know-how—and they can mentor us on clinical cases and decision-making.

Senior ophthalmologists would be very good at mentoring young ophthalmologists when it comes to advocacy and leadership in the profession and practice, she adds.

"YOs, in turn, could help bring the practice 'up to date' with more efficient use of technology, assisting in clinic flow and improving the patient experience, especially by using apps," continues Dr. Law. "Web marketing and social media promotion would benefit the practice and can certainly be a notable contribution that the YO can make. We can also spearhead the selection and implementation of an electronic medical records system for the practice."

"Here's an example," Dr. Law says. "I recently went to a doctor's appointment. I checked in online (like a hotel) paid my outstanding $11 bill via an app (like my bank app), made a follow-up appointment (as I do with my hairdresser), and got a text reminder so I could put the follow-up appointment in my calendar (like a secretary/assistant). All of that was easy. Millennials can make sure that it works this way for the practices in which they work."

Both Sides Now

Like any other generational differences, many of the ones that separate these two groups may never go away.

"I think that senior ophthalmologists should expect younger ophthalmologists to push back. I mean that is

Ophthalmologists by Practice Type and Gender

Primary Practice Type	Number of U.S. Practicing Ophthalmologists / AAO Members*	Percent Females **	Percent Males **	Unknown/ Declined to say
Solo Practice	3,543	17.7%	82.2%	0.1%
Ophthalmology Group Practice	7,112	19.8%	80.2%	0.1%
Multispecialty Group Practice (e.g., group with ophthalmology and other specialties)	1,781	22.6%	77.3%	0.1%
Academic Institution	2,308	37.7%	62.3%	---
Hospital/Health Care System	807	42.8%	57.1%	0.1%
Government/Military	336	33.3%	66.7%	---
Other	327	27.0%	73.0%	---
Unknown	1,928	34.0%	65.5%	0.5%
Total	18,142	----	----	

*Source: American Academy of Ophthalmology membership data, as of Nov. 5, 2019. Some members may practice in more than one practice modality. The Academy asks members to select the practice type where they spend more than half of their work time.
** Source: AAO's 2018 year-end membership data.

just going to happen," says Dr. Law. "Young ophthalmologists are committed to medicine but not in the same way as senior ophthalmologists. They don't have their doctor identities turned on every night or on the weekends."

But in the long run, say the thought leaders interviewed for this article, these differences will strengthen the profession. "The millennials have different goals than us at times," acknowledges Dr. George Williams, who counts eight millennials among the 27 doctors at his multispecialty practice. "When it comes to maternity leave, flexibility in scheduling and other work/home balance issues, they very well may be the ones who are right. I have confidence in their ability to do the things that I have to do: be good doctors and take great care of their people. That is what we all do." REVIEW

1. Pavarini PA, Schaff MF. New barbarians at the gate? What private equity wants from medical practices and how to advise clients. Presentation given at American Health Lawyers Association Physicians and Hospitals Law Institute, Orlando, Florida, 1–3 February 2017.
2. Casalino LP, Saiani R, Bhidya S, Khullar D, O'Donnell E. Private equity acquisition of physician practices. Ann Intern Med 2019 Jan;170:2:114-115.

REVIEW News

(Continued from p. 6)

Forecasting IOP with A.I.?

Techniques that identify individuals in whom ocular hypertension is likely to progress to open-angle glaucoma may be able to assist clinicians with deciding on the frequency of monitoring and the potential benefit of early treatment. In a study from the University of Michigan, researchers tested whether Kalman filtering, a machine-learning technique, could accurately forecast intraocular pressure values five years into the future for individuals with OHT.[1]

The cohort study was a secondary analysis of data from individuals with OHT from the Ocular Hypertension Treatment Study. In it, individuals underwent tonometry and perimetry every six months for up to 15 years. Scientists trained, validated and tested a KF-OHT model to assess how well it could forecast IOP at up to five years, and compared the forecasts with results from the actual trial. They compared the KF for OHT with a previously developed KF for subjects with high-tension glaucoma (KF-HTG) and three traditional forecasting algorithms. Main outcomes were prediction error and root-mean-square error at 12, 24, 36, 48 and 60 months for mean deviation, pattern standard deviation and IOP.

Among 1,407 eligible participants (2,806 eyes), 809 (57.5 percent) were female and the mean (SD) age at baseline was 57.5 (9.6) years.

• For 2,124 eyes with sufficient measurements, KF-OHT was able to forecast MD values 60 months into the future within 0.5 dB of the actual value for 696 eyes (32.8 percent), 1 dB for 1,295 eyes (61 percent) and 2.5 dB for 1,980 eyes (93.2 percent).

• Among the five forecasting algorithms tested, KF-OHT achieved the lowest root-mean-square error (1.72 vs. 1.85 to 4.28) for MD values 60 months into the future.

• For eyes that progressed to open-angle glaucoma, KF-OHT and KF-HTG forecast MD values 60 months into the future within 1 dB of the actual value for 30 eyes (68.2 percent; CI, 54.4 to 82 percent) and achieved the lowest RMS error among all models.

Scientists wrote that the findings suggested that algorithms such as KF could forecast MD, pattern SD and IOP five years into the future for many individuals with OHT. They added that these algorithms may aid clinicians in managing OHT in patients. REVIEW

1. Garcia GP, Lavieri MS, Andrews C, et al. Accuracy of Kalman filtering in forecasting visual field and IOP trajectory in patients with ocular hypertension. JAMA Ophthalmol 2019; Nov 14. [Epub ahead of print].

Trifocals and EDOFs: Where Do They Stand?

Christine Leonard, Associate Editor

Surgeons discuss two of the latest lens technologies for increasing range of vision.

Two recent presbyopia-correcting intraocular lens technologies, trifocals and extended-depth-of-focus lenses, aim at increasing the range of vision without compromising vision quality. In particular, both trifocals and EDOFs offer good quality vision at the intermediate range.

"Intermediate vision is a really valuable working distance for a lot of patients," says Dagny Zhu, MD, FAAO, managing partner at Hyperspeed LASIK in Rowland Heights, California, and volunteer attending and lecturer at Los Angeles County+University of Southern California department of ophthalmology. "I've put in a lot of [bifocal] multifocals, and I've found that patients really appreciate the near vision, but some will notice that they struggle with anything around the intermediate range. If you look at the defocus curve for [bifocal] multifocals, it really drops off for anything between near and far," she says. Some activities that benefit from good intermediate vision include computer work, looking at a GPS while driving, checking price tags and cooking. The challenge of producing good intermediate vision, however, lies in the fact that extending range of vision usually decreases overall image quality.

In this article we'll take a look at some aspects of trifocals and EDOFs—how their lens materials contribute to visual performance and potential dysphotopsias, and how thorough patient counseling can improve overall satisfaction.

Trifocals and EDOFs

Alcon's PanOptix trifocal, which gained FDA approval in August, is the only trifocal option currently available in the United States. Unlike bifocal multifocal IOLs, which split light in two ways to give near and distance vision, trifocals split light three ways to provide an intermediate focal point, typically around 80 cm (about 31 inches). The PanOptix trifocal's intermediate point, however, is around 60 cm (24 inches). "Trifocals aren't quite continuous [in terms of focus], but they're better than [bifocal] multifocal IOLs and bifocal glasses," says Daniel Chang, MD, of Empire Eye and Laser in Bakersfield, California, and member of the ASCRS Refractive Surgery Clinical Committee.

Trifocals were found to provide better intermediate vision than multifocals with two focal points, according to a meta-analysis literature study conducted in 2017 that compared the two lens types' clinical performance.[1] In a similar study in 2018, researchers in South Korea found that trifocals out-

This article has no commercial sponsorship.

performed bifocal multifocals in intermediate vision and provided similar or better distance and near vision without compromising visual quality.[2]

Dr. Zhu performed about 60 cases with trifocals in the two months following PanOptix's approval by the FDA. She says her preliminary results have been fairly favorable, with many patients seeing 20/20 at distance, intermediate and near at one week postoperatively. "That's just not been my experience with [bifocal] multifocals, which again do not give the same level of intermediate vision as trifocals," she says. "It's been quite excellent."

Figure 1. The Alcon PanOptix trifocal IOL.

Prior to the trifocal, the EDOF lens was the latest iteration of presbyopia-correcting lens technology. "In the U.S., the only true EDOF lens that we have is the Tecnis Symfony," Dr. Zhu notes. "Unlike multifocals, which split light for specific focal distances, the EDOF extends the range of focus, so there's no splitting of light at a discrete distance. In that sense, it gives the patient a more continuous range of vision without dropping out in between specific focal points." However, while the Symfony provides good distance and intermediate vision, it doesn't provide the same quality of near vision as a multifocal or a trifocal IOL, according to Dr. Zhu.

The bulk of the literature on trifocals has been published outside the United States, where the trifocal has been in use longer. "A couple of studies say different things, so I don't think we can necessarily conclude anything in particular," Dr. Zhu says. "The only thing that's accepted is that the Symfony does not provide as much good near vision as the PanOptix trifocal. In terms of quality of distance vision and intermediate vision, I've seen studies saying it's about the same among both. In terms of the degree of contrast sensitivity, I've seen some say it's better, and some say it's the same, so I don't really think a conclusion can be drawn about that.

"The Symfony EDOF uses a completely different technology from multifocals," Dr. Zhu continues. "[Bifocal] and trifocal multifocals tend to offer really good near vision at around 15 inches or 40 cm. I would say the Symfony is closer to 20 inches, so definitely not as much near vision."

A 2019 prospective, consecutive, non-randomized study in New Delhi, India, compared the visual outcomes and clinical performance of diffractive trifocal and EDOF lenses over six months in 160 eyes of 80 patients who had bilateral cataract surgery with implantation of either a trifocal (FineVision, PhysIOL, not approved in the United States) (n=40) or an EDOF (Tecnis Symfony) (n=40).[3] The study found that the trifocals performed better in near visual acuity, and that trifocals and EDOFs demonstrated comparable "excellent" distance and intermediate visual acuity and a high percentage of spectacle independence with minimal levels of disturbing photic phenomena.

A 2018 study in France compared binocular and monocular uncorrected distance, intermediate and near visual acuity in patients randomized to receive trifocals—either FineVision or AcrySof IQ PanOptix—or the Tecnis Symfony EDOF. The researchers found that all three IOLs provided good distance visual acuity and reported that patients had few visual symptoms. They also found that the trifocal IOLs provided statistically better near vision than the EDOF IOL.[4]

"I'm sure down the road we'll be able to offer extended depth of range up to a closer point," says Dr. Zhu. "That would be ideal."

Dr. Chang says he hasn't implanted any trifocals yet; he currently uses the Symfony EDOF in his patients to offer intermediate vision. "EDOF lenses try to spread vision more evenly so that the overall quality of vision and night vision symptoms can be improved," Dr. Chang explains. Expanding the depth of field and reducing night vision symptoms comes at the expense of some near vision, he notes.

A study conducted by university hospital researchers in Madrid and Alicante, Spain, found that the Symfony EDOF lens showed statistically significantly better subjective and objective depth of field than the Mini Well (SIFI MedTech) EDOF, the FineVision (PhysIOL) and AT LISA Tri (Carl Zeiss Meditec) trifocals and the Tecnis ZMB and ZLB (Abbott Laboratories) bifocals.[5]

Torics

Dr. Chang says the toric versions of the Symfony EDOF and PanOptix trifocal are welcome additions to the surgeon's armamentarium. "It's good to be able to correct astigmatism with a lens instead of separate incisions on the cornea," he adds.

Knowledge of astigmatic tolerance of IOLs is important for surgical planning and can help avoid the need for secondary management after implantation.[6] It's been estimated that multifocal IOLs in general can tolerate about 0.75 D of astigmatism,[7] compared to EDOFs' tolerance, which was found to be slightly better at 1 D in a study that compared relative indications and contraindications for implantation. The study also reported that trifocal users can tolerate about 0.5 D of astigmatism.[8] "EDOF technology doesn't give you as much range as a trifocal," says Dr. Chang, "but the range it does give, at least in theory and in my experience, tends to be better. So even if you miss a little bit of astigmatism or

Figure 2. The Tecnis Symfony extended-depth-of-focus IOL.

the lens is positioned off by a little bit, it'll tend to do a little better than a toric multifocal or a trifocal, in which nailing the alignment is really important."

He points to another recent study that compared EDOFs to trifocals in terms of induced astigmatic defocus on visual performance.[6] The study compared the reduction of mean monocular visual acuity at all defocus levels relative to no defocus and found it was significantly lower in the IC-8 (AcuFocus) EDOF group, compared to the FineVision, AT LISA and enVista (Bausch + Lomb), supporting other studies' findings that EDOFs tend to provide a greater tolerance of induced astigmatic defocus.

