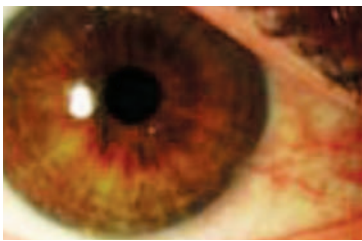


Clinical Diagnosis

OCULAR PAIN: NOCICEPTIVE OR NEUROPATHIC?



CORNEAL neuropathic pain seems to be a “neglected stepchild” compared with nociceptive pain in that it is under-evaluated by cornea specialists. Though the two disorders are different with different causes, both can occur concomitantly in patients. Both pain syndromes can result in patients presenting complaints of dry, burning, and aching eyes, and ophthalmologists should not limit their investigations to the ocular surface in patients with dry eye symptoms, says Anat Galor, MD, MSPH.

(See story on page 14 : Ocular pain)

Surgery

HIGH- VERSUS MEDIUM-ADD MULTIFOCAL IOLS

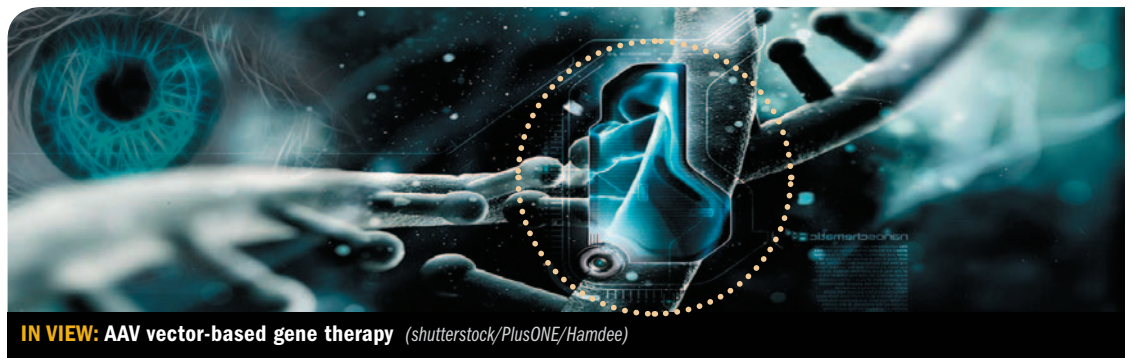
MEDIUM-ADD multifocal IOLs address the most likely source of dissatisfaction with contemporary multifocal IOLs: intermediate vision. High levels of success with presbyopia-correcting IOLs are dependent on choosing the IOLs that will maximize the patient’s bilateral visual performance at distance, intermediate, and near; aggressively treating residual refractive error (≤ 0.50 D of residual sphere and astigmatism); and aggressively managing the ocular surface, explains Frank A. Bucci Jr., MD.

(See story on page 29 : Intermediate)

► OphthalmologyTimes.com

OPHTHALMIC YEAR IN REVIEW

Ophthalmology benefiting from active programs for innovative product development in 2018 and onward



IN VIEW: AAV vector-based gene therapy (shutterstock/PlusONE/Hamdee)

By Cheryl Guttman Krader

THE 12 MONTHS between Oct. 1, 2017 and Sept. 30, 2018 was a banner period for new entries into the ophthalmic therapeutic armamentarium with the FDA approving nine original New Drug Applications/Biologic License Applications (NDA/BLA) and a first gene therapy. In addition, seven devices for use in ophthalmology received Premarket Approval Application (PMA) approvals during the same time interval.

This article recaps the new product entries and takes a look at some emerging therapies that are advancing in clinical development.

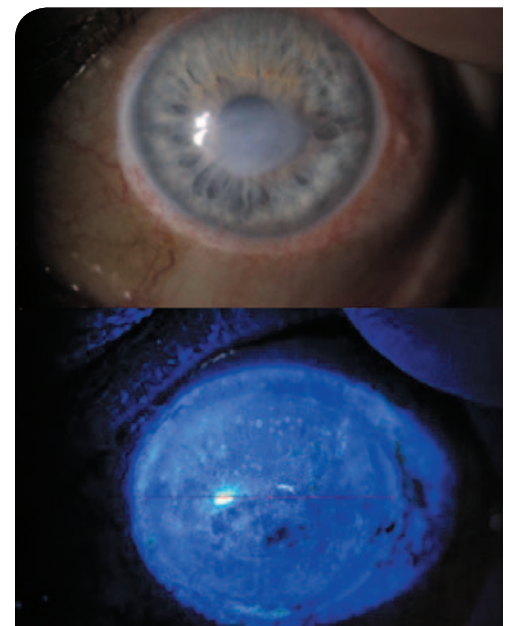
APPROVED PRODUCTS

► GLAUCOMA

Three new medications for IOP reduction were among the NDA approvals.

LATANOPROSTENE BUNOD 0.024% (Vyzulta, Bausch + Lomb) is indicated for the reduction of IOP in patients with open-angle glaucoma or ocular hypertension. It is a prostaglandin analog administered once daily, and the first prostaglandin analog that has nitric oxide as a metabolite. Nitric oxide increases outflow through the

(Continues on page 26 : Year in review)



IN VIEW: Healing of a neurotrophic corneal ulcer in a patient treated with cenegeermin. (Bonini S, Lambiase A, Rama P, et al, for the Reparo Study Group. Phase II randomized, double-masked, vehicle-controlled trial of recombinant human nerve growth factor for neurotrophic keratitis. *Ophthalmology*. 2018;125:1332-43. Permalink: <https://doi.org/10.1016/j.ophtha.2018.02.022>. © 2018 by the American Academy of Ophthalmology; reproduced under Creative Commons license CC BY-NC-ND 4.0)

Clinical Diagnosis

14 IS IT NOCICEPTIVE OR NEUROPATHIC EYE PAIN?

Dry eye signs and symptoms may point to a culprit outside of the ocular surface, says Anat Galor, MD, MSPH.

Surgery

29 HIGH- VERSUS MEDIUM-ADD MULTIFOCAL IOLS

Medium-add lenses may address a source of dissatisfaction with contemporary IOLs: Intermediate vision.

Focal Points

34 'TIS THE SEASON FOR BEAUTY-RELATED DRY EYE

With holiday festivities right around the corner, make sure patients know these dos and don'ts.

In This Issue

10 GUEST EDITORIAL

34 FOCAL POINTS

30 MARKETPLACE

What's Trending

See what the ophthalmic community is reading on *OphthalmologyTimes.com*

1 Laser cataract surgery uses expand

OphthalmologyTimes.com/Laser

2 7 pearls for penetrating keratoplasty in pediatrics

OphthalmologyTimes.com/KeratoplastyPearls

3 Adalimumab therapy safe in open-label uveitis study

ModernRetina.com/Adalimumab

4 Exploring tocilizumab for giant cell arteritis cases

OphthalmologyTimes.com/GiantCell

Video



Erin D. Stahl, MD, discusses why it is important to diagnose and treat children with keratoconus at the earliest signs of development for the most successful outcomes during the 2018 AAO meeting. Go to <http://bit.ly/2EclUfW>

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Optic Relief

Even ophthalmologists have difficulty spelling it sometimes.



"Mom, I think it's cool that you're an ophthalmologist, but why didn't you choose something easier to spell?"

Illustration by Jon Carter

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DECEMBER 2018 ■ VOL. 43, NO. 20

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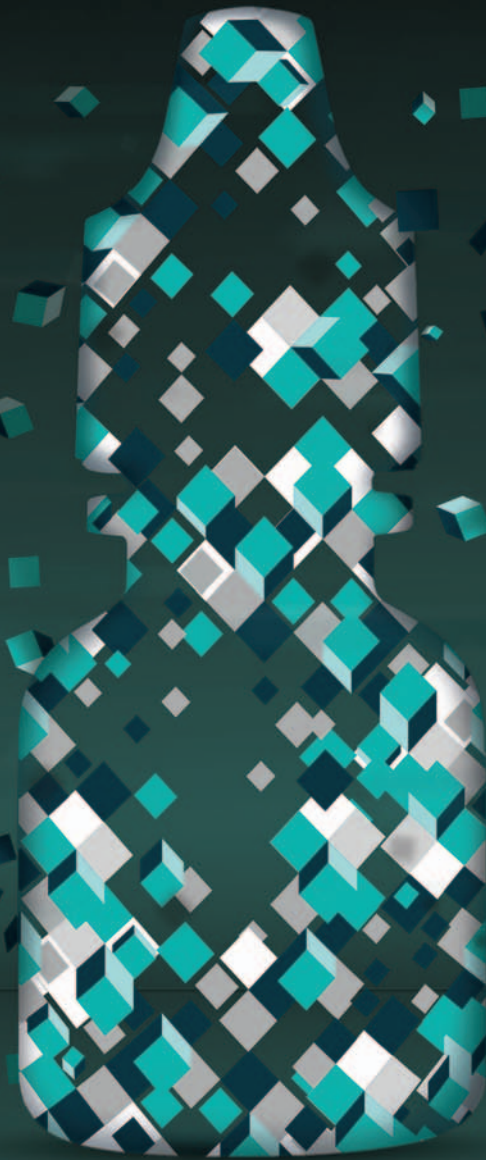
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Therapies, trends make waves in neuro-ophthalmology

Promising steps in place for previously untreatable diseases

By Timothy J. McCulley, MD, and Melissa W. Ko, MD, FAAN, CPE

On behalf of the North American Neuro-Ophthalmology Society (NANOS)

THESE ARE exciting times for neuro-ophthalmologists and our patients. We are refining existing therapies, and 2018 marked a time of revolutionary breakthroughs in the management of previously untreatable diseases.

For instance, promising steps have been taken toward viral vector-delivered gene therapy for patients with Leber's hereditary optic neuropathy.^{1,2}

Additionally, not only has sleep apnea been identified as a probable risk factor for non-arteritic anterior ischemic optic neuropathy (NAION), its management has been shown to reduce the risk of second eye involvement.^{3,4}

Each year, we are finding novel uses for optical coherence tomography (OCT), and 2018 was certainly no different. In addition to its well-established role in the assessment of patients with optic neuropathies, recent innovations include utilization of the ganglion cell layer thickness to estimate the potential for visual recovery in patients with optic nerve compression.⁵

A rapidly evolving and intriguing application is in the diagnosis and monitoring of patients with various forms of dementia.⁶

CENTRAL RETINAL ARTERY OCCLUSION

Best practices in the management of central retinal artery occlusion (CRAO) continues to be a topic of interest. Fueled largely by anecdotal accounts, trends are leaning toward treating CRAO with thrombolysis,⁷ and this perception is supported by a recent meta-analysis.⁸ But controversy remains and will likely persist until an adequately powered, prospective study sheds light.

In addition to these more-focused innovations, numerous diseases are being attacked from multiple angles. Management of multi-

ple sclerosis and related demyelinating disease have improved by leaps and bounds.

For example, we are recognizing subsets of disease including patients with neuromyelitis optica (NMO) in whom antibodies directed against aquaporin-4 are detectable.⁹

More recently, a subgroup has been identified in whom harbor antibodies directed against myelin oligodendrocyte glycoprotein (MOG)¹⁰ aid in assigning prognosis and tailoring therapy. Moving forward, precision in our understanding of disease pathophysiology will enable development of targeted immunotherapy.

TARGETED THERAPY

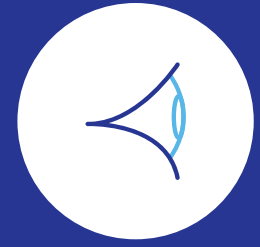
Concerning targeted therapy, one of the most impactful developments in clinical medicine is the commercial availability of therapeutically designed recombinant monoclonal antibodies. These antibodies are engineered to target specific antigens, most commonly on tumor or inflammatory cells.

The most well known among these is rituximab. Targeting CD-20, rituximab has found an invaluable role in the treatment of lymphoproliferative disease. With regard to neuro-ophthalmology, success with rituximab has been described in the treatment of Graves' ophthalmopathy, demyelinating disease, and orbital inflammation.¹¹

Teprotumumab, a monoclonal antibody targeting insulin-like growth factor I receptor (IGF-IR), has shown promise in reducing orbital involvement in patients with Graves' disease. Data continue to be made available from an ongoing clinical trial, spearheaded by Raymond Douglas.¹² Thanks to these efforts, in the near future we may be able to prevent the life-altering consequences of Graves' ophthalmopathy.

