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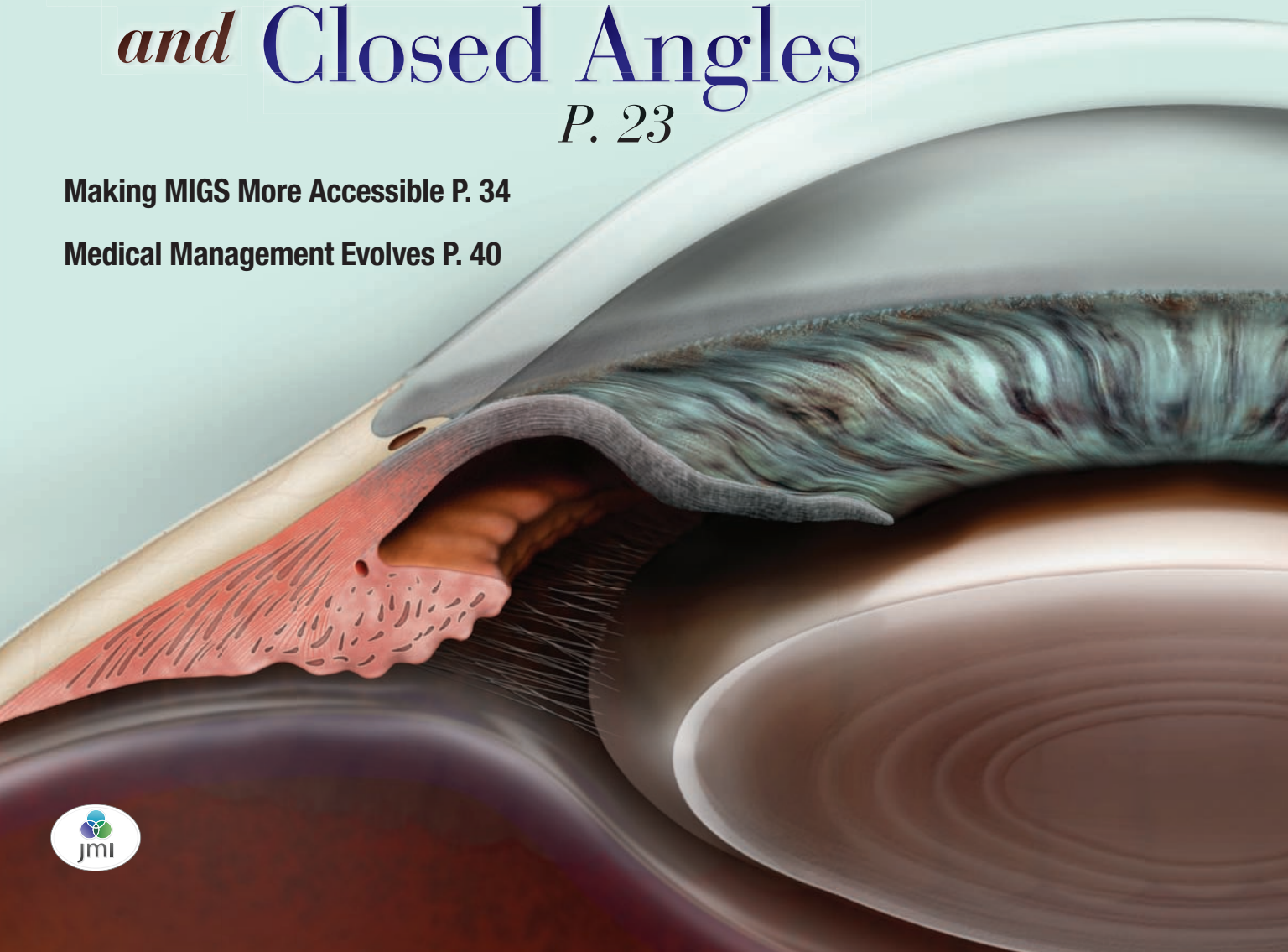

jmi

NEW

For the treatment of elevated IOP

UNLOCK NEW TREATMENT POSSIBILITIES

SIMBRINZA™ Suspension provided additional 1-3 mm Hg IOP lowering compared to the individual components[1]

- IOP measured at 8 AM, 10 AM, 3 PM, and 5 PM was reduced by **21-35%** at Month 3[2-4]
- Efficacy proven in two pivotal Phase 3 randomized, multicenter, double-masked, parallel-group, 3-month, 3-arm, contribution-of-elements studies[2,3]
- The most frequently reported adverse reactions (3-5%) were blurred vision, eye irritation, dysgeusia (bad taste), dry mouth, and eye allergy[1]
- Only available beta-blocker-free fixed combination[2,3]

INDICATIONS AND USAGE

SIMBRINZA™ (brinzolamide/brimonidine tartrate ophthalmic suspension) 1%/0.2% is a fixed combination indicated in the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.

Dosage and Administration

The recommended dose is one drop of SIMBRINZA™ Suspension in the affected eye(s) three times daily. Shake well before use. SIMBRINZA™ Suspension may be used concomitantly with other topical ophthalmic drug products to lower intraocular pressure. If more than one topical ophthalmic drug is being used, the drugs should be administered at least five (5) minutes apart.

IMPORTANT SAFETY INFORMATION

Contraindications

SIMBRINZA™ Suspension is contraindicated in patients who are hypersensitive to any component of this product and neonates and infants under the age of 2 years.

Warnings and Precautions

Sulfonamide Hypersensitivity Reactions—Brinzolamide is a sulfonamide, and although administered topically, is absorbed systemically. Sulfonamide attributable adverse reactions may occur. Fatalities have occurred due to severe reactions to sulfonamides. Sensitization may recur when a sulfonamide is readministered irrespective of the route of administration. If signs of serious reactions or hypersensitivity occur, discontinue the use of this preparation.

Corneal Endothelium—There is an increased potential for developing corneal edema in patients with low endothelial cell counts.

Severe Hepatic or Renal Impairment (CrCl <30 mL/min)—SIMBRINZA™ Suspension has not been specifically studied in these patients and is not recommended.

Adverse Reactions

In two clinical trials of 3 months' duration with SIMBRINZA™ Suspension, the most frequent reactions associated with its use occurring in approximately 3-5% of patients in descending order of incidence included: blurred vision, eye irritation, dysgeusia (bad taste), dry mouth, and eye allergy. Adverse reaction rates with SIMBRINZA™ Suspension were comparable to those of the individual components. Treatment discontinuation, mainly due to adverse reactions, was reported in 11% of SIMBRINZA™ Suspension patients.

Drug Interactions—Consider the following when prescribing SIMBRINZA™ Suspension:

Concomitant administration with oral carbonic anhydrase inhibitors is not recommended due to the potential additive effect. Use with high-dose salicylate may result in acid-base and electrolyte alterations. Use with CNS depressants may result in an additive or potentiating effect. Use with antihypertensives/cardiac glycosides may result in additive or potentiating effect on lowering blood pressure. Use with tricyclic antidepressants may blunt the hypotensive effect of systemic clonidine and it is unknown if use with this class of drugs interferes with IOP lowering. Use with monoamine oxidase inhibitors may result in increased hypotension.

For additional information about SIMBRINZA™ Suspension, please see Brief Summary of full Prescribing Information on adjacent page.

References: 1. SIMBRINZA™ Suspension Package Insert. **2.** Katz G, DuBiner H, Samples J, et al. Three-month randomized trial of fixed-combination brinzolamide, 1%, and brimonidine, 0.2% [published online ahead of print April 11, 2013]. *JAMA Ophthalmol.* doi:10.1001/jamaophthalmol.2013.188. **3.** Nguyen QH, McMenemy MG, Realini T, et al. Phase 3 randomized 3-month trial with an ongoing 3-month safety extension of fixed-combination brinzolamide 1%/brimonidine 0.2%. *J Ocul Pharmacol Ther.* 2013;29(3): 290-297. **4.** Data on file, 2013.

NEW

SIMBRINZA™

(brinzolamide/brimonidine tartrate ophthalmic suspension) 1%/0.2%

ONE BOTTLE. NEW POSSIBILITIES.

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BRIEF SUMMARY OF PRESCRIBING INFORMATION
INDICATIONS AND USAGE

SIMBRINZA™ (brinzolamide/brimonidine tartrate ophthalmic suspension) 1%/0.2% is a fixed combination of a carbonic anhydrase inhibitor and an alpha 2 adrenergic receptor agonist indicated for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.

DOSAGE AND ADMINISTRATION

The recommended dose is one drop of SIMBRINZA™ Suspension in the affected eye(s) three times daily. Shake well before use. SIMBRINZA™ Suspension may be used concomitantly with other topical ophthalmic drug products to lower intraocular pressure. If more than one topical ophthalmic drug is being used, the drugs should be administered at least five (5) minutes apart.

DOSAGE FORMS AND STRENGTHS

Suspension containing 10 mg/mL brinzolamide and 2 mg/mL brimonidine tartrate.

CONTRAINDICATIONS

Hypersensitivity - SIMBRINZA™ Suspension is contraindicated in patients who are hypersensitive to any component of this product.

Neonates and Infants (under the age of 2 years) - SIMBRINZA™ Suspension is contraindicated in neonates and infants (under the age of 2 years*) see Use in Specific Populations*

WARNINGS AND PRECAUTIONS

Sulfonamide Hypersensitivity Reactions - SIMBRINZA™ Suspension contains brinzolamide, a sulfonamide, and although administered topically is absorbed systemically. Therefore, the same types of adverse reactions that are attributable to sulfonamides may occur with topical administration of SIMBRINZA™ Suspension. Fatalities have occurred due to severe reactions to sulfonamides including Stevens-Johnson syndrome, toxic epidermal necrolysis, fulminant hepatic necrosis, agranulocytosis, aplastic anemia, and other blood dyscrasias. Sensitization may recur when a sulfonamide is re-administered irrespective of the route of administration. If signs of serious reactions or hypersensitivity occur, discontinue the use of this preparation *[see Patient Counseling Information]*

Corneal Endothelium - Carbonic anhydrase activity has been observed in both the cytoplasm and around the plasma membranes of the corneal endothelium. There is an increased potential for developing corneal edema in patients with low endothelial cell counts. Caution should be used when prescribing SIMBRINZA™ Suspension to this group of patients.

Severe Renal Impairment - SIMBRINZA™ Suspension has not been specifically studied in patients with severe renal impairment (CrCl < 30 mL/min). Since brinzolamide and its metabolite are excreted predominantly by the kidney, SIMBRINZA™ Suspension is not recommended in such patients.

Acute Angle-Closure Glaucoma - The management of patients with acute angle-closure glaucoma requires therapeutic interventions in addition to ocular hypotensive agents. SIMBRINZA™ Suspension has not been studied in patients with acute angle-closure glaucoma.

Contact Lens Wear - The preservative in SIMBRINZA™, benzalkonium chloride, may be absorbed by soft contact lenses. Contact lenses should be removed during instillation of SIMBRINZA™ Suspension but may be reinserted 15 minutes after instillation *[see Patient Counseling Information]*.

Severe Cardiovascular Disease - Brimonidine tartrate, a component of SIMBRINZA™ Suspension, has a less than 5% mean decrease in blood pressure 2 hours after dosing in clinical studies; caution should be exercised in treating patients with severe cardiovascular disease.

Severe Hepatic Impairment - Because brimonidine tartrate, a component of SIMBRINZA™ Suspension, has not been studied in patients with hepatic impairment, caution should be exercised in such patients.

Potentiation of Vascular Insufficiency - Brimonidine tartrate, a component of SIMBRINZA™ Suspension, may potentiate syndromes associated with vascular insufficiency. SIMBRINZA™ Suspension should be used with caution in patients with depression, cerebral or coronary insufficiency, Raynaud's phenomenon, orthostatic hypotension, or thromboangitis obliterans.

Contamination of Topical Ophthalmic Products After Use - There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products. These containers have been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial surface *[see Patient Counseling Information]*.

ADVERSE REACTIONS

Clinical Studies 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 the rates in the clinical studies of another drug and may not reflect the rates observed in practice.

SIMBRINZA™ Suspension - In two clinical trials of 3 months duration 435 patients were treated with SIMBRINZA™ Suspension, and 915 were treated with the two individual components. The most frequently reported adverse reactions in patients treated with SIMBRINZA™ Suspension occurring in approximately 3 to 5% of patients in descending order of incidence were blurred vision, eye irritation, dysgeusia (bad taste), dry mouth, and eye allergy. Rates of adverse reactions reported with the individual components were comparable. Treatment discontinuation, mainly due to adverse reactions, was reported in 11% of SIMBRINZA™ Suspension patients.

Other adverse reactions that have been reported with the individual components during clinical trials are listed below.

Brinzolamide 1% - In clinical studies of brinzolamide ophthalmic suspension 1%, the most frequently reported adverse reactions reported in 5 to 10% of patients were blurred vision and bitter, sour or unusual taste. Adverse reactions occurring in 1 to 5% of patients were blepharitis, dermatitis, dry eye, foreign body sensation, headache, hyperemia, ocular discharge, ocular discomfort, ocular keratitis, ocular pain, ocular pruritus and rhinitis.

The following adverse reactions were reported at an incidence below 1%: allergic reactions, alopecia, chest pain, conjunctivitis, diarrhea, diplopia, dizziness, dry mouth, dyspnea, dyspepsia, eye fatigue, hypertonia, keratoconjunctivitis, keratopathy, kidney pain, lid margin crusting or sticky sensation, nausea, pharyngitis, tearing and urticaria.

Brimonidine Tartrate 0.2% - In clinical studies of brimonidine tartrate 0.2%, adverse reactions occurring in approximately 10 to 30% of the subjects, in descending order of incidence, included oral dryness, ocular hyperemia, burning and stinging, headache, blurring, foreign body sensation, fatigue/drowsiness, conjunctival follicles, ocular allergic reactions, and ocular pruritus.

Reactions occurring in approximately 3 to 9% of the subjects, in descending order included corneal staining/erosion, photophobia, eyelid erythema, ocular ache/pain, ocular dryness, tearing, upper respiratory symptoms, eyelid edema, conjunctival edema, dizziness, blepharitis, ocular irritation, gastrointestinal symptoms, asthenia, conjunctival blanching, abnormal vision and muscular pain.

The following adverse reactions were reported in less than 3% of the patients: lid crusting, conjunctival hemorrhage, abnormal taste, insomnia, conjunctival discharge, depression, hypertension, anxiety, palpitations/arrhythmias, nasal dryness and syncope.

Postmarketing Experience - The following reactions have been identified during postmarketing use of brimonidine tartrate ophthalmic solutions in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. The reactions, which have been chosen for inclusion due to either their seriousness, frequency of reporting, possible causal connection to brimonidine tartrate ophthalmic solutions, or a combination of these factors, include: bradycardia, hypersensitivity, iritis, keratoconjunctivitis sicca, miosis, nausea, skin reactions (including erythema, eyelid pruritus, rash, and vasodilation), and tachycardia.

Apnea, bradycardia, coma, hypotension, hypothermia, hypotonia, lethargy, pallor, respiratory depression, and somnolence have been reported in infants receiving brimonidine tartrate ophthalmic solutions *[see Contraindications]*.

DRUG INTERACTIONS

Oral Carbonic Anhydrase Inhibitors - There is a potential for an additive effect on the known systemic effects of carbonic anhydrase inhibition in patients receiving an oral carbonic anhydrase inhibitor and brinzolamide ophthalmic suspension 1%, a component of SIMBRINZA™ Suspension. The concomitant administration of SIMBRINZA™ Suspension and oral carbonic anhydrase inhibitors is not recommended.

High-Dose Salicylate Therapy - Carbonic anhydrase inhibitors may produce acid-base and electrolyte alterations. These alterations were not reported in the clinical trials with brinzolamide ophthalmic suspension 1%. However, in patients treated with oral carbonic anhydrase inhibitors, rare instances of acid-base alterations have occurred with high-dose salicylate therapy. Therefore, the potential for such drug interactions should be considered in patients receiving SIMBRINZA™ Suspension.

CNS Depressants - Although specific drug interaction studies have not been conducted with SIMBRINZA™, the possibility of an additive or potentiating effect with CNS depressants (alcohol, opiates, barbiturates, sedatives, or anesthetics) should be considered.

Antihypertensives/Cardiac Glycosides - Because brimonidine tartrate, a component of SIMBRINZA™ Suspension, may reduce blood pressure, caution in using drugs such as antihypertensives and/or cardiac glycosides with SIMBRINZA™ Suspension is advised.

Tricyclic Antidepressants - Tricyclic antidepressants have been reported to blunt the hypotensive effect of systemic clonidine. It is not known whether the concurrent use of these agents with SIMBRINZA™ Suspension in humans can lead to resulting interference with the IOP lowering effect. Caution is advised in patients taking tricyclic antidepressants which can affect the metabolism and uptake of circulating amines.

Monoamine Oxidase Inhibitors - Monoamine oxidase (MAO) inhibitors may theoretically interfere with the metabolism of brimonidine tartrate and potentially result in an increased systemic side-effect such as hypotension. Caution is advised in patients taking MAO inhibitors which can affect the metabolism and uptake of circulating amines.