Chromatic Aberration

Contrast sensitivity improves when chromatic aberration is reduced. Dr. Chang explains that as light passes through a lens, it breaks into its component colors. Each wavelength focuses differently because the index of refraction of the lens affects each one differently. "With a good lens system, you can focus the image sharply," he says. "But if you have too much separation of colors, you end up with a blurring effect—that's chromatic aberration."

The material of an IOL contributes to chromatic aberration. Both the Symfony and the PanOptix are built on proprietary hydrophobic acrylic platforms. Hydrophobic foldable acrylics are made of a series of copolymers of acrylate and methacrylate derived from PMMA to make them foldable and durable, and they have a refractive index between 1.44 and 1.55.[9] Due to a high refractive index and low anterior curvature, hydrophobic acrylic tends to be associated with dysphotopsias more often than other acrylics, such as hydrophilic acrylic (typical refractive index: 1.43).[9] However, materials with a high refractive index can be made much thinner, allowing, as in the case of the AcrySof material, the lens to have a full 6-mm refractive optic, even as the IOL power increases. In contrast, other materials may require a reduction of the effective refractive zone of the optic as the power increases in order to prevent variation in the lens' central thickness.

The PanOptix lens material has an index of refraction of 1.55 and an abbe value of 37. The Tecnis lens material, a type of UV-blocking hydrophobic acrylic, has an index of refraction of 1.47 and an abbe number of 55.[10]

Dr. Chang says that chromatic aberration is often the culprit for unsatisfied patients. "We don't see chromatic aberration at the slit lamp, and patients may not necessarily tell us, 'I have a chromatic-aberration problem,' " he says. "But when there's a dissatisfaction with image quality in spite of good Snellen acuity, you could be dealing with either a higher-order aberration, such as spherical aberration, or chromatic aberration. In my practice, I like to use a material that provides chromatic aberration correction to make it as little of an issue as possible. For any material, the higher the index of refraction, the higher the chromatic aberration."

Dr. Chang says that patients may not notice chromatic aberration as much with monofocal lenses, but with diffractive lenses, image quality can become an issue.

Some image-quality issues and dysphotopsias are common to all multifocal lenses, including trifocals, notes Dr. Zhu. And even with EDOF lenses, patients still experience dysphotopsias such as glare, halo and starbursts.

Dysphotopsias

While trifocals and EDOFs aim for reducing dysphotopsias, unwanted photic phenomena occur whenever the range of vision is extended. Dr. Chang says that these dysphotopsias are more evident in dim environments, particularly with night driving. "The amount of off-axis light is directly related to the amount of near vision that you get with a particular lens," he says. "So if you look at the PanOptix versus the ReSTOR +3 D, I would expect more near and intermediate vision with PanOptix, and of course, a greater number of night-vision symptoms. If you look at the EDOF Symfony versus the Tecnis multifocal, I would expect fewer night-vision symptoms but not quite as much near vision."

Dr. Zhu notes that the results from the PanOptix FDA trials showed that it had no more dysphotopsias than other trifocal or multifocal lenses. "Around the same level of decrease in contrast sensitivity was observed as well, which is common to all multifocal lens technology," she says.

One of the common benefits cited in regard to EDOF lenses is that they have fewer dysphotopsias than multifocal IOLs. The [EDOF] AT LARA 829MP pre-clinical study report makes this claim, saying this EDOF's diffractive optical design, called "light bridge," corrects spherical and chromatic aberration and causes fewer visual disturbances than multifocal IOLs. For the Symfony, Johnson & Johnson reports a low incidence of visual symptoms.

A 2019 study in Heidelberg, Germany, evaluated the functional results and photic phenomena of the Mini Well Ready IOL (SIFI MedTech)—

Binocular Defocus Curve Comparisons

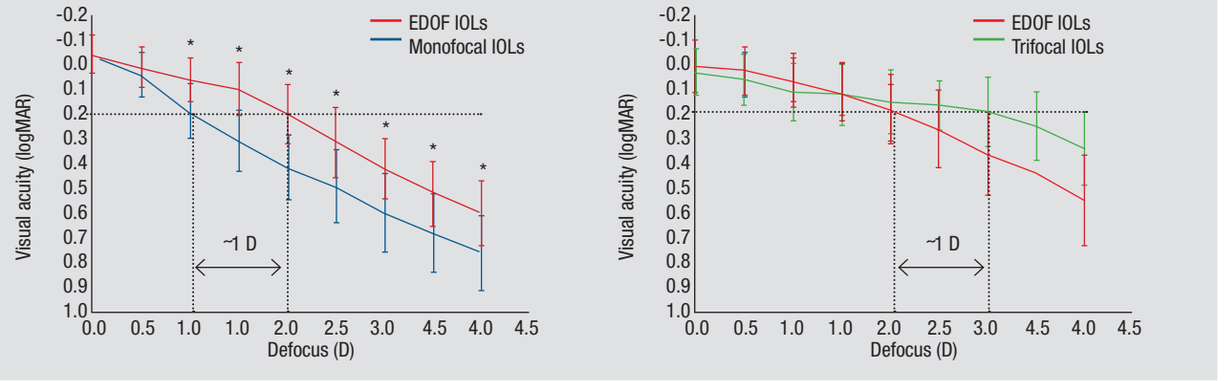


Figure 3. Binocular defocus curves for EDOF and monofocal IOLs (three trials of 215 subjects) (left) and for EDOF and trifocal IOLs (four trials of 159 subjects) (right), based on six studies in a meta-analysis review of EDOFs conducted by researchers in Tianjin, China.[12]

a single-piece hydrophilic acrylic EDOF with a hydrophobic surface that relies on spherical aberrations of opposite signs to create an elongated focus[11]—and found that it provided good distance and intermediate vision, improved reading-distance visual acuity and few to no dysphotopsias.

According to a meta-analysis of randomized and nonrandomized controlled studies by researchers in Tianjin, China, compared to monofocals, EDOFs provided better intermediate and near visual acuity, but more contrast reduction and more frequent halos; compared to trifocals, EDOFs had better contrast sensitivity and comparable halo incidence.[12] The researchers say they used only the Tecnis Symfony EDOF, due to a lack of studies on other EDOF lenses.

Patient Counseling

At the end of the day, all these lenses have some visual side effects, particularly at night. However, Dr. Chang says those side effects shouldn't discourage qualified patients from seeking presbyopia-correcting IOLs. EDOF and trifocal IOLs may be safer alternatives to bifocal spectacles, which have been associated with a 2.3-fold increased risk of tripping and falling in the elderly because they throw off depth perception. Traumatic falls are the number one cause of injury and death among elderly Americans.[13]

"Right now the most important thing for surgeons to keep in mind is the kind of night-vision symptoms each lens produces so they can describe them appropriately to patients," says Dr. Chang. He elaborates, saying that the Symfony produces different night-vision symptoms than other lenses. He explains that with traditional multifocals, there's glare, which is blurring of light around a light source, and halo, which manifests as a ring around the light source due to the IOL's single add power. On the other hand, in addition to some glare, the Symfony primarily produces multiple fine halos—depending on the color of the light—and also starbursts, which are streaks of light emanating from the light source. "It's commonly been described as a spider web, Ferris wheel, daisy or digital pattern. Spider web is the most common term I use," Dr. Chang says.

Dr. Chang adds that counseling patients and illustrating and explaining specific symptoms—whether it's halos, glare, single or multiple halos or spider-web patterns—helps patients tolerate them better. "It can be disorienting for patients if they're not prepared for it," he says. "If we simply say glare and halos, patients may not necessarily know what we mean. They'll say, 'No, it's not glare. There are big lines coming out.' In my experience, when limitations are expected, patients tolerate them pretty well."

Contraindications

"In general, the same exclusion criteria can be applied to both types of lenses," says Dr. Zhu. She says that patients with any ophthalmic pathology, either in the macula, the optic nerve or the cornea, probably shouldn't receive EDOFs or multifocals. "For all of these lenses there's some decrease in contrast sensitivity," she says. "You don't want to use them in a patient who already has vision problems." She says this is due to the fact that these lenses were designed to work in perfect eyes. "If the eye is malfunctioning in one way or another, patients probably won't get the full value of the lens," she adds. "When I advise patients and tell them they're not candidates for EDOFs, [bifocal] multifocals or trifocals because of their pathology, I usually recommend using a monofocal lens and reading glasses for anything close up.

Results of a Meta-analysis of Defocus Curves

Defocus levels	MD [95% CI]	*P* value	Heterogeneity	
			I^2 (%)	$P_{heterogeneity}$
EDOF vs. Monofocal IOLs				
–0.01	–0.00 (–0.10, 0.08)	0.81	89	0.0001
–0.50	–0.04 (–0.09, 0.00)	0.07	25	0.26
–1.00	–0.16 (–0.21, –0.12)	< 0.00001	0	0.65
–1.50	–0.22 (– 0.31, – 0.13)	< 0.00001	63	0.07
–2.00	–0.24 (– 0.29, – 0.19)	< 0.00001	8	0.34
–2.50	–0.22 (– 0.27, – 0.16)	< 0.00001	0	0.45
–3.00	–0.25 (– 0.31, – 0.18)	< 0.00001	37	0.20
–3.50	–0.21 (– 0.26, – 0.16)	< 0.00001	0	0.94
–4.00	–0.21 (–0.26, –0.16)	< 0.00001	0	0.73
EDOF vs. Trifocal IOLs				
0.00	–0.02 (–0.07, 0.03)	0.40	59	0.06
–0.50	–0.03 (–0.08, 0.01)	0.17	52	0.10
–1.00	–0.04 (–0.10, 0.01)	0.11	55	0.08
–1.50	–0.01 (–0.08, 0.07)	0.88	76	0.006
–2.00	0.03 (–0.01, 0.07)	0.19	0	0.96
–2.50	0.10 (0.06, 0.15)	< 0.00001	0	0.79
–3.00	0.17 (0.09, 0.26)	< 0.0001	65	0.04
–3.50	0.19 (0.07, 0.30)	0.002	68	0.04
–4.00	0.21 (0.07, 0.35)	0.003	79	0.008

MD: mean difference, CI: confidence interval, I^2: extent of inconsistency

Figure 4. Mean difference in visual acuity, expressed in logMAR, between EDOFs and monofocal or trifocal lenses. Negative values indicate that EDOFs performed better, and positive values indicate that the comparison lens performed better. (See defocus curves graph on previous page.) The meta-analysis conducted by researchers in Tianjin, China, found that in the six studies reporting binocular distance-corrected defocus curves, visual acuity was found to be significantly better in EDOFs than monofocal IOLs in defocus levels from -1 to -4 D. Visual acuity in trifocal IOLs was significantly better than EDOFs from -2.5 to -4 D.[12]

"Another strategy is to leave patients with a little monovision—a little myopia in their nondominant eye," Dr. Zhu continues. "Those patients are typically still able to do a lot of things close up. They may still need reading glasses for very fine print, but most patients are okay with that; they understand that that's the best option available, given their situation."

There are also some patients whose pathology prevents their receiving traditional multifocals but for whom an EDOF might be the answer. Dr. Chang says that the chromatic aberration correction in the Symfony lens makes it a possible alternative to multifocals in some cases because the patient's visual quality won't be degraded to the same degree as it would be with a traditional multifocal.

A Personalized Approach

Intraocular lens selection is not a one-size-fits-all procedure, experts say. Focal points and ranges are just two dimensions of a lens that bear consideration in the process of lens selection. "We as surgeons need to learn about and understand all the lens options we have so we can use them in a customized fashion for our patients," Dr. Chang says. "Instead of saying, 'This is what I do,' we need to have an approach for each patient based on who they are and what they do. The first eye may receive something a little different than the second eye, for example."

In Dr. Zhu's clinical practice, she talks to patients to get a sense of the visual distances that are important to them. "You really have to talk to the patients about what their day-to-day life is like," Dr. Zhu says. "What do they do for a living? What do they value in terms of type of work and activities they do? There are some patients for whom I'll favor implanting a trifocal lens over a [bifocal] multifocal lens—those who can't sacrifice their intermediate vision, like chefs who need to cook at arm's length or people who are on the computer quite a bit. At the same time, an EDOF would probably do very well in these same patients, but, if the patient also requires a lot of good near vision—because they like to read a lot, for example—then probably the trifocal would be better than the EDOF because you won't sacrifice as much near vision."

"There's Snellen acuity and there's patient happiness, and patient happiness may not necessarily reflect in your Snellen acuity data," Dr. Chang says. "We all know of products out there that have been taken off the market or lost popularity—not because of poor objective outcomes, but because patients just aren't quite happy with their quality of vision. It's hard to capture that, even with contrast data. Sometimes a patient with 20/25 vision is happy and one with 20/20 is not so happy."