Continues on page 13 : **Neuro updates**

THE CYCLE OF INFLAMMATION IN DRY EYE DISEASE²



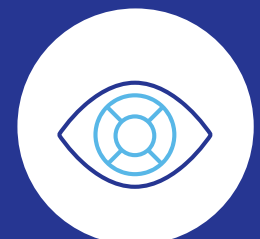
Ocular Surface Stress



Inflammation



Tear Film Instability



Signs & Symptoms



XIIDRA MAY INTERRUPT THE CYCLE OF INFLAMMATION CENTRAL TO DRY EYE DISEASE^{1,2}

The exact mechanism of action of Xiidra in Dry Eye Disease is not known.¹

Xiidra blocks the interaction of ICAM-1 and LFA-1, which is a key mediator of the inflammation central to Dry Eye Disease. *In vitro* studies have shown that Xiidra may inhibit the recruitment of previously activated T cells, the activation of newly recruited T cells, and the release of pro-inflammatory cytokines.¹

.....
Check out Xiidra-ECP.com
.....

.....
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.

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):269-275.





BRIEF SUMMARY:

Consult the Full Prescribing Information for complete product information.

INDICATIONS AND USAGE

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

DOSAGE AND ADMINISTRATION

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

CONTRAINDICATIONS

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

ADVERSE REACTIONS

Clinical Trials Experience

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

Postmarketing Experience

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

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

USE IN SPECIFIC POPULATIONS

Pregnancy

There are no available data on Xiidra use in pregnant women to inform any drug associated risks. Intravenous (IV) administration of lifitegrast to pregnant rats, from pre-mating through gestation day 17, did not produce teratogenicity at clinically relevant systemic exposures. Intravenous administration of lifitegrast to pregnant rabbits during organogenesis produced an increased incidence of omphalocele at the lowest dose

tested, 3 mg/kg/day (400-fold the human plasma exposure at the recommended human ophthalmic dose [RHOD], based on the area under the curve [AUC] level). Since human systemic exposure to lifitegrast following ocular administration of Xiidra at the RHOD is low, the applicability of animal findings to the risk of Xiidra use in humans during pregnancy is unclear.

Animal Data

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

Lactation

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

Pediatric Use

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

Geriatric Use

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

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: Animal studies have not been conducted to determine the carcinogenic potential of lifitegrast.

Mutagenesis: Lifitegrast was not mutagenic in the *in vitro* Ames assay. Lifitegrast was not clastogenic in the *in vivo* mouse micronucleus assay. In an *in vitro* chromosomal aberration assay using mammalian cells (Chinese hamster ovary cells), lifitegrast was positive at the highest concentration tested, without metabolic activation.

Impairment of fertility: Lifitegrast administered at intravenous (IV) doses of up to 30 mg/kg/day (5400-fold the human plasma exposure at the recommended human ophthalmic dose (RHOD) of lifitegrast ophthalmic solution, 5%) had no effect on fertility and reproductive performance in male and female treated rats.



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NEURO UPDATES

(Continued from page 10)

Another recent breakthrough that may transform the management of giant cell arteritis (GCA) is the FDA approval of tocilizumab, which targets interleukin-6 (IL-6).

Results from a large, multicenter clinical trial demonstrated the benefits of tocilizumab as a steroid-sparing agent over prednisone alone.¹³ Although we are still fine-tuning tocilizumab's optimal role in patients suffering ophthalmic involvement of GCA, these initial results are very promising.

NORDIC RESEARCH

The Neuro-Ophthalmology Research Disease Investigator Consortium (NORDIC) is a collaborative group of researchers—including neuro-ophthalmologists, biostatisticians, clinical trial experts, and a robust administrative team—who are supported by the National Eye Institute (NEI) of the National Institutes of Health (NIH).

Results from a number of NORDIC-led

projects are already available and a number of trials are either ongoing or about to initiate enrollment, including studies assessing treatment of NAION and idiopathic intracranial hypertension (IIH).

ADVANCES IN TREATMENT OF IIH

NORDIC's most substantial contribution to date relates to the treatment of IIH.¹⁴⁻¹⁶ Results from a trial assessing the use of acetazolamide, labeled the Idiopathic Intracranial Hypertension Treatment Trial, continue to be published.

Beyond initial results demonstrating therapeutic benefits, this year an assessment of optic disc size and papilledema grade was released.¹⁷

The next phase is the Surgical IIH Treatment Trial (or SIGHT Trial). This study is designed to compare optic nerve sheath fenestration with cerebrospinal fluid (CSF) shunting. Enrollment to this multicenter trial will commence throughout the country in the near future. Information about this and other clinical trials are available at www.nordicclinicaltrials.com.

Another advance in the treatment of IIH is

transverse sinus stenting.^{18,19} There is a subset of patients with IIH with narrowing of the transverse sinus, detected with cerebral angiography. Within this group, in some patients intracranial pressure can be normalized with stenting of the transverse sinus.

Presently, we lack precision to identify which individuals will benefit. This is a very active area of interest and transverse sinus stenting is sure to play a valuable role in managing patients with IIH. Most importantly, we have to figure how to best identify appropriate candidates.

HEALTHCARE DELIVERY

A final noteworthy achievement of the neuro-ophthalmology community is our contribution to healthcare delivery. No subspecialty in ophthalmology struggles more to meet patients' demands. With financial pressures, cumbersome regulations, and the complexity of neuro-ophthalmic patients, our ability to provide optimal care to all in need is dependent on improving efficiency and expanding our workforce.

Some departments are adding depth to their neuro-ophthalmology divisions with the addition of optometrists, orthoptists, and physicians with dual training.²⁰ Other innovations include providing remote screening via fundus photography.^{21,22} As healthcare delivery evolves, so, too, is neuro-ophthalmology.

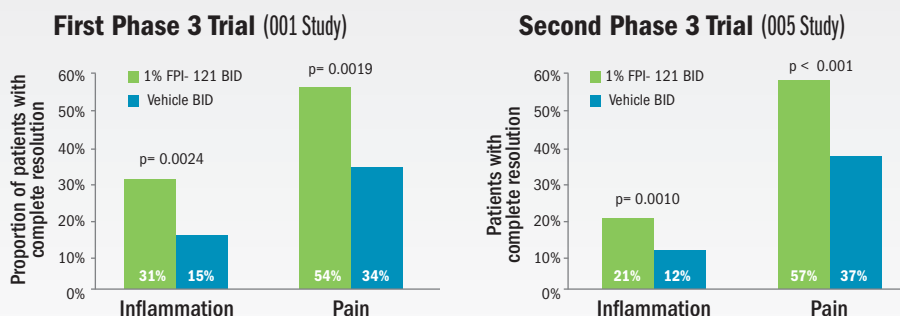
In closing, the rapidly changing face of modern healthcare comes with challenges and opportunities.

The practice of neuro-ophthalmology is rising to the challenge and expanding like never before. This year has seen many exciting innovations, and many more are expected in the near future. ■

Correction

The graphic accompanying the article "Novel steroid approval benefits ocular surgery" featured data for the dry eye candidate rather than the steroid data for loteprednol etabonate ophthalmic suspension 1% (KPI-121 1%) (INVELTYS, Kala Pharmaceuticals) (*Ophthalmology Times*, Oct. 15, 2018, Page 40). The correct graphic appears here.

KPI-121 1% for Post-surgical Inflammation, Pain Statistical Significance for Both Primary Endpoints in Two Phase 3 Trials



STANDARD CLINICAL DESIGN UTILIZED FOR POST-SURGICAL STEROIDS

- Two-week dosing in patients with intraocular inflammation one day after cataract surgery (N=380 in 001 Study, N=520 in 005 Study)
- Primary endpoints:
 - Proportion of patients with complete resolution of anterior chamber cells at postoperative Day 8 maintained through end of study with no need for rescue medication
 - Proportion of patients with complete resolution of pain (grade = 0) at postoperative Day 8 maintained through end of study with no need for rescue medication

(Table courtesy of Terry Kim, MD)

OT

For article references, go to
OphthalmologyTimes.com/Neuro2018



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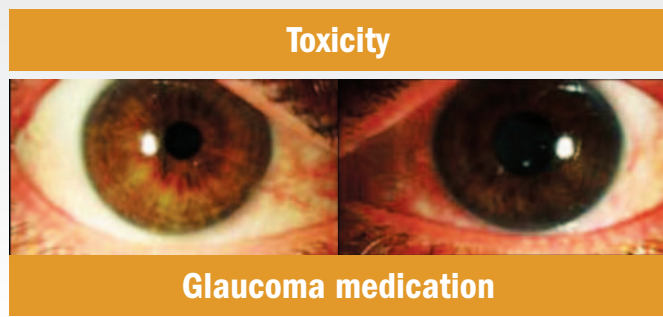
Center, SUNY Upstate Medical University, Syracuse, New York. She has no proprietary interest to declare.

Differentiating ocular pain: Nociceptive or neuropathic

Look beyond ocular surface dysfunction for clues, causes of dry eye pain

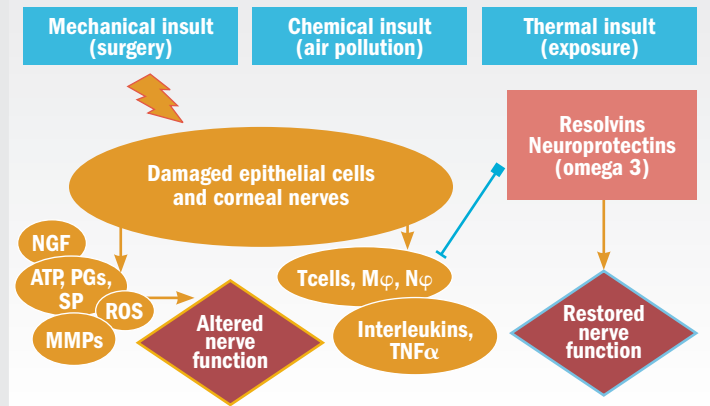
By Lynda Charters; Reviewed by Anat Galor, MD, MSPH

What Causes Nociceptive Eye Pain?



(FIGURE 1) Ocular pathologies—such as toxicity from glaucoma medication, tear film issues that cause increases in osmolarity, and pterygia—can be the culprits with nociceptive pain. (Figures courtesy of Anat Galor, MD, MSPH)

What Causes Neuropathic Eye Pain?



(FIGURE 2) Neuropathic pain is not a reaction to noxious stimuli, but rather a result from an insult to the nervous system.

Corneal neuropathic pain seems to be a “neglected step-child,” compared with nociceptive pain, in that it is undervalued by cornea specialists. Though the two disorders are different with different causes, both can occur concomitantly in patients.

Both pain syndromes can result in patients presenting with complaints of dry, burning, and aching eyes, said Anat Galor, MD, MSPH, associate professor of ophthalmology, Bascom Palmer Eye

limit their investigations to the ocular surface when patients present with dry eye symptoms.

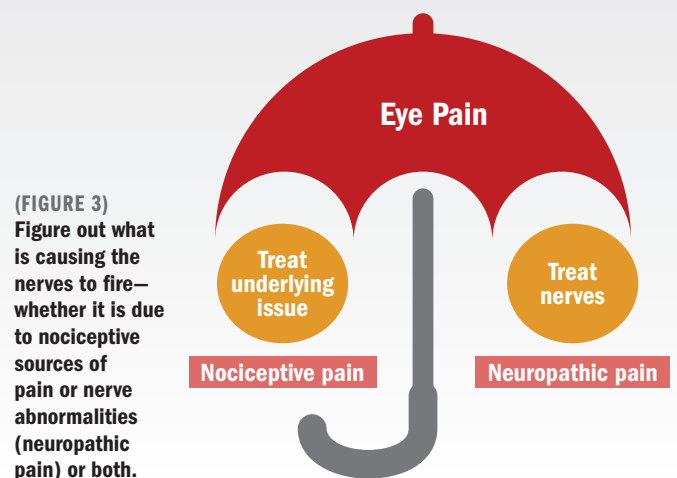
“Focusing on the ocular surface alone is a disservice to the patient,” she said.

Nociceptive pain is triggered by noxious stimuli, which can trigger nociceptors to fire and cause the painful sensation. Ocular pathologies—such as pterygia, conjunctivochalasis, tear film issues that cause increases in osmolarity, environmental factors, and toxicity from glaucoma medication—can be the culprits.