USE IN SPECIFIC POPULATIONS

Pregnancy - *Pregnancy Category C:* Developmental toxicity studies with brinzolamide in rabbits at oral doses of 1, 3, and 6 mg/kg/day (20, 60, and 120 times the recommended human ophthalmic dose) produced maternal toxicity at 6 mg/kg/day and a significant increase in the number of fetal variations, such as accessory skull bones, which was only slightly higher than the historic value at 1 and 6 mg/kg. In rats, statistically decreased body weights of fetuses from dams receiving oral doses of 18 mg/kg/day (180 times the recommended human ophthalmic dose) during gestation were proportional to the reduced maternal weight gain, with no statistically significant effects on organ or tissue development. Increases in unossified sternebrae, reduced ossification of the skull, and unossified hyoid that occurred at 6 and 18 mg/kg were not statistically significant. No treatment-related malformations were seen. Following oral administration of ^{14}C-brinzolamide to pregnant rats, radioactivity was found to cross the placenta and was present in the fetal tissues and blood.

Developmental toxicity studies performed in rats with oral doses of 0.66 mg brimonidine base/kg revealed no evidence of harm to the fetus. Dosing at this level resulted in a plasma drug concentration approximately 100 times higher than that seen in humans at the recommended human ophthalmic dose. In animal studies, brimonidine crossed the placenta and entered into the fetal circulation to a limited extent.

There are no adequate and well-controlled studies in pregnant women. SIMBRINZA™ Suspension should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers - In a study of brinzolamide in lactating rats, decreases in body weight gain in offspring at an oral dose of 15 mg/kg/day (150 times the recommended human ophthalmic dose) were observed during lactation. No other effects were observed. However, following oral administration of ^{14}C-brinzolamide to lactating rats, radioactivity was found in milk at concentrations below those in the blood and plasma. In animal studies, brimonidine was excreted in breast milk.

It is not known whether brinzolamide and brimonidine tartrate are excreted in human milk following topical ocular administration. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from SIMBRINZA™ (brinzolamide/brimonidine tartrate ophthalmic suspension) 1%/0.2%, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use - The individual component, brinzolamide, has been studied in pediatric glaucoma patients 4 weeks to 5 years of age. The individual component, brimonidine tartrate, has been studied in pediatric patients 2 to 7 years old. Somnolence (50-83%) and decreased alertness was seen in patients 2 to 6 years old. SIMBRINZA™ Suspension is contraindicated in children under the age of 2 years *[see Contraindications]*.

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

OVERDOSAGE

Although no human data are available, electrolyte imbalance, development of an acidotic state, and possible nervous system effects may occur following an oral overdose of brinzolamide. Serum electrolyte levels (particularly potassium) and blood pH levels should be monitored.

Very limited information exists on accidental ingestion of brimonidine in adults; the only adverse event reported to date has been hypotension. Symptoms of brimonidine overdose have been reported in neonates, infants, and children receiving brimonidine as part of medical treatment of congenital glaucoma or by accidental oral ingestion. Treatment of an oral overdose includes supportive and symptomatic therapy; a patent airway should be maintained.

PATIENT COUNSELING INFORMATION

Sulfonamide Reactions - Advise patients that if serious or unusual ocular or systemic reactions or signs of hypersensitivity occur, they should discontinue the use of the product and consult their physician.

Temporary Blurred Vision - Vision may be temporarily blurred following dosing with SIMBRINZA™ Suspension. Care should be exercised in operating machinery or driving a motor vehicle.

Effect on Ability to Drive and Use Machinery - As with other drugs in this class, SIMBRINZA™ Suspension may cause fatigue and/or drowsiness in some patients. Caution patients who engage in hazardous activities of the potential for a decrease in mental alertness.

Avoiding Contamination of the Product - Instruct patients that ocular solutions, if handled improperly or if the tip of the dispensing container contacts the eye or surrounding structures, can become contaminated by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions *[see Warnings and Precautions]*. Always replace the cap after using. If solution changes color or becomes cloudy, do not use. Do not use the product after the expiration date marked on the bottle.

Intercurrent Ocular Conditions - Advise patients that if they have ocular surgery or develop an intercurrent ocular condition (e.g., trauma or infection), they should immediately seek their physician's advice concerning the continued use of the present multidose container.

Concomitant Topical Ocular Therapy - If more than one topical ophthalmic drug is being used, the drugs should be administered at least five minutes apart.

Contact Lens Wear - The preservative in SIMBRINZA™, benzalkonium chloride, may be absorbed by soft contact lenses. Contact lenses should be removed during instillation of SIMBRINZA™ Suspension, but may be reinserted 15 minutes after instillation.

U.S. Patent No:
6,316,441

ALCON LABORATORIES, INC.
Fort Worth, Texas 76134 USA
1-800-757-9195
alcon.medinfo@alcon.com

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AREDS2 Provides Clarity on Vision and Supplements

Adding omega-3 fatty acids did not improve a combination of nutritional supplements commonly recommended for treating age-related macular degeneration, according to the AREDS2 study from the National Institutes of Health. The plant-derived antioxidants lutein and zeaxanthin also had no overall effect on AMD when added to the combination; however, they were safer than the related antioxidant beta-carotene, according to the study, published online in May in the *Journal of the American Medical Association*.

Millions of older Americans take nutritional supplements to protect their sight without clear guidance regarding benefit and risk," said NEI director Paul A. Sieving, MD, PhD. "This study clarifies the role of supplements in helping prevent advanced AMD, an incurable, common and devastating disease that robs older people of their sight and independence."

The Age-Related Eye Disease Study, which was led by NIH's National Eye Institute and concluded in 2001, established that daily high doses of vitamins C and E, beta-carotene, and the minerals zinc and copper—called the AREDS formulation—can help slow the progression to advanced AMD. The American Academy of Ophthalmology now recommends use of the AREDS formulation to reduce the risk of advanced AMD. However, beta-carotene use has been linked to a heightened risk of lung cancer in smokers. And there have been concerns that the high zinc dose in AREDS could cause minor side effects, such as stomach upset, in some people.

In 2006 the NEI launched AREDS2, a five-year study designed to test whether the original AREDS formulation could be improved by adding omega-3 fatty acids; adding lutein and zeaxanthin; removing beta-carotene; or reducing zinc. The study also examined how different combinations of the supplements performed. Omega-3 fatty acids are produced by plants, including algae, and are present in oily fish such as salmon. Lutein and zeaxanthin are carotenoids, a class of plant-derived vitamins that includes beta-carotene; both are present in leafy green vegetables and, when consumed, they accumulate in the retina. Prior studies had suggested that diets high in lutein, zeaxanthin and omega-3 fatty acids protect vision. Before the AREDS2 study finished, manufacturers began marketing supplements based on the study design.

In AREDS2, participants took one of four AREDS formulations daily for five years. The original AREDS included 500 milligrams vitamin C, 400 international units of vitamin E, 15 mg beta-carotene, 80 mg zinc and 2 mg copper. Other groups took AREDS with no beta-carotene, AREDS with low zinc (25 mg), or AREDS with no beta-carotene and low zinc. Participants in each AREDS group also took one of four additional supplements or combinations: these included lutein/zeaxanthin (10 mg/2 mg), omega-3 fatty acids (1,000 mg), lutein/zeaxanthin and omega-3 fatty acids, or placebo. Progression to advanced AMD was established by examination of retina photographs or treatment for advanced AMD.

In the first AREDS trial, participants with AMD who took the AREDS formulation were 25 percent less likely to progress to advanced AMD over the five-year study period, compared with participants who took a placebo. In AREDS2, there was no overall additional benefit from adding omega-3 fatty acids or a 5-to-1 mixture of lutein and zeaxanthin to the formulation. However, the investigators did find some benefits when they analyzed two subgroups of participants: those not given beta-carotene, and those who had very little lutein and zeaxanthin in their diets.

"When we looked at just those participants in the study who took an AREDS formulation with lutein and zeaxanthin but no beta-carotene, their risk of developing advanced AMD over the five years of the study was reduced by about 18 percent, compared with participants who took an AREDS formulation with beta-carotene but no lutein or zeaxanthin," said Emily Chew, MD, deputy director of the NEI Division of Epidemiology and Clinical Applications and the NEI deputy clinical director. "Further analysis showed that participants with low dietary intake of lutein and zeaxanthin at the start of the study, but who took an AREDS formulation

with lutein and zeaxanthin during the study, were about 25 percent less likely to develop advanced AMD compared with participants with similar dietary intake who did not take lutein and zeaxanthin."

Because carotenoids can compete with each other for absorption in the body, beta-carotene may have masked the effect of the lutein and zeaxanthin in the overall analysis, Dr. Chew said. Indeed, participants who took all three nutrients had lower levels of lutein and zeaxanthin in their blood compared to participants who took lutein and zeaxanthin without beta-carotene.

Removing beta-carotene from the AREDS formulation did not curb the formulation's protective effect against developing advanced AMD, an important finding because several studies have linked taking high doses of beta-carotene with a higher risk of lung cancer in smokers. Although smokers were not given a formulation with beta-carotene in AREDS2, the study showed an association between beta-carotene and risk of lung cancer among former smokers. About half of AREDS2 participants were former smokers. "Removing beta-carotene simplifies things," said Wai T. Wong, MD, PhD, chief of the NEI Neuron-Glia Interactions in Retinal Disease Unit and a co-author of the report. "We have identified a formulation that should be good for everyone regardless of smoking status," he said. Adding omega-3 fatty acids or lowering zinc to the AREDS formulation also had no effect on AMD progression.

More than 4,000 people, ages 50 to 85 years, who were at risk for advanced AMD participated in AREDS2 at 82 clinical sites across the country.

In a separate study, published online in *JAMA Ophthalmology*, the AREDS2 Research Group evaluated the effect of the various AREDS formulas on cataract. As reported in

2001, the original AREDS formulation does not protect against cataract. In AREDS2, none of the modified formulations helped reduce the risk of progression to cataract surgery, although a subgroup of participants with low dietary lutein and zeaxanthin gained some protection. "While a healthy diet promotes good eye health and general well-being, based on overall AREDS2 data, regular high doses of antioxidant supplements do not prevent cataract," Dr. Chew said.

Scientists are unsure how supplements in the AREDS formulation exert their protective effects. However, an April 2013 report in *Ophthalmology* by the AREDS Research Group shows the beneficial effects of taking the AREDS vitamins are long-lasting. In a follow-up study of AREDS participants, those who took the AREDS formulation during the initial five-year trial were 25 to 30 percent less likely to develop advanced AMD—mostly due to a reduction in the number of neovascular AMD cases—over the next five years, compared with participants who took placebo during AREDS. Seventy percent of all participants were taking the original AREDS formula by the end of the follow-up period.

"Long-term use of AREDS supplements appears safe and protective against advanced AMD," said Dr. Chew. "While zinc is an important component of the AREDS formulation, based on evidence from AREDS2 it is unclear how much zinc is necessary. Omega-3 fatty acids and beta-carotene clearly do not reduce the risk of progression to advanced AMD; however, adding lutein and zeaxanthin in place of beta-carotene may further improve the formulation."

VEGF Implicated In Trab Scarring

The most common cause of failure after glaucoma surgery is scarring at the surgical site, so researchers are actively looking for ways to minimize or prevent scar formation. Previous work had suggested that vascular endothelial growth factor activates fibrosis, whereas VEGF inhibition results in reduced scar formation and better surgical results. In a series of studies using a rabbit model of glaucoma surgery, investigators have determined that VEGF probably exerts its effects through induction of transforming growth factor (TGF)-β1, which may open up a new target for therapies to improve glaucoma surgical outcomes. This study is published in the June 2013 issue of the *American Journal of Pathology*.

"The cytokine TGF-β1 is a key mediator of wound healing and is critically involved in postoperative scarring," says Chan Kee Park, MD, PhD, Department of Ophthalmology and Visual Science of Seoul St. Mary's Hospital and the College of Medicine of the Catholic University of Korea. "Our present study shows that VEGF induces TGF-β1 production, and inhibiting VEGF reduces TFG-β1 levels … and decreases subconjunctival fibrosis after trabeculectomy."

In this study of 32 white rabbits, some underwent trabeculectomy and others remained unoperated as controls. Immediately after surgery, some rabbits received intraocular injections of 0.2 ml of VEGF at doses ranging from 1 to 50 μg/mL, while others were injected with the VEGF inhibitor bevacizumab in the subconjunctival space.

One of the questions addressed by the researchers was whether VEGF triggers the transformation of fibroblasts to myofibroblasts in the subconjunctiva, since myofibroblasts play a significant role in fibrosis. Using immunohistochemical staining, the researchers found that trabeculectomy activated myoblast transformation as measured by levels of Smad-positive and Snail-positive cells in the conjunctiva and subconjunctiva. This effect increased after VEGF stimulation. Similarly, Western blot analysis of proteins showed increased levels of Smad, phosphorylated Smad and Snail after surgery, which was intensified by VEGF and inhibited by bevacizumab.

"Our findings suggest that VEGF has potential effects on the TGF-β1/Smad/Snail pathway involved in myoblast transformation. Our study gives an experimental basis for the use of anti-VEGF agents in glaucoma surgery," says Dr. Park.

Freeing Cholesterol To Combat AMD

A central feature of age-related macular degeneration is an accumulation of cholesterol in the macrophages, which has been shown to cause the abnormal blood vessel growth characteristic of AMD.

To discover why cholesterol builds up in the macrophages of AMD patients, researchers looked at macrophages from older mice and humans with AMD. Both the older mice and human AMD patients had low levels of the cholesterol transporter ABCA1. Without appropriate amounts of ABCA1, macrophages were unable to move cholesterol out of the eyes and could not prevent abnormal blood vessels from forming.

Experimenting with two cholesterol regulators called Liver X Receptor and microRNAs-33, researchers found that both medications helped to move cholesterol out of the macrophages and reduce abnormal blood vessel growth in the eyes of older mice.

Furthermore, the drugs can be administered via eye drops or injection. It is even hoped that delivering medications through eye drops will reduce the number of possible side effects. REVIEW

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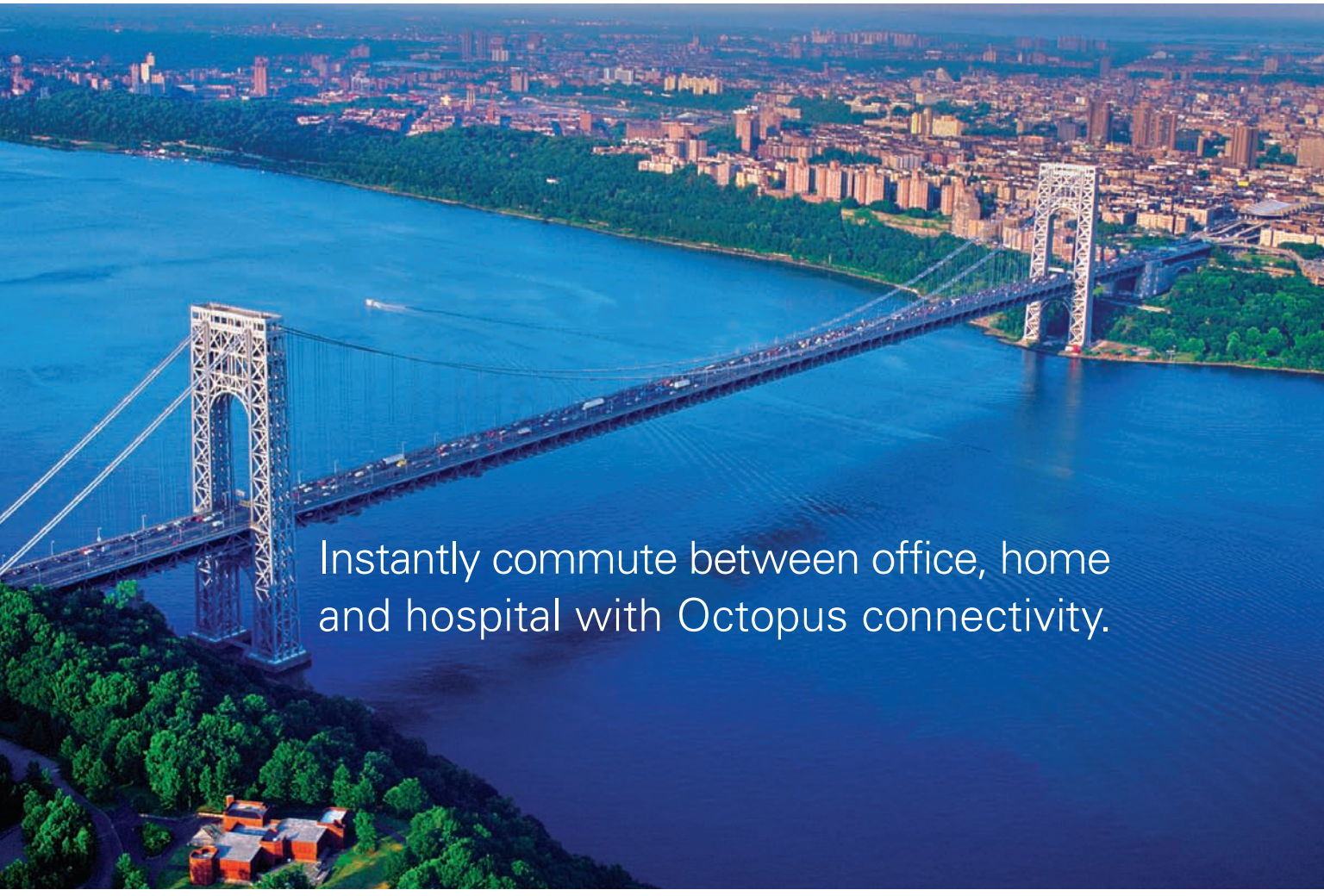