Are Two Lenses Better than One?

Dr. Chang says that trifocal and EDOF lens technologies have been shown to have varying performance in different areas. "There have been

some head-to-head studies comparing EDOFs to trifocals, and so far each tends to have comparable performance in certain areas and better performance in others," Dr. Chang says.

He says some studies have examined combining lens technologies, such as implanting an EDOF in one eye and a multifocal in the other eye to get the strengths of both lenses. Other options may include implanting an EDOF and a toric lens for added depth of focus.[14]

Some enterprising companies are even combining the two technologies in one lens. For instance, a few years ago, a trifocal lens with EDOF features, the Acriva Reviol Tri-ED (VSY Biotechnology), was developed in the Netherlands. One study found that it provided good distance, intermediate and near vision.[15] The study authors said that based on the clinical outcomes, they believe EDOF elements can be incorporated into a multifocal visual system. Long-term studies will have to be done to bear this out.

Ultimately, all intraocular lenses have benefits and drawbacks, says Dr. Chang. "It's a matter for the surgeon to figure out what will work best for which patients." REVIEW

Dr. Zhu reports no financial disclosures. Dr. Chang is a consultant and investigator for Johnson & Johnson. He's also a clinical researcher for AcuFocus' IC-8 lens.

1. Xu Z, Cao D, Chen X et al. Comparison of clinical performance between trifocal and bifocal intraocular lenses: A meta-analysis. PLoS One 2017 Oct 26;12:10:e0186522. PMID 29073156.
2. Yoon CH, Shin IS, Kim MK. Trifocal versus bifocal diffractive intraocular lens implantation after cataract surgery or refractive lens exchange: A meta-analysis. J Korean Med Sci 2018 Sept 27;33:44:e275. PMID 30369857.
3. Singh B, Sharma S, Dadia S, Bharti N et al. Comparative evaluation of visual outcomes after bilateral implantation of a diffractive trifocal intraocular lens and an extended depth of focus intraocular lens. Eye Contact Lens 2019 July 5. [Epub ahead of print.] PMID: 31283552.
4. Cochener B, Boutillier G, Lamard M and Auberger-Zagnoli C. A comparative evaluation of a new generation of diffractive trifocal and extended depth of focus intraocular lenses. J Refract Surg 2018;34:8:507-14.
5. Palomino-Bautista C, Sánchez-Jean R, Carmona-González D, et al. Subjective and objective depth of field measures in pseudophakic eyes: Comparison between extended depth of focus, trifocal and bifocal intraocular lenses. Int Ophthalmol 2019 Oct 3. Epub ahead of print. PMID: 31583551.
6. Ang RE. Comparison of tolerance to induced astigmatism in pseudophakic eyes implanted with small aperture, trifocal, or monofocal intraocular lenses. Clin Ophthalmol 2019;13:905-911. [Epub ahead of print.] PMID 31213762.
7. Braga-Mele R, Chang D, Dewey S et al [ASCRS Cataract Clinical Committee]. Multifocal intraocular lenses: Relative indications and contraindications for implantation. J Cataract Refract Surg 2014; 40;2:313-22.
8. Carones F. Residual astigmatism threshold and patient satisfaction with bifocal, trifocal and extended range of vision intraocular lenses (IOLs). Open J Ophthalmol 2017;7:1.
9. Bellucci R. An introduction to intraocular lenses: Material, optics, haptics, design and aberration. Cataract: ESASO Course Series. Basel, Karger 2013:3:38-55.
10. Abbe number and longitudinal chromatic aberration (LCA). Bausch Surgical. Accessed Nov 4 2019. https://bauschsurgical.eu/blog-learning/blog/abbe-number-and-longitudinal-chromatic-aberration-lca/
11. Giers B, Khoramnia R, Caradi D, Wallek H et al. Functional results and photic phenomena with new extended-depth-of-focus intraocular lens. BMC Ophthalmol 2019;19:197.
12. Liu J, Dong Y, Wang Y. Efficacy and safety of extended depth of focus intraocular lenses in cataract surgery: A systematic review and meta-analysis. BMC Ophtahlmol 2019;19;198.
13. Falls prevention facts. National Council on Aging. https://www.ncoa.org/new/resources-for-reporters/get-the-facts/falls-prevention-facts. Accessed 8 Nov 2019.
14. Calogero D. New categories of IOLs for improved near and intermediate performance. FDA/AAO Workshop: Developing novel endpoints for premium intraocular lenses. March 28 2014. https://www.fda.gov/media/88004/download.
15. Acar BT, Duman E, Simsek S. Clinical outcomes of a new diffractive trifocal intraocular lens with enhanced depth of focus (EDOF). BMC Ophthalmol 2016;16:208. PMID: 27899084.


How Many Topical Drops are Too Many?

Not every patient can deal with a complex regimen, but options such as combination drops are making things easier.

Janet B. Serle, MD, New York City

As clinicians, we're problem solvers. Today, we have many tools we can use to manage glaucoma and help preserve our patients' vision, so one question we constantly strive to answer is: Which tools are the right ones for solving this patient's problem? And, how many of those tools should we use to get the best possible outcome?

Topical medications remain a mainstay of glaucoma treatment, and today we have more varieties to choose from than ever before. Currently, seven classes of compounds are available:

- prostaglandin analogues, including a nitric-oxide-donating prostaglandin (instilled once a day);
- rho kinase inhibitors (once a day);
- beta blockers (once a day);
- alpha agonists (two or three times a day);
- carbonic anhydrase inhibitors (two or three times a day);
- miotics (one to four times a day); and
- nonselective adrenergic agonists (twice a day).

For most patients, topical drops are a less-risky way to manage glaucoma than traditional surgeries such as trabeculectomy and tube shunt implantation. For that reason, most surgeons would agree that if drops can control the disease, prevent progression and be consistently administered and tolerated by the patient, then that's the option of choice. (MIGS surgeries, now added to our treatment options, need to be carefully assessed in comparison to medical management, in terms of efficacy and side effects, for each individual patient.)

This proliferation of glaucoma drugs, particularly with the recent addition of new medications—the nitric-oxide-donating prostaglandin Vyzulta, which is a co-drug, and the rho kinase inhibitor Rhopressa (as well as the fixed-dose combination of netarsudil and latanoprost, Rocklatan)—has raised important questions: How many medications should we be asking our patients to use? How many will be well-tolerated? And how many will be effective?

Multi-drop-related Issues

Asking patients to use multiple drops raises a host of potential concerns, ranging from how well the drops will perform when added to an existing regimen, to how managing multiple drops will affect compliance. Here's what we know about these issues, based on the published literature:

- ***You won't get as much pressure reduction when using a drop as a second or third medication.*** When we use a drug by itself, we have a pretty good idea how much IOP reduction we'll get. For example, with beta blockers alone you'll probably get a 25 to 28 percent IOP reduction. But if you add a beta blocker to latanoprost as a second medication, the effect will be smaller. In short, the second, third and fourth drugs in a patient's regimen won't give you the same bang for the buck that you'd get using them first-line. We've seen this in randomized clinical trials, typically Phase III, usually comparing one medication to another (often timolol).[1]
- ***The beneficial effect of a second, third or fourth medication may not last.*** Data in the literature suggests that the effect of an added

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medication wanes over time.[2] However, it's important to note that this conclusion is based on data from a population of patients; an individual patient may not mirror these findings. For that reason, treating each patient is somewhat trial and error. You prescribe a drug and see if it works, and if so, how long it works. Whatever the outcome, your next patient could have a different reaction.

• ***A complex regimen with multiple medications may undercut compliance.*** Many patients will find it frustrating to manage multiple medications; some will simply find it difficult to remember to take them. Other possible issues include the increased cost associated with more medications, side effects that patients dislike and the age of the patient. Young patients who don't take many pharmaceuticals may not take the regimen as seriously as they should. Older patients may have mental status changes or difficulty instilling the drops. In addition, we know that level of education and health literacy can be barriers to compliance.[3]

• ***Nocturnal efficacy can be an issue.*** Overnight studies involving glaucoma drugs have revealed that several classes of compounds are less effective at night than during the day.[4] That lack of efficacy at night may lead to progression in patients who appear to be well-controlled in daytime office IOP measurements. For that reason, when we design a regimen, we have to make sure we include medications that work at nighttime as well as during the day. Furthermore, if there's any question that progression is occurring, it's important to consider the possibility that the progression may be due to nocturnal IOP fluctuation. If so, reorganize the regimen to make sure that nighttime IOP is being addressed.

• ***Chronic medical therapy may lead to conjunctival changes and ocular surface disease.*** This happens, in part, as a result of inflammation of the conjunctiva. We know the changes can be related to the preservatives, the drugs themselves and/or the frequency of dosing. These conjunctival changes can have multiple consequences, including visual blurring and discomfort for patients.[5] They may also lead to a reduced rate of success in subsequent incisional surgery.[6] So, the fewer drops we can prescribe and still prevent progression, the better.

Despite the caveats just mentioned, it's clear that clinicians treating glaucoma use all the treatment options available. We can see this in the literature. Patients enrolled in the AGIS trial, which was conducted before the advent of prostaglandins, alpha adrenergic agonists and topical CAIs, were on a mean number of 2.7 medications at baseline enrollment.[7] In the mid-90s, those three classes of compounds were approved; the number of baseline medications in similar patient populations participating in subsequent clinical trials was more than three.[8,9] Current peer-reviewed articles and case reports confirm even higher numbers of baseline medications—3.6 up to as many as five.[10-12] So despite being aware of the limitations of multiple drops, we still tend to use a good number of medications in patients when we believe they need them to lower IOP.

Efficacy of Adding a 3rd or 4th IOP-lowering Medication

Drug name (brand name) No. of eyes (type of trial)	Duration of efficacy	Mean IOP decrease	Baseline no. of meds
Ripasudil (Glanatec) 39 (prospective)[10]	12 months	15.5% 69% of patients	3.6
Netarsudil (Rhopressa) 172 (retrospective)[14]	3 months	3.9 ±4.8 mmHg	<3 and ≥3 similar efficacy
Brimonidine (Alphagan) 53 (retrospective)[2]	12 months	20% 53% of patients	3
Latanoprost (Xalatan) 61 (prospective)[15]	22 months (13.9 ±5.7)	36% 30% of patients	3.6 ±1.1
Latanoprost (Xalatan) 65 (prospective)[16]	12 months (11.3 ±4.1)	>20% 25% of patients	2.4 ±0.5

Third and Fourth Drops

That being said, what do we know about adding a third or fourth medication to a patient's regimen? A few studies in the literature have addressed this question. (*See table, above.*) For example:

• One prospective, 12-month study conducted in Japan monitored the effect of Ripasudil (a rho kinase inhibitor drop administered twice a day that's only available in Japan) when added to the regimens of patients with a mean baseline of 3.6 medications. This was the fourth or fifth medication for some of these patients, but more than two-thirds of them had an additional IOP reduction of almost 16 percent.[10]

• A retrospective 12-month study in which brimonidine was added to a baseline regimen of three medications found that slightly more than half of the patients had an additional 20-percent reduction in IOP.[2]

• Another study followed 172 eyes for three months after netarsudil was added to baseline regimens. The result was an additional mean pressure reduction of about 4 mmHg. Of note, the efficacy of the addition

of netarsudil was similar, regardless of whether patients were on fewer or more than three medications at baseline.[13]

• Several prospective studies have looked at adding latanoprost to patients already on anywhere from 2.4 to 3.6 medications.[14,15] In these studies, additional IOP reductions were observed, ranging from a little more than 20 percent to 36 percent. However, this was only observed in a minority of patients (25 to 30 percent). So, latanoprost didn't provide as robust an additional IOP reduction as had been anticipated.

What about using fixed-combination drops as third and fourth medications? We know that fixed-combination regimens may help address efficacy, compliance and surface toxicity. It turns out that they may also reduce intra-day and inter-day IOP fluctuations,[16] which may contribute to progression.[17] This could be the result of better compliance, since fewer drops need to be managed, or the result of eliminating the issue of the second drop washing out the first drop if the second is instilled too quickly after the first. (This is obviously not a concern with a combination drop.)

Today we have several fixed-dose combination therapies available in the United States:

1. a fixed-dose combination of netarsudil and latanoprost, (Rocklatan, approved 2018)
2. a fixed-dose combination of brinzolamide and brimonidine (Simbrinza, approved 2013)
3. a fixed-dose combination of a topical CAI and a beta blocker (Cosopt, approved 1998);
4. a fixed-dose combination of brimonidine and a beta blocker (Combigan, approved 2007); and
5. the co-drug latanoprostene bunod, a nitric-oxide-donating prostaglandin (Vyzulta, approved 2017).