On the other hand, neuropathic pain is not a reaction to noxious stimuli, but rather a result from an insult to the nervous system.

“Mechanical (surgery), chemical (air pollution), and thermal (expo-

Determine the Appropriate Treatment



(FIGURE 3) Figure out what is causing the nerves to fire—whether it is due to nociceptive sources of pain or nerve abnormalities (neuropathic pain) or both.

sure) insults can damage epithelial cells and corneal nerves, with subsequent upregulation of nerve growth factor and matrix metalloproteinase, among others,” Dr.

Galor said. “This can lead to alterations in corneal nerve function.”

The body can repair itself after an acute insult (often with the help of omega-3-derived lipid mediators

TAKE-HOME

► Dry eye signs and symptoms may point to a culprit outside of the ocular surface.

Institute, University of Miami Miller School of Medicine, and staff physician, Miami Veterans Affairs Medical Center.

Ophthalmologists should not

Understanding Pain

Eye pain (dry, burning, shooting)

■ “Unhappy” nerves

Figure out why the nerves are “unhappy”

- Environment (nociceptive)
- Dysfunction (neuropathic)

such as neuroprotectins and resolvins), she noted.

“However, sometimes due to a severe or ongoing insult or genetic predisposition, corneal nerves can become permanently dysfunctional, resulting in neuropathic ocular pain,” Dr. Galor said.

When nerves become dysfunctional, they fire spontaneously or at a lower threshold—causing both spontaneous and evoked eye pain that may be characterized as “dryness” or often described using terms such as “burning,” “aching,” and “tenderness.” Ocular pain in these cases is often provoked by wind and/or light.

FOUR-STEP DIAGNOSTIC APPROACH

The key to making the distinction between the two pain disorders is determining the level at which pain occurs. Here are four steps Dr. Galor uses:

- **Step 1.** Conduct a standardized work-up evaluating both symptom severity and chronicity, breaking symptoms into categories of pain (dryness, spontaneous, and evoked pain) and visual complaints.
- **Step 2.** Ask the patient about the presence of systemic issues that include systemic autoimmune conditions, depression and anxiety, chronic pain, medication use, and the use of a continuous, positive-airway pressure system for sleep apnea.
- **Step 3.** Conducts an ocular surface examination.
- **Step 4.** Ask the patient if he or she feels persistent pain after instillation of an anesthetic agent.

OTHER CONSIDERATIONS

Some clues are recognition of the risk factors for neuropathic pain, which include LASIK and the presence of pain elsewhere in the body. Another clue is a disconnect between symptoms and signs of disease, with symptoms outweighing signs, Dr. Galor noted.

For patients in whom dry eye medications are not effective, an underlying nerve issue should also be considered.

“A need in the field is to develop better tests that can quantify corneal nerve function and develop specific therapies for neuropathic ocular pain,” she said.

The take-home points are that eye symptoms characterized as “dryness,” “burning,” and “shooting pain” indicate that nerves are firing, she said.

“The important factor is to figure out what is causing the nerves to fire—whether it is due to nociceptive sources of pain or nerve abnormalities (neuropathic pain) or both,” Dr. Galor said.


Not all symptoms of dryness are driven by “dry eye,” i.e., aqueous tear deficiency, she added.

“The key to achieving happy patients is to determine the cause of pain and to treat it appropriately.” Dr. Galor concluded. ■

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Dr. Galor is a consultant to Allergan, Dompe, Novaliq, and Shire.



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YEAR IN REVIEW & TOP OPHTHALMIC CHALLENGES FOR 2019

HIGHLIGHTING CUTTING-EDGE ADVANCEMENTS IN CLINICAL DIAGNOSIS, SURGERY, DRUG THERAPY, AND TECHNOLOGY



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Professor of Ophthalmology and Lou Higgins Chair in Ophthalmology, Bascom Palmer Eye Institute University of Miami Miami, FL



Peter J. McDonnell, MD
Director, Wilmer Eye Institute Johns Hopkins University Baltimore, MD; Chief Medical Editor - *Ophthalmology Times*



Robert Ritch, MD, FACS, FARVO
Shelley and Steven Einhorn Distinguished Chair Professor of Ophthalmology New York Eye and Ear Infirmary of Mount Sinai, New York, NY



Pravin U. Dugel, MD
Retinal Consultants of Arizona, Phoenix; Clinical Professor, USC Roski Eye Institute, Keck School of Medicine Los Angeles



Randall J. Olson, MD
Chairman, Department of Ophthalmology and Visual Sciences; CEO, John A. Moran Eye Center, University of Utah, Salt Lake City



Ehsan "Ethan" Sadri, MD, FACS
Private Practice Newport Beach, CA



Robert K. Maloney, MD
Director, Maloney Vision Institute; Clinical Professor of Ophthalmology, David Geffen School of Medicine at UCLA Los Angeles



Mark Packer, MD
Mark Packer MD Consulting Boulder, CO

TOP OPHTHALMIC CHALLENGES IN 2019

Ophthalmology Times' Editorial Advisory Board members share their thoughts on what to watch in year ahead

From OT Staff Reports

take-home

► As 2018 ends, members of the *Ophthalmology Times* Editorial Advisory Board share their thoughts on the most important advances and innovations over the past 12 months and the challenges to be faced in the new year.

A

s 2018 comes to its end, members of *Ophthalmology Times'* Editorial Advisory Board share their perspectives on the most important ophthalmic advances over the past 12 months and the challenges to be faced in the new year.

Reflecting on the past year, what advances and innovations come to mind?

DR. CULBERTSON: There were several notable advances in the past year, including those involving the femtosecond laser adjustable IOL (Perfect Lens), topical treatments for the reduction and/or prevention of cataracts, low-dose atropine for retarding myopia progression, and FDA approval of ReLex SMILE (Carl Zeiss

Meditec) for correction of myopic astigmatism.

The challenge of bringing diabetic retinopathy surveillance and treatment to rural areas is being addressed through the combination of fundus photographs in health clinics and artificial intelligence screening of these photographs. Deep learning of large numbers of retinal photographs has proved to be as accurate as ophthalmoscopy by ophthalmologists in detecting diabetic retinopathy.

Similarly, machine review of retinal and nerve fiber layer OCT images will provide accurate and rapid diagnosis of both retinal and glaucoma-based disorders. These advances should save time and money for patients and ophthalmologists and supplement both in-office and telemedicine settings for providing efficient and appropriate patient care.

To me, however, the most interesting development is the progress that has been made in endothelial cell layer repopulation with both injected cultured endothelial cells as described by Kinoshita et al. and the Descemet stripping only procedure. Both approaches may be enhanced by the adjunctive use of rho-kinase inhibitors that may encourage both proliferation and migration of endothelial cells.

The possibility of enhancing attachment of injected cells selectively to the back of the cornea using a corneal magnet and endothelial cells as described by Goldberg et al. holds in-

Continues on page 19 : **Innovation**

NEW

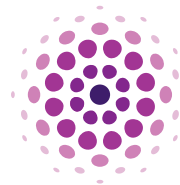
The first and only FDA-approved, single-dose, sustained-release, intracameral steroid for the treatment of postoperative inflammation¹⁻³

For Post-Cataract Surgery Inflammation Target Within¹⁻³

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

- The percentage of patients who received DEXYCU (517 mcg) who had anterior chamber cell clearing on day 8 was 60% (N=94/156) vs 20% (N=16/80) in the placebo group¹
- The cumulative percentage of subjects receiving rescue medication of ocular steroid or nonsteroidal anti-inflammatory drug (NSAID) at day 30 was significantly lower in the DEXYCU 517 mcg treatment group (20%; N=31/156) compared to placebo (54%; N=43/80)¹

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



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DEXYCU™

(dexamethasone intraocular suspension) 9%

Visit DEXYCU.com for more details.

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. July 2018. 2. Donnenfeld E, Holland E. Dexamethasone intracameral drug-delivery suspension for inflammation associated with cataract surgery: a randomized, placebo-controlled, phase III trial. *Ophthalmology*. 2018;125(6):799-806. 3. Data on file. EyePoint Pharmaceuticals, Inc.



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480 Pleasant Street, Suite B300, Watertown, MA 02472

10/2018
DEX0031

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 breast-feeding 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

Special Report) YEAR IN REVIEW & TOP OPHTHALMIC CHALLENGES FOR 2019

INNOVATION

(Continued from page 16)

interesting potential. Alternatives on this theme that involve plating cultured endothelial cells on autologous Descemet membrane or other membranes that are placed on the back of the cornea “DMEK-style” is also interesting.

The progress that has been made in treating endothelial dysfunction and corneal edema over the last 10 to 15 years has been phenomenal and will continue to offer fairly non-invasive alternatives providing rapid restoration of vision.

DR. DUGEL: This past year has been a banner year for retina and next year promises to be even better. The most important advancements for treatment of neovascular age-related macular degeneration (nAMD) have been with the next generation anti-VEGFA drugs, led by brodalumab (Novartis), a single-chain antibody fragment that achieved positive results in the phase III HAWK and HARRIER trials.

Faricimab (Roche/Genentech), a unique and elegant bi-specific drug that simultaneously inhibits VEGFA and angiopoietin-2 is also advancing. In addition, conbercept, the first Chinese drug, may make its way to the United States with the initiation of the Panda trial. Conbercept is a fusion protein with impressive binding characteristics.

For dry AMD, the complement C3 inhibitor, APL-2 (Appellis), showed impressive results for slowing the progression of geographic atrophy in a phase II trial, but with a side effect of increasing choroidal neovascular membrane conversion that is concerning. The phase III trial for APL-2 will be illuminating.

The next-generation anti-VEGFA drugs are also exciting potential new treatments for diabetic macular edema/ diabetic retinopathy (DME/DR) as is AKB-9778 (Aerpio Pharmaceuticals), a subcutaneously administered Tie2 activator, which may also have benefit renal function.

DR. MALONEY: This year has brought a slowdown in private equity activity. Sophisticated financiers have discovered, once again, that it is hard for anyone to run a practice better than the owner-ophthalmologists. I still think the future of private equity is bright, but good deals will be done at lower valuations with shared governance that extracts the more limited value from economies of scale rather than monetizing an income stream.

DR. MCDONNELL: The launch of voretigene neparvovec-rzyl (Luxturna, Spark Therapeutics) for the treatment of confirmed biallelic RPE65 mutation-associated retinal dystrophy was an exciting advance because it represents

proof-of-concept of gene therapy for eye disease. While only a limited number of people are affected by the condition for which it is indicated, I think this first gene therapy gives us a window into exciting future therapies for ocular disease.

DR. OLSON: The entire field of post-refractive IOL adjustment is heating up and, I predict, will be a game-changer. The Light Adjustable Lens (RxSight), approved towards the end of 2017, is showing impressive results. In particular, with the opportunity to do custom spherical aberration adjustment with guaranteed centration, it would appear to offer a superior depth of focus approach for presbyopia. In addition, refractive index shaping is moving along nicely with Perfect Lens soon to show efficacy in humans, and the Rochester variation is not far behind.

The future will be less about surgical accuracy and more about adjustment postoperatively. With all of the current unknowns, such as effective lens position and posterior cornea impact, postoperative adjustment will guarantee refractive precision that will take us to a new level.

DR. PACKER: Although it cannot be considered new technology because its origins date back to the beginning of the last decade, the long-awaited FDA approval of the Visian Toric ICL (STAAR Surgical) represents a significant step forward for U.S. refractive surgeons. Outside the United States, the increased adoption of the EVO Visian ICL (STAAR Surgical) with its innovative central port design that eliminates the requirement for preoperative YAG iridotomies reflects both outstanding safety and “optically superb correction of relatively high degrees of ametropia” as noted by McLeod in a published editorial [McLeod SD. *JAMA Ophthalmol.* 2016;134:494-495]. Once EVO is approved here, I believe we will witness its utilization increase here as well and across a broader range of refractive errors, including low to moderate myopia. In addition, STAAR has mentioned that there is a prospective clinical evaluation of an extended depth of focus ICL, which suggests a potential new entrant in the quest for a safe and effective surgical treatment of presbyopia. Given the retrenchment we have seen this year among presbyopia devices, this is welcome news.