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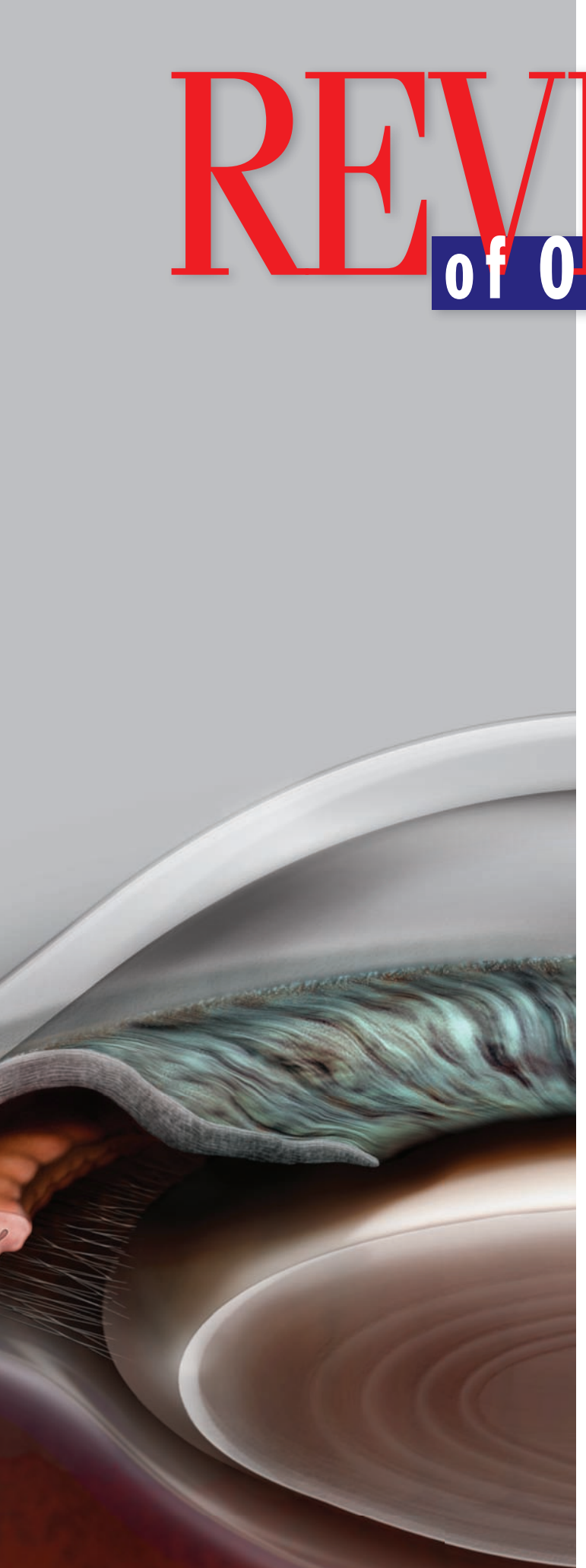

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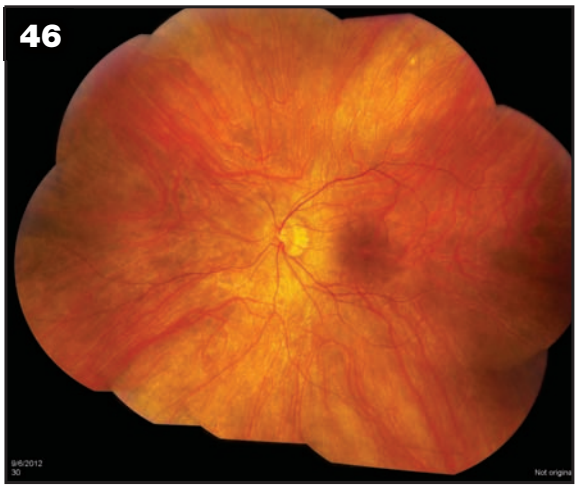

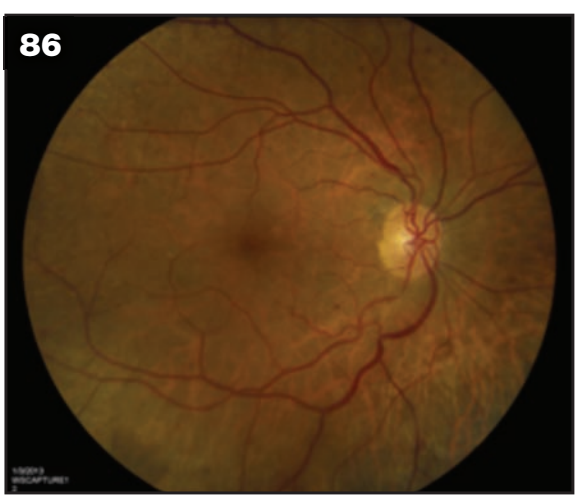

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References: 1. Bacitracin Ophthalmic Ointment [Package Insert]. Locust Valley, NY; Fera Pharmaceuticals, LLC;2009. **2.** Kowalski RP, Karenchak LM, Romanowski EG. Infectious disease: changing antibiotic susceptibility. *Ophthalmol Clin N Am* 2003;16:1-9. **3.** Freidlin J, Acharya N, Lietman TM, Cevallos V, Whitcher JP, Margolis TP. Spectrum of eye disease caused by methicillin-resistant *Staphylococcus aureus*. *Am J Ophthalmol* 2007;144:313-315. **4.** Recchia FM, Busbee BG, Pearlman RB, Carvalho-Recchia CA, Ho AC. Changing trends in the microbiologic aspects of postcataract endophthalmitis. *Arch Ophthalmol* 2005;123:341-346. **5.** http://fingertipformulary.com/drugs/Bacitracinopthalmicointment/

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REVIEW Editor's Page

Christopher Glenn, Editor in Chief

A Long Way to Go on EHR's Potential

Sometimes you pull on a thread and all you get is a hole. Other times …

Of all the concepts in this month's issue, the one I least suspected I'd be coming back to was from our superb Medicare expert, Donna McCune. In this month's column, she offers sage advice that may not strike you as earth-shaking at first glance but could save you quite a bit of money: Be very careful with those macros and other automated chart-filling helpers on many EHR systems. See p. 16 for a further discussion of why all this may matter mightily to you.

I pulled the EHR thread a little further. Remember 2004 when that visionary George Bush set 2014 as the goal for all Americans to have an EHR? OK, not there yet, but we passed a milestone this month with a Health and Human Services report confirming that we have passed the halfway mark: 50 percent of physicians have received Medicare or Medicaid incentive payments for adopting or meaningfully using EHRs, and HHS has met and exceeded its goal for 50 percent of doctor offices and 80 percent of eligible hospitals to have EHRs by the end of 2013, a rate more than double that of 2012.

I gave it another tug. Perhaps in celebration of the milestone, Farzad Mostashari, MD, the national coordinator for health information technology at HHS, was out and about winning lots of press coverage. In one interesting exchange, Dr. Mostashari told a Washington gathering, "We're about halfway through the process of computerizing and digitizing America's hospitals and doctor's offices," but "we're about 5 percent of the way through changing workflows and redesigning care to take advantage of those technologies."

Dr. Mostashari revealed his Bushian vision of the as-yet unrealized potential of EHR systems by citing three ways an effectively integrated EHR system can impact care of diabetic patients: by truly engaging patients in the process and reducing the rate of patients lost to follow-up; by streamlining and automating communication about such matters as cholesterol tests, freeing the doctor from having to remember everything in an eight-minute visit; and by using protocol-based defaults for choices about care options, such as what steps come next after a diabetic patient has tried unsuccessfully to reduce blood pressure and cholesterol with diet and exercise.

While he was talking about diabetic patients, I couldn't help but think—patients with poor or lost follow-up, with an inadequate knowledge base about their disease, and a myriad of treatment choices and options for their physicians—glaucoma! Which brings us back to this month's issue.

Thanks, Donna!

Donna McCune, CCS-P, COE

Unanticipated Issues Implementing EHRs

A new survey suggests that electronic health records can affect productivity and introduce new errors in patient charts.

Q How do physicians view the implementation of electronic health records in their practices?

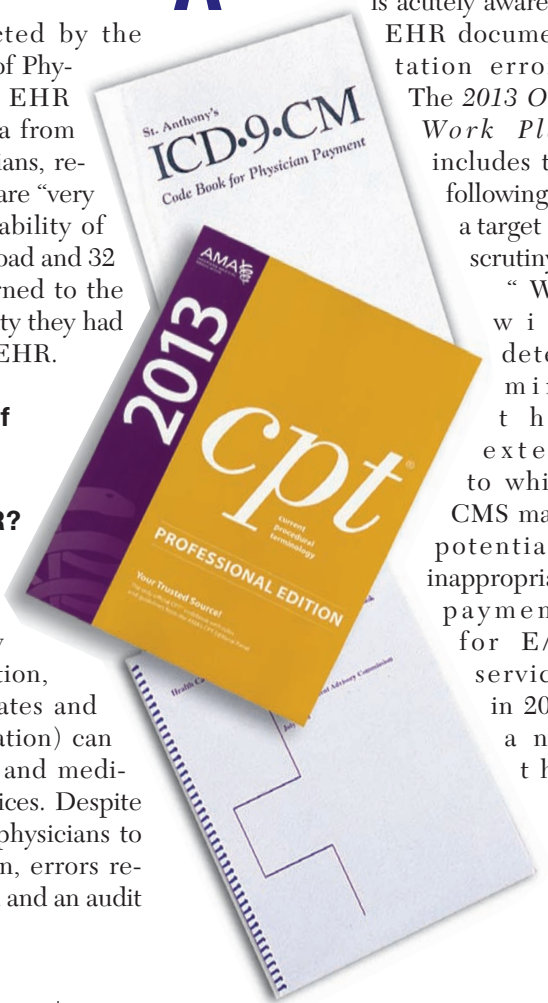
A A survey conducted by the American College of Physicians and American EHR Partners evaluated data from a survey of 4,200 clinicians, revealing that 34 percent are "very dissatisfied" with the ability of EHR to decrease workload and 32 percent have not returned to the same level of productivity they had pre-implementation of EHR.

Q What are some of the unintended consequences associated with EHR?

A What appear to be attractive options with EHR (e.g., carry forward, auto-completion, comprehensive templates and macros for documentation) can result in inaccuracies and medically inappropriate services. Despite the best intentions by physicians to improve documentation, errors result, claims are overpaid and an audit could result.

Q What types of errors have been noted by regulators?

A The Office of Inspector General is acutely aware of EHR documentation errors. The *2013 OIG Work Plan* includes the following as a target for scrutiny[1]: "We will determine the extent to which CMS made potentially inappropriate payments for E/M services in 2010 and the consistency of E/M medical review determinations. We will also review multiple E/M services for the same providers and beneficiaries to identify electronic health records (EHR) documentation practices associated with potentially improper payments. Medicare contractors have noted an increased frequency of medical records with identical documentation across services. Medicare requires providers to select the code for the service on the basis of the content of the service and have documentation to support the level of service reported."



It has also been shown that EHR users have an increased utilization of level 4 and 5 Evaluation and Management services due to robust charting with much more information in the history and exam[2]; prepayment audits of CPT 99204 have been initiated by some Medicare Administrative Contractors.[3]

Q Is it necessary to populate every exam element at each encounter documented on the EHR?

A No. When learning how to use the EHR, users learn to populate all of the cells, so it appears

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that every exam is comprehensive. To speed the process, some EHR programs pre-populate the eye exam with "normal" findings, which the physician modifies with pertinent positives where abnormalities are identified. This technique, known as charting by exception, can lead to errors when some parts of the eye were not examined, but presumed to be normal. In addition, if every exam appears to be comprehensive, there is doubt that the physician did the work and that it was necessary to do it all on each encounter. Best practices utilize templates with exam elements and complete only those elements that are pertinent to the patient's chief complaint and associated findings.

Q Do macros—long, detailed notes triggered by a single word or keystroke, placing information in the patient medical record about a discussion related to a specific disease or treatment—present any issues?

A They can. Although they're comprehensive in nature, it is unrealistic to believe that this amount of information is shared with each patient diagnosed with a particular condition. This documentation may cause an audit risk—as described above—but also represents a risk management concern related to the quality of care and informed consent.

Q Are there any concerns with the copy-paste or copy-forward functions that are available in some EHR programs?

A Yes. Copy-paste or copy-forward is an attractive feature for EHR users because it speeds charting, but it does create the potential for numerous problems. This approach creates "cloned" notes. When used indiscriminately, the integrity of the medical record is doubtful because chart notes on successive records are identical. The potential for mistakes is also very high with this tool. It is best to minimize use of copy features, and ensure that any copied notations are edited with new information. If no new information exists, verify every copied notation.

Q Can corrections be made in EHRs?

A There are several different types of "corrections" that can be made to an EHR. A correction is a change of the information in an old entry, after it is closed, to fix inaccuracy. Significantly, the old information must not be destroyed. The correction should stand out, be separately dated and time stamped, and individually signed. Practices should develop a policy as to who has the authority to "unlock" a record for this purpose. The privilege should be restricted to a small number of individuals and used sparingly.

An amendment is a note added to an old entry, after it is closed, to clarify the record. It should stand out, be separately dated and time stamped, and individually signed. An addendum is a new entry, with a new date/time and provider signature, that contains a separate notation that corrects or amplifies the prior note. The old entry is not re-opened, thereby avoiding criticism of altered records.

Q Has the Centers for Medicare & Medicaid Services published any guidance regarding the proper procedure for correcting errors found during reviews of EHRs?

A Yes. In December 2012, CMS updated the *Medicare Program Integrity Manual*, Chapter 3 – Verifying Potential Errors and Taking Corrective Actions section 3.3.2.5 – Amendments, Corrections and Delayed Entries in Medical Documentation in Transmittal 442, effective January 8, 2013. The information applies to those conducting audits and reminds them to consider the recordkeeping principles when conducting a review. An excerpt[4] states:

"Regardless of whether a documentation submission originates from a paper record or an electronic health record, documents submitted to MACs, CERT, Recovery Auditors, and ZPICs containing amendments, corrections or addenda must:

1. Clearly and permanently identify any amendment, correction or delayed entry as such, and
2. Clearly indicate the date and author of any amendment, correction or delayed entry, and
3. Not delete but instead clearly identify all original content."

Additionally, records that have been sourced from electronic systems that "contain corrections or amendments, as well as delayed entries, must:

a. Distinctly identify any amendment, correction or delayed entry, and

b. Provide a reliable means to clearly identify the original content, the modified content, and the date and authorship of each modification of the record." REVIEW

Ms. McCune is vice president of the Corcoran Consulting Group. Contact her at DMcCune@corcorancg.com.

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Grading the Ocular Surface with the iPod

How a group of corneal specialists constructed an effective way to image the ocular surface without breaking the bank.

Walter Bethke, Managing Editor

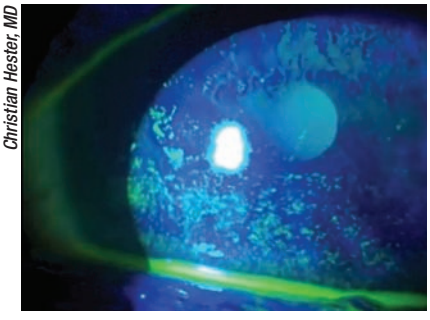
If you've ever been involved in a dry-eye trial in which many patients needed to have their ocular surface evaluated, or had a patient with ocular surface disease who might benefit from an evaluation by an expert at a remote site, the cornea experts at the Baylor College of Medicine may have hit upon an economical but effective method that may be able to make these tasks easier. Using a slit lamp, an iPod Touch and readily available adapters and software applications, the physicians were able to document ocular surface findings and produce sharp, useful images. Here's a look at how they did it, how well it worked and how you can use your iDevice to take slit-lamp photos and videos.

The System

Stephen Pflugfelder, MD, the James and Margaret Elkins Chair of ophthalmology at Baylor, and his corneal fellow Christian Hester, MD, say there are several keys to achieving the best images at the slit lamp with an iDevice, which in their case began with the iPod Touch.

• ***Maximum megapixels.*** "We've been comparing the iPod Touch and the iPhone 4S, and we've found you want at least a 5-megapixel camera," says Dr. Hester. "You'll notice an increase in the camera's sharpness with more megapixels, and an improvement in the camera's optics, as well." He says the Samsung Galaxy's camera actually has more megapixels than the iPhone, but the trade-off is that it doesn't have software that can enhance the camera's exposure to achieve optimal imaging of the ocular surface.