In addition, several prostaglandin agonist/beta blocker combinations are commercially available outside of the United States (for example, Xalcom).

IOP-lowering Regimens of Three to Five Medications Daily

Bottle 1	Bottle 2	Bottle 3	No. of Daily Drops	No. of Meds
NO-donating PGA	Netarsudil or Timolol		2	3
NO-donating PGA	Netarsudil	Timolol	3	4
NO-donating PGA	FDC Dorzolamide/ Timolol, or FDC brinzolamide/ brimonidine		3	4
NO-donating PGA	FDC brinzolamide/ brimonidine	Timolol	4	5
FDC Netarsudil/Latanoprost	Timolol		2	3
FDC Netarsudil/Latanoprost	FDC Dorzolamide/ Timolol, or FDC brinzolamide/ brimonidine		3	4
FDC Netarsudil/Latanoprost	FDC brinzolamide/ brimonidine, or FDC brinzolamide/ brimonidine	Timolol	4	5

The challenge we face is that there are few—and only retrospective—studies to date involving the additivity of the newer combination drugs to existing regimens.[13,18] Of course, we do know a fair amount about their use as single agents from the numerous phase III clinical trials that have been published.[19-21]

Counting the Drops

One concern with prescribing multiple drops is how to evaluate the burden a given regimen places on the patient. I propose that rather than counting the medications or number of bottles a patient is using, we should be counting the number of daily eye drop instillations the patient has to make. That, I think, relates best to what a patient can comply with.

Using that perspective, today's co-drug and fixed-dose combinations can allow us to prescribe more medications without increasing the number of drops, which can make a big difference to many patients. For example, if we prescribe latanoprostene bunod (Vyzulta) with either netarsudil (Rhopressa) or timolol, that would mean two drops a day providing three medications. Both Vyzulta and Rhopressa would be taken in the evening, which for some patients would make the regimen easy to comply with. Typically, timolol would be used in the morning, so combining that with Vyzulta would mean one drop in the morning and one in the evening. Another regimen of two drops a day that would provide three medications is the fixed-dose combination of netarsudil/latanoprost (Rocklatan) which is taken in the evening, with timolol taken in the morning.

Any of these regimens gives the patient three medications with only two drops a day. The same logic could be used to provide four medications with three drops a day,

or five medications with four drops a day. (*See table, facing page.*) In short, the combination drugs give us better options for addressing the issue of patient compliance.

It's worth asking whether our patients can be expected to reliably administer three or more topical drops per day. In fact, we know from our own practices that many of our patients manage to use three or more drops and are well-controlled. (Admittedly, compliance is difficult to measure; but the surrogate for compliance is our IOP measurement in the office and the stability of visual fields, the optic nerve exam and our nerve fiber layer evaluations.) So a regimen consisting of multiple drops can work for some patients. The issue is knowing when such a regimen isn't working.

Should We Adjust Therapy?

Several things should be considered warning signs that a complex regimen isn't working out for one of our patients:

• ***The patient says, "I'm going to do better.*** You'll see—my pressure will be better next time." That's a red flag that you need to think about alternatives.

• ***The pressure varies a lot from visit to visit.*** The reason could involve compliance or the medications not working; either way, you need to move on to other treatment options.

• ***The patient hasn't asked for a refill in a year.*** That tells you that for some reason, the patient isn't taking—or isn't buying—the medications.

• ***The patient doesn't show up for scheduled appointments.*** If the patient is poorly compliant with office visits, he or she is probably also poorly compliant with medications.

You should also be on the lookout for a problem if your patient is elderly. Some elderly patients will have tremors or difficulty squeezing a bottle. In that situation, you should have an honest discussion: Is there someone else in their home, or a caregiver, who can assist with instilling the medications? If there isn't, then it's up to you to consider other options such as simplifying the regimen or choosing a laser or surgical option.

My rule of thumb is that if the patient has no complaints and is stable, it's OK to leave well enough alone. However, even if all seems fine, there are two options you may want to consider. First, it may be possible to simplify the regimen. If you can lessen

(Continued from page 35)

Back in the Driver's Seat

All of this can be boiled down to 10 key points:

1. Take the problem of burnout seriously. Make dealing with this a priority in your practice and in your life.

2. If you recognize that you're showing signs of burnout, don't wait for a crisis before addressing the problem.

3. Be aware that unusually difficult periods in your life put you at greater risk; ask for help dealing with your situation.

4. Do more socializing with your peers. Don't become isolated.

5. Take advantage of the resources around you. Investigate the concepts in the "mindfulness" curriculum; if possible, take a course. In addition, take the online version of Yale University's "happiness class."

6. Find ways to offload day-to-day burdens in the office that you might have previously overlooked.

7. Instead of resisting changes in the profession that you dislike, look for ways to turn them to your advantage.

8. Don't take on the role of victim; doing so takes away your ability to change things for the better. Focus on what you can change, not the things beyond your control.

9. Take the time to do things you love. Do things that remind you why you went into medicine—even if it means a loss of some income.

10. Give people you trust permission to provide feedback on how you're doing.

"Again, it's important for doctors to understand: If you're suffering from burnout, you need to get help," says Dr. Pearl. "You didn't do anything wrong. You need to make changes that will bring you happiness and fulfillment, not because the problem is your fault, but because this is your life."

Dr. Connolly says that perhaps the most important way to avoid burnout is to take a moment each day and remember why you became a doctor—and why you chose ophthalmology in particular. "Even with all of the hassles and the ways in which medicine has changed, it's still one of the best professions," she points out. "It's truly an amazing thing to be doing. Every single day, we physicians have the unique opportunity to make eye contact with other another human being. We have the opportunity to interact with people in a deep and meaningful way and make a difference in their lives. That truly is a great privilege.

"At the end of the day, if we can simply remember that, it will make the whole thing worthwhile," she concludes. "The rest of it is just paraphernalia. If we can shift our focus back to all the positive things that are still here, we'll not only be able to withstand the negative things, we'll extinguish burnout and reignite our joy in medicine." REVIEW

Dr. Piso is the author of the book "Healthy Power." Dr. Pearl is the author of the bestseller "Mistreated: Why We Think We're Getting Good Health Care and We're Usually Wrong." All profits from the sale of Dr. Pearl's book go to Doctors Without Borders.

the number of drops the patient has to use by switching to a combination drop—assuming cost issues are not a problem—then offer that option to the patient.

Second, if the patient has been stable for some time, it might be worth considering conducting a reverse therapeutic trial. It's possible that one of the drops your patient is using may no longer be making much of a difference. If that's the case, you'll be doing the patient a favor by eliminating it.

For example, if a patient has been well-controlled on three medications for several months or years, you may wonder if one could be removed. If the patient is interested in simplifying the regimen, you can suggest stopping one medication for two to four weeks; then, the patient can return for a checkup to see if all is still well. (If the patient is unhappy because of a side effect, this is also a way to determine if that medication is the cause.)

The challenge with reverse therapeutic trials is that patients often don't want to make the extra visits to the office. It may be difficult to convince a patient to stop a medication and return for follow-up if he's not sufficiently bothered by the regimen or side effects. In that case, you should simply stay the course.

No Easy Answers

Is there a "best" regimen? No. The maximum number of medications that's effective, tolerated and doesn't undercut compliance varies dramatically. What might be an excellent treatment regimen for one patient could be intolerable for another.

At this point in time we don't have a clear explanation, but there is certainly an individual response to medical therapy, just as there is to surgery or any other treatment. So for clinicians, finding the best regimen is a process of trial and error. What works best for a given patient will rarely match the result of a clinical study; he or she will be somewhere on the curve. That's something that we as clinicians must be sensitive to.

Perhaps our biggest current challenge is that we have limited data about the efficacy of the newer drugs when they're used in combination with other drugs, and whether or not these combinations will help to delay surgery. But—as noted earlier—we do know that in many situations adding even a fourth or fifth drop will provide additional pressure lowering. And we can assume that if we do get a pressure reduction, that will delay any potential surgical interventions for as long as the drugs are effective and tolerated.

What works best for a given patient will rarely match the result of a clinical study; he or she will be somewhere on the curve. That's something we as clinicians must be sensitive to.

As clinicians, it's our job to make sure the target pressure is achieved, the glaucoma is stable, and the patient is compliant and adherent. Whatever number of drops makes that happen, that's the right number for that patient. REVIEW

Dr. Serle is Professor Emeritus of Ophthalmology at the Icahn School of Medicine at Mount Sinai in New York. She is a consultant to and equity owner in Aerie Pharmaceuticals, a consultant to Allergan and Bausch + Lomb, and receives grant support from Ocular Therapeutix.

1. Jampel HD, Chon BH, Stamper R, et al. Effectiveness of intraocular pressure-lowering medication determined by washout. JAMA Ophthalmol 2014;132:4:390-5.
2. Bro T, Lindén C. The more, the better? The usefulness of brimonidine as the fourth antiglaucoma eye drop. J Glaucoma 2018;27:7:643-646.
3. Spencer SKR, Shulruf B, McPherson ZE, et al. Factors affecting adherence to topical glaucoma therapy. Ophthalmol Glaucoma 2019;2:86-93.
4. Weinreb RN, Bacharach J, Fechtner RD, et al. 24-hour intraocular pressure control with fixed-dose combination brinzolamide 1%/brimonidine 0.2%: A multicenter, randomized trial. Ophthalmology 2019;126:8:1095-1104.
5. Banitt M, Jung H. Ocular surface disease in the glaucoma patient. Int Ophthalmol Clinics 2018;58:3:23-33.
6. de Fendi LI, Oliveira TC, et al. Additive effect of risk factors for trabeculectomy failure in glaucoma patients: A risk-group from a cohort study. J Glaucoma 2016;25:10;e879-883.
7. Ederer F, Gaasterland DE, Sullivan EK; AGIS Investigators. The Advanced Glaucoma Intervention Study (AGIS): 1. Study design and methods and baseline characteristics of study patients. Control Clin Trials 1994;15:4:299-325.
8. Gedde SJ, Schiffman JC, Feuer WJ, et al. Treatment outcomes in the Tube Versus Trabeculectomy (TVT) study after five years of follow-up. Am J Ophthalmol 2012;153:5:789-803.
9. Christakis PG, Tsai JC, Zurakowski D, Kalenak JW, et al. The Ahmed Versus Baerveldt study: Design, baseline patient characteristics, and intraoperative complications. Ophthalmology 2011;118:2172-9.
10. Inazaki H, Kobayashi S, Anzai Y, et al. One-year efficacy of adjunctive use of Ripasudil, a rho-kinase inhibitor, in patients with glaucoma inadequately controlled with maximum medical therapy. Graefes Arch Clin Exp Ophthalmol 2017;255:2009-15.
11. Weinreb R, Feldman RM, et al. MIGS: When maximum medical therapy is not enough. Eyenet Supplement 2018.
12. Serle JB, Goldberg JL, Herndon LW, et al. Changing the course of glaucoma: Clinical implications of new therapies for IOP control. Eyenet Supplement 2018.
13. Ustaoglu M, Shiuey E, Sanvicente C, et al. The efficacy and safety profile of Netarsudil 0.02% in glaucoma treatment: Real-world outcomes. Invest. Ophthalmol. Vis. Sci.. 2019; 60(9):2393.
14. Shin DH, McCracken MS, Bendel RE, et al. The additive effect of latanoprost to maximum-tolerated medications with low-dose, high-dose, or no pilocarpine therapy. Ophthalmology 1999;106:386-390.
15. Bayer A, Tas A, Sobaci G, Henderer JD. Efficacy of latanoprost additive therapy on uncontrolled glaucoma. Ophthalmologica 2002;216:443-8.
16. Feldman RM, Bell NP, Nagi KS. Control of intraocular pressure fluctuation: Are combination drugs more effective? Exp Review Ophthalmol 2011;6:2:151-4.
17. Kim JH, Caprioli J. Intraocular pressure fluctuation: Is it important? J Ophthalmic Vis Res 2018;13:170-4.
18. Lamberg H, Kumar N,Reed D, et al. Early clinical experience with latanoprostene bunod. IOVS 2019;60:2395.
19. Kahook MY, Serle JB, Mah FS, et al. Long-term safety and ocular hypotensive efficacy evaluation of netarsudil ophthalmic solution. Am J Ophthalmol 2019;200:130-137.
20. Radell JE, Serle JB. Netarsudil/latanoprost fixed dose combination for the treatment of open-angle glaucoma or ocular hypertension. Drugs of Today 2019;55:9:1-12.
21. Weinreb RN, Liebmann JM, Martin KR, et al. Latanoprostene bunod 0.024% in subjects with open-angle glaucoma or ocular hypertension, pooled phase 3 study findings. J Glaucoma 2018;27:1:7-15.