DR. RITCH: Advanced imaging modalities that allow early detection of glaucoma have been an important advance because early detection is the cornerstone for appropriate treatment and management of glaucoma. Ophthalmic imaging has come a long way from disc photos to OCT for detecting and documenting glaucomatous damage. The finer and more accurate

the detection tool, the higher the chance of detecting disease in its very early stages with the potential to halt its progression.

Functional imaging that can identify malfunctioning retinal cells before they are lost is a new development in this domain. A combination of highly sensitive anatomical imaging and functional imaging will make the ideal ophthalmic imaging tool to detect glaucoma in its earliest stage.

DR. SADRI: Several recent innovations will advance cataract surgery by making our procedures faster and better with improved outcomes. They include the miLOOP/ miPORT (Iantech), Zepto (Mynosys), and the Light Adjustable Lens. In addition, the iLUX Device (Tearfilm Innovations) is an important new option for treating meibomian gland dysfunction.

What do you consider as some of the top remaining challenges?

CATARACT SURGERY

REFRACTIVE CATARACT SURGERY

DR. CULBERTSON: An ongoing challenge is the necessity to achieve the refractive target (usually plano) when implanting a multifocal IOL. In contrast to monofocal IOL surgery, small amounts of residual spherical or astigmatic refractive error after multifocal IOL implantation result in substantial patient dissatisfaction postoperatively.

We may be at our practical limit for getting closer to this goal with present diagnostic devices and formulas because of unpredictable anterior-posterior positioning, centration, rotation, and tilt of the IOL after the healing period. The potential ability to effect postoperative adjustment of the IOL power after stabilization of the lens position using refractive index modification of acrylic lenses with the femtosecond laser should increase patient satisfaction with all IOLs, especially multifocals.

DR. MCDONNELL: We need an accommodating IOL. Although multifocal IOLs benefit many patients, the optical aberrations associated with this type of technology tell us that multifocal IOLs are unlikely to become broadly accepted.

DR. OLSON: I believe we are starting to hit the wall for improving refractive prediction. Once intraoperative aberrometry, the effect of the posterior cornea, the latest IOL formulas, and formula customization are employed, further improvement in prediction error will increasingly add little gain for a lot of effort. This is the reason why modalities for postsurgical refractive adjustment will be so important.

Continues on page 20 : **Advances**

Special Report) YEAR IN REVIEW & TOP OPHTHALMIC CHALLENGES FOR 2019

ADVANCES

(Continued from page 19)

Patient outcomes expectations are continuing to climb, and our demanding patients will be impatient for this next level of precision.

DR. PACKER: While the rate of cataract surgery is increasing, the proportion of refractive cataract surgery procedures, including cases involving implantation of toric and presbyopia-correcting IOLs, has remained relatively flat. These data points suggest to me that surgeons face an ongoing challenge in counseling patients regarding their options at the time of surgery.

While the profit motive has been a friend to encourage advances in IOL design and cataract extraction technology on industry's part, it has also driven adoption of premium surgery at the practice level. However, profit in the practice accrues primarily to owners, and the trend towards employed surgeons may be further hindering growth of the premium channel.

Practicing the art and science of refractive cataract surgery requires not only motivation, intellect, and surgical skill, but also the ability to communicate the value proposition to patients, manage their expectations effectively, and remain steadfast when problems arise. In this world, satisfaction and success go hand in hand, but achieving both means taking necessary risks. If there isn't an appropriate reward, those risks can appear daunting, and I will be sorry if that means many surgeons will not start down this road.

In addition, if our goal is to achieve improved outcomes, then the first step is to examine current outcomes because it is impossible to make progress without understanding the current state of affairs. Tracking surgical outcomes should be a required element of clinical practice, but few surgeons allow time for themselves or their employees to record outcomes, and surgeons who co-manage extensively may never know their postoperative outcomes, such as their surgically induced astigmatism (SIA).

As the medical monitor of a recent clinical trial, we required participating surgeons to complete a spreadsheet to calculate their SIA. The investigators were selected because of their competence as refractive cataract surgeons, yet none had performed this exercise until it was mandated for their participation in the trial. Once the data were collected, some of the surgeons were quite surprised at the outcomes (one even insisted that we repeat the exercise). The point is that one doesn't know until one collects the data.

It remains a major challenge to find the re-

sources for outcomes analysis because the time is not directly reimbursed by revenue. The time and effort, however, represent an investment in the future—a future of better surgical outcomes, and we should all be willing to make that investment.

ECONOMIC, LEGAL, AND REGULATORY CHALLENGES

DR. CULBERTSON: One of the most important challenges is the attempt by insurers to eliminate anesthesia standby (monitored anesthesia care) in cataract surgery. Although this is commonplace in third-world countries, it does not have a place in the modern medical environment.

Cataract surgery, or any ocular surgery, is an anxiety-laced experience for patients, especially cataract patients who are typically older. Often, these individuals have fragile cardiovascular and/or respiratory status, and they must be monitored closely if given sedation to recognize and/or prevent rapid decompensation. The ophthalmologist cannot simultaneously give sedation, maintain supervision of the patient's general medical status, and concentrate fully on the intraocular surgery. If the patient becomes anxious, disoriented, or unmanageable during surgery, the outcome could be disastrous for the eye. As a profession, we must make insurers aware of the importance of monitored anesthesia to produce an optimal result.

Cataract surgeons in the United States also continue to face regulatory, legal, and economic barriers to performing bilateral same day cataract surgery in the United States. Bilateral surgery has been performed in Canada and at Kaiser Permanente Northern California without complications that are related to same day surgery. The time and resources consumed by patients, families, and health care providers in association with cataract surgery are significant and could be consolidated by allowing same-day bilateral surgery without adverse consequences to the patient.

The tradition of separating contralateral eye surgery dates to a time when cataract incisions were large (10 mm versus <3.0 mm), the possibility of endophthalmitis was significant (1/300 versus 1/2,000 cases) and postoperative lifestyle was limited by pain and slow return of vision (1 month versus 1 day). Today, when surgery on the first eye has been uneventful and there are no predictable risk factors for complications in the second eye, it should be safe and ethical to proceed with same-day surgery in the fellow eye.

DR. OLSON: Declining reimbursement will continue to be a challenge as the technical

fee will continue to be downgraded. We have been and will continue to be punished for our success with cataract surgery. There will be a push to do surgery in our clinics, and that will come with another steep cut in pay per procedure. The upside is that more surgeons will see that premium IOLs can add real value, and this technology will become an increasingly important consideration. A downside, however, will be the particularly poor reimbursement for difficult cases to the point that many surgeons will see no reason for tackling them, leaving fewer surgeons to take on more such cases at an increasing loss.

DR. PACKER: Demographics pose an ongoing challenge for the provision of high-quality, cost-effective care for cataract patients. Data show a steady increase in the incidence of visually significant cataracts as the population ages. The increased demand for services must be met with increased efficiencies in the delivery of care, including both operational and financial aspects of clinical practice. I believe these demands are in part driving the trends towards practice consolidation and corporate ownership, which may look particularly appealing to cataract surgeons in the waning years of their careers.

For younger surgeons, the appetite for practice ownership appears to continue to wane, so that working as an employed ophthalmologist has become a more common practice model. Nevertheless, it remains to be seen if these practice models will have the necessary innovative mindset to cope with future demographic demands.

CORNEA

DR. CULBERTSON: Severe progressive ulcerative keratitis remains a diagnostic and therapeutic challenge. Referral eye-care centers deal with cases in which the etiologic diagnosis is elusive and treatment involves months of painful topical drops (e.g., fortified antibiotics and anti-*Acanthamoeba* agents), injections, expensive oral medications (e.g., voriconazole), and eventual high-risk keratoplasties. The patients and their families suffer visual loss and loss of income because of visual debilitation, pain, and ophthalmologist visits.

The advent of corneal crosslinking with ultraviolet light and riboflavin has offered some hope in these refractory cases for both eradicating the offending organism, including bacteria, fungi, and *Acanthamoeba*, as well as making the cornea more resistant to collagenase degradation melting. Similarly, photodynamic therapy using rose bengal and green light has helped cure infectious cases resistant to con-

Continues on page 22 : **Therapy**

Announcing the winners of the 2018

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Angela Verkade, MD

*"The Patient Who Presents with
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*"Successful Outcome of an Extended Depth of Focus Intraocular
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Michael Yen, MD

*"Diplopia After Uncomplicated Implantation of a
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Special Report) YEAR IN REVIEW & TOP OPHTHALMIC CHALLENGES FOR 2019

THERAPY

(Continued from page 20)

ventional therapies. These options have broad application and are not dependent on the etiologic agent or stage of the disease. They can bring rapid resolution to advanced cases and could possibly be used even as initial therapy.

GLAUCOMA

DETECTING AND PREDICTING PROGRESSION

DR. RITCH: Glaucoma is a heterogeneous entity of diseases with the final pathway leading to retinal ganglion cell loss and resultant visual field loss. Due to its diverse phenotypes, stopping progression or slowing the rate at which ganglion cells are lost differ among the glaucomas and can differ from patient to patient, depending on the presence of risk factors other than IOP.

More attention to the discovery of causative genes and cellular mechanisms/pathophysiology (e.g., autophagy in exfoliation syndrome) is needed. Non-IOP-lowering treatment modalities require investigation based upon these underlying mechanisms.

Predicting which patient is “prone” to fast progression and which patient is not also is a remaining challenge. Instead of waiting to see scotoma formation on visual field testing or thinning of the retinal nerve fiber layer with OCT, it would be advantageous to know in advance which patients should be treated more aggressively and to what extent. As of now, no such algorithm exists for predicting the development or course of glaucoma in different patients with different types of glaucoma.

ADDRESSING UNMET THERAPEUTIC NEEDS

DR. RITCH: Although the armamentarium of a glaucoma specialist is now well equipped with multiple anti-glaucoma drops, lasers, minimally invasive glaucoma surgeries (MIGS), shunts, and more invasive glaucoma surgeries, there are patients who fail every treatment and continue to lose vision. Decisions regarding which treatment to choose first, how to move from one category to another, and how to manage the challenge of treatment refractory patients is still a puzzle to solve. The development of therapies directed at risk factors other than IOP is a much-needed advance.

The ultimate goal for glaucoma patients is to restore lost vision. The complicated neural network and cellular hierarchy of the retina has made it the “mission impossible” until now. Artificial retinal implants are now available for age-related macular degeneration and

retinitis pigmentosa and are still in an early age. Electric stimulation of the visual system to reverse visual field loss is just developing. The ideal strategy would be to regenerate retinal ganglion cells and guide their axons to the lateral geniculate nucleus where they synapse with the neurons leading to the visual cortex. However, it remains unknown whether stem cells are present in the lateral geniculate to enable regrowth of these neurons.

COST BARRIERS

DR. RITCH: The cost per bottle of new anti-glaucoma medications may be as much as \$400. Medication costs in the United States can be far greater than for the same medication in other countries, and many insurance companies refuse to cover many of the newer medications. The relevance of this problem becomes more pronounced when a patient does not respond to other drops market, becomes treatment-resistant, or develops an allergic reaction. Medical therapy is not the only part of the cost of treatment that can put a burden on patients. The coverage of new surgical treatments, such as MIGS, can also be exorbitant. The hands of government are tied when it comes to negotiating prices for Medicare patients.

REFRACTIVE SURGERY

DR. MALONEY: One of the top challenges for refractive surgery is the need to teach a new crop of ophthalmology residents to be competent refractive surgeons in the setting of stagnant volumes. We also need to lay the groundwork for refractive surgery to become the standard treatment for poor vision, just as braces are the standard treatment for crooked teeth.

Broader integration of the ICL into refractive practice is needed because it is a better option for correcting high myopia. Answering the occasional bad press about LASIK, despite objective evidence of the remarkable safety of the procedure also remains a challenge. In addition, introduction of new procedures is challenging because modern LASIK with its outstanding results has set a high bar for entry.

RETINA

DR. MCDONNELL: We need an anti-VEGF agent that can be administered just once or twice a year because the burden of monthly or bi-monthly intravitreal injections for AMD, DR, and DME is simply not sustainable.

DR. DUGEL: We need treatments for dry AMD and wet AMD that give better early efficacy and better and/or sustained long-term efficacy. Treatments are also needed for DME that provide greater sustainability and efficacy in patients who are poor responders to anti-VEGF therapy.