• ***A good adapter.*** The adapter is the interface by which the iPod/iPhone attaches to the slit lamp. Dr. Hester says they use an adapter from EyePhotoDoc (eyephotodoc.com), which was designed by Clifford Terry, MD. "It slides on easily," says Dr. Hester. "I've used a number of different adapters, and imaging is a more pleasurable experience when you have the right one." Other adapters are available from Keeler (keelerusa.com), Tiger Lens (tigerlens.com) and Zarf Enterprises (zarfenterprises.com).



Christian Hester, MD

A yellow filter and an app that optimizes exposure help detect subtle changes in the ocular surface, say physicians.

• ***Illumination, the ProCamera app and a filter.*** "Initially, I was taking terrible pictures that didn't look like the images in the texts," recalls Dr. Hester. "But then I realized it all had to do with the lighting, which is important to optimize. For fluorescein exams especially, we use an app called ProCamera that lets us precisely adjust the exposure in order to capture the optimum image. Dr. Pflugfelder also showed me that it's important to incorporate a yellow barrier filter. When you use the yellow filter and optimize the exposure with ProCamera, you can really begin to pick up subtle surface changes." ProCamera is available at the Apple App Store.

In terms of a light source for staining evaluation, the physicians' Haag-Streit slit lamp has what they need.

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1. LASTACAFT® Prescribing Information. **2.** Torkildsen G, Shedden A. The safety and efficacy of alcaftadine 0.25% ophthalmic solution for the prevention of itching associated with allergic conjunctivitis. *Curr Med Res Opin.* 2011;27(3):623-631. **3.** Data on file, Allergan, Inc., 2005.

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"We played around with various light sources but, in the end, found that you can actually get good images with the standard cobalt blue light that's on the Haag-Streit slit lamp that we use," says Dr. Hester. "We then optimize the lighting in the ProCamera app." Putting these elements together cost the ophthalmology department about $600 to $700.

Getting the Best Shots

As with anything, you can assemble the best equipment but you need hands-on experience to make the most of it.

"We'll use some slit lamps where we have to turn up the light intensity a little bit, and others where you don't need such an intense light source," explains Dr. Hester. "But the ProCamera app lets you compensate for the variations among the slit lamps in your clinic by moving the yellow exposure circle around on the screen to get the optimum lighting. You don't have to enter a numeric value—it's all done visually. So, when the image looks right, you tap the circle to keep that exposure. We literally tried 15 to 20 apps before finding this one that makes it that simple."

For traditional, white-light photography at the slit lamp, Dr. Hester says illumination looms large again. "To get an image of the entire eye, you need an external illumination source," he says. "You can get one of these from your slit lamp manufacturer, and EyePhotoDoc also makes one. However, what I do 90 percent of the time is just hold a transilluminator next to the slit lamp and illuminate the eye with that.

"Also, Dr. Pflugfelder showed me that you can get a nice overall image of the eye using a diffuser," Dr. Hester continues. "You can get a pack of five diffusers for $50 or so, and using one really softens the light and makes for a good overview picture of the eye. And, if you want that classic image in which the entire eye is visible with a thin slit beam on it and there's diffuse illumination, you hold up the transilluminator and use a thin light slit on medium intensity oriented between a 30- and 60-degree angle." The physicians say that diffusers are available from their slit-lamp company's website, but, in a pinch, a piece of translucent scotch tape or a piece of 3M Transpore surgical tape placed over the slit-lamp mirror can also work.

Dr. Pflugfelder explains that sclerotic scatter can help capture very subtle findings, such as fine diffuse lamellar keratitis, on the iPod/iPhone. "You decenter the slit beam to the limbus and let the internal reflection within the cornea highlight those features," he says. "Something like basement membrane disease shows up fairly well in that way. You can also capture images with retroillumination: With a dilated pupil, the illumination will create a diffuse red glow off the retina that will backlight corneal

opacities. Using a combination of those two methods should let you capture something that you can't catch with direct white-light illumination."

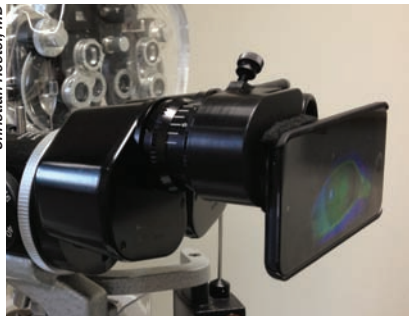
The other key element is focusing the image. "This is one of the things that drives people crazy when they first start taking slit-lamp photos," says Dr. Hester. "What works best is using the blue focus square in ProCamera. You use your finger to move the blue square over what you want to focus on and, once it's there, you lock the focus. You can then control fine adjustments to the focus using the slit lamp as you would normally during an exam. Using this method, with a thin slit beam on the high-intensity setting and a 60-degree angle, we've been able to capture the posterior capsule, which is about 5 to 10 µm thick. The precision you can attain with the focus is amazing."

Studying the System

Drs. Pflugfelder and Hester, along with their colleague Mitchell Weikert, MD, used the iPod/slit-lamp system for a study of ocular surface grading that they presented at the 2012 meeting of the American Society of Cataract and Refractive Surgery, and say they achieved intriguing results.

"Our goal for the study was to determine if we could take images with an iDevice, in this case the iPod Touch, and grade the severity of corneal fluorescein staining, tear-film breakup time and lissamine green staining compared to their grading in real time at the slit lamp by a physician," says Dr. Pflugfelder. "If the grading corresponded, we knew that someone could capture the images and video at a remote site and send them to a reading center where they could be anonymously graded by a reader. So, one of us graded the staining at the slit lamp and captured the staining video from 14 patients, then a naïve reviewer would evaluate the video and images and grade them."

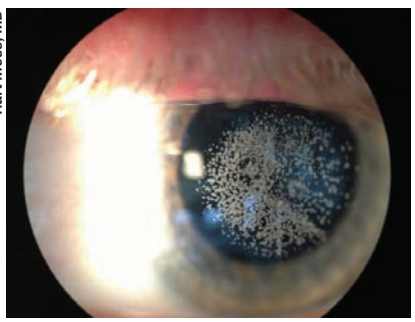
Christian Hester, MD



You use an adapter to attach the iPod or smartphone to the slit lamp.

Dr. Hester says they found a correlation, but also variability. "We found a very high correlation between tear-film breakup time as graded visually in real time and as graded through viewing the iPod video," he says. "We had a similar finding with the lissamine green staining. But, there was more variability in the fluorescein staining, which was an interesting finding. The gradings still related to each other very well and weren't statistically different from each other and had a high correlation, but there was also more variability in them. In some cases, we'd sit down after grading some of them and watch the video together and ask each other how we'd grade that particular eye. Even then, when we were watching the same video, we'd come up with different scores. Part of this is because there's a certain amount of subjectivity in grading the fluorescein scores, which have a larger range in their numbering system. You can grade fluorescein from zero to 21, but the lissamine green scale is just zero to six, and TBUT—you know it the second you call it. Recording these high-quality videos is interesting because you might be able to eliminate that bias from research studies if you take the videos and send them to a centralized reading center for grading."

Hart Moss, MD



Using sclerotic scatter with the iDevice allows sharp pictures for certain diseases, such as this image of granular dystrophy.

In addition to its use at centralized reading centers, the physicians say such a system could provide other benefits. "I receive e-mails from India on a regular basis, and have talked with others involved with international ophthalmology," says Dr. Hester. "After speaking with them I think this could serve as an important resource for areas that can't afford to install a $5,000 or $6,000 camera. The other thing is that it's portable. Instead of having to move patients to the room with the imaging system in it, you can put this in your pocket and carry it to your exam rooms."

Dr. Pflugfelder says it's allowed care to be more convenient for some of his patients, as well. "We practice in Houston, so we have a wide referral area," he says. "Some patients live four to five hours away. In some instances, these far-off patients would call in with an eye problem such as irritation or redness, and Dr. Hester would have them take images of their eyes with their phones and e-mail them to us. This has saved patients a long trip on a number of occasions."

Ultimately, Dr. Hester says that taking the time to clear the relatively short learning curve can pay off. "I used to try to take pictures at the slit lamp with a digital SLR camera and couldn't do a very good job," he says. "This makes it easier, but just because it's an iPhone it's not magic, and won't make you automatically start taking amazing photos. It still takes work, but I think it takes a whole lot less work, and less photographic knowledge, than trying to do it with traditional slit-lamp photography." REVIEW

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Managing Narrow Angles and Glaucoma

Christopher Kent, Senior Editor

This form of the disease may be more common than many clinicians realize. Here, experts provide a management update.

Although angle-closure glaucoma is less prevalent around the world than open-angle glaucoma, its contribution to vision loss and blindness is significant. Furthermore, the diagnosis and treatment of angle closure raise issues unique to this type of problem.

With that in mind, three clinicians who have done extensive research in this area share their experience and latest thinking on angle closure: how it happens; why it happens; and what clinicians can do to manage it to—hopefully—prevent vision loss.

A Major Health Issue

"Glaucoma is the second leading cause of blindness globally, and angle closure accounts for close to half of the blindness caused by the disease," notes David S. Friedman, MD, MPH, director of the Dana Center for Preventive Ophthalmology, and the Alfred Sommer Professor of Ophthalmology at the Wilmer Eye Institute of Johns Hopkins University School of Medicine. "It's less common than open-angle glaucoma, but a large number of population-based studies have shown that people who have angle-closure glaucoma typically have more severe damage than people who have open-angle glaucoma.

"Angle-closure glaucoma develops because the anterior part of the eye is crowded," he continues. "That is reflected in many different measurements that we do. Also, the length from the front to the back of the eye in these patients, on average, is a little bit shorter. However, that doesn't mean that a short eye will necessarily develop angle closure, or that people with longer-than-average eyes are immune to it. It's really the way the anterior segment structures are positioned that causes the disease."

Dr. Friedman notes that there's a misunderstanding that in China narrow angle glaucoma is more common than open-angle glaucoma. "That's not the case," he says. "Angle-closure glaucoma is still less common. It's just that angle closure is much more common than it is here. People used to say it was 10 times more common among the Chinese, which is also not true; it's probably two or three times more common. In any case, because the population at risk is so large and aging, there's a big public health issue developing."

Categories of Closure

"Like open-angle glaucoma, angle-closure glaucoma comes in many forms," notes Jeffrey M. Liebmann,

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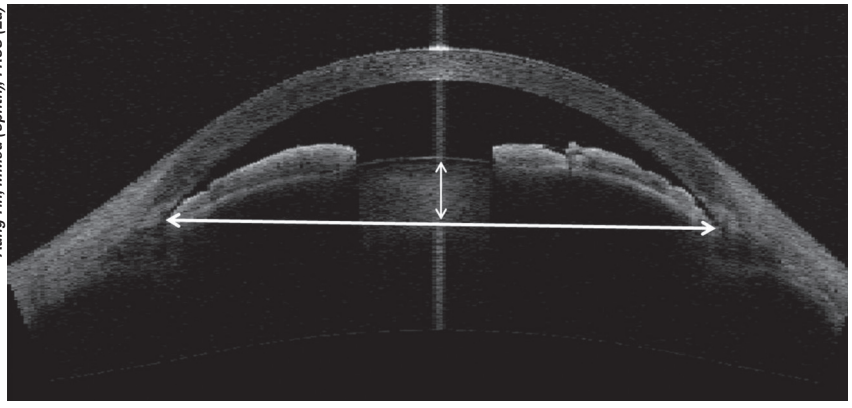

Aung Tin, MMed (Ophth), FRCS (Ed)

Using optical coherence tomography to visualize and measure the angle is becoming increasingly common. Here, OCT reveals an abnormally large lens vault (vertical arrow). One study found that lens vault correlated more closely with angle closure than any other factor measured, including iris thickness and anterior chamber width.[1]

MD, clinical professor of ophthalmology at New York University School of Medicine, adjunct professor of clinical ophthalmology at New York Medical College and director of glaucoma services at Manhattan Eye, Ear, and Throat Hospital and New York University Medical Center. "It's not just one disorder—a series of different conditions can lead to anatomically narrow angles, angle closure and acute angle-closure attacks. Given that fact, the most important thing doctors can do is develop a systematic approach to the angle-closure glaucomas, just as they would for primary open-angle glaucoma, to try to determine the cause of the angle closure. Once you know the cause, you can direct the treatment to that cause."

Dr. Friedman agrees that it's useful to categorize people with angle closure as different types. "That will allow us to look at various treatments and interventions and see if one is better at helping a given type," he notes. However, when it comes to categorizing subtypes of angle closure, he points out that some of the older terminology is no longer very useful. "A term like 'intermittent angle closure' isn't very helpful," he says. "It's not that such a thing doesn't exist; it's just that a lot of people have intermittent symptoms who've never had an attack and don't have acute angle closure. Other terms such as 'latent' or 'creeping' angle closure never seemed very well-defined, either.

"Another widely used term I think we should avoid is 'occludable angle,' referring to an eye we think might occlude," he continues. "In reality, we have very little understanding of who occludes and who will have an acute attack. I think using accurate names to describe what we see is important because when we give something a name, we often then feel compelled to act on it. If it sounds like it might kill you, you'll probably feel that you need to do something, when in fact it would make more sense to say, 'I don't really know what's going on, so let's keep an eye on it.' "

In terms of anatomy, Dr. Friedman says a few factors seem to be key. "Some individuals have their lens very anterior to the scleral spur, pushing into the anterior segment," he says. "We can measure that by marking the scleral spur and then seeing how much farther forward the lens is, which we call lens vault. A greater-than-average lens vault can be the dominant factor in closing the angle." *(See example, above.)*

Dr. Friedman says he now prefers to divide angle closure patients into four major categories. "The largest category is people who are anatomically narrow—they look closed, but if you press on the eye with gonioscopy you can open the angle," he explains. "There's no scarring and the pressure's normal. These eyes raise our suspicions, but there's no apparent crisis. The second category is a group that has similarly narrow angles but also has synechiae in the angle and/or high pressures. *(See example, p. 26.)* We consider these individuals more worrisome, as they have the appearance of early disease development, although we don't have a lot of natural history data on this group. The third category is those who clearly have glaucoma and closed angles. Finally, there's a fourth group; those who present with an acute symptomatic attack of angle closure and high eye pressure. This is the simple new approach to categorizing these patients that we've been using."

Causal Factors

In the majority of cases, angle closure in these patients is attributed to pupillary block and addressed by laser iridotomy, which reopens the angle. However, Dr. Liebmann notes that a number of other causes can underlie angle closure.

"In patients with plateau iris, the ciliary body configuration is abnormal," he says. "The abnormally positioned ciliary body physically holds the peripheral iris to the trabecular meshwork. When laser iridotomy is performed in plateau iris, the angle usually opens only a very small amount and there is persistent appositional closure of the iris to the meshwork. This can be seen during indentation gonioscopy. If the iris is still touching the trabecular meshwork, you should then determine whether or not the patient requires further intervention such as a peripheral iridoplasty.