“I didn’t realize STARS were little dots that twinkled”

—Misty L, *RPE65* gene therapy recipient

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PCV: An Important Subtype of Wet AMD

An in-depth look at the entity known as polypoidal choroidal vasculopathy.

Gregg T. Kokame, MD, MMM, Jase N. Omizo, BS, and Kelli A. Kokame, BA
Honolulu and Aiea, Hawaii

The most common cause of central vision loss in the developed world is leaking and bleeding due to the development of subretinal neovascularization. This abnormal leaking and bleeding is typically found under the retina, as well as below the retinal pigment epithelium, and it's most commonly caused by choroidal neovascularization associated with exudative age-related macular degeneration. An important subtype of exudative AMD involves CNV, in which subretinal aneurysmal dilations are a part of the lesion. This entity has been called polypoidal choroidal vasculopathy, or subretinal aneurysmal neovascularization. This article will discuss why the diagnosis of this polypoidal or aneurysmal subtype is the most impactful of all subtypes in terms of affecting treatment decisions for exudative AMD, and provide answers to the pertinent questions about the disease.

1 What is PCV?

Although PCV was initially theorized to be a choroidal vascular abnormality,[1-2] optical coherence tomography studies have usually localized this lesion between Bruch's membrane and the RPE.[3-4] In the anatomic classification of Gass for subretinal neovascularization,[5] this would be a type I subretinal neovascularization under the RPE and above Bruch's membrane. (The other anatomic classifications are Type II, in which subretinal neovascularization occurs above the RPE and in the subretinal space,[5] and Type III, in which neovascularization or retinal angiomatous proliferation includes an intraretinal component.[5])

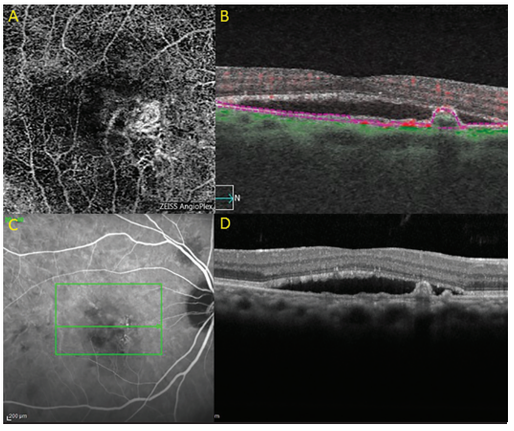

Figure 1. A: OCTA showing branching vascular network, but the polypoidal and aneurysmal dilations don't appear as clearly. B: Corresponding B-scan OCT showing the location of OCTA images in the area between RPE and Bruch's membrane, as noted by purple tracing lines in figure B. Note the prominent subretinal fluid and lack of intraretinal cystic changes more common in PCV. C: ICGA showing vascular complex with hyperfluorescent dilations. D: Multimodality imaging with corresponding B-scan showing typical inverted U-shaped elevation with heterogenous reflectivity consistent with a polypoidal lesion.

The clinical presenting features of this aneurysmal form of CNV look very similar to what is seen with exudative AMD. There is subretinal fluid and blood, as well as associated subretinal exudate and retinal pigment epithelial detachment. PCV has some distinguishing clinical features,[6] such as more subretinal fluid, greater height of subretinal fluid, more RPED, less intraretinal fluid and macular edema and a higher frequency of subretinal hemorrhage. However, unlike typical exudative AMD, the PCV diagnosis can't be made purely based on a fundus examination or fluorescein angiography.[7] In most cases, FA in PCV shows

This article has no commercial sponsorship.

occult leakage or occult CNV, often associated with RPED.

2 Isn't PCV mainly an Asian disease, since prevalence has been noted to be as high as 50 percent or more in eyes presenting with exudation and bleeding from subretinal neovascularization?

PCV has been diagnosed with high prevalence in Asian populations. However, PCV in Caucasian populations has been underdiagnosed due to a lack of access to indocyanine green angiography or lack of interest in ICGA diagnosis of PCV. Initial studies reported the prevalence of PCV in Caucasian patients to be less than 10 percent,[8-9] but these studies were done with digital fundus camera ICGA, which is much less sensitive than ICGA done with a scanning laser ophthalmoscope.[10] When SLO ICGA was used in Caucasian studies, for example, the prevalence of ICGA ranged from 20 percent in the PROTECT study from Duke,[11] to 24.5 percent in a study from Brazil on patients of predominantly European ancestry,[12] and as high as 31 percent in a Caucasian population in Hawaii.[13]

What makes ICGA the best way to diagnose PCV is its ability to delineate the aneurysmal lesions in the CNV complex with the highest sensitivity possible. The aneurysmal lesions are best seen three to five minutes after the injection of ICG dye and are often surrounded by a hypofluorescent ring. If video ICGA is performed with the SLO, the infrequent but dramatic finding of pulsations of the polypoidal lesions can be seen and is diagnostic of PCV. RPED is a frequent finding associated with PCV, and the RPED may mask the aneurysmal lesions, especially with the usual lack of hyperfluorescence within the RPED using the SLO. PCV lesions often appear at the edge of the RPED or at a notch in the RPED. There is often a branching vascular network (BVN) connecting to the polypoidal lesions. The ICGA SLO can visualize both polypoidal lesions and the BVN, which makes it more suitable for diagnosing PCV than flash fundus camera ICGA.[10]

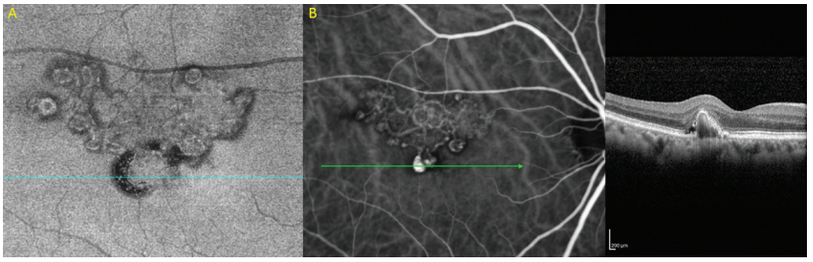

Figure 2. A: En face OCT using a slab localized between RPE and Bruch's membrane showing diagnostic branching vascular network and aneurysmal dilations typical of PCV. B: Corresponding ICGA showing the PCV complex and characteristic BVN and aneurysmal dilations. Note the characteristic inverted U-shaped elevation of the RPE on B-scan OCT, typical of a polypoidal lesion.

3 Why is it important to diagnose PCV or subretinal aneurysmal neovascularization? Doesn't it respond in ways similar to wet AMD to anti-VEGF drugs, our current standard-of-care?

Presently, there are no genetic markers for anti-VEGF resistance. However, there is one phenotypic marker that does predict anti-VEGF resistance, and that is subretinal aneurysmal lesions in the CNV complex, or PCV. While this was first recognized in case studies,[14,15] subsequent studies have confirmed a significantly higher rate of persistent disease activity in eyes with PCV when treated with the currently available anti-VEGF agents. This was seen in a study of PRN treatment in Sweden with ranibizumab.[16] This was also seen in a retrospective study in the United States, which defined anti-VEGF resistance as lack of clinical response after four consecutive anti-VEGF injections. It showed a statistically significantly higher prevalence of PCV in eyes with anti-VEGF resistance in PCV patients in general, and in both Asian and Caucasian patients specifically.[13]

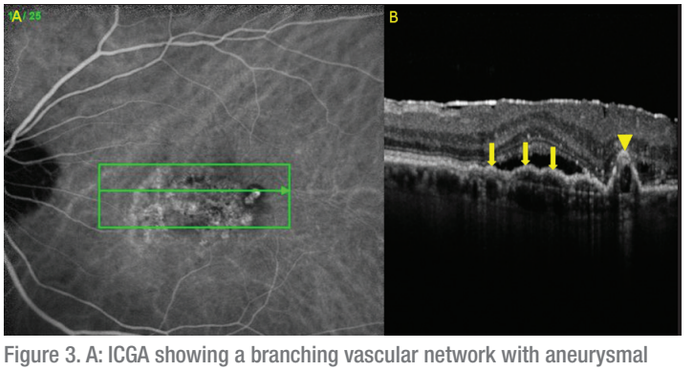

Figure 3. A: ICGA showing a branching vascular network with aneurysmal dilations typical of PCV. Note the characteristic hypofluorescent ring around the temporal aneurysmal dilation. B: B-scan OCT corresponding to the location of the green line with the arrow shown in figure 3A. Note the double-line sign with shallow elevation of the RPE corresponding to the BVN (arrows) and the higher inverted U-shaped lesion corresponding to the polypoidal lesion temporally (arrowhead).

Subretinal aneurysmal or polypoidal lesions noted on angiogram in the subretinal neovascularization are thus the one phenotypic marker that predicts resistance to the current standard-of-care therapy for exudative AMD: anti-VEGF medications.

4 Why is this important? Is there

another treatment option that may be useful in anti-VEGF resistant eyes?

Since PCV may not respond to anti-VEGF medications as well, alternative treatments may need to be considered, especially if a patient exhibits a poor response to therapy. The recent multicenter clinical trial, EVEREST II, showed that primary treatment using combined photodynamic therapy and anti-VEGF injections was superior to anti-VEGF monotherapy, both in terms of clinical and visual response. In addition, eyes that are initially treated with anti-VEGF medications and have a poor response may have a better outcome with less of a treatment burden when treating in conjunction with PDT.[17] *(See case examples below.)*

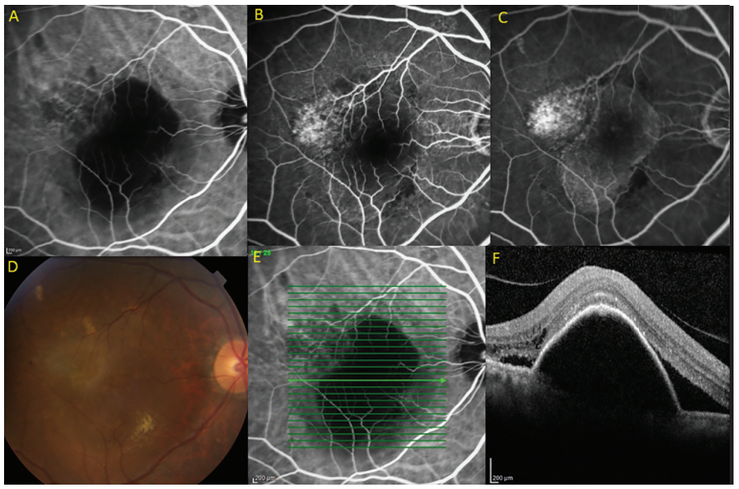

Figure 4. Initial presentation of PCV with vascularized RPE detachment in the right eye. Visual acuity is 20/60. A: ICGA showing superotemporal polypoidal vascular complex with adjacent hypofluorescent RPED. Note that the RPED is hypofluorescent on the scanning laser ophthalmoscopic ICGA. B & C: Early- and late-phase fluorescein angiogram showing occult hyperfluorescence superotemporally. D: Color photo showing elevated RPED and inferonasal exudate. E: Raster scan OCT over an ICGA image in which the green line with the arrow corresponds to the chosen OCT B-scan segment shown in F. F: B-scan OCT showing an RPED, subretinal fluid, temporal intraretinal edema and cystic changes.