PRACTICE DECISIONS

DR. PACKER: Integrating new technology into practice requires foresight, investment, and dedication to improving outcomes. Surgeons who own and direct their own practice and surgery center have the ability to weigh and consider new opportunities and educate staff appropriately in order to make new technology a success, whether they introduce presbyopia-correcting IOLs, a new electronic medical record (EMR) system or SMILE. Employed surgeons or those serving in a corporate ownership model may have additional challenges in persuading those with the power of the purse to invest in new technology.

In ophthalmology we have witnessed many amazing advances and a few notable failures. This year, in particular, has seen retrenchment in both the correction of presbyopia and MIGS. Ophthalmologists face the challenge of thinking critically and making decisions to benefit both their patients and their practices. ■

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Dr. Ritch wishes to acknowledge Ahmad Najafi, MD, Glaucoma Research Fellow, New York Eye and Ear Infirmary of Mount Sinai, who contributed.

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Dr. Sadri is an investor in Visionary Fund, which owns equity in IamTECH, Myrosis, and RxSite.

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AAO 2018: IRD Experts

Interviews with experts on the latest news and information from AAO Chicago 2018 on the topic of Gene Therapy for Inherited Retinal Disease.



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What is Inherited Retinal Disease (IRD)?

IRD is a class of single-gene disorders that represent the major cause of familial blindness in the Western world, and until recently, have been untreatable.

This website hosts a series of CME/CE-accredited educational activities that present updated guidelines for diagnosis, referral patterns, and treatment, all of which have changed dramatically in the past year. It is also where busy clinicians can find valuable resources, which will include video interviews from the 2018 AAO Conference with the leading subject matter experts on gene therapy for IRD.



These educational activities were planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education (ACCME) by the Institute for Continuing Healthcare Education. The Institute for Continuing Healthcare Education is accredited by the ACCME to provide continuing medical education for physicians.

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These activities are supported by an unrestricted educational grant from Spark Therapeutics.

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Refractive Cataract Surgery: Success through TECNIS Personalized Vision

Keith A. Walter, MD



Dr. Walter is professor of ophthalmology, Wake Forest School of Medicine, Winston-Salem, NC. He is a paid consultant to Johnson & Johnson Surgical Vision, Inc.

Patients presenting for cataract surgery represent a heterogeneous group in regard to goals for postoperative vision. In general, today's cataract surgery patients are more interested than previous generations in wearing glasses less often postoperatively. Different patients, however, have different vision needs because of their individual lifestyles.

Recognizing this diversity within the cataract surgery patient population, I have found a personalized approach to pseudophakic correction that is consistent with the different functional profiles of available presbyopia-correcting intraocular lenses (IOLs) with patients' vision needs, provides an effective strategy for meeting their goals, and achieves satisfaction after surgery. This personalized approach uses the TECNIS® portfolio of presbyopia-correcting lenses as its foundation and the TECNIS Symfony® IOL as its cornerstone.

TECNIS Symfony® IOL

The TECNIS Symfony® IOL is built on the familiar platform of other TECNIS® IOLs and is made of the same time-tested, clear hydrophobic acrylic material. Featuring a novel diffractive optic that combines two complementary proprietary diffractive technologies and includes compensation for positive corneal spherical aberration, the TECNIS Symfony® IOL is an extended-depth-of-focus lens that has been designed to provide quality vision over a continuous range from distance to near.

Unlike the bifocal optic of diffractive multifocal IOLs that splits light into two discrete foci, the TECNIS Symfony® IOL optic incorporates an echelette design elongating the focus, which results in a defocus curve with a single broad peak (Figure).¹ Its second diffractive technology serves to enhance visual quality by reducing the eye's intrinsic chromatic aberration, which causes blur and loss of contrast. As with all TECNIS® IOLs, the TECNIS

Symfony® has $-0.27 \mu\text{m}$ of negative spherical aberration on its anterior surface that offsets the full spherical aberration of the average cornea for better quality of vision.¹ With a toric version of the TECNIS Symfony® IOL available in cylinder powers of +1.50 D to +3.75 D at the IOL plane, I can offer the benefits of this presbyopia-correcting lens to patients with significant pre-existing corneal astigmatism.

Results from the pivotal trial in the United States investigating the TECNIS Symfony® IOL show that it provides excellent uncorrected vision at intermediate and far distances.¹ It also provides functional uncorrected vision at near, with a low incidence of nighttime visual symptoms.¹

The personalized strategy

Gathering information about a patient's vision needs and goals is the first step in creating a personalized vision strategy. In my practice, patients who schedule a presurgical consultation visit are sent a packet that includes information about surgical and IOL options. The cover letter asks patients to review the materials and explains that there have been a lot of advances in cataract surgery recently and that new technologies are being used, including a laser for performing certain surgical steps and special lens options allowing patients to wear glasses less after the surgery.

The packet also contains the Johnson & Johnson Vision cataract patient survey. Featuring seven questions, this simple tool gives helpful insights into a patient's vision needs, goals, current problems, and personality. More specifically to my practice, it allows

me to start the conversation about IOL options at the consultation visit.

Patient responses on the cataract patient survey are consistent with the idea that more people are staying active as they age, continuing to work and drive, and relying on electronic devices (eg, computers, cellphones, tablets). Consequently, a large segment of cataract surgery patients are particularly motivated to have good uncorrected vision at far and intermediate distances. If these patients are willing to accept a need for glasses when reading fine print, I recommend bilateral TECNIS Symfony® IOL implantation.

For patients who depend more on near vision and are interested in wearing glasses less for all distances postoperatively, implanting the TECNIS Symfony® IOL bilaterally in a micromonovision approach or the TECNIS Symfony® IOL in the dominant eye and a TECNIS® multifocal IOL +3.25 D in the nondominant eye are excellent solutions in my experience. This personalized approach combining the TECNIS Symfony® IOL and the TECNIS® multifocal IOL +3.25 D is also supported by findings from a study conducted by Dr. Jeffrey Machat.² The Canadian study included 24 patients who were followed prospectively. Results from binocular visual acuity testing performed at 90 days after surgery showed that 96% of patients saw 20/20 or better uncorrected at distance, the same percentage achieved 20/25 uncorrected intermediate vision, and 91% of patients saw 20/25 or better uncorrected at near.²

Night vision needs are another consideration when recommending surgery with the TECNIS Symfony® and TECNIS® multifocal IOLs. Because the TECNIS Symfony® IOL is a diffractive lens, patients may perceive halos, glare, or starbursts around light sources at night. All patients are informed about these potential symptoms preoperatively. I explain that these are inherent to the lens design for improving near and intermediate vision and may improve with time. Patients who believe they might be significantly bothered by these symptoms may not be good candidates for the TECNIS Symfony® or TECNIS® multifocal IOLs.

Creating and refining the surgical plan

Delivering the desired functional outcome for patients involves choosing the right refractive target and hitting it postoperatively. When the goal is to maximize uncorrected intermediate and distance vision and I am implanting the TECNIS Symfony® IOL bilaterally, I generally aim for plano in both eyes. I also aim for plano in both eyes when combining a TECNIS Symfony® IOL with the TECNIS® multifocal IOL +3.25 D for patients wanting better reading vision. When planning to implant a TECNIS Symfony® IOL bilaterally in the latter cases, I plan plano in the dominant eye and low myopia, about -0.5 D , in the nondominant eye.

Although I try to set expectations for near vision with the TECNIS Symfony® IOL during the preoperative consultation, it is not until

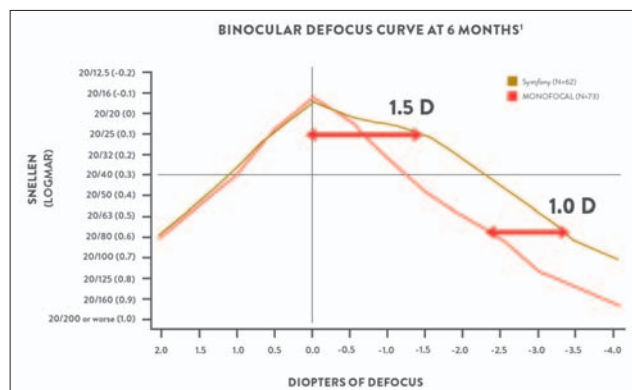


Figure. Binocular defocus curve at 6 months from the multicenter, bilateral, randomized clinical trial evaluating the TECNIS Symfony® IOL shows sustained mean visual acuity of 20/25 or better through 1.5 D of defocus and an increase of 1.0 D in range of vision throughout the defocus curve relative to the comparator monofocal IOL.

patients are able to experience the functional result that they can truly judge whether the lens will meet their needs. Therefore, I spend time evaluating visual performance and patient satisfaction after the first eye procedure and use the information to assess whether I should modify my original IOL strategy.

If I have planned for bilateral TECNIS Symfony® IOL implantation with a plano target in both eyes and the patient wants a little better reading vision but is still prioritizing quality vision for distance and intermediate, I will still implant the TECNIS Symfony® IOL in the second eye but aim for slight myopia. Alternatively, I will switch to the TECNIS® multifocal IOL +3.25 D if a patient expresses a strong interest in better reading vision.

To optimize refractive outcome predictability, I take care in all cases to get accurate measurements for the IOL power calculation. For IOL power calculation in nontoric cases, I use the Barrett Universal II formula unless the patient has a history of corneal refractive surgery, in which case I use the Barrett True-K formula. When implanting a toric IOL, I use the Barrett toric formula and my personal value for surgically induced astigmatism.

Refractive outcome predictability can also be improved by using data from refractive measurements to refine personal lens constants. It is important to note that a “push plus” technique should be used when refracting a patient with a TECNIS Symfony® IOL (**Table**). Because of the chromatic aberration compensation in this lens, refraction measured with an autorefractor is not recommended.

Table. Steps for measuring refraction after TECNIS Symfony® IOL implantation

1. Start with a sphere of +1.50 D and assess visual acuity
2. Start reducing in steps of -0.25 D until the patient sees the most number of letters with the least amount of minus
3. Affirm if after reducing sphere by another step or two of -0.25 D, visual acuity remains the same

Conclusion

The personalized vision approach to IOL selection using the TECNIS® portfolio of lenses is a patient-centered strategy that optimizes outcomes by taking advantage of the different performance profiles of the various IOLs. Being successful, however, also requires spending time with patients to explain the options, understand their needs, and assess their outcomes. Listening to patients is the key to their satisfaction. Not only is it the basis for creating a personalized surgical plan that will meet patient goals but it also has value for improving patient perceptions of the entire care experience.

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1. TECNIS Symfony® IOL DFU.
2. DOF2018CT4021.

INDICATIONS and IMPORTANT SAFETY INFORMATION for TECNIS SYMFONY and TECNIS SYMFONY TORIC EXTENDED RANGE OF VISION IOLs

Rx Only

INDICATIONS FOR USE

The TECNIS Symfony Extended Range of Vision IOL, Model ZXR00, is indicated for primary implantation for the visual correction of aphakia, in adult patients with less than 1 diopter of pre-existing corneal astigmatism, in whom a cataractous lens has been removed. The lens mitigates the effects of presbyopia by providing an extended depth of focus. Compared to an aspheric monofocal IOL, the lens provides improved intermediate and near visual acuity, while maintaining comparable distance visual acuity. The Model ZXR00 IOL is intended for capsular bag placement only. The TECNIS Symfony Toric Extended Range of Vision IOLs, Models ZXT150, ZXT225, ZXT300, and ZXT375, are indicated for primary implantation for the visual correction of aphakia and for reduction of residual refractive astigmatism in adult patients with greater than or equal to 1 diopter of preoperative corneal astigmatism, in whom a cataractous lens has been removed. The lens mitigates the effects of presbyopia by providing an extended depth of focus. Compared to an aspheric monofocal IOL, the lens provides improved intermediate and near visual acuity, while maintaining comparable distance visual acuity. The Model Series ZXT IOLs are intended for capsular bag placement only.

WARNINGS Patients with any of the conditions described in the Directions for Use may not be suitable candidates for an intraocular lens because the lens may exacerbate an existing condition, may interfere with diagnosis or treatment of a condition, or may pose an unreasonable risk to the patient's eyesight. Lenses should not be placed in the ciliary sulcus. May cause a reduction in contrast sensitivity under certain conditions, compared to an aspheric monofocal IOL; fully inform the patient of this risk before implanting the lens. Special consideration should be made in patients with macular disease, amblyopia, corneal irregularities, or other ocular disease. Inform patients to exercise special caution when driving at night or in poor visibility conditions. Some visual effects may be expected due to the lens design, including: a perception of halos, glare, or starbursts around lights under nighttime conditions. These will be bothersome or very bothersome in some people, particularly in low-illumination conditions, and on rare occasions, may be significant enough that the patient may request removal of the IOL.