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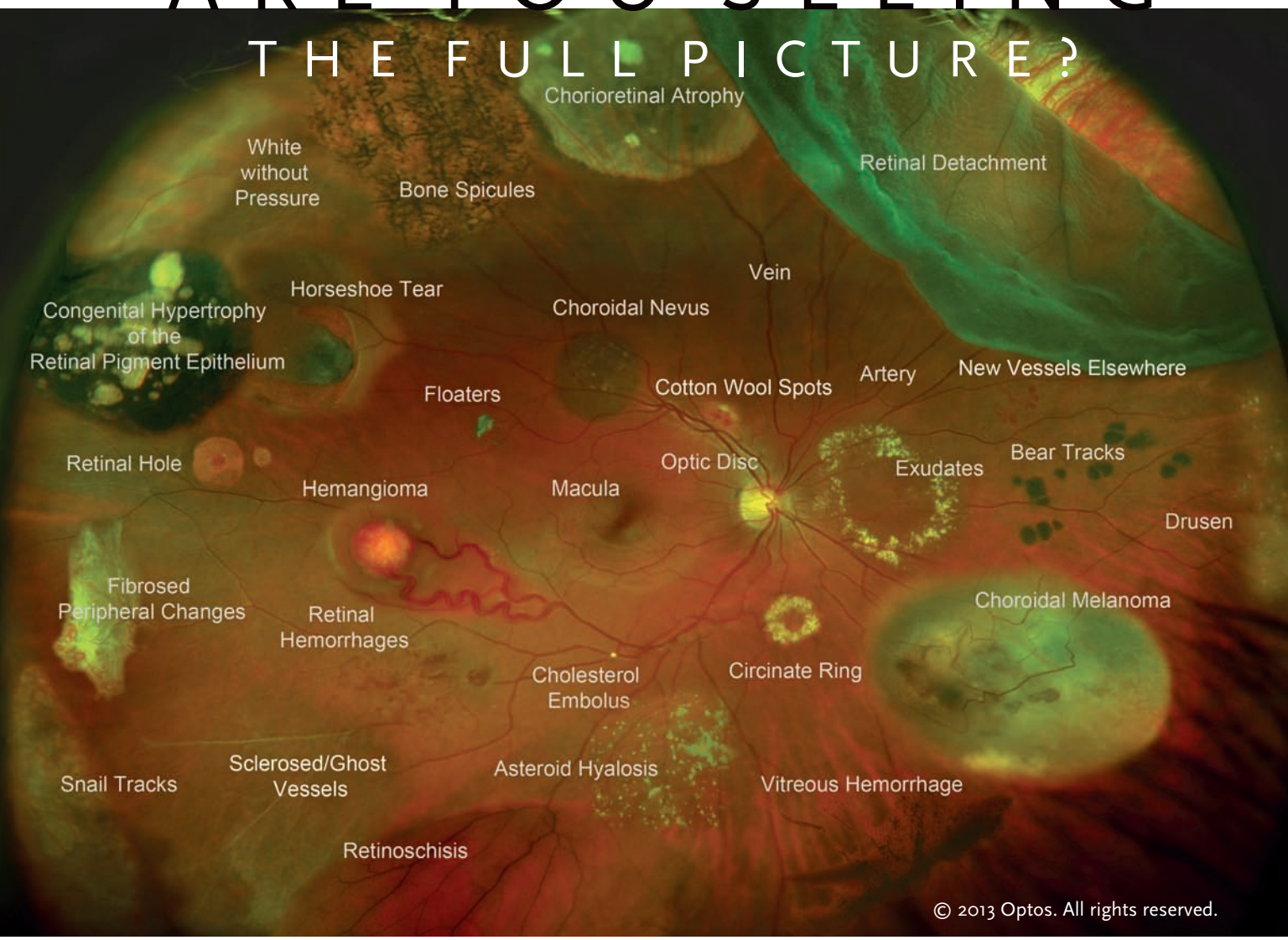

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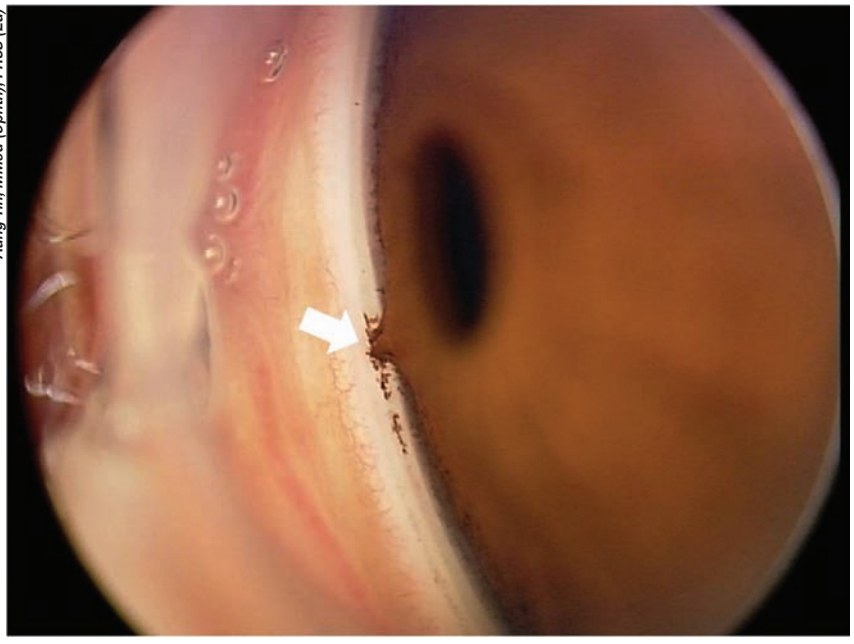


Aung Tin, MMed (Ophth), FRCS (Ed)

Most surgeons still consider gonioscopy to be the gold standard for examining the angle. Here, gonioscopy reveals peripheral anterior synechiae in the angle.

Fortunately, relatively few patients will require that."

Dr. Friedman has mixed feelings about categorizing a patient as having plateau iris. "I look at angle-closure mechanisms as being multifactorial," he says. "The iris might be thick or have an anterior insertion; the ciliary body could pushing the iris upwards. A number of factors probably play a role in angle closure, so labeling one case as plateau iris and another not seems like a little bit of an artificial construct. I think a mix of components is likely to be responsible.

"When we looked at clinic patients with angle closure to identify plateau iris using ultrasound biomicroscopy, very few people had plateau iris in all four quadrants," he continues. "Most of them only had it in one or two quadrants. Furthermore, a lot of people who had plateau iris before iridotomy didn't have it after, and a lot of people who didn't have plateau iris before iridotomy did have it after. I think there are various mechanisms at play, so you can't dismiss pupillary block as being a component even when you think it's a case of plateau iris. That's why I still emphasize doing an iridotomy in angle closure, as a necessary part of the treatment, regardless of the appearance of plateau iris."

Dr. Liebmann notes that causes of angle closure may also lie farther back in the eye. "Disorders of the lens can cause angle closure, including enlargement of the lens as the cataract process advances," he says. "In this case, the physical size of the lens is pushing the iris into the trabecular meshwork. Closure could also happen if the lens is subluxed or loose. The most common cause of zonular laxity is exfoliation syndrome; while exfoliation is a common cause of open-angle glaucoma, 10 percent of all patients who have exfoliation syndrome will have an angle-closure glaucoma component.

"Causes can also lie in the posterior segment," he continues. "You can have angle closure related to disorders of the vitreous and the retina, and patients can develop angle closure after scleral buckling surgery. Still another angle closure currently of interest to doctors is malignant glaucoma. This form of angle closure, most often occurring after intraocular surgery, is characterized by flattening of the anterior chamber and high intraocular pressure; it's relieved by rupturing the anterior hyaloid face using the YAG laser or vitrectomy. The pathogenesis of this disorder is an area of intense discussion among glaucomatologists. Finally, there are other more unusual potential causes of angle closure, such as ciliary cysts, but these are relatively uncommon."

Diagnosis: Gonioscopy

In terms of clinical diagnosis, the three approaches most commonly used to examine the angle are gonioscopy, ultrasound biomicroscopy and optical coherence tomography. "I do both gonioscopy and OCT, but the reference standard is gonioscopy," says Shan C. Lin, MD, professor of clinical ophthalmology and co-director of glaucoma at the University of California San Francisco. "Unfortunately, gonioscopy is currently not done at least half the time in patients who have glaucoma or glaucoma suspicion, and those are the ones who really need gonioscopy. Arguably, everybody deserves at least one gonioscopic exam in order to really determine what's going on with the angle.

"As to whether a patient needs treatment," he adds, "in the United States the criterion is that if you can't see the posterior trabecular meshwork for 180 degrees or more, that's considered to be an occludable angle and the patient should receive prophylactic laser."

Dr. Friedman notes that one reason identifying angle closure is still a challenge is that gonioscopy is subjective. "It's also uncomfortable for patients, and doctors frequently don't perform it," he points out. "We've looked at charts across the United States from health-care plans, and the charts of at least half of the people diagnosed

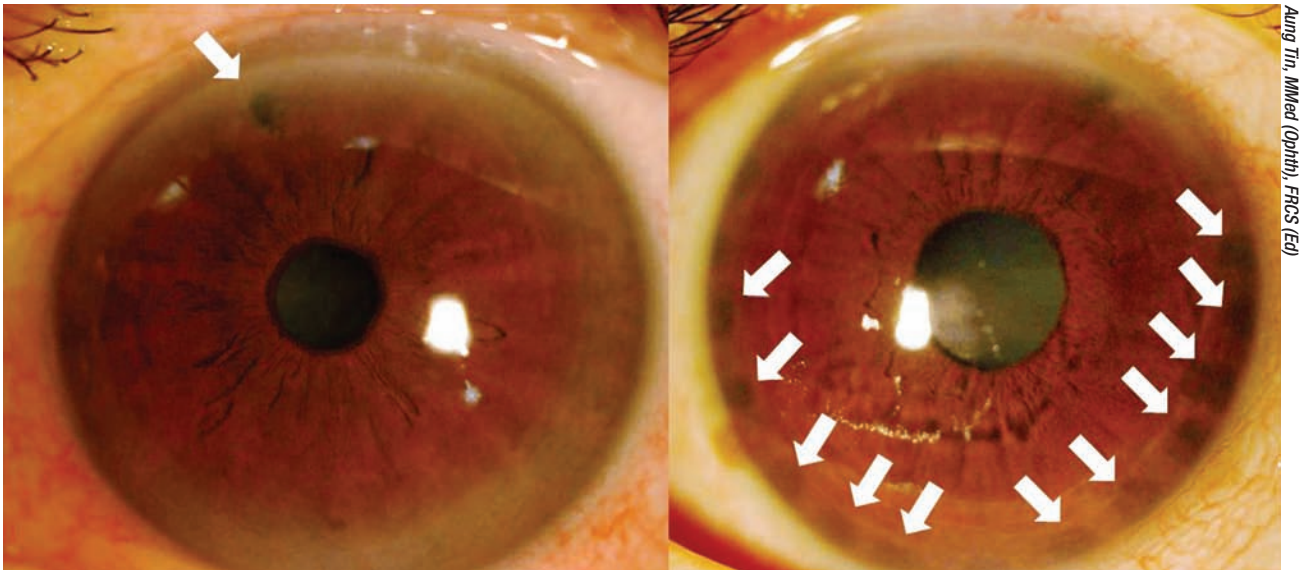
with glaucoma contained no evidence that the patient had undergone gonioscopy. But doctors can't really know that they're dealing with open-angle glaucoma unless they look at the angle to see whether it's open."

"Gonioscopy is the single most important thing the ophthalmologist can do to detect angle closure," agrees Dr. Liebmann. "It allows us to determine whether the angle is just narrow, or whether there is actual apposition of the iris to the trabecular meshwork. We recommend that every patient—at least the first time he's examined by an ophthalmologist—have gonioscopy. Indentation gonioscopy does not require any coupling gels and it only takes a very short time to perform.

"One of the key things about gonioscopy is to perform it in relatively dark conditions," he adds. "If a bright slit beam is directed through the pupil, the pupil constricts and the angle opens. Gonioscopy should be performed with the room lights out, using a small beam of light directed through the gonioprism mirror to look at the angle. Care needs to be taken to avoid shining it through the pupil. As the pupil dilates with darkening room conditions there's a better chance of making a diagnosis of angle closure if it is present."

Diagnosis: Imaging the Angle

"In recent years we've done a lot of research on the mechanisms of angle closure because there are a number of excellent imaging technologies now available that have allowed us to see much more of what's going on," notes Dr. Friedman. "The first technology that helped in this regard was ultrasound biomicroscopy, which appeared 20 or 25 years ago. That allowed one quadrant of the filtering part of the eye to be seen in tremendous detail, giving us a lot more insight into the angle-closure mechanism. More recently we've had the anterior segment



Aung Tin, MMed (Ophth), FRCS (Ed)

Laser iridotomy (left) is commonly used to relieve the pupillary block component of angle closure when the iris is found to be touching the trabecular meshwork. Iridoplasty (right) is sometimes used as a follow-up procedure if iridotomy isn't effective, although clinical data has not definitively proven that iridoplasty is universally effective.

OCT devices, which allow us to see the entire anterior segment from side to side in slices. That provides a lot of information about the relationship of various structures to each other. Even more recently, the development of three-dimensional imaging has allowed us to see the whole anterior segment as a unit. All of this is allowing us to learn much more about the mechanisms and causes of this condition."

Dr. Friedman observes that one of the benefits of imaging technology is that it can often simplify complicated information through algorithmic analyses. "For example," he says, "we have a manuscript in submission describing software that can take a single slice of an anterior segment OCT and say with 95-percent accuracy whether if you do gonioscopy you'll find the angle to be open or closed. That's with minimal physician input. The only thing you need to do to make the algorithm work is identify the scleral spur in the angle images. Of course, that identification can be an issue with some technologies—you can't always identify the scleral spur in an image. But tests of this algorithm done in two populations found that it was very accurate. We hope that at some point this will lead to a Star Trek-style device that you can simply place over the eye; it will tell you whether the angle is open or closed. I think that's where we're headed."

Despite his optimism, Dr. Friedman notes that use of imaging technology currently has limitations. "Is there information in these scans? Certainly," he says. "Do we have enough data on which to base clinical recommendations from various tests like these? I don't think so, although we're working in that direction. Just because you have the technology, it doesn't necessarily mean that you're going to do better applying it in the clinic."

Dr. Lin notes that OCT technology provides a more objective evaluation of the angle. "In a way, it's a verification of my gonioscopy," he says. "I'd say that most doctors don't use it for assessing the angle, probably because the stand-alone device that's specific for that purpose—the Visante OCT from Zeiss—is quite expensive. But in recent years several manufacturers have incorporated anterior segment imaging into their standard Fourier domain OCTs, which should make this more accessible to clinicians.

"It's arguable that imaging may be better than gonioscopy for determining how narrow an angle is," he continues. "Gonioscopy is very subjective and dependent upon training; it's variable from doctor to doctor. We have debates at meetings sometimes about whether imaging or gonioscopy is better, and some people have decided that imaging is the better way to go. For one thing, it doesn't involve touching the patient and potentially altering the anatomy. It's reproducible and quantifiable. It's also easier for the patient; the patient just sits there and gets a picture of his or her eye."

Dr. Lin notes that one of the most useful pieces of information obtainable with OCT is lens vault. "This is the factor that seems to be mathematically most correlated with angle closure," he says. "A group in Singapore looked at all the factors associated with angle width in their population. They found that, statistically, lens vault was the most closely correlated, even taking into consideration other factors

such as iris thickness and area and anterior chamber width.[1] Of course, you may be able to tell that lens vault is significant just by looking at the patient or by doing gonioscopy, but AS-OCT allows you to quantify that.

"Despite the advantages of OCT, many doctors still see gonioscopy as the gold standard," he adds. "You could argue that it has some advantages beyond the cost issue, some of which are related to the disadvantages. For example, when doing gonioscopy you can end up pushing on the eye and altering the anatomy. But that can also be used as an advantage, to see whether the eye has peripheral anterior synechiae, for example. Being able to do that can lead to a different classification of the patient and different management."

A Question of Intervention

"For most patients with angle closure, it's a slow disease process," says Dr. Liebmann. "At first the iris intermittently touches the trabecular meshwork; then you see more chronic apposition, pigment deposition on the trabecular meshwork and synechiae formation. Only then does the pressure start to rise. As far as an acute attack, there's no way of determining who's going to have one or when it will occur.

"Once the pressure rises in angle closure, the cat's out of the bag and the meshwork has been significantly damaged," he notes. "The pressure usually rises slowly over time in most patients who go on to develop chronic angle-closure glaucoma, but in some patients it fluctuates with the position of the iris. Widely fluctuating IOP in a patient previously thought to have open-angle glaucoma could be indicative of an angle-closure process.

"For me, the time to intervene is when the iris is touching the trabecular meshwork," he continues. "Once angle closure is identified we recommend laser iridotomy to relieve the pupillary block component of the disease process for all those patients, regardless of whether they have a secondary cause of angle closure. On the other hand, we don't usually intervene when the angle is narrow but open. In rare cases there are patients in whom we don't see apposition, but the angle is slit-like and other conditions are present that might require frequent dilation (e.g., diabetes or macular degeneration); laser iridotomy might be indicated in selected cases."

Dr. Friedman is a lead investigator on a trial taking place in China to determine whether or not iridotomy is beneficial for people who are anatomically narrow but have no scarring and have normal pressures. "We've randomized treatment to one eye, leaving the other eye untreated in more than 900 people who look suspicious," he explains. "There's another similar project in Singapore that I'm co-investigator on; that one involves a smaller number of subjects, but has been going on a little longer. The findings produced by these studies will be very important for public health purposes. The question we hope to answer is: Should we be doing an iridotomy—something potentially harmful—in all of these people, when nearly 20 percent of all people over the age of 50 in China have this finding? That's an enormous number of people."

Iridoplasty is often chosen as a follow-up procedure when iridotomy has failed to produce results, but Dr. Lin isn't convinced that it's effective. "I think the jury is still out about iridoplasty," he says. "We still need a good prospective study so see whether it's helpful. The studies I've seen to date haven't really answered that question."

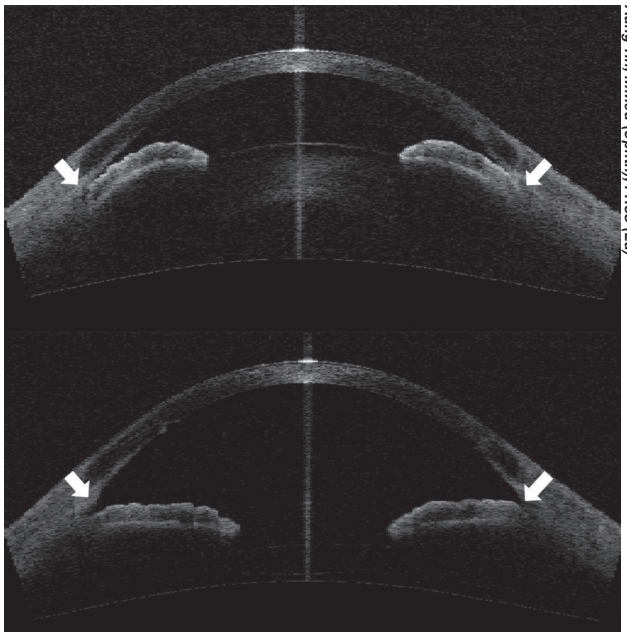
The Cataract Surgery Option

"After you do an iridotomy, about 30 percent of eyes still have narrow or closed angles," says Dr. Lin. "The

primary reason, in several studies, has been plateau iris; this acts as a secondary mechanism keeping the angle narrow or closed. On the other hand, recent studies have shown that even in people with plateau iris, everybody opened up after cataract surgery.[2,3] Therefore you'd surmise that cataract surgery would improve eye pressure and help prevent angle-closure glaucoma in these patients.