5 How do we best diagnose the polypoidal or aneurysmal lesions within the subretinal neovascularization?

Historically, ICGA has been the gold standard for the diagnosis of the polypoidal subretinal aneurysmal lesions in the subretinal neovascular complex.[7,10,18] In addition, as previously discussed, ICGA using SLO is more sensitive than digital-camera ICGA.[10] However, if ICGA isn't available, the diagnosis can be made using multimodality imaging with high specificity but lower sensitivity than ICGA. OCTA images the BVN well, although the aneurysmal or polypoidal lesions are less well-imaged due to slower blood flow within the polypoidal lesions *(Figure 1)*. En face OCT imaging also can often demonstrate the BVN and the aneurysmal dilations associated with PCV anatomically *(Figure 2)*,[19-22] but again, it's less sensitive than ICGA. Both OCTA and en face OCT have higher sensitivity when correlated with B-scan OCTs showing subretinal fluid and blood associated with the polypoidal lesions. The polypoidal lesions appear as inverted U-shaped lesions with heterogeneous reflectivity, while the BVN appears as a shallow elevation of the RPE above Bruch's membrane (double-line sign).[4]

Practically, we recommend using any diagnostic means available in a practice to identify subretinal aneurysmal lesions, especially if there is poor response to anti-VEGF therapy. Start with the OCT B-scan images, and don't look just at the change images or the OCT map. Look at the individual horizontal and vertical scans for areas suspicious for the BVN, often with overlying fluid, and see if there's a double-line sign *(Figure 3)*. Then, look for possible polyps and analyze a B-scan going through the polyp to look for an inverted U-shaped elevation with heterogeneous reflectivity *(Figures 1-3)*. The best way to fully evaluate an area with OCT is to perform the sequential raster scan, which allows you to scroll down through the OCT. Then use the en face mode on the OCT scanner to scan a layer between the RPE and Bruch's membrane. This may allow imaging of the BVN with polypoidal lesions or aneurysmal dilated protrusions, which are diagnostic of PCV. OCTA localized to the area below the RPE and above Bruch's membrane may provide very characteristic

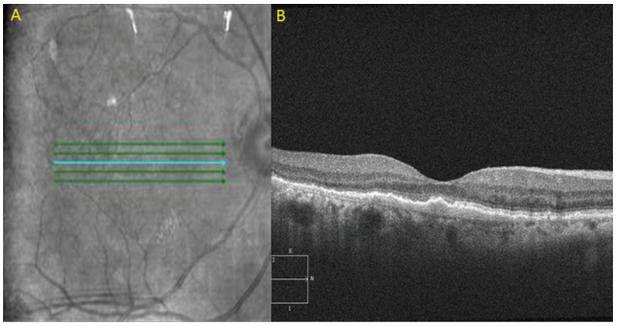

Figure 5. Resolution of RPED and subretinal fluid after treatment with combined PDT and anti-VEGF injections. A: Infrared photo showing the raster scan; the blue line with the arrow shows the location of the B-scan OCT through the fovea shown in B. B: Marked resolution of intraretinal edema, RPED and subretinal fluid.

or diagnostic pictures *(Figure 1)*, but the polypoidal lesions tend to be low-flow and may not be easily visualized with OCTA.[19] However, the polypoidal lesions may be identified with multimodality imaging when the OCTA is unable to image the aneurysmal dilations *(Figure 1)*.

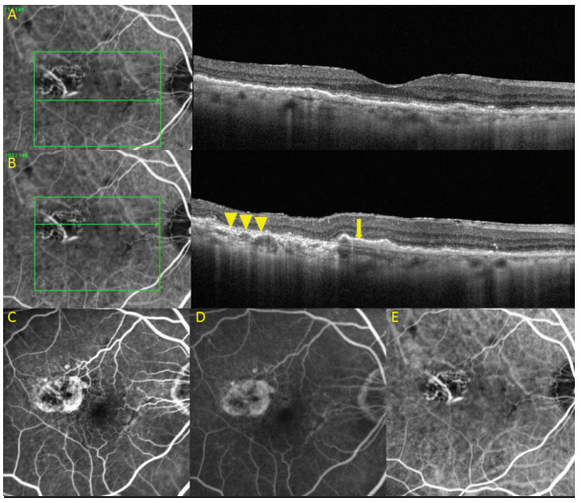

Figure 6. No recurrence of leakage six years after combined PDT/anti-VEGF without the need for continuing intravitreal injections. Visual acuity is 20/40. A: ICGA showing a superotemporal RPE scar with the corresponding OCT through the fovea. Note the lack of RPED and subretinal fluid. B: The corresponding OCT goes through the area of the superotemporal RPE scar and the area of the previous PCV. Note the area of RPE atrophy corresponding to the scar (arrowheads) and the double-line sign corresponding to the residual BVN (arrow). C,D: Fluorescein angiogram, early (C) and late (D), showing lack of leakage. E: ICGA showing regression of the PCV complex but residual BVN.

6 How is overall treatment specifically different for PCV, compared to typical wet AMD?

Based on the EVEREST II Study, it's reasonable to offer either anti-VEGF alone or combined with PDT for PCV that involves the central fovea. Practically, if vision is still very good—20/40 to 20/50 or better—then it's reasonable to start with anti-VEGF therapy. However, if vision is 20/50 to 20/60 or worse, it's also very reasonable to start with combined PDT and anti-VEGF therapy, since results in the EVEREST II Study were better with regard to treatment burden and visual recovery for combination PDT and anti-VEGF treatment for PCV. In the EVEREST II study there weren't any cases of sudden vision loss after PDT, but there's a potential risk of choroidal ischemia or subretinal hemorrhage, so this small risk may be avoided in eyes with good vision. However, if lesions are extrafoveal and the PDT lesion spot can avoid the fovea, it's very reasonable to begin with combination PDT and anti-VEGF therapy with the laser spot size sparing the fovea.

7 Why doesn't PCV respond as well to the standard-of-care therapy for exudative AMD of intravitreal anti-VEGF injections?

The response of typical exudative AMD to anti-VEGF therapy has been significantly better than the natural course of the disease, resulting in markedly less subretinal hemorrhage and leakage and better overall visual outcomes. However, the PCV subtype has been shown in case series and in retrospective studies to have a higher risk of anti-VEGF resistance.[13-16] There's more persistent disease activity in eyes with PCV on anti-VEGF therapy. This makes the subretinal aneurysmal lesions diagnostic of PCV the only phenotypic marker for anti-VEGF resistance in eyes presenting with exudative AMD.

8 How are PDT and combination treatment performed for PCV? Is it different from the protocol we traditionally used for typical exudative AMD?

Traditionally, in the early 2000s, for typical wet AMD, FA was utilized to determine lesion size and the area of leakage was encircled. The greatest linear dimension was calculated based on leakage detected by the FA. For typical exudative AMD, the initial recommendation was to use a treatment spot 1,000 µm larger than the GLD leakage on the FA. Treatment for PCV lesions is very different, as the spot size for PDT is based on the ICGA, not the FA. The area of the BVN and the polypoidal lesions is encircled. The greatest linear dimension is then determined on the ICGA. Some experts use a treatment spot size exactly the size of the PCV lesion on ICGA. However, it's reasonable to add a 300-µm border around the lesion on ICGA.

For verteporfin (Bausch + Lomb, Rochester, New York), an intravenous dose of 6 mg per square meter of body surface is given and the diode laser (689 nm) is directed to the treatment area 15 minutes after IV infusion of dye. If the PCV lesion is extrafoveal, we recommend full fluence PDT (50 J/cm^2 of light at 600 mW/cm^2 for 83 seconds). If the lesion is subfoveal and vision is good, then reduced fluence PDT (25 J/cm^2 of light at 300 mW/cm^2) can be considered. Laser spot duration is 83 seconds for both full-fluence and reduced-fluence treatments, but the settings of the laser are different, as noted above. If vision is 20/50 to 20/60 or worse, full-fluence treatment is reasonable for subfoveal lesions, based on EVEREST II.

Case Examples

Following are two cases showing the treatment course of PCV.

• ***Case 1: Primary combination PDT.*** This patient was an 85-year-old male who presented with blurred vision in the right eye for five months. Visual acuity was 20/60 and there was

an RPED, serous retinal detachment, pachydrusen and subretinal exudates. ICGA revealed a BVN and polypoidal aneurysmal lesions in the superotemporal macula. The patient refused to start frequent intravitreal anti-VEGF injections, and specifically requested a therapy that could minimize the treatment burden and injections. As a result, he underwent full-fluence PDT with intravitreal bevacizumab 1.25 mg and dexamethasone 400 µg. The lesion responded dramatically. There was a slight residual RPED and subretinal fluid, but after two subsequent injections of intravitreal bevacizumab 1.25 mg and dexamethasone 400 µg, the RPED, subretinal fluid and exudate all resolved *(Figure 5)*. His vision recovered to 20/30 and there hasn't been a need for further injections or PDT in six years *(Figure 6)*.

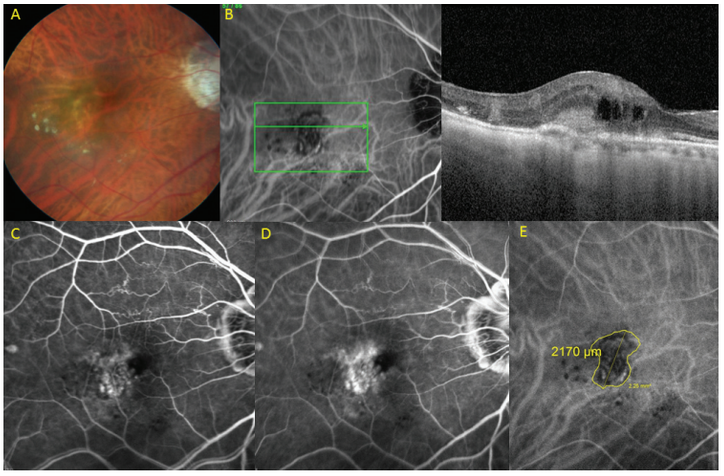

Figure 7. PCV in an eye with previous poor response to anti-VEGF therapy. A: A color fundus photograph showing persistent macular edema and temporal subretinal exudates after monthly intravitreal aflibercept injections. B: ICGA with correlated OCT showing intraretinal edema with cystic changes and SHRM. C, D: Early- and late-phase FA showing persistent occult leakage. E: ICGA showing a PCV lesion with BVN and visible inferior polypoidal lesions. Note that the lesion size can be determined on the ICGA by circumscribing it on the scan in order to determine its greatest linear dimension (2,170 µm in this instance). This ICGA lesion size is used as the target for the PDT laser treatment.

If an eye with exudative AMD has already been treated with standard-of-care anti-VEGF injections but there's persistent disease activity, a combination therapy of PDT and anti-VEGF may be very helpful in decreasing the treatment burden and improving the anatomic results.

• ***Case 2: Combination PDT after previous anti-VEGF therapy.*** A 96-year-old male was diagnosed with exudative AMD with a vascularized RPED, subretinal fluid, macular cystic changes and subretinal hyperreflective material (SHRM). Fluorescein angiography showed occult leakage. He started monthly intravitreal aflibercept injections but there was persistent subretinal fluid, subretinal hemorrhage, RPED and exudates. Due to persistent disease activity, ICGA was performed, and he was diagnosed with the polypoidal subtype of exudative AMD. This ICG was used to guide PDT treatment and to measure the spot size *(Figure 7)*. Vision was 20/40, and the lesion was subfoveal, so reduced-fluence PDT was performed, but there was persistent leakage and his vision was 20/60. Three months after the first PDT, a second full-fluence PDT was performed, combined with same-day injection of bevacizumab 1.25 mg and dexamethasone 400 µg. There was marked resolution of the RPED, macular edema and subretinal fluid, and he now requires aflibercept injections only every 10 weeks; the RPED, subretinal fluid and disease activity have completely resolved *(Figure 8)*. Vision has recovered to 20/40.

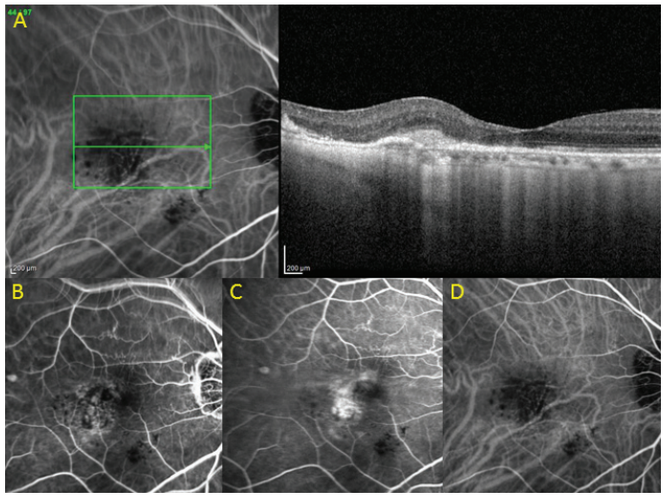

Figure 8. After two combination PDT treatments with anti-VEGF and decadron, the vision is 20/40 and there's resolution of macular edema and exudates with extension of the aflibercept treatment interval from four weeks out to 10 weeks. A: OCT showing recovery of the foveal depression with resolution of intraretinal edema and temporal subretinal fibrosis, with an intact subfoveal photoreceptor layer. B, C: FA shows staining of subretinal fibrosis temporally and superiorly. D: ICGA showing marked resolution of the PCV complex after combination PDT.