Rotation of the TECNIS Symfony Toric IOLs away from their intended axis can reduce their astigmatic correction, and misalignment >30° may increase postoperative refractive cylinder. If necessary, lens repositioning should occur as early as possible prior to lens encapsulation.

PRECAUTIONS Interpret results with caution when refracting using autorefractors or wavefront aberrometers that utilize infrared light, or when performing a duochrome test. Confirmation of refraction with maximum plus manifest refraction technique is recommended. The ability to perform some eye treatments (e.g. retinal photocoagulation) may be affected by the optical design. Target emmetropia for optimum visual performance. Care should be taken to achieve IOL centration, as lens decentration may result in a patient experiencing

visual disturbances under certain lighting conditions. For the TECNIS Symfony Toric IOL, variability in any preoperative surgical parameters (e.g. keratometric cylinder, incision location, surgeon's estimated surgically induced astigmatism and biometry) can influence patient outcomes. Carefully remove all viscoelastic and do not over-inflate the capsular bag at the end of the case to prevent lens rotation.

SERIOUS ADVERSE EVENTS The most frequently reported serious adverse events that occurred during the clinical trial of the TECNIS Symfony lens were cystoid macular edema (2 eyes, 0.7%) and surgical reintervention (treatment injections for cystoid macular edema and endophthalmitis, 2 eyes, 0.7%). No lens-related adverse events occurred during the trial.

ATTENTION: Reference the Directions for Use for a complete listing of Indications and Important Safety Information.

INDICATIONS AND IMPORTANT SAFETY INFORMATION FOR THE TECNIS Multifocal Family of 1-Piece IOLs

Rx Only

INDICATIONS: The TECNIS Multifocal 1-Piece intraocular lenses are indicated for primary implantation for the visual correction of aphakia in adult patients with and without presbyopia in whom a cataractous lens has been removed by phacoemulsification and who desire near, intermediate, and distance vision with increased spectacle independence. The intraocular lenses are intended to be placed in the capsular bag.

WARNINGS: Physicians considering lens implantation should weigh the potential risk/benefit ratio for any conditions described in the Directions for Use that could increase complications or impact patient outcomes. Multifocal IOL implants may be inadvisable in patients where central visual field reduction may not be tolerated, such as macular degeneration, retinal pigment epithelium changes, and glaucoma. The lens should not be placed in the ciliary sulcus. Inform patients about the possibility that a decrease in contrast sensitivity and an increase in visual disturbances may affect their ability to drive a car under certain environmental conditions, such as driving at night or in poor visibility conditions.

PRECAUTIONS: Prior to surgery, inform prospective patients of the possible risks and benefits associated with the use of this device and provide a copy of the patient information brochure to the patient. The long term effects of intraocular lens implantation have not been determined. Secondary glaucoma has been reported occasionally in patients with controlled glaucoma who received lens implants. Do not reuse, resterilize or autoclave.

ADVERSE EVENTS: The rates of surgical re-interventions, most of which were non-lens related, were statistically higher than the FDA grid rate for both the ZMB00 (+4.00 D) and ZLB00 (+3.25 D) lens models. For the ZMB00, the surgical re-intervention rates were 3.2% for first eyes and 3.3% for second eyes. The reintervention rate was 3.3% for both the first and second eyes in the ZLB00 group.

ATTENTION: Reference the Directions for Use for a complete listing of Indications and Important Safety Information.

Special Report) YEAR IN REVIEW & TOP OPHTHALMIC CHALLENGES FOR 2019

YEAR IN REVIEW

(Continued from page 1)

trabecular meshwork and Schlemm's canal. The phase III study compared latanoprostene bunod with timolol. In the phase II VOYAGER study, latanoprostene bunod 0.024% was associated with significantly greater IOP reduction than latanoprost 0.005% (Xalatan, Pfizer).

NETARSUDIL 0.02% (Rhopressa, Aerie Pharmaceuticals) is a rho kinase inhibitor indicated for the reduction of elevated IOP in patients with open-angle glaucoma or ocular hypertension. The first approved rho kinase inhibitor, netarsudil is administered once daily and believed to reduce IOP by increasing aqueous outflow through the trabecular meshwork.

Aerie Pharmaceuticals has also filed an NDA for a fixed-dose combination of **NETARSUDIL/LATANOPROST OPHTHALMIC SOLUTION** 0.02%/0.005% (Roclatan). At month 12 in the MERCURY 1 clinical trial, IOP was ≤ 18 mm Hg in 82% of patients treated with netarsudil/latanoprost versus 66% of patients treated with latanoprost and 57% of those receiving netarsudil alone.

A new **LATANOPROST OPHTHALMIC EMULSION**, 0.005% (Xelpros, Sun Pharma) product is the first and only benzalkonium chloride-free formulation of latanoprost. It is indicated for reduction of elevated IOP in patients with open-angle glaucoma or ocular hypertension.

► CORTICOSTEROIDS

LOTEPREDNOL etabonate ophthalmic suspension 1% (Inveltys, Kala Pharmaceuticals) is a corticosteroid indicated for the treatment of postoperative inflammation and pain following ocular surgery. The product is based on proprietary mucus penetrating particle (MPP) technology (AMPPLIFY) that enhances drug delivery through the mucus barrier, enabling twice-daily dosing. In the pivotal trial, the novel loteprednol product demonstrated statistical superiority to placebo in analyses of proportions of patients with complete resolution of ocular inflammation at day 8 and day 15 and pain at days 4, 8, and 15.

DEXAMETHASONE INTRAOCULAR SUSPENSION 9% (Dexycu, EyePoint Pharmaceuticals) is a corticosteroid indicated for the treatment of postoperative inflammation. It

uses a proprietary bioerodible sustained-delivery system (Verisome) and administered as a single 5 μ L dose behind the iris at the end of the surgical procedure. In the pivotal trial, anterior chamber cell clearing was achieved by 60% of patients receiving the intraocular dexamethasone injection compared with 20% of placebo-treated controls.

EyePoint Pharmaceuticals gained a second FDA approval in October 2018 for its **FLUOCINOLONE ACETONIDE INTRAVITREAL IMPLANT** 0.18 mg (Yutiq) with an indication for the treatment of chronic non-infectious uveitis affecting the posterior segment. It uses a non-bioerodible intravitreal micro-insert that is designed for consistent release of fluocinolone over a period of 36 months and can be given as an in-office injection using a single-dose preloaded applicator.

► **TOPICAL, INJECTION, AND MORE CYCLOSPORINE OPHTHALMIC SOLUTION** 0.09% (Cequa, Sun Pharma) was approved to increase tear production in patients with keratoconjunctivitis sicca. This topical product incorporates nanomicellar technology to improve cyclosporine solubility and bioavailability.

CENEGERMIN-BKBJ OPHTHALMIC SOLUTION 0.002% (Oxervate, Dompé farmaceutici) is a recombinant form of human nerve growth factor indicated for the treatment of neurotrophic keratitis. Results from two randomized, masked controlled clinical trials showed that cenegermin-bkjb was safe, well-tolerated, and significantly more effective than vehicle for restoring corneal epithelial integrity in eyes with stage 2 (moderate, persistent epithelial defect) or stage 3 (severe, corneal ulcer) neurotrophic keratitis.

VORETIGENE NEPARVOVEC-RZYL INTRAOCULAR SUSPENSION for subretinal injection (Luxturna, Spark Therapeutics) is an adeno-associated virus vector-based gene therapy indicated for the treatment of patients with confirmed biallelic RPE65 mutation-associated retinal dystrophy who have viable retinal cells as determined by the treating physician(s). It is the first gene therapy approved to treat an inherited disease and the first gene therapy in ophthalmology. Clinical trial results showed that

voretigene neparvovec-rzyl had an acceptable safety profile and resulted in rapid improvements in functional vision and visual function that were sustained with follow-up to 2 years.

BRIMONIDINE TARTRATE 0.025% (Lumify, Bausch + Lomb) was approved as an over-the-counter product to relieve redness of the eye due to minor eye irritations.

BENOXINATE HCL AND FLUORESCIN SODIUM, 0.25%/0.4% (Altafluor Benox, Altaire Pharmaceuticals) offers a fixed combination of the disclosing agent and local ester anesthetic and is indicated for use in procedures requiring both agents.

DEVICE APPROVALS

The device approvals included a variety of products lens products.

Seven devices for use in ophthalmology received PMA approvals in the year. STAAR Surgical received FDA approval to market the toric version of its phakic IOL (**VI-SIAN TORIC ICL**), opening opportunity to treat myopic patients with astigmatism.

In the pseudophakic IOL space, approval of the **ENVISTA TORIC IOL** (Model MX60T) gave manufacturer Bausch + Lomb its first hydrophobic acrylic IOL for astigmatism correction. The IOL has

an aberration-free aspheric optic with fenestrated, step-vaulted, modified C-loop haptics.

The **LIGHT ADJUSTABLE LENS AND LIGHT DELIVERY DEVICE** (RxSight) also received FDA approval. It is the first medical device system that can make small adjustments to the pseudophakic lens power after cataract surgery.

A new disposable, extended-wear contact lens that can be worn continuously for up to six nights and seven days (**SAMFILCON A; Ultra**, Bausch + Lomb) was also approved.

After granting Breakthrough Device Designation, the FDA approved the **CUSTOMFLEX ARTIFICIAL IRIS** (HumanOptics/Clinical Research Consultants) for the treatment of full or partial aniridia resulting from congenital aniridia, acquired defects, or other conditions associated with full or partial aniridia. Patients with a missing or damaged iris. The prosthetic device is made of medical-grade silicone. It is thin, foldable, individually customized for size and iris color, and can be used in children and adults. In premarketing evaluation, the artificial iris was associated with high patient satisfaction and demonstrated benefit for reducing light sensitivity.

Continues on page 28 : Innovation

take-home

► The 12 months between Oct. 1, 2017 and Sept. 30, 2018 was a banner period for new entries into the ophthalmology therapeutic armamentarium with the FDA approving nine original New Drug Applications/Biologic License Applications and a first gene therapy. In addition, seven devices for use in ophthalmology received Premarket Approval Application approvals during the same time interval.

Members of the *Ophthalmology Times* Editorial Advisory Board share their thoughts about the most important advances and innovations over the past 12 months, with a look to the challenges to be faced in the year ahead. See Page 16



I didn't realize
STARS
were little dots that twinkled

—Misty L, *RPE65* gene therapy recipient

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Special Report) YEAR IN REVIEW & TOP OPHTHALMIC CHALLENGES FOR 2019

INNOVATION

(Continued from page 26)

Two micro-invasive glaucoma surgery (MIGS) devices intended to be implanted during cataract surgery to reduce IOP in patients with primary open-angle glaucoma were approved. The **ISTENT INJECT TRABECULAR MICRO-BYPASS SYSTEM** (Glaukos) introduces two stents using a dedicated injector. The Hydrus Microstent (Ivantis) also creates a bypass through the trabecular meshwork.

There were two de novo approvals. The **TRUE-TEAR INTRANASAL TEAR NEUROSTIMULATOR** (Allergan) provides a temporary increase in tear production to improve dry eye symptoms in adults with severe dry eye symptoms.

Approval of the **IDX-DR** (IDx) represents the first FDA-approved autonomous artificial intelligence-based diagnostic device. It is indicated for use by health care providers to automatically detect more than mild diabetic retinopathy in adults with diabetes who have not been previously diagnosed with diabetic retinopathy. It is indicated for use with the TRC-NW400 robotic fundus camera (Topcon Medical).

PIPELINE PRODUCTS

► DRY EYE

More than 30 companies are developing treatments for dry eye disease (DED). In this space is **KP-121** from Kala Pharmaceuticals, which is a lower-concentration version (0.025%) of its approved loteprednol etabonate ophthalmic suspension with MPP technology. Two phase III trials have been completed and a third is ongoing.

TopiVert is developing **TOP1630**, a non-systemic multikinase inhibitor that targets several kinases that are upregulated in DED. In a placebo-controlled phase I/IIa study, TOP1630 improved signs and symptoms by day 15.