"Whether to do cataract surgery as the primary surgery for people who have primary angle-closure glaucoma is a hot-button issue," he notes. "A few years ago we published a paper in which we looked at nonglaucomatous patients who had cataract surgery.[4] We found that the amount the angle opened up correlated proportionally to the amount that the eye pressure went down. That suggests that the main mechanism by which cataract surgery lowers eye pressure is allowing the angle to open up, which makes sense.

"In fact, we recently submitted a paper on a case series of clear lens extractions for angle-closure glaucoma," he continues. "We had five angle-closure cases at our county hospital where the pressures were high and the patients were on maximum medications; if left untreated they would almost certainly have needed glaucoma surgery. A trabeculectomy would have carried a high risk of complications, so we decided to proceed with clear lens extraction. Four of the five cases improved; one remained unchanged. That would seem to suggest that this is a reasonable alternative for treating angle-closure glaucoma, especially in comparison to a significant glaucoma surgery that has a high chance of failure."



Aung Tin, MMed (Ophth), FRCS (Ed)

Cataract surgery opens closed angles, although that will not necessarily lower the intraocular pressure. Above: Iris position changes dramatically from preop (top) to postop (bottom).

"There's good evidence that removing the lens causes the intraocular pressure to drop in some people with angle closure," notes Dr. Friedman. "It may be that the people that have lens vault as a dominant factor are the ones who need cataract surgery to help get the pressure down. Those who have cataract surgery and don't have much eye pressure lowering may have other angle-closure mechanisms having more to do with the location of the ciliary body or the configuration of the iris."

Dr. Friedman feels there may be a bit of excessive optimism about using cataract surgery to treat angle-closure glaucoma. "The lens is clearly a very important part of angle closure, and if you remove the lens, you eliminate angle closure," he says. "However, that's not the same as curing the glaucoma.

"In individuals who have had chronic angle closure longer-term, taking out the lens doesn't always lower the pressure that much," he continues. "It does seem to work if you start with a higher pressure, or if you've had an acute attack recently, in which case it's definitely indicated and is beneficial. But the trials that have looked at more chronic forms of glaucoma find that just removing the lens provides only some benefit; it's not the be-all and end-all at this point. I think there may still be room for additional therapies at the time of cataract surgery, especially as we get better at some of the newer outflow procedures."

Dr. Friedman notes that there's also the issue of risk. "Cataract surgery is effective and generally safe, but it's not perfect," he points out. "A small number of people get endophthalmitis and lose vision, and 1 or 2 percent have significant negative outcomes like macular edema or retinal detachment after cataract surgery. So if you're considering applying this very widely and very early, you need to be a little cautious. In fact, there's a very large clinical trial called the EAGLE trial being done, centered in Aberdeen, Scotland. They're taking out clear lenses in people around the world who don't have much cataract, to see whether that's an effective way to treat angle-closure glaucoma."

New Thoughts on Causes

In recent years, several new observations have been made regarding angle closure that may eventually help explain why some patients have the problem and others don't. For example, work done by Harry Quigley, MD, and colleagues, including Dr. Friedman, has shown that the iris is a sponge, rapidly losing half its volume during dilation, thus avoiding "bunching up" and closing the angle. Eyes with angle closure, however, lose less volume when dilating than eyes with-

out angle closure.[5,6]

"I definitely think that there are dynamic factors that play a role in who does and doesn't have angle-closure problems," says Dr. Friedman. "Some of my earliest research showed differences in the pupil's response to light and dark. For example, in eyes with closed angles the pupils open less in response to lower light or pilocarpine. So there's something about the physiology of the structure in the front of the eye in these individuals that alters that responsiveness.

"There's no question that the iris has to lose some fluid when it jams itself into the angle during dilation," he continues. "One of the hypotheses about this is that the iris in narrow-angle patients may have a different conduction of fluid in and out, and there's some very good research showing that this is the case. So I think the sponge theory is legitimate, although we need a little more basic data to show exactly how that works.

"Unfortunately, for now, the static aspects of angle closure are easier to quickly capture, analyze and think about," he adds. "And even if the iris behavior does differ in these patients, it's not clear whether knowing that will help us manage the disease."

Another avenue of exploration is centering around the discovery that choroidal expansion might be a factor in angle closure; choroidal effusion, measured by UBM, was found in 58 percent of eyes that underwent an acute angle-closure attack; 23 percent of fellow eyes; 20 percent of eyes with primary angle closure but no acute attack; and 1 percent of eyes with open-angle glaucoma.[7]

"It's an interesting idea and it makes a lot of sense that it could be part of the causal mechanism," says Dr. Friedman. "Harry Quigley has done a body of research that supports this, and given that imaging the choroid is not easy, the fact that he was able to show differences means that they're likely to be real. The challenge will be figuring out how to use that information clinically."

"I think these ideas that are sort of outside the box are great," says Dr. Lin. "They could very well be correct. However, it's too early for this to be of much use in the clinic. To measure these things will require advanced technology, and even if we measure the iris or choroid, how will it help us directly diagnose angle-closure glaucoma? We'll still need to do gonioscopy and look at the angle. I suspect it will end up being like corneal thickness. Corneal thickness doesn't tell you if a patient has glaucoma, but if a

patient does have a thin cornea, your ears perk up a little bit and you look a little more carefully."

Angle Closure in the Clinic

Based on their experience, Drs. Friedman, Liebmann and Lin offer these suggestions:

• ***Always consider the possibility of angle closure.*** "I think there's a lot more angle closure in our clinics than people realize," says Dr. Friedman. "So the first step is to always look for it as a possibility. If the patient flow in your clinic doesn't permit everybody to be gonioscoped, look at the limbal anterior chamber depth, because that's a very easy way to tell that an angle is likely to be narrow. If you look at the limbus and the iris is very close to or touching the cornea, you know there's not a lot of angle opening. At a minimum, everybody should be doing that."

Dr. Liebmann agrees. "We believe there's an underdiagnosis of angle-closure glaucoma," he says. "That's unfortunate because it's better to intervene earlier rather than later. If you can intervene earlier you can keep people off chronic medical therapy, reducing costs to the medical system and avoiding issues of patient adherence to treatment. We'd rather prevent this disease than have to treat it."

• ***Be aware of demographic and biometric risk factors.*** "For example, angle closure is more common in smaller eyes," says Dr. Liebmann. "Patients with hyperopia are at greater risk—and the greater the hyperopia, the greater the risk. Some ethnic groups are at greater risk, including people of Chinese ancestry and people of African descent."

• ***Learn to be facile with the gonioprism.*** "Once you do that, you can perform gonioscopy in 15 seconds," notes Dr. Liebmann. "It's not a difficult thing to do."

• ***Don't just do an iridotomy and assume all is well.*** "In the majority of cases, the first line of treatment is to do a peripheral iridotomy, but it's crucial to reassess these patients afterwards and see whether the angle is improved," Dr. Lin points out. "If it isn't, you have to think about what else you might do, and follow them closely. It's true that many of these patients get relief after having a patent iridotomy, but almost 30 percent of them are still narrow afterwards. That's almost a third who need to be reassessed."

> *"I think there's a lot more angle closure in our clinics than people realize. So the first step is to always look for it as a possibility."*
> *— David Friedman, MD*

• ***If the patient has had an acute attack, perform cataract surgery.*** "The vast majority of patients who have had an acute attack of angle closure will benefit from cataract surgery," notes Dr. Friedman. "It's probably a good idea to do this about a month after the attack. It will decrease the likelihood that the patient will go on to develop high eye pressures and glaucoma."

• ***Avoid trabeculectomy in these patients.*** "Trabeculectomy is fairly risky in angle-closure patients," says Dr. Friedman. "If you don't need to achieve too low a pressure, taking out the lens is a reasonable first option for many patients."

Keeping It Simple

"Although some of the research is complex and there's a lot we don't yet understand, I like to keep it simple when I'm practicing," says Dr. Liebmann. "Keeping it simple means identifying that the angle is closed and then identifying the cause of the block.

"First, I determine whether the iris is touching the trabecular meshwork," he continues. "Second, I determine the level of the block. Most often it's pupillary block, so I perform laser iridotomy. Once you've done that, you've taken care of the vast majority of the cases; a patient only becomes challenging and complex when the angle remains closed. For the most part, you don't have to get into the other mechanisms—the plateau iris, the posterior segment ones.

"In most cases, once you've performed laser iridotomy, management is similar to open-angle glaucoma," he adds. "If the angle fails to open after iridotomy, other causes should be sought." REVIEW

Drs. Friedman and Lin have received non-financial research support from Zeiss via the loan of equipment, but have no financial connection to the company. Dr. Liebmann has no financial interest in any of the technologies discussed.

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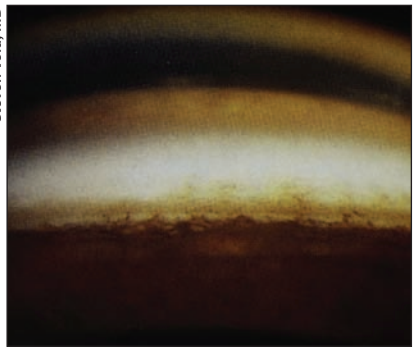
MIGS and the General Ophthalmologist

Walter Bethke, Managing Editor

What you need to know about the minimally invasive surgical options for glaucoma.

The advent of minimally invasive glaucoma surgery has the potential to shift a good portion of glaucoma management toward the side of the comprehensive ophthalmologist, since MIGS is often performed in conjunction with cataract surgery for mild to moderate glaucoma patients. However, surgeons have to weigh the pros and cons of the currently available MIGS procedures before they can decide if MIGS fits into the way they manage their patients. Here, experts familiar with MIGS procedures discuss what the comprehensive ophthalmologist needs to know about the procedures in general, and discuss possible impediments to widespread adoption of the procedures as they stand today.



Steven Vold, MD

Part of the learning curve for the iStent is knowing the anatomy of the angle, surgeons say.

Today's MIGS

For the purposes of this article, MIGS will be defined as a Food and Drug Administration-approved, minimally invasive, *ab interno* procedure that is performed through a small incision, usually corneal, that spares the conjunctiva. The procedure is aimed at decreasing intraocular pressure in mild to moderate glaucoma patients. Here are the general ophthalmologist's current MIGS options:

• ***iStent.*** The Glaukos iStent is the most recent addition to the minimally invasive armamentarium, having just been approved for use in the United States in 2012. It's an extremely small titanium device implanted into Schlemm's canal during cataract surgery in patients with open-angle glaucoma who could benefit from IOP lowering below that normally associated with cataract surgery. The iStent comes preloaded in an inserter.

The FDA trial of the iStent looked at the results from 116 patients receiving the device during cataract surgery vs. 123 undergoing cataract surgery alone. After 12 months, 68 percent of the iStent/cataract surgery group were at or below 21 mmHg without glaucoma medications, vs. 50 percent of the cataract surgery group. The difference

Preservative Toxicity Can Complicate Glaucoma Treatment

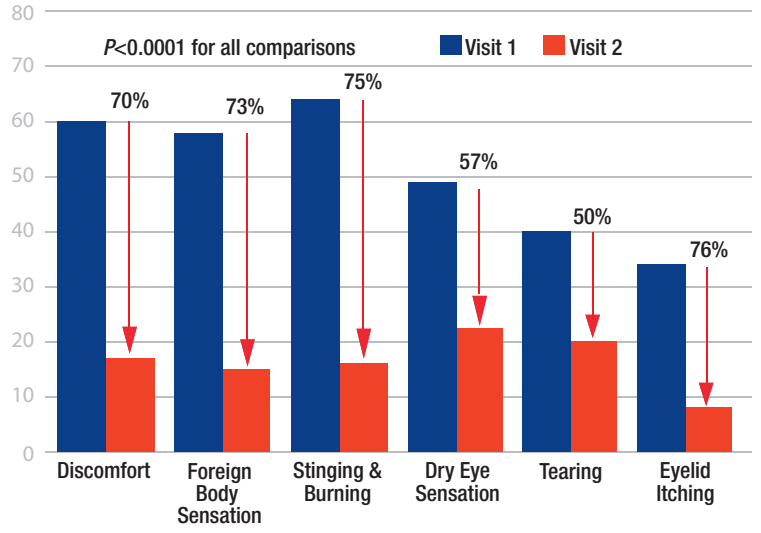
Preservative toxicity in glaucoma medications may complicate treatment. Eyes may present with subclinical fibroses due to the cumulative effect of years of dosing with multiple preserved glaucoma eyedrops.[1-3] Preservatives can break the tight junctions in the apical epithelial cells in the cornea, with some cytotoxic activity, and impact the barrier function in the cornea. As cells start to be lost from the apical cornea, the ability of the cornea to hold the tear film diminishes.[4] As the tear film becomes more unstable, the eye becomes dry and patients may complain of blurred and fluctuating vision.[5]

While some clinicians will treat OSD in glaucoma patients by adding steroids or other anti-inflammatories, an alternative approach is the "subtractive strategy"—to take the patient off the preserved medications that may further exacerbate OSD symptoms.

Preservative-free glaucoma treatment is an established option in Europe where preservative-free beta blockers have been available for many years. Large epidemiologic surveys in Europe have shown the significant impact ($P<0.0001$) of switching to a preservative-free medication, or reducing the preservative load by switching out just the preserved beta blocker in patients on multiple IOP-lowering therapies.[6] With the recent availability of new preservative-free glaucoma medications in the U.S., physicians have the opportunity to prescribe completely preservative-free medication regimens.

Preservative-free TIMOPTIC® (timolol maleate 0.5%) in OCUDOSE® (dispenser) is indicated in the treatment of elevated intraocular pressure in patients with glaucoma.

Reduction of symptoms in a switch from preserved to preservative-free timolol



Reports of symptoms of surveyed patients on multiple preserved medications at visit 1, and after having a switch to a preservative-free timolol at visit 2, thereby reducing the number of preserved glaucoma drops (n=981)[6]

Preservative-free TIMOPTIC® in OCUDOSE® may be used when a patient is sensitive to the preservative in Timoptic (timolol maleate ophthalmic solution), benzalkonium chloride, or when use of a preservative-free topical medication is advisable.[7]

IMPORTANT SAFETY INFORMATION
TIMOPTIC® in OCUDOSE® is contraindicated in patients with: bronchial asthma; a history of bronchial asthma; severe chronic obstructive pulmonary disease; sinus bradycardia; second or third degree atrioventricular block; overt cardiac failure; cardiogenic shock; hypersensitivity to any component of this product. This drug is absorbed systemically. The same adverse reactions found with systemic administration of beta-adrenergic blocking agents may occur with topical administration. Severe respiratory or cardiac reactions, including death, have been reported following systemic or ophthalmic administration of timolol maleate. TIMOPTIC® in OCUDOSE® should be used with caution in patients with cerebrovascular insufficiency. The most frequently reported adverse experiences have been burning and stinging upon instillation.

In patients being considered for add-on therapy after monotherapy with a prostaglandin analog, it makes sense to avoid adding to the preservative load. Preservative-free TIMOPTIC® in OCUDOSE® provides an option for adjunctive therapy when use of a preservative-free topical medication is advisable. When paired with a preservative-free prostaglandin, TIMOPTIC® in OCUDOSE® can be part of a truly preservative-free medication regimen.

Please see reverse side for the Brief Summary of full Prescribing Information for TIMOPTIC® in OCUDOSE®.

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Brief Summary of Prescribing Information

ATON PHARMA

PRESERVATIVE-FREE STERILE OPHTHALMIC SOLUTION
in a Sterile Ophthalmic Unit Dose Dispenser

TIMOPTIC®
0.25% AND 0.5%
(TIMOLOL MALEATE OPHTHALMIC SOLUTION)
in OCUDOSE®
(DISPENSER)

CONTRAINDICATIONS

Preservative-free TIMOPTIC in OCUDOSE is contraindicated in patients with (1) bronchial asthma; (2) a history of bronchial asthma; (3) severe chronic obstructive pulmonary disease (see WARNINGS); (4) sinus bradycardia; (5) second or third degree atrioventricular block; (6) overt cardiac failure (see WARNINGS); (7) cardiogenic shock; or (8) hypersensitivity to any component of this product.

WARNINGS

As with many topically applied ophthalmic drugs, this drug is absorbed systemically.

The same adverse reactions found with systemic administration of beta-adrenergic blocking agents may occur with topical administration. For example, severe respiratory reactions and cardiac reactions, including death due to bronchospasm in patients with asthma, and rarely death in association with cardiac failure, have been reported following systemic or ophthalmic administration of timolol maleate (see CONTRAINDICATIONS).

Cardiac Failure

Sympathetic stimulation may be essential for support of the circulation in individuals with diminished myocardial contractility, and its inhibition by beta-adrenergic receptor blockade may precipitate more severe failure.

In Patients Without a History of Cardiac Failure continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of cardiac failure, Preservative-free TIMOPTIC in OCUDOSE should be discontinued.