9 Is there a role for macular laser photocoagulation of polyps when treating PCV?

If the diagnosis of PCV is made with extrafoveal

polyps resulting in leakage, it's reasonable to consider focal macular laser treatment of the polyps with or without supplemental anti-VEGF therapy. This may result in long-term stabilization of the leakage with good vision. The goal of using thermal laser is to close the polypoidal lesion and prevent further leakage or bleeding.[23]

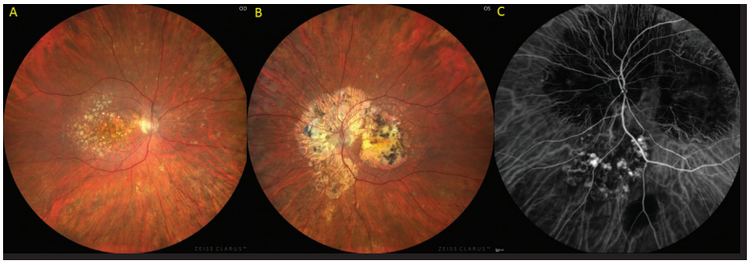

Figure 9. A: Color fundus photograph of a Caucasian patient, with PCV in the left eye, showing significant soft drusen and geographic atrophy in the fellow eye. B: Fundus photograph of significant peripapillary scarring and macular scarring in the eye with PCV. The PCV complex started along the superior edge of the nerve, then moved nasally and inferiorly, initially sparing the macula. C: ICGA showing the most recent inferior recurrence, revealing polypoidal lesions in the inferior PCV complex.

10 Are the presenting characteristics of PCV different in different ethnic populations?

PCV was initially described as a peripapillary, often bilateral, disease in Caucasian and black patients.[9] However, more recent studies in Caucasian patients show that PCV does primarily affect the macula.[24] However, when there's peripapillary disease, a characteristic peripapillary scarring occurs around the nerve *(Figure 9B)*, which isn't usually seen in Asian patients with this disease. Note that there can also be significant drusen and geographic atrophy in the fellow eye of Caucasian patients with unilateral PCV *(Figure 9A)*.

Although typical exudative AMD has long been known to be more frequent in females, PCV has a strong male predilection in Asian patients; it doesn't show the usual female predominance typical of exudative AMD in Caucasian patients.[13,24] PCV in black patients often has larger-caliber vessels, and is more often peripapillary.[9]

11 Ultimately, how can diagnosing PCV in exudative AMD patients help me in my practice?

Although most patients with exudative AMD are started on anti-VEGF intravitreal injections as first-line therapy, PCV is the one subtype of exudative AMD that may predict anti-VEGF resistance. So, if there is a poor response, alternative therapy with combinated PDT and an anti-VEGF injection can be considered. However, after long-term anti-VEGF therapy, polypoidal or aneurysmal lesions may regress, so it may be more difficult to make the diagnosis of PCV. In addition, the EVEREST II study has shown that combination therapy with PDT should be considered as a primary therapy for PCV, as it allows better vision and anatomic results than anti-VEGF therapy with ranibizumab alone.[17]

Finally, PCV may be more responsive to certain anti-VEGF medications, since aflibercept is the treatment of choice in Asia for PCV and the drug has shown a significantly better response in some eyes treated previously with other anti-VEGF agents.[4] In the future, there could also be differences in treatment response with new medications, including the newly-approved Beovu (brolucizumab; Novartis, Basel, Switzerland), which was studied in the setting of PCV in both the HAWK and HARRIER trials for treatment-naïve, exudative AMD and is being analyzed in the ongoing MERLIN trial for previously treated exudative AMD.

In conclusion, PCV is the most impactful subtype of exudative AMD because it provides a marker for anti-VEGF resistance, which may affect therapeutic planning for treatment-naïve eyes as well as eyes responding poorly to anti-VEGF therapy. Combining PDT with anti-VEGF therapy can significantly decrease treatment burden and improve anatomic and visual outcomes. Although ICGA with the SLO is the gold standard for diagnosing PCV, retina physicians should use all modalities, including B-scan OCT, en face OCT and OCTA, to make the diagnosis of PCV—modalities that will continue to improve. PCV isn't only common in Asian patients, but it's also more common than previously thought in Caucasian patients (a 20- to 30-percent prevalence), which means that it's present in a very significant number of the patients presenting with exudative AMD throughout the world. REVIEW

Dr. Kokame is a clinical professor at the University of Hawaii John A. Burns School of Medicine, and medical director of the Hawaii Macula and Retina Institute. Mr. Omizo and Ms. Kokame, BA, are employed at Retina Consultants of Hawaii.

No authors have any financial interest in any of the methods or materials presented. Dr. Kokame receives research support from Genentech and Regeneron, and is a consultant for Genentech, Santen, Regeneron, Bayer, Bausch + Lomb, Zeiss and Allergan. He's a speaker for Regeneron, Bayer, Second Sight and Bausch + Lomb. Ms. Kokame and Mr. Omizo have no such financial interests to disclose.

1. Yannuzzi LA. Idiopathic choroidal vasculopathy. Presented at: Macula Society Annual Meeting, February 5, 1982; Miami.

(Continued on p. 66)

New Hope for Battling Myopia Development

As myopia reaches epidemic proportions around the globe, clinicians just received a new weapon to aid them in the fight against it: CooperVision received U.S. Food and Drug Administration approval for the MiSight (omafilcon A) daily wear single use soft contact lens, designed for the correction of myopia and for slowing the progression of myopia.

MiSight is indicated for use in children with healthy eyes, who at the initiation of treatment are 8 to 12 years old and have a spherical equivalent refraction between -0.75 and -4 D with no more than 0.75 D of astigmatism.

According to an FDA description of the device, when it's placed on the eye, one part of the MiSight contact lens corrects the refractive error to improve distance vision in nearsighted eyes, while concentric peripheral rings in the lens focus part of the light in front of the retina. This latter effect is believed to reduce the stimulus causing the progression of myopia.

The approval of MiSight was based on data obtained from a prospective clinical trial at four clinical sites and "real-world evidence." The trial showed that over a three-year period, the progression in myopia of children wearing MiSight lenses was less than those wearing conventional soft contact lenses. In addition, subjects who used MiSight had less change in the axial length of the eyeball at each annual checkup. Over the course of the trial, there were no serious ocular adverse events in either arm of the study, and the rate of corneal ulcers was "comparable" to that in adults who wear daily contact lenses. The company says the lens will be available in spring of 2020, and, as part of the approval of MiSight, it will conduct a postmarket study of the contact lenses to further evaluate the safety and effectiveness of the product. For information, visit https://coopervision.com/contact-lenses/misight-1-day.

The MiSight contact lens uses peripheral rings to focus some incoming light in front of the retina in an attempt to slow the development of myopia.

Optos Unveils Silverstone

If you've been looking for an ultra-widefield optical coherence tomographer that uses swept-source technology, Optos has a new device for you. The company recently launched Silverstone, an imaging system combining ultra-widefield retinal imaging with integrated, image-guided, swept-source OCT.

Optos says that Silverstone produces a 200-degree, single-capture Optomap image with guided OCT, enabling OCT imaging anywhere across the retina, from posterior pole to the far periphery. It has features such as a 3-in-1 Color Depth Imaging, which provides clinical data from the retinal surface through the choroid, Optos says. For more information, visit https://www.optos.com/en/products/silverstone.

Mini but Mighty

If your AMD patients have trouble swallowing normal-sized gels or tablets, Bausch + Lomb may have a solution: PreserVision AREDS 2 Formula mini-gels, which will replace the previously offered soft gels. The company says that the vitamins contain the same National Eye Institute-recommended formula for moderate to advanced age-related macular degeneration.

For information on the new gels, visit https://www.bausch.com/our-products/eye-vitamins/age-related-eye-vitamins. REVIEW

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REVIEW Advertising Index

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A young boy presents with a strange constellation of symptoms, prompting an evaluation at Wills' Ocular Oncology Service.

Louis Cai, MD, Sara Lally, MD, Carol L. Shields, MD

Presentation

An asymptomatic 8-year-old Asian Indian male was seen for a routine examination by the local ophthalmologist. On fundus evaluation, the physician noted a choroidal pigmentary abnormality in both eyes and referred the patient for evaluation at the Ocular Oncology Service at Wills Eye Hospital to rule out malignancy.

Medical History

This patient was the product of a full-term pregnancy with uncomplicated prenatal, perinatal and postnatal courses. Past medical and surgical histories were unremarkable. Iris heterochromia was noted at 1 month of age with a blue iris in the right eye and brown iris in the left. When the patient was 6 years old, his primary ophthalmologist noticed choroidal pigmentary abnormalities in both eyes and recommended observation. Family history was remarkable for diabetes mellitus and hypertension on the maternal side. He had no known allergies or medications. There was no family history of vitiligo, albinism, Waardenburg syndrome or other pigmentary abnormalities. There was no family history of cancer.

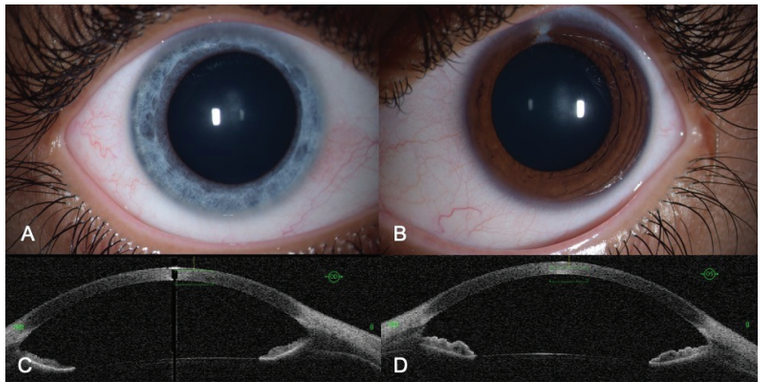

Figure 1. A brilliant blue iris in the right eye (A) and an area of sectoral hypopigmentation superiorly in the left eye (B). Anterior segment optical coherence tomography shows thinning of the right iris (C) compared to the left iris (D).

Examination

On ocular examination, visual acuity was 20/20 OU. Both pupils were round, equal and reactive. Intraocular pressure was normal to finger tension OU. Confrontation visual fields and ocular motility were full bilaterally. The anterior segment examination of the right eye revealed a "brilliant-blue" iris, despite his Asian Indian heritage *(Figure 1A)*. The left iris was homogeneously brown with a focal segment of pigment loss superiorly, appearing blue *(Figure 1B)*. The rest of the anterior segment examination was unremarkable.

On funduscopic examination, patchy diffuse

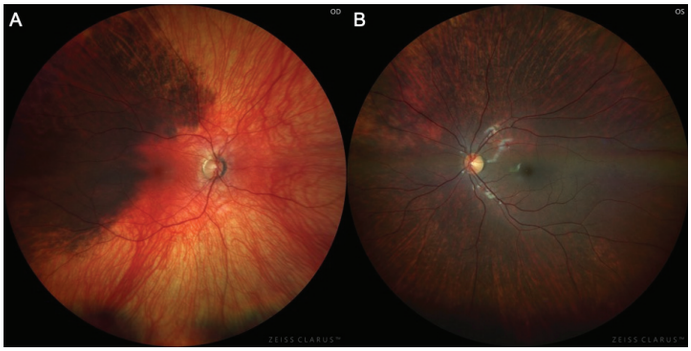

Figure 2. Fundus photography demonstrating (A) patchy hypopigmentation of the right choroid nasally and inferiorly. Normal pigmentation is seen in the left choroid (B), with minor pigment abnormalities superonasally.

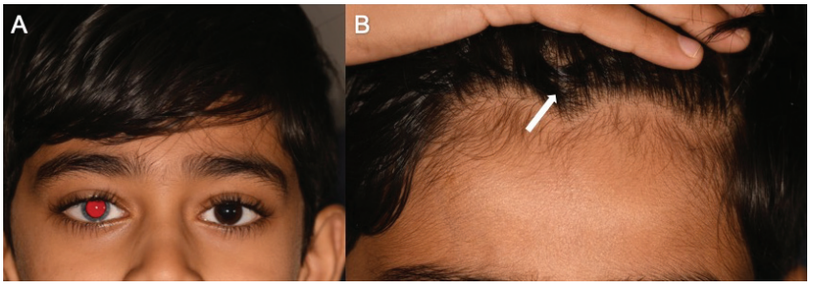

Figure 3. External photography documenting heterochromia with a blue iris in the right eye and a brown iris in the left eye as well as synophrys of the eyebrows (A). Upon lifting the frontal hairs, strands of white hairs (arrow) are noted, a mild documentation of white forelock.

choroidal hypopigmentation was noted with preserved normal pigmentation superotemporally in the right eye *(Figure 2A)*. There was no subretinal fluid, orange lipofuscin pigment, choroidal mass, retinal pigment epithelial abnormalities or peripheral drusen. The left fundus had normal pigmentation with subtle, wedge-shaped hypopigmentation superonasally *(Figure 2B)*.