Aldeyra Therapeutics reported data from a phase IIb study of **REPROXALAP**, a small-molecule reactive aldehyde species scavenger, showing statistically significant superiority to placebo for improving ocular dryness and ocular staining.

OysterPoint Pharma is developing a novel **NICOTINE ACETYLCHOLINE RECEPTOR AGONIST** that is delivered as an intranasal spray and acts to stimulate natural tear production by depolarizing intranasal trigeminal nerves. Phase III studies are being planned based on encouraging phase IIb data.

MC2 Therapeutics is developing **TOPICAL CYCLOSPORINE** using its proprietary delivery system (PAD Technology). Positive data were

achieved in a phase II vehicle-controlled study.

SHP640, an ophthalmic suspension containing povidone-iodine 0.6% and dexamethasone 0.1%, is being developed by Shire as a treatment for adenoviral conjunctivitis. Phase III studies are ongoing.

► PRESBYOPIA

Several pharmacotherapies for presbyopia are being investigated in clinical trials. These treatments include **EV06** (Novartis) that aims to restore crystalline lens flexibility. Compared with placebo, EV06 demonstrated benefit in a phase I/II study in an analysis of the proportion of participants who achieved 20/40 or better near UCVA at day 90. Novartis is undertaking a reformulation before moving ahead in clinical studies.

Allergan released phase IIa data from a study comparing **OXYMETAZOLINE** (AGN-199201), low-dose **PILOCARPINE** (AGN-190584), and both agents together. Data from additional phase II studies are expected.

Orasis Pharmaceuticals is developing **CSF-1**, a proprietary combination product designed to increase depth of focus and improve near vision via a pinhole effect. It showed promise in a small phase IIa placebo-controlled study, and a comprehensive phase IIb study is expected to begin soon.

Presbyopia Therapies is developing a **TOPICAL TREATMENT FOR PRESBYOPIA** that formulates miotic agents in a proprietary vehicle.

Viewpoint Therapeutics has conducted pre-clinical studies of **VP1-001**, a first-in-class compound that disaggregates crystallin. In a canine cataract model, VP1-001 reversed lens opacity. By softening the lens, it might also have benefit as a treatment for presbyopia.

► MYOPIA

Studies showing the safety and efficacy of low-dose atropine for slowing myopia progression have motivated three companies to undertake development of products for commercialization. **NVK-002** from Nevakar is being investigated in a two-stage, three-arm, randomized, multicenter, double-masked, placebo-controlled crossover study.

Sydnexis has a patent-protected, **LOW-DOSE ATROPINE FORMULATION** and plans to initiate a phase III trial in 2019. Eyenovia is developing a low-dose atropine that is sprayed onto the ocular surface using a proprietary, piezo-print microdose technology. It is also expected to begin a phase III study in 2019.

► RETINA

RANIBIZUMAB delivered via the Port Delivery System (Genentech) is now being evalu-

ated in a phase III study for the treatment of neovascular age-related macular degeneration. In the phase II LADDER study, 80% of patients who received the highest dose went 6 months or longer without needing an implant refill.

BROLUCIZUMAB (Novartis) is a single-chain variable fragment anti-VEGFA agent that demonstrated robust visual gains in patients with neovascular (nAMD). In the phase III study, 50% of patients were treated every 12 weeks and brolicizumab was non-inferior to aflibercept.

GB-102 (Graybug Vision) is a depot formulation of sunitinib malate, a tyrosine kinase inhibitor that is a pan-VEGF receptor antagonist. A phase Ib/IIa switching study is ongoing enrolling treatment-responsive patients with nAMD.

RGX-314 (Regenxbio) is a gene therapy approach to anti-VEGF therapy for nAMD. It is hoped to offer a one-time subretinal treatment and showed promise in an early study.

FARICIMAB (Roche/Genentech) is a unique bi-specific drug that simultaneously inhibits VEGFA and Ang-2. It is being evaluated in phase III studies as a treatment for diabetic macular edema (DME) and nAMD.

OPT-302 (Ophthea) is a soluble form of human VEGF receptor-3 that blocks VEGF-C and VEGF-D. It is being evaluated for use in combination with an anti-VEGF-A agent.

PAN-90806 (PanOptica) is being developed as a topical treatment for neovascular diseases, including nAMD and proliferative diabetic retinopathy plus diabetic macular edema (DME). PAN-90806 blocks activation of the VEGF receptor 2 by inhibiting the receptor's tyrosine kinase activity. Phase I/II studies for both indications were completed in 2016. Results from a study enrolling patients with treatment-naïve nAMD are expected in 2019.

RISUTEGANIB (formerly known as Luminate, Allegro Ophthalmics) is a first-in-class anti-integrin that is being developed as a treatment for DME and nonexudative AMD. In phase II research, risuteganib demonstrated particular benefit for improving vision and anatomic outcomes in patients with DME who were suboptimal responders to previous anti-VEGF therapy.

AKB-9778 (Aerpio Therapeutics) is a small-molecule tie-2 activator administered by subcutaneous injection. Data from a study investigating AKB-9778 for treatment of patients with moderate/severe non-proliferative diabetic retinopathy is expected in 2019. ■

Editor's Note: This article is based on a presentation by Emmett Cunningham, MD, at the 2018 OIS@AAO meeting. It provides an overview, but not an all-inclusive list, of ophthalmic approvals and emerging therapies and devices.

Regression analysis: High- vs medium-add multifocal IOLs

Variables related to intermediate vision significant predictors of overall patient satisfaction

By Frank A. Bucci Jr., MD; Special to Ophthalmology Times

The goal with presbyopic implant surgery is to achieve high levels of patient satisfaction and spectacle independence. This means providing excellent distance, intermediate and near vision (in both dim and bright light), with an acceptable level of light phenomenon while driving at night.

The challenge for cataract surgeons is we must also have the communication skills to determine patients' visual needs and enough knowledge about IOL technology to understand the strengths and weaknesses of each lens.

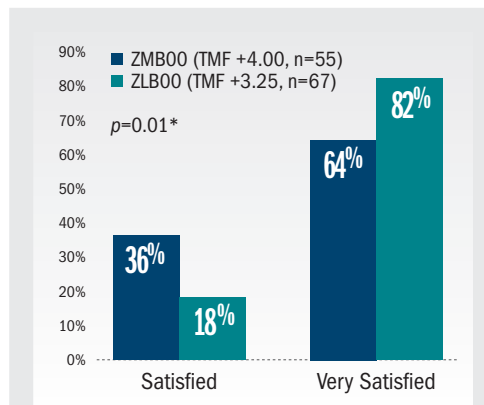
I have implanted nearly 6,000 presbyopia-correcting IOLs. We developed a multivariate regression analysis model to evaluate how presbyopic lenses fare when implanted bilaterally or in various combinations. The model now includes more than 40 independent variables, including a wide range of objective clinical metrics and subjective patient responses related to performance of common visual tasks.

ANALYSIS MODEL EXAMPLE

I used this model to determine predictors of overall patient satisfaction in cohorts of patients implanted bilaterally with either ZMB00 (Tecnis Multifocal +4.00, Johnson & Johnson Vision) or ZLB00 (Tecnis Multifocal +3.25, Johnson & Johnson Vision) IOLs.

Both cohorts comprised "best case" patients: They were all at least 6 months postoperative so that any neuroadaptation had already occurred; all necessary Nd:YAG procedures had been completed; residual refractive error, if any, had been treated; and the ocular surface was well managed. The same regression analysis methodology was applied to both cohorts.

In both cohorts, 100% of subjects rated themselves either "satisfied" or "very satisfied" overall. If one evaluated a cohort including patients with dry eye or uncorrected astigmatism, the spread of results would be greater, but it would also be impossible to know whether their re-



(FIGURE 1) Overall satisfaction 6 months after bilateral implantation. (Figures and tables courtesy of Frank A. Bucci Jr., MD)

	ZMB00 (TMF +4.00, N = 55)	ZKB00 (TMF +3.25, N = 67)
Distance	3.44	3.53
Intermediate	2.96	3.32
Near	3.44	3.44

p = 0.02

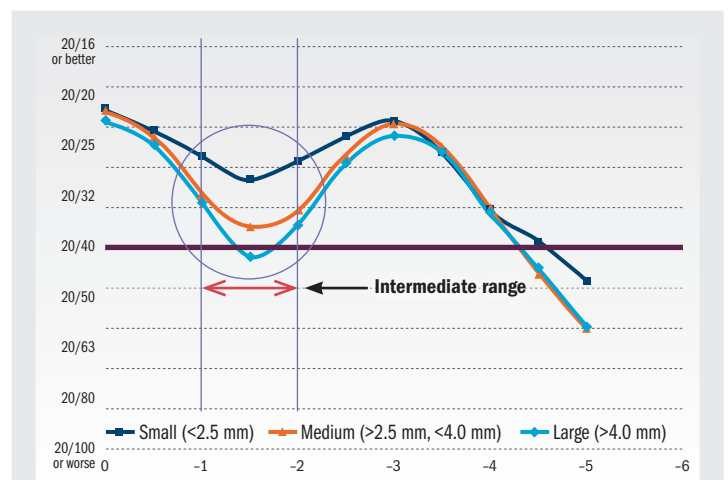
sponses were related to the IOL.

There was a statistically significant increase in the rate of "very satisfied" patients in the bilateral +3.25 cohort (82%) versus the bilateral +4.00 (64%) cohort (Figure 1).

Satisfaction with intermediate vision improved significantly in the +3.25 cohort compared with the +4.00 cohort, while satisfaction scores for distance and near vision were equivalent between the two (Table 1).

SUCCESS PREDICTORS

Regression analysis revealed that three variables related to intermediate vision were statistically significant predictors of overall patient satisfaction in the ZMB00/+4.00 cohort: Ability to "read a newspaper" without glasses ($p < 0.005$); ability to "work at a com-



(FIGURE 2) Tecnis Multifocal Defocus Curve* — Mean visual acuity at each defocus level for Tecnis multifocal IOL subjects by pupil size groups: small: ≤ 2.5 mm; medium: >2.5 mm, <4.0 mm; large: ≥ 4.0 mm. Intermediate VA defined at 67 cm for average pupil size defined as 2.5-4.0 mm.

*TECNIS Multifocal 1-Piece IOL, Model ZMB00, Directions for Use.

puter" without glasses ($p < 0.005$); and "intermediate visual acuity at the patient's preferred focal distance" ($p = 0.05$). Next, I made "intermediate visual acuity at the preferred focal dis-

Continues on page 33 : Intermediate vision

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Ophthalmology Times

INTERMEDIATE VISION

(Continued from page 29)

tance” an independent variable to see if any of the regression factors would predict who would achieve better intermediate vision. Smaller “mesopic pupils” ($p < 0.005$) and better “IOL centration” ($p = 0.02$) were statistically significant predictors of superior intermediate vision. This observation was beyond the pinhole effect because better distance and near vision were not correlated with decreasing mesopic pupils.

A unique design feature of the Tecnis family of multifocal IOLs helps to explain the regression findings related to smaller mesopic pupils. These lenses have a central 1.0-mm button with half the add power of the total near add (Table 2).

As the mesopic pupil decreases, the percentage of light being processed through the central intermediate button increases, thereby enhancing intermediate vision. Results from the FDA clinical trial for the ZMB00 model demonstrate this same effect: Subjects with smaller pupils also achieved better intermediate vision in that study (Figure 2 on Page 29).

In the +3.25 cohort, data strongly suggest the improved intermediate vision is responsible for the increased percentage of patients responding at the “very satisfied” level (82%/+3.25 versus 64%/+4.00). The raw scores for ranking intermediate vision were significantly higher without any difference in the raw scores for distance or near vision. The increased focal length of the +3.25 IOL (17 inches versus 14 inches for the +4.00) is likely responsible for the improved intermediate vision.

Regression revealed that preoperative mesopic pupil size is a reliable predictor of postoperative intermediate vision. This information is powerful for preoperative planning. For example, if you were initially planning to implant two +3.25 IOLs, but preoperative testing re-

Table 2: Characteristics of Tecnis Multifocal IOLs of Varying Add Powers

TMF MODEL	NOMINAL ADD POWER (IOL PLANE)	ADD POWER (SPECTACLE PLANE)	CENTRAL BUTTON ADD POWER (SPEC PLANE)	NEAR FOCAL POINT (APPROX)
ZMB00	+4.00	+3.00	+1.50	14 in
ZLB00	+3.25	+2.37	+1.20	17 in
ZKB00	+2.75	+2.00	+1.00	20 in

vealed large mesopic pupils, which may result in less than optimal intermediate vision, you should consider changing your surgical plan.