Obstructive Pulmonary Disease

Patients with chronic obstructive pulmonary disease (e.g., chronic bronchitis, emphysema) of mild or moderate severity, bronchospastic disease, or a history of bronchospastic disease (other than bronchial asthma or a history of bronchial asthma, in which TIMOPTIC in OCUDOSE is contraindicated [see CONTRAINDICATIONS]) should, in general, not receive beta-blockers, including Preservative-free TIMOPTIC in OCUDOSE.

Major Surgery

The necessity or desirability of withdrawal of beta-adrenergic blocking agents prior to major surgery is controversial. Beta-adrenergic receptor blockade impairs the ability of the heart to respond to beta-adrenergically mediated reflex stimuli. This may augment the risk of general anesthesia in surgical procedures. Some patients receiving beta-adrenergic receptor blocking agents have experienced protracted severe hypotension during anesthesia. Difficulty in restarting and maintaining the heartbeat has also been reported. For these reasons, in patients undergoing elective surgery, some authorities recommend gradual withdrawal of beta-adrenergic receptor blocking agents.

If necessary during surgery, the effects of beta-adrenergic blocking agents may be reversed by sufficient doses of adrenergic agonists.

Diabetes Mellitus

Beta-adrenergic blocking agents should be administered with caution in patients subject to spontaneous hypoglycemia or to diabetic patients (especially those with labile diabetes) who are receiving insulin or oral hypoglycemic agents. Beta-adrenergic receptor blocking agents may mask the signs and symptoms of acute hypoglycemia.

Thyrotoxicosis

Beta-adrenergic blocking agents may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta-adrenergic blocking agents that might precipitate a thyroid storm.

PRECAUTIONS

General

Because of potential effects of beta-adrenergic blocking agents on blood pressure and pulse, these agents should be used with caution in patients with cerebrovascular insufficiency. If signs or symptoms suggesting reduced cerebral blood flow develop following initiation of therapy with Preservative-free TIMOPTIC in OCUDOSE, alternative therapy should be considered.

Choroidal detachment after filtration procedures has been reported with the administration of aqueous suppressant therapy (e.g. timolol).

Angle-closure glaucoma: In patients with angle-closure glaucoma, the immediate objective of treatment is to reopen the angle. This requires constricting the pupil. Timolol maleate has little or no effect on the pupil. TIMOPTIC in OCUDOSE should not be used alone in the treatment of angle-closure glaucoma.

Anaphylaxis: While taking beta-blockers, patients with a history of atopy or a history of severe anaphylactic reactions to a variety of allergens may be more reactive to repeated accidental, diagnostic, or therapeutic challenge with such allergens. Such patients may be unresponsive to the usual doses of epinephrine used to treat anaphylactic reactions.

Muscle Weakness: Beta-adrenergic blockade has been reported to potentiate muscle weakness consistent with certain myasthenic symptoms (e.g., diplopia, ptosis, and generalized weakness). Timolol has been reported rarely to increase muscle weakness in some patients with myasthenia gravis or myasthenic symptoms.

Information for Patients

Patients should be instructed about the use of Preservative-free TIMOPTIC in OCUDOSE.

Since sterility cannot be maintained after the individual unit is opened, patients should be instructed to use the product immediately after opening, and to discard the individual unit and any remaining contents immediately after use.

Patients with bronchial asthma, a history of bronchial asthma, severe chronic obstructive pulmonary disease, sinus bradycardia, second or third degree atrioventricular block, or cardiac failure should be advised not to take this product. (See CONTRAINDICATIONS.)

Drug Interactions

Although TIMOPTIC (timolol maleate ophthalmic solution) used alone has little or no effect on pupil size, mydriasis resulting from concomitant therapy with TIMOPTIC (timolol maleate ophthalmic solution) and epinephrine has been reported occasionally.

Beta-adrenergic blocking agents: Patients who are receiving a beta-adrenergic blocking agent orally and Preservative-free TIMOPTIC in OCUDOSE should be observed for potential additive effects of betablockade, both systemic and on intraocular pressure. The concomitant use of two topical beta-adrenergic blocking agents is not recommended.

Calcium antagonists: Caution should be used in the coadministration of beta-adrenergic blocking agents, such as Preservative-free TIMOPTIC in OCUDOSE, and oral or intravenous calcium antagonists, because of possible atrioventricular conduction disturbances, left ventricular failure, and hypotension. In patients with impaired cardiac function, coadministration should be avoided.

Catecholamine-depleting drugs: Close observation of the patient is recommended when a beta blocker is administered to patients receiving catecholamine-depleting drugs such as reserpine, because of possible additive effects and the production of hypotension and/or marked bradycardia, which may result in vertigo, syncope, or postural hypotension.

Digitalis and calcium antagonists: The concomitant use of beta-adrenergic blocking agents with digitalis and calcium antagonists may have additive effects in prolonging atrioventricular conduction time.

CYP2D6 inhibitors: Potentiated systemic beta-blockade (e.g., decreased heart rate, depression) has been reported during combined treatment with CYP2D6 inhibitors (e.g., quinidine, SSRIs) and timolol.

Clonidine: Oral beta-adrenergic blocking agents may exacerbate the rebound hypertension which can follow the withdrawal of clonidine. There have been no reports of exacerbation of rebound hypertension with ophthalmic timolol maleate.

Injectable epinephrine: (See PRECAUTIONS, General, Anaphylaxis)

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a two-year oral study of timolol maleate administered orally to rats, there was a statistically significant increase in the incidence of adrenal pheochromocytomas in male rats administered 300 mg/kg/day (approximately 42,000 times the systemic exposure following the maximum recommended human ophthalmic dose). Similar differences were not observed in rats administered oral doses equivalent to approximately 14,000 times the maximum recommended human ophthalmic dose.

In a lifetime oral study in mice, there were statistically significant increases in the incidence of benign and malignant pulmonary tumors, benign uterine polyps and mammary adenocarcinomas in female mice at 500 mg/kg/day (approximately 71,000 times the systemic exposure following the maximum recommended human ophthalmic dose), but not at 5 or 50 mg/kg/day (approximately 700 or 7,000 times, respectively, the systemic exposure following the maximum recommended human ophthalmic dose). In a subsequent study in female mice, in which postmortem examinations were limited to the uterus and the lungs, a statistically significant increase in the incidence of pulmonary tumors was again observed at 500 mg/kg/day.

The increased occurrence of mammary adenocarcinomas was associated with elevations in serum prolactin which occurred in female mice administered oral timolol at 500 mg/kg/day, but not at doses of 5 or 50 mg/kg/day. An increased incidence of mammary adenocarcinomas in rodents has been associated with administration of several other therapeutic agents that elevate serum prolactin, but no correlation between serum prolactin levels and mammary tumors has been established in humans. Furthermore, in adult human female subjects who received oral dosages of up to 60 mg of timolol maleate (the maximum recommended human oral dosage), there were no clinically meaningful changes in serum prolactin.

Timolol maleate was devoid of mutagenic potential when tested *in vivo* (mouse) in the micronucleus test and cytogenetic assay (doses up to 800 mg/kg) and *in vitro* in a neoplastic cell transformation assay (up to 100 mcg/mL). In Ames tests the highest concentrations of timolol employed, 5,000 or 10,000 mcg/plate, were associated with statistically significant elevations of revertants observed with tester strain TA100 (in seven replicate assays), but not in the remaining three strains. In the assays with tester strain TA100, no consistent dose response relationship was observed, and the ratio of test to control revertants did not reach 2. A ratio of 2 is usually considered the criterion for a positive Ames test.

Reproduction and fertility studies in rats demonstrated no adverse effect on male or female fertility at doses up to 21,000 times the systemic exposure following the maximum recommended human ophthalmic dose.

Pregnancy: Teratogenic Effects — Pregnancy Category C.: Teratogenicity studies with timolol in mice, rats and rabbits at oral doses up to 50 mg/kg/day (7,000 times the systemic exposure following the maximum recommended human ophthalmic dose) demonstrated no evidence of fetal malformations. Although delayed fetal ossification was observed at this dose in rats, there were no adverse effects on postnatal development of offspring. Doses of 1000 mg/kg/day (142,000 times the systemic exposure following the maximum recommended human ophthalmic dose) were maternotoxic in mice and resulted in an increased number of fetal resorptions. Increased fetal resorptions were also seen in rabbits at doses of 14,000 times the systemic exposure following the maximum recommended human ophthalmic dose, in this case without apparent maternotoxicity.

There are no adequate and well-controlled studies in pregnant women. Preservative-free TIMOPTIC in OCUDOSE should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Timolol maleate has been detected in human milk following oral and ophthalmic drug administration. Because of the potential for serious adverse reactions from timolol in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

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

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

ADVERSE REACTIONS

The most frequently reported adverse experiences have been burning and stinging upon instillation (approximately one in eight patients).

The following additional adverse experiences have been reported less frequently with ocular administration of this or other timolol maleate formulations:

BODY AS A WHOLE: Headache, asthenia/fatigue, and chest pain.

CARDIOVASCULAR: Bradycardia, arrhythmia, hypotension, hypertension, syncope, heart block, cerebral vascular accident, cerebral ischemia, cardiac failure, worsening of angina pectoris, palpitation, cardiac arrest, pulmonary edema, edema, claudication, Raynaud's phenomenon, and cold hands and feet.

DIGESTIVE: Nausea, diarrhea, dyspepsia, anorexia, and dry mouth.

IMMUNOLOGIC: Systemic lupus erythematosus.

NERVOUS SYSTEM/PSYCHIATRIC: Dizziness, increase in signs and symptoms of myasthenia gravis, paresthesia, somnolence, insomnia, nightmares, behavioral changes and psychic disturbances including depression, confusion, hallucinations, anxiety, disorientation, nervousness, and memory loss.

SKIN: Alopecia and psoriasiform rash or exacerbation of psoriasis.

HYPERSENSITIVITY: Signs and symptoms of systemic allergic reactions including anaphylaxis, angioedema, urticaria, and localized and generalized rash.

RESPIRATORY: Bronchospasm (predominantly in patients with preexisting bronchospastic disease), respiratory failure, dyspnea, nasal congestion, cough and upper respiratory infections.

ENDOCRINE: Masked symptoms of hypoglycemia in diabetic patients (see WARNINGS).

SPECIAL SENSES: Signs and symptoms of ocular irritation including conjunctivitis, blepharitis, keratitis, ocular pain, discharge (e.g., crusting), foreign body sensation, itching and tearing, and dry eyes; ptosis; decreased corneal sensitivity; cystoid macular edema; visual disturbances including refractive changes and diplopia; pseudopemphigoid; choroidal detachment following filtration surgery (see PRECAUTIONS, General); and tinnitus.

UROGENITAL: Retroperitoneal fibrosis, decreased libido, impotence, and Peyronie's disease.

The following additional adverse effects have been reported in clinical experience with ORAL timolol maleate or other ORAL beta blocking agents, and may be considered potential effects of ophthalmic timolol maleate: *Allergic:* Erythematous rash, fever combined with aching and sore throat, laryngospasm with respiratory distress; *Body as a Whole:* Extremity pain, decreased exercise tolerance, weight loss; *Cardiovascular:* Worsening of arterial insufficiency, vasodilatation; *Digestive:* Gastrointestinal pain, hepatomegaly, vomiting, mesenteric arterial thrombosis, ischemic colitis; *Hematologic:* Non-thrombocytopenic purpura; thrombocytopenic purpura; agranulocytosis; *Endocrine:* Hyperglycemia, hypoglycemia; *Skin:* Pruritus, skin irritation, increased pigmentation, sweating; *Musculoskeletal:* Arthralgia; *Nervous System/Psychiatric:* Vertigo, local weakness, diminished concentration, reversible mental depression progressing to catatonia, an acute reversible syndrome characterized by disorientation for time and place, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics; *Respiratory:* Rales, bronchial obstruction; *Urogenital:* Urination difficulties.

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was statistically significant (p=0.004).

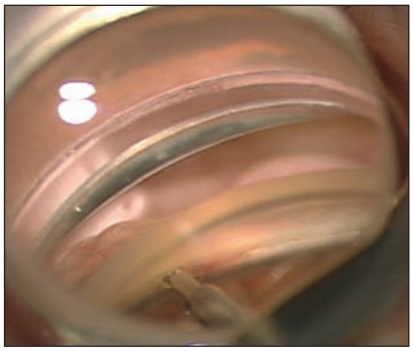
"Work by Richard Lindstrom and Tom Samuelson showed that cataract surgery alone could decrease IOP by at least a couple of points," says Jason Bacharach, MD, director of glaucoma clinics at Cal Pacific Medical Center in San Francisco. "So, with the addition of a MIGS procedure, it might be possible to expand the number of patients that a cataract surgeon could treat in his practice by being able to control the IOP at the same time he's taking out the cataract, as well as potentially reduce the number of medications the patient is using postop."

• ***Trabectome.*** The NeoMedix Trabectome uses bipolar cautery on a disposable handpiece, inserted into the anterior chamber through a clear corneal incision, to ablate a certain number of clock hours of trabecular meshwork to increase aqueous outflow. The handpiece is equipped with irrigation and aspiration ports.

Brian Francis, MD, associate professor of ophthalmology at the University of California's Keck School of Medicine/Doheny Eye Institute, says that the pressure-lowering potential of the Trabectome depends on where the patient starts. "It will generally get the patient into the mid-teens," he avers. "If the patient is at 30 mmHg preop, for example, he will get to the mid-teens. If he's already at 16 mmHg but is on two or three medications, he may stay at 16 but be able to get off of one or more of the medications."

• ***Endocyclophotocoagulation***. The Endo Optiks ECP system uses a laser and an endoscopic viewing system, inserted through either a corneal or limbal incision when combined with cataract surgery, or a limbal or pars plana incision when done alone, to ablate the ciliary processes and reduce aqueous production.

In a retrospective study, researchers in the United Kingdom reviewed 58 cases of ECP combined with cataract surgery that were followed for two years. They report that the average preop IOP of 21.54 mmHg was reduced to 14.44 mmHg at two years. The mean decrease from baseline to 18 and 24 months was 7.1 mmHg, and there was a statistically significant decrease in IOP at all time points.[1]



The Trabectome goes through a clear corneal incision and uses bipolar cautery to open up parts of the trabecular meshwork.

Dr. Francis says one of the benefits of ECP is flexibility. "For Trabectome and iStent, you need to have an open angle, but since ECP isn't trying to enhance aqueous outflow, you're not concerned whether the angle is closed or not," he says.

Complications

One of the purported strong suits of MIGS procedures is their safety. Here's what surgeons have to say about adverse events and how to avoid them.

• ***iStent.*** In 160 eyes in the FDA study (112 from the randomized and 48 from the non-randomized treatment groups), there were 23 intraoperative complications related to implanting the stent, the most frequent of which was touching the iris with the device (11 eyes, 7 percent), failure to implant (three eyes, 2 percent), contacting the endothelium (two eyes, 1 percent) and stent malposition (two eyes, 1 percent). Postop, there were 12 cases of adverse events related to the stent, composed of seven cases of stent obstruction and five of stent malposition.

To prevent failure to implant the stent, Steven Vold, MD, of Fayetteville, Ark., says it's key to keep the tip of the inserter up. "When you take the insertion device out of the packaging, you have to keep the tip up," he says. "If you're not careful you can hit it on the edge of the packaging or something and you can knock it off. I'm also careful not to hit it on the corneal wound during insertion. Since these devices cost about $1,000 each, you don't want to drop one."

To avoid malpositioning, Dr. Vold says it's important to know the anatomy. "A lot of comprehensive ophthalmologists have never done angle surgery before and maybe don't do gonioscopy in the clinic, so they really need to practice their gonioscopy," he says. "They should do little things, like learn the corneal wedge technique to know which pigment line is the trabecular meshwork. Also, in the OR, for patients with a little shallower anterior chamber, removal of the cataract before you put the stent in can also be helpful because it'll deepen the anterior chamber." Postop, Dr. Vold says you have to look out for the infrequent case of the stent being occluded by iris or pigment. He adds that there have been anecdotal reports of stents coming loose in the anterior chamber, but he hasn't experienced that. "You just want to make sure they're in place," he says. "If I was concerned about it moving around the anterior chamber I'd just go in and remove it."

• ***Trabectome.*** The most common complication with Trabectome is hyphema, which occurred in about 78 percent of 304 patients in a prospective case series.[2] The hyphema resolved in a few days. Another study found delayed-onset hyphema in 12 of 262 cases (4.5 percent), that occurred at a median of 8.6 months postop. Most of these hyphemas resolved in one to two weeks.[3]

Dr. Francis says to avoid problems intraoperatively, it's important to always maintain a clear view. "You want

to place the handpiece where you have a clear view and not try to go off to the side where you're not sure that you're actually in Schlemm's canal," he says. "If you try to push the treatment to the extreme edges you could damage other ocular tissues."

• ***ECP.*** Fairfield, Conn., surgeon Robert Noecker says that IOP spikes are the most common adverse event after ECP, so he focuses on prophylaxis. "For all these patients, I'll give them Diamox and Alphagan postoperatively," he says. "The other risk that we worry about when doing ECP is ocular inflammation above that of regular cataract surgery. So I treat inflammation very aggressively. I give them intravenous steroids at the time of the procedure as well as intraocular steroids, and treat them topically a little more aggressively for the first week. If we get them through that first week, the inflammation won't be a problem."