An external examination found mild synophrys with eyebrow hairs over the upper nasal bridge *(Figure 3A)*. Upon careful examination of his scalp hair, there was trace evidence of a white forelock *(Figure 3B, arrow)*. Otherwise there was no displacement of the medial canthi, no broad nasal root or any other dermal or palatal hyper- or hypopigmentation. There was no skeletal deformation, and a hearing test was normal.

What is your diagnosis? What further workup would you pursue? The diagnosis appears below.

Workup, Diagnosis and Treatment

Further ancillary imaging was performed. Optical coherence tomography displayed normal foveal features OU, with subfoveal choroidal thickness at 210 µm OU, but the right eye demonstrated increased light transmission into deeper structures. Autofluorescence demonstrated mild scleral unmasking of autofluorescence in the right eye in the area of hypopigmentation compared to the left *(Figure 4 A and B)*. By anterior segment OCT there was slight thinning of the iris stroma with loss of crypt architecture OD as compared to OS *(Figure 1 C and D)*. There was no retinal or choroidal elevation on ultrasonography OU *(Figure 4 C and D)*.

On further questioning, the patient's mother revealed that she had a white central portion of hair that she had routinely dyed since the age of 12 years. With the presence of iris hypopigmentation, choroidal hypopigmentation, synophrys, and a personal and family history of white forelock, the patient was diagnosed clinically with Waardenburg syndrome. As congenital deafness can be present in this condition, a complete auditory evaluation was performed and found to be normal.

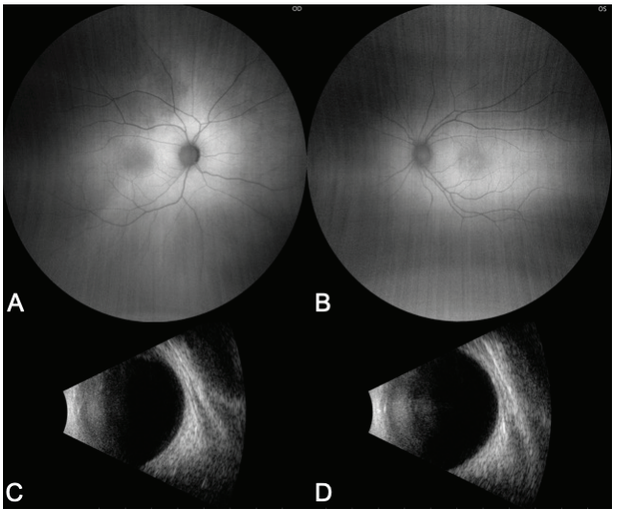

Figure 4 Fundus autofluorescence showing mild peripapillary hyperautofluorescence in the depigmented areas of the right eye compared to the left (A). By B-scan ultrasonography there was no mass in either eye (B).

Discussion

Waardenburg syndrome is a relatively rare congenital disease that occurs in one in 40,000 births.[1] It was first described in 1951.[2] This condition is composed of six defining features, including telecanthus or dystopia canthorum (displacement of the medial canthi), broad nasal root synophrys of the eyebrows, white forelock in the scalp, iris heterochromia and congenital sensorineural deafness.[2] Dystopia canthorum is quantified using a "W

Index," which incorporates inner canthal distance, interpupillary distance and outer canthal distance. W Index values greater than 1.95 are considered abnormal.[4] In 1966, researchers detailed the findings associated with WS and found a correlation between hypopigmentation of the iris and hypopigmentation of the choroid.[3] Most recently, one of this report's authors, Dr. Shields, and colleagues described these findings in detail and found both iris and choroid hypopigmented regions to be thinner on AS-OCT and posterior segment OCT, respectively.[4] The hypopigmentation and thinning is believed to be related to abnormal neural crest migration and melanin production.[5]

Ocular melanocytosis is a close mimicker of WS, as the pigmentary abnormality can affect the uveal tract in both a sectoral and diffuse pattern.[6] Unlike WS, melanocytosis is a hyperpigmentation and not a hypopigmentation. Additionally, ocular melanocytosis can manifest with increased pigmentation of the sclera, skin and palate. By AS-OCT, melanocytosis demonstrates iris thickening with loss of crypts and presence of mammillations from overabundant melanocytes, whereas WS shows thinning and loss of crypts. One further point is that WS can be hereditary and affect multiple family members, whereas melanocytosis isn't hereditary. This distinction is important, as ocular melanocytosis is associated with secondary glaucoma and an increased likelihood of development of uveal melanoma, unlike WS.[7]

Four distinct types of WS have been described. WS1 and WS2 are inherited in an autosomal dominant fashion and are likely related to the originally described syndrome.[4] There's a large variability of phenotypic expression, and individuals will typically show only a few of the classical features. WS3 and WS4 seem to have an autosomal recessive pattern of inheritance. WS3 is associated with malformations of the upper limbs, and WS4 is associated with Hirschsprung disease.[8] Multiple genes have been associated with WS, including EDN3, EDNRB, MITF, PAX3 and SOX10. The exact functions of these genes have yet to be elucidated.[9] Genetic testing for individuals suspected to have WS may help confirm the diagnosis. Ultimately, patients with WS have a preserved visual prognosis and require annual ophthalmic examination. It's important to remember that Waardenburg Syndrome accounts for 2 to 5 percent of all patients with congenital hearing loss.[1]

In conclusion, in patients who present with diffuse choroidal hyper- or hypopigmentation in both eyes, consider that the lighter areas may represent WS, rather than the dark areas of ocular melanocytosis, a close mimicker. Examination for classical features of WS including telecanthus (dystopia canthorum), synophrys of the eyebrows, white forelock, broad nasal root, heterochromia and congenital deafness can lead to the diagnosis. And don't forget that a detailed family history—including asking questions about the dyeing of hair—can be revealing, as in this case. REVIEW

1. Zaman A, Capper R, Daddoo W. Waardenburg syndrome: More common than you think! Clin Otolaryngol 2015;40:1:44-8.
2. Waardenburg PJ. A new syndrome combining developmental anomalies of the eyelids, eyebrows and nose root with pigmentary defects of the iris and head hair and with congenital deafness. Am J Hum Genet 1951;3:3:195-253.
3. Goldberg MF. Waardenburg's syndrome with fundus and other anomalies. Arch Ophthalmol 1966;76:6:797-810.
4. Shields CL, Nickerson SJ, Al-Dahmash S, Shields JA. Waardenburg syndrome: Iris and choroidal hypopigmentation: Findings on anterior and posterior segment Imaging. JAMA Ophthalmol 2013;131:9:1167–1173.
5. Mullaney PB, Parsons MA, Weatherhead RG, Karcioglu ZA. Clinical and morphological features of Waardenburg syndrome type II. Eye (Lond) 1998;12:3a:353-357.
6. Shields CL, Qureshi A, Mashayekhi A,et al. Sector (partial) oculo(dermal) melanocytosis in 89 eyes. Ophthalmology 2011;118:12:2474-2479.
7. Singh AD, De Potter P, Fijal BA, et al. Lifetime prevalence of uveal melanoma in Caucasian patients with oculo(dermal) melanocytosis. Ophthalmology 1998;105:195–8.
8. Pingault V, Ente D, Dastot-Le Moal F, et al. Review and update of mutations causing Waardenburg syndrome. Hum Mutat 2010;31:4:391-406.
9. Tachibana M. A cascade of genes related to Waardenburg syndrome. J Investig Dermatol Symp Proc 1999;4:2:126-29.

(Continued from p. 61)

2. Yannuzzi LA, Sorensen J, Spaide RF, Lipson B. Idiopathic polypoidal choroidal vasculopathy. Retina 1990;10:1:1–8.
3. Khan S, Engelbert M, Imamura Y, Freund KB. Polypoidal choroidal vasculopathy. Simultaneous indocyanine green angiography and eye-tracked spectral domain optical coherence tomography findings. Retina 2012;32:6:1057–1068.
4. Kokame GT. Prospective evaluation of subretinal location in polypoidal choroidal vasculopathy (PCV) and response of exudative and hemorrhagic PCV to high dose anti-angiogenic therapy (An American Ophthalmological Society Thesis). Trans Am Ophthalmol Soc 2014;112:74–93.
5. Gass JDM. Stereoscopic atlas of macular diseases: Diagnosis and treatment. 4th ed. St. Louis: Mosby, 1997.
6. Ozawa S, Ishikawa K, Ito Y, et al. Differences in macular morphology between polypoidal choroidal vasculopathy and exudative age-related macular degeneration detected by optical coherence tomography. Retina 2000;29:6:793–802.
7. Kokame GT. Polypoidal choroidal vasculopathy: An important diagnosis to make with therapeutic implications. Retina 2012;32:8:1446–8.
8. Lafaut BA, Leys AM, Snyers B, et al. Polypoidal choroidal vasculopathy in Caucasians. Graefes Arch Clin Exp Ophthalmol 2000;238:9:752–9.
9. Yannuzzi LA, Wong DW, Sforzolini BS, G, et al. Polypoidal choroidal vasculopathy and neovascularized age-related macular degeneration. Arch Ophthalmol 1999;117:1503–10.
10. Cheung CM, Lai TY, Chen SJ, et al. Understanding indocyanine green angiography in polypoidal choroidal vasculopathy: The group experience with digital fundus photography and scanning laser ophthalmoscopy. Retina 2014;34:2397–2406.
11. Mettu PS, Allingham MJ, Nicholas PC, et al. Neovascular morphology by ICG angiography and response to loading-dose anti-VEGF therapy in patients with neovascular age-related macular degeneration: Results of the PERSIST Study. Invest Ophthalmol Vis Sci 2016;57:12.
12. Pereira FB, Veloso CE, Kokame GT, Nehemy MB. Characteristics of neovascular age-related macular degeneration in Brazilian patients. Ophthalmologica 2015;234:4:233-42.
13. Kokame GT, de Carlo TE, Kaneko KN, et al. Anti-VEGF resistance in exudative macular degeneration and PCV. Ophthalmology Retina 2019;3:9:744-752.
14. Stangos AN, Gandhi JS, Nair-Sahni J, et al. Polypoidal choroidal vasculopathy masquerading as neovascular age-related macular degeneration refractory to ranibizumab. Am J Ophthalmol 2010;150:5:666-673.
15. Cho M, Barbazetto IA, Freund KB. Refractory neovascular age-related macular degeneration secondary to polypoidal choroidal vasculopathy. Am J Ophthalmol 2009;148:1:70-81.
16. Hatz K, Prunte C. Polypoidal choroidal vasculopathy in Caucasian patients with presumed neovascular age-related macular degeneration and poor ranibizumab response. Br J Ophthalmol 2014;98:2:188-94.
17. Koh A, Lai TY, Takahashi K, et al. Efficacy and safety of ranibiuzmab with or without verteporfin photodynamic therapy for polypoidal choroidal vasculopathy. A randomized clinical trial. JAMA Ophthalmol 2017;135:1206-1213.
18. Cheung CMG, Lai TYY, Ruamviboonsuk P, et al. Polypoidal choroidal vasculopathy: Definition, pathogenesis, diagnosis, and management. Ophthalmol 2018;1255:708-24.
19. deCarlo T, Kokame GT, Kaneko KN, Lian R, Lai JC, Wee R. Sensitivity and specificity of detecting polypoidal choroidal vasculopathy with en face OCT and OCT angiography. Retina 2019;39:7:1343-1352.
20. deCarlo T, Kokame GT, Shantha JG, et al. Spectral domain OCTA for the diagnosis and evaluation of polypoidal choroidal vasculopathy. Ophthalmologica 2018;239:103e109.
21. Kokame GT, Hirai K, Yanagihara R. Polypoidal choroidal vasculopathy: Imaging by indocyanine green angiography and en face optical coherence tomography. JAMA Ophthalmol 2015;133:e151886.
22. Sayahagi K, Gomi F, Akiba M, et al. En-face high penetration optical coherence tomography imaging in polypoidal choroidal vasculopathy. Br J Ophthalmol 2015;99:1:29-35.
23. Kokame GT. Polypoidal choroidal vasculopathy–A type I polypoidal subretinal neovasculopathy. Open Ophthalmol J 2013;7:82-84.
24. Kokame GT, Liu K, Kokame KA, et al. Clinical characteristics of polypoidal choroidal vasculopathy and anti-vascular endothelial growth factor treatment response in Caucasians. Ophthalmologica 2019. [Pending publication].

xiidra® (lifitegrast ophthalmic solution)5%

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

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

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

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

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

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

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

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

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

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

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

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

Shire

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

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xiidra® (lifitegrast ophthalmic solution)5%

THERE'S NO SUBSTIITUTE

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

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

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

References:

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

Indication

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

Important Safety Information

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

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

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

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

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

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

Shire