This patient would likely achieve greater overall patient satisfaction if one of the +3.25 lenses was replaced with a Symfony or Symfony Toric IOL which would enhance the overall bilateral intermediate function. If the patient had small mesopic pupils you should stick with the bilateral +3.25 lenses, which would maximize the near vision while achieving excellent intermediate vision in both eyes because of the small pupils. We are currently applying the regression evaluation method to our +3.25/Symfony cohort which appears to be achieving very high levels of patient satisfaction.

CONCLUSIONS

In summary, this study revealed:

- 1 A significantly greater level of “very satisfied” patients in the bilateral +3.25 cohort versus the bilateral +4.00 cohort;
- 2 Improved intermediate vision was responsible for the higher levels of satisfaction;
- 3 The intermediate vision was improved without sacrificing the quality of either near or distance vision;
- 4 The increased focal length of 17 inches in the +3.25 group versus 14 inches in the +4.00 group and subsequent improved intermediate vision did not “wash out” the meso-

pic pupil effect in the +3.25 patients. Smaller mesopic pupils still strongly correlated with enhanced intermediate vision in the +3.25 patients as observed in the +4.00 cohort, and

5 Our findings of increased satisfaction in the +3.25 cohort with improved intermediate vision without sacrificing near vision, along with the mesopic pupillary effect, strongly support further efforts at customization of the preoperative surgical plan like the combination of a +3.25 with the Symfony or Symfony toric.

Finally, high levels of success with presbyopia-correcting IOLs are dependent on choosing the IOLs that will maximize the patient’s bilateral visual performance at distance, intermediate, and near; aggressively treating residual refractive error (≤ 0.50 D of residual sphere and astigmatism); and aggressively managing the ocular surface. ■

Reference

Bucci FA. Regression analysis of patient satisfaction in patients receiving bilateral +3.25 vs. bilateral +4.00 multifocal IOLs. Poster presented at: Meeting of the American Academy of Ophthalmology, Chicago, 2018.



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PA. He is a consultant to Johnson & Johnson Vision, although the

studies described herein were independent and not funded by industry.

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'Tis the season for patient beauty-related dry eye

With holiday festivities around the corner, make sure your patients know these dos, don'ts

By *Melissa Toyos, MD*

The holiday season bring lots of good cheer and also worsens dry eyes. Indoor heat lowers already low winter humidity levels. On top of that, patients are getting dressed up for events and parties where beauty-related dry eye problems abound.

Makeup is a major offender. Some patients with severe dry eye often find it virtually impossible to wear eye makeup. However, the majority of dry eye sufferers do try to glam up. We can help them by making recommendations for products and treatments that can facilitate their holiday season and improve their resilience to the season's challenges.

BEAUTY PRODUCT PROBLEMS

For many of my patients, makeup and beauty products are not optional. I try to minimize dry eye problems related to these products by telling them my recommendations for cosmetics and reminding them to always remove all makeup before bed, no matter how late they're getting there.

■ **MASCARA** We've all seen mascara flecks in the tear film on slit lamp exams. There is no question that these products take their toll chemically, with a host of chemical ingredients. Mechanically, the flecks are uncomfortable and can be abrasive. "Thickening" and "lengthening" mascaras are particularly problematic because they incorporate fibers to create the desired effect, and the fibers can irritate the eyes.

■ **EYELINER** Eyeliner can irritate the eye and contribute to dry eye simply because it is used on the eyelids. At the base of the lashes, it can harbor bacteria and be difficult to remove completely. Using eyeliner on the inside of the upper or lower eyelids can dramatically define the look of the eye, but it also can adversely affect the meibomian glands and tear film.

■ **EYE SHADOW AND POWDER** Any powdered makeup—eye shadow, face powder, bronzer, glitter, and so on—inevitably ends up in the eyes, causing problems that are similar to mascara flakes. People with dry eye may prefer to stick to cream-based products instead of powder.

■ **LASH GROWTH PRODUCTS** Lash growth products containing prostaglandins are known to be pro-inflammatory—in fact, I reported on the first case of MGD associated with them. However, many of my patients consider these products mandatory, so I adjust with additions of high-quality fish oil, topical anti-inflammatories, and/or intense pulsed light (IPL) to reduce inflammation and reverse the damage.

■ **EYEMAKEUP REMOVER** Virtually all eye makeup removers contain detergents, which break up the tear film's lipid layer. Currently, there are no great alternatives, but I steer my patients toward non-petroleum, oil-based products.

■ **EYE CREAM** Patients with dry eye need to eliminate drying agents like retinoids, especially near the eye. I recommend creams without retinoids that instead contain peptides, which activate collagen-building fibroblasts. Hyaluronic acid is great to use in this delicate area too. (Yes, hyaluronic acid is good.) I try to minimize preservatives and fragrances in this delicate area.

■ **EYEWHITENERS** To make tired eyes look whiter, brighter, and more radiant, I recommend brimonidine tartrate ophthalmic solution 0.025% (Lumify, Bausch + Lomb), an FDA-approved eye whitener. One drop works within minutes and lasts up to 8 hours.

TREATMENT FOR HEALTHY EYES

In addition to educating patients about beauty products, the best defense is to make sure that they start the season with the healthiest eyes

'There is no question that these products take their toll chemically, with a host of chemical ingredients.'

— *Melissa Toyos, MD*

possible. I use IPL therapy (Optima IPL, Lumenis), which allows us to solve several issues simultaneously. IPL rejuvenates skin in the eye area, reduces ocular surface inflammation, closes off lid margin telangiectasias, improves meibomian gland function, and can even increase the number of working glands over time.

I also prescribe cyclosporine (Restasis, Allergan; Cequa, Sun Pharma) and lifitegrast (Xiidra, Shire), as well as loteprednol (Lotemax, Bausch + Lomb) for acute flares. I offer platelet-rich plasma tears made with an advanced centrifuge technology (Genius PRP, Reinvent Biologics) and a natural preservative-free tear product containing chamomile, aloe vera, and other natural anti-inflammatories. With dry eye disease under control—and, hopefully, some beauty tips heeded—patients can sail through the holidays with fresh, clear, and healthy eyes. ■



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for Valeant and Sun; researcher for Kala, Lumenis, Magellan, Novaliq, Opternative, and

Sun; speaker, consultant, and researcher for Shire, Mallinckrodt, and Mixto Lasering;

and consultant and researcher for DigSight.



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Not actual patients.

INDICATIONS AND IMPORTANT SAFETY INFORMATION

Rx Only

ATTENTION: Reference the Directions for Use for a complete listing of Indications and Important Safety Information. **INDICATIONS:** The TECNIS® 1-Piece Lens is indicated for the visual correction of aphakia in adult patients in whom a cataractous lens has been removed by extracapsular cataract extraction. These devices are intended to be placed in the capsular bag. **WARNINGS:** Physicians considering lens implantation should weigh the potential risk/benefit ratio for any conditions described in the TECNIS® 1-Piece IOL Directions for Use that could increase complications or impact patient outcomes. The TECNIS® 1-Piece IOL should not be placed in the ciliary sulcus. **PRECAUTIONS:** Do not reuse, resterilize, or autoclave. **ADVERSE EVENTS:** In 3.3% of patients, reported adverse events of cataract surgery with the 1-Piece IOL included macular edema. Other reported reactions occurring in less than 1% of patients were secondary surgical intervention (pars plana vitrectomy with membrane peel) and lens exchange (due to torn lens haptic).

*Compared against AcrySof® IQ (SN60WF), HOYA AF-1™ FY-60AD and enVista® IOLs (MX60).

Reference: 1. Data on file. Chromatic aberration of the TECNIS® Symphony IOL. Johnson & Johnson Surgical Vision, Inc. Santa Ana, CA.

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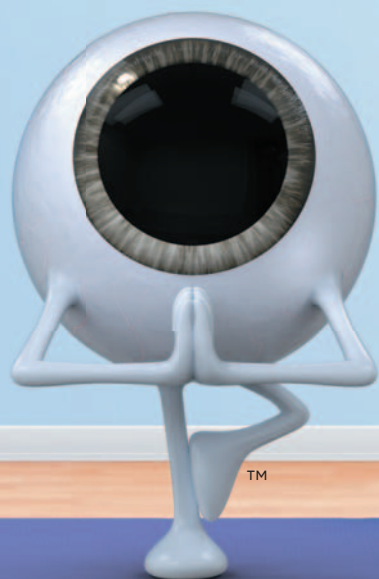
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OMIDRIA® (phenylephrine and ketorolac intraocular solution) 1% / 0.3% is added to ophthalmic irrigating solution used during cataract surgery or intraocular lens replacement and is indicated for maintaining pupil size by preventing intraoperative miosis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

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

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

- Prevents Intraoperative Floppy Iris Syndrome (IFIS)¹
- Reduces complication rates (epinephrine comparator)²
- Decreases use of pupil-expanding devices (epinephrine comparator)²⁻⁷
- Reduces surgical times (epinephrine comparator)^{2,4,6,7}
- Prevents miosis during femtosecond laser-assisted surgery (epinephrine comparator)^{5,8}
- Improves uncorrected visual acuity on day after surgery (epinephrine comparator)²
- Delivers NSAID to the anterior chamber and related structures better than routine preoperative topical drug administration, resulting in effectively complete postoperative inhibition of COX-1 and COX-2^{9,10}

Separately reimbursed under Medicare Part B

Contact your OMIDRIA representative today or visit omidria.com to learn more

IMPORTANT SAFETY INFORMATION

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

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

Systemic exposure of phenylephrine may cause elevations in blood pressure.

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

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

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

You are encouraged to report Suspected Adverse Reactions to the FDA.

Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

References: 1. Silverstein SM, Rana V, Stephens R, Segars L, Pankratz J, Shivani R, et al. Effect of phenylephrine 1.0%-ketorolac 0.3% injection on tamsulosin-associated intraoperative floppy-iris syndrome. *J Cataract Refract Surg.* 2018;44(9):1103-1108. 2. Rosenberg ED, Nattis AS, Alevi D, et al. Visual outcomes, efficacy, and surgical complications associated with intracameral phenylephrine 1.0%/ketorolac 0.3% administered during cataract surgery. *Clin Ophthalmol.* 2018;12:21-28. 3. Bucci FA Jr, Michalek B, Fluet AT. Comparison of the frequency of use of a pupil expansion device with and without an intracameral phenylephrine and ketorolac injection 1%/0.3% at the time of routine cataract surgery. *Clin Ophthalmol.* 2017;11:1039-1043. 4. Visco D. Effect of phenylephrine/ketorolac on iris fixation ring use and surgical times in patients at risk of intraoperative miosis. *Clin Ophthalmol.* 2018;12:301-305. 5. Walter K, Delwadia N. Miosis prevention in femtosecond cataract surgery using a continuous infusion of phenylephrine and ketorolac. Presented at: 2018 American Society of Cataract and Refractive Surgery (ASCRS) and American Society of Ophthalmic Administrators (ASOA) Annual Meeting; April 13-17, 2018; Washington, DC. 6. Matossian C. Clinical outcomes of phenylephrine/ketorolac vs. epinephrine in cataract surgery in a real-world setting. Presented at: American Society of Cataract and Refractive Surgery (ASCRS) and American Society of Ophthalmic Administrators (ASOA) Annual Meeting; April 13-17, 2018; Washington, DC. 7. Al-Hashimi S, Donaldson K, Davidson R, et al. Medical and surgical management of the small pupil during cataract surgery. *J Cataract Refract Surg.* 2018;44:1032-1041. 8. Gayton JL. E-poster presented at: 15th International Congress on Vision Science and Eye; 2017 Aug 10-11; London, UK. 9. Katsev DA, Katsev CC, Pinnow J, Lockhart CM. Intracameral ketorolac concentration at the beginning and end of cataract surgery following preoperative topical ketorolac administration. *Clin Ophthalmol.* 2017;11:1897-1901. 10. Waterbury LD. Alternative drug delivery for patients undergoing cataract surgery as demonstrated in a canine model. *J Ocul Pharmacol Ther.* 2018;34:154-160.



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intraocular solution)
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