Hurdles to Clear

While the current MIGS procedures offer the comprehensive ophthalmologist attractive, low-risk options, but there are still some obstacles to widespread adoption that may be keeping surgeons from committing to them.

Though the Trabectome and the ECP unit can be used by themselves or in conjunction with cataract surgery, they involve a capital expenditure for the equipment that surgeons may not be ready to make. "Any time you have a capital expenditure, that can be a roadblock," says Dr. Francis. "Surgeons also have to learn a new procedure, which takes an investment of time. If you're a busy cataract surgeon, learning something from scratch can be daunting. But I think it's important for surgeons to keep challenging themselves, pushing themselves."

Regarding Trabectome, on an operative report it is described as "trabeculotomy *ab interno*, but Kevin Corcoran, a consultant whose firm specializes in reimbursement and coding, notes that there is no CPT code with the description "trabeculotomy *ab interno*." He adds that a well-informed biller would probably choose CPT 65820 (goniotomy) although, he says, "It's apparent that some billers unfamiliar with Latin nomenclature choose CPT 65850 (trabeculotomy *ab externo*) instead." Alternately, he notes, some billers might choose a miscellaneous code (66999) although he says the administrative hassles with these codes are well-known. He adds that experts acknowledge that coding for this procedure is not crystal clear, and a new code for trabeculectomy *ab interno* is probably needed.

The obstacles to widespread iStent adoption revolve around its labeling and reimbursement, which limit surgeons from using it on a wider variety of patients. "Right now we only do it in Medicare patients," says Dr. Noecker. "Commercial payors and Medicaid have not been paying for it regularly, though once in a while we can get one through, so that restricts your patient population. The other thing is it's only indicated for the code 36511, primary open-angle glaucoma, so if the patient has any other type of glaucoma, it's not covered. And it can only be done in conjunction with cataract surgery; it won't get reimbursed as a stand-alone procedure. Also, it can only be for mild or moderate patients, so if a patient is coded as having severe glaucoma he doesn't qualify for payment. In addition, you can only put in one iStent."

In terms of payment, Mr. Corcoran says that the 2013 Medicare iStent reimbursement rate for the facility is $2,978 for a hospital outpatient department and $1,671 for an ambulatory surgery center. "The physician's reimbursement is variable because there's no specific value assigned to the CPT code 0191T in the Medicare Physician Fee Schedule," he says. "Various Medicare Administrative Contractors have allowed $252 to $1,235. The average is around $850."

Another issue, which Dr. Noecker alluded to, is the movement to use more than one iStent in the belief that this will yield better results. "I think many patients do need multiple stents, but right now it's only approved for one stent," says Dr. Vold. Also, the way reimbursement is structured, if a surgeon were to implant an additional stent, it would cost the facility more than it would make from reimbursement, so it wouldn't make sense to do it. As far as FDA is concerned, implantation of two or more iStents concurrently hasn't been studied in a clinical trial, so an investigational or experimental procedure is almost always not covered by Medicare or other third-party payers, though there are exceptions like Avastin for wet AMD. Mr. Corcoran says that, until more studies are completed, it's best to stick with the present directions for use.

With all the activity in the MIGS arena, Dr. Noecker thinks the comprehensive ophthalmologist will have no shortage of options. "Though the efficacy of MIGS procedures isn't as good as trabeculectomy, their risk is lower," he says, "I think this space will just continue to grow. And the nice thing about these procedures is you might still be able to do a trabeculectomy afterward." REVIEW

Dr. Noecker was an investigator for Glaukos' FDA study and is on the medical advisory board of Endo Optiks; Dr. Francis is a consultant to NeoMedix and is on the advisory board of Endo Optiks; and Dr. Bacharach is a consultant to Glaukos. Dr. Vold is a consultant to Glaukos and NeoMedix.

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2. Francis BA, Minckler D, Dustin L, et al. Combined cataract extraction and trabeculotomy by the internal approach for coexisting cataract and open-angle glaucoma: Initial results. J Cataract Refract Surg 2008;34:7:1096-103.
3. Ahuja Y, Malihi M, Sit AJ. Delayed-onset symptomatic hyphema after ab interno trabeculotomy surgery. Am J Ophthalmol 2012; 154:3:476-480.

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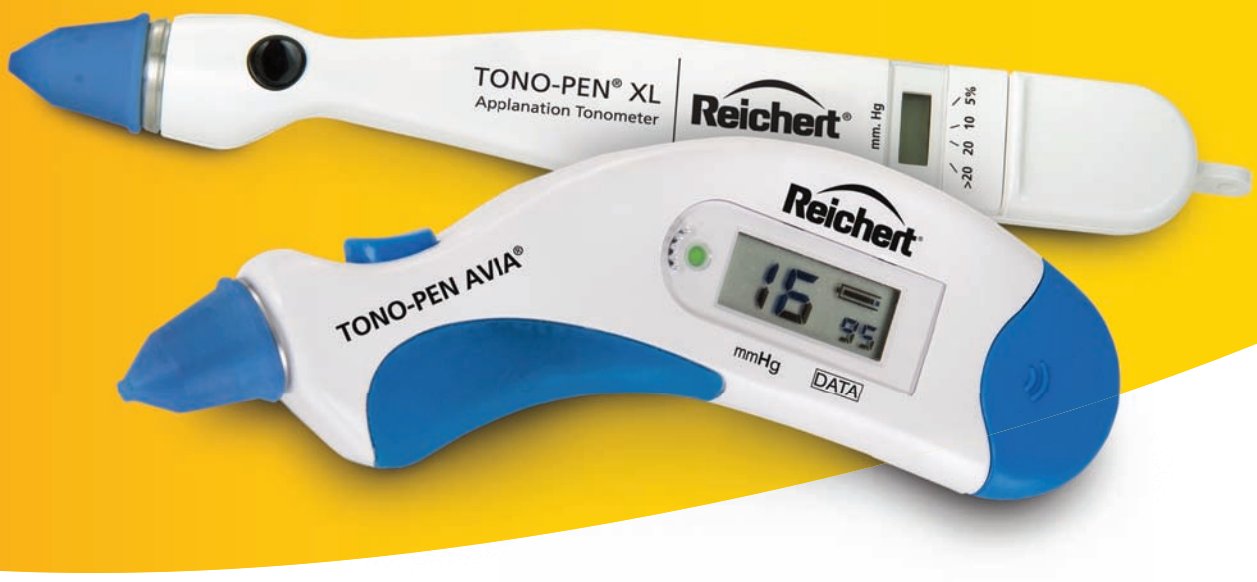

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Medical Management Continues Evolution

Michelle Stephenson, Contributing Editor

New topical glaucoma medications and delivery systems are on the horizon.

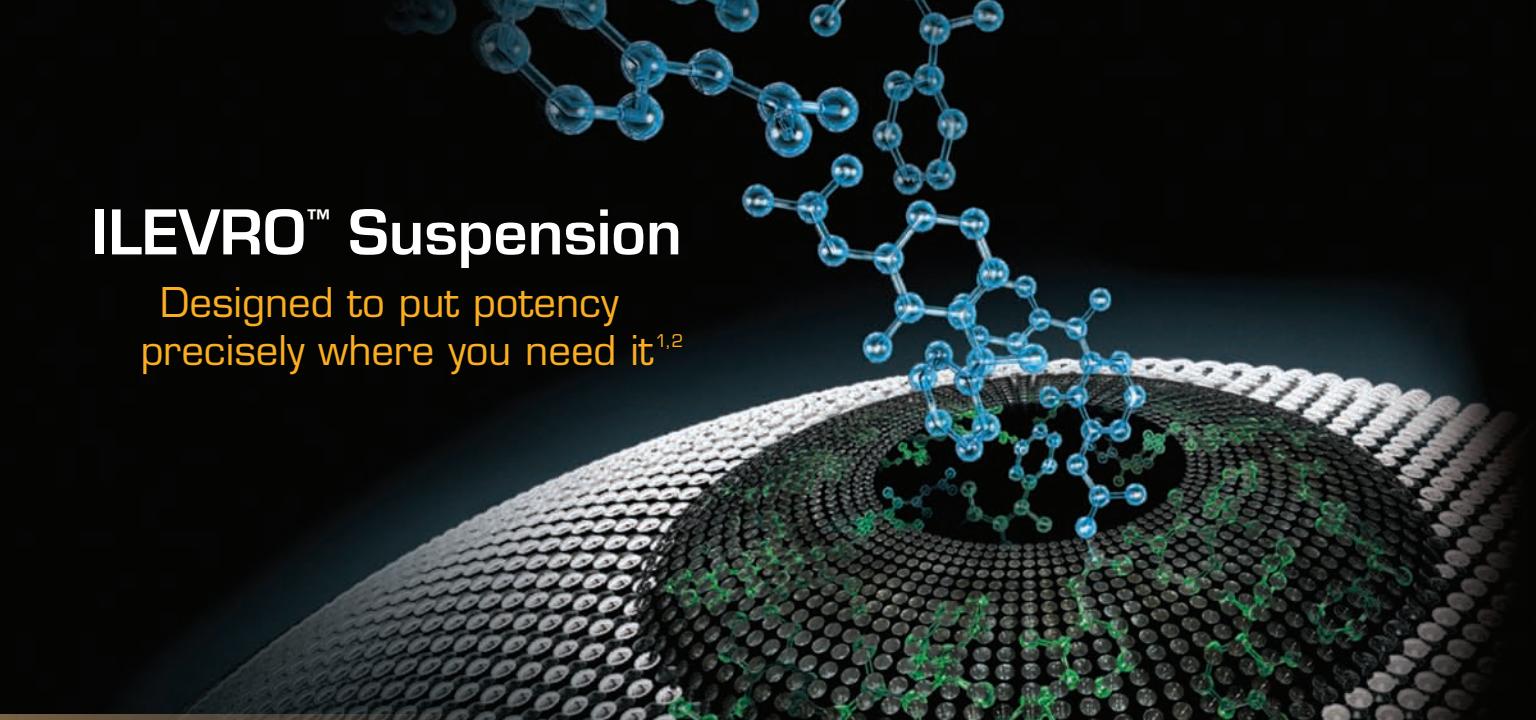
Despite being less than ideal, topical medications continue to be a mainstay in the treatment of glaucoma. The main issue with topical glaucoma medications is patient noncompliance. Some patients simply forget to instill the drops, while others are noncompliant because they cannot afford the medications.

"More than half of patients require more than one medication, so the biggest issue is compliance," says Michael Stiles, MD, who is in private practice in Overland Park, Kan. One way that drug companies have tried to address this issue is by developing combination medications. Unfortunately, combination medications also have downsides.

"There are pluses and minuses to the new combination medications that are coming out these days," says Mildred M.G. Olivier, MD, who is in private practice in Hoffman Estates, Ill. "They can help to facilitate patient compliance. However, when new medications are released, the cost needs to be factored into the equation, and that's a struggle for a lot of patients. The drugs may be on the market, but out of reach for many. Individuals with low income, or who have lost their jobs in this economy, may not always be able to afford the newest medication on the market due to increasingly high co-pays, being on fixed incomes, being a Medicare patient who has reached the 'donut hole,' or tiers established by the insurance companies."

A recent study conducted at the University of Toronto found that low-income patients are less likely to be compliant when using eye drops (*Leung V, et al. To Investigate the Relationship between Socio-demographic Factors and Non-persistence with Topical Glaucoma Medications. Abstract #99. Presented at the 23rd Annual Meeting of the American Glaucoma Society, 2013*). In this study, 61 patients completed a questionnaire about socioeconomic status. They answered questions about income and whether or not their basic needs for food, shelter and transportation were being met on a monthly basis. Pharmacy records were used to assess medication compliance. The researchers found that 54 percent of the glaucoma patients in the study were noncompliant, and those who reported not having their basic needs met were less likely to refill and take their medications.

Patients are driving the call for less expensive glaucoma drugs, and many are requesting generics. Unfortunately, generics often do not stand up well against their brand-name counterparts. "Often, patients have



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One drop should be applied once daily beginning 1 day prior to surgery through 14 days post-surgery, with an additional drop administered 30 to 120 minutes prior to surgery[3]

Use of ILEVRO™ Suspension more than 1 day prior to surgery or use beyond 14 days post-surgery may increase patient risk and severity of corneal adverse events[3]

INDICATIONS AND USAGE

ILEVRO™ Suspension is a nonsteroidal, anti-inflammatory prodrug indicated for the treatment of pain and inflammation associated with cataract surgery.

Dosage and Administration

One drop of ILEVRO™ Suspension should be applied to the affected eye one-time-daily beginning 1 day prior to cataract surgery, continued on the day of surgery and through the first 2 weeks of the postoperative period. An additional drop should be administered 30 to 120 minutes prior to surgery.

IMPORTANT SAFETY INFORMATION

Contraindications

ILEVRO™ Suspension is contraindicated in patients with previously demonstrated hypersensitivity to any of the ingredients in the formula or to other NSAIDs.

Warnings and Precautions

- Increased Bleeding Time – With some nonsteroidal anti-inflammatory drugs including ILEVRO™ Suspension there exists the potential for increased bleeding time. Ocularly applied nonsteroidal anti-inflammatory drugs may cause increased bleeding of ocular tissues (including hyphema) in conjunction with ocular surgery.
- Delayed Healing – Topical nonsteroidal anti-inflammatory drugs (NSAIDs) including ILEVRO™ Suspension may slow or delay healing. Concomitant use of topical NSAIDs and topical steroids may increase the potential for healing problems.
- Corneal Effects – Use of topical NSAIDs may result in keratitis. In some patients, continued use of topical NSAIDs may result in epithelial breakdown, corneal thinning, corneal erosion, corneal ulceration or corneal perforation. These events may be sight threatening. Patients with evidence of corneal epithelial breakdown should immediately discontinue use.

  Patients with complicated ocular surgeries, corneal denervation, corneal epithelial defects, diabetes mellitus, ocular surface diseases (e.g., dry eye syndrome), rheumatoid arthritis, or repeat ocular surgeries within a short period of time may be at increased risk for corneal adverse events which may become sight threatening. Topical NSAIDs should be used with caution in these patients.

  Use more than 1 day prior to surgery or use beyond 14 days post-surgery may increase patient risk and severity of corneal adverse events.
- Contact Lens Wear – ILEVRO™ Suspension should not be administered while using contact lenses.

Adverse Reactions

The most frequently reported ocular adverse reactions following cataract surgery occurring in approximately 5 to 10% of patients were capsular opacity, decreased visual acuity, foreign body sensation, increased intraocular pressure, and sticky sensation.

For additional information about ILEVRO™ Suspension, please refer to the brief summary of prescribing information on adjacent page.

References: 1. Ke T-L, Graff G, Spellman JM, Yanni JM. Nepafenac, a unique nonsteroidal prodrug with potential utility in the treatment of trauma-induced ocular inflammation, II: In vitro bioactivation and permeation of external ocular barriers. *Inflammation*. 2000;24(4):371-384. **2.** Data on file. **3.** ILEVRO™ Suspension package insert.

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BRIEF SUMMARY OF PRESCRIBING INFORMATION

INDICATIONS AND USAGE
ILEVRO™ Suspension is indicated for the treatment of pain and inflammation associated with cataract surgery.

DOSAGE AND ADMINISTRATION
Recommended Dosing
One drop of ILEVRO™ Suspension should be applied to the affected eye one-time-daily beginning 1 day prior to cataract surgery, continued on the day of surgery and through the first 2 weeks of the postoperative period. An additional drop should be administered 30 to 120 minutes prior to surgery.

Use with Other Topical Ophthalmic Medications
ILEVRO™ Suspension may be administered in conjunction with other topical ophthalmic medications such as beta-blockers, carbonic anhydrase inhibitors, alpha-agonists, cycloplegics, and mydriatics. If more than one topical ophthalmic medication is being used, the medicines must be administered at least 5 minutes apart.

CONTRAINDICATIONS
ILEVRO™ Suspension is contraindicated in patients with previously demonstrated hypersensitivity to any of the ingredients in the formula or to other NSAIDs.

WARNINGS AND PRECAUTIONS
Increased Bleeding Time
With some nonsteroidal anti-inflammatory drugs including ILEVRO™ Suspension, there exists the potential for increased bleeding time due to interference with thrombocyte aggregation. There have been reports that ocularly applied nonsteroidal anti-inflammatory drugs may cause increased bleeding of ocular tissues (including hyphemas) in conjunction with ocular surgery. It is recommended that ILEVRO™ Suspension be used with caution in patients with known bleeding tendencies or who are receiving other medications which may prolong bleeding time.

Delayed Healing
Topical nonsteroidal anti-inflammatory drugs (NSAIDs) including ILEVRO™ Suspension, may slow or delay healing. Topical corticosteroids are also known to slow or delay healing. Concomitant use of topical NSAIDs and topical steroids may increase the potential for healing problems.

Corneal Effects
Use of topical NSAIDs may result in keratitis. In some susceptible patients, continued use of topical NSAIDs may result in epithelial breakdown, corneal thinning, corneal erosion, corneal ulceration or corneal perforation. These events may be sight threatening. Patients with evidence of corneal epithelial breakdown should immediately discontinue use of topical NSAIDs including ILEVRO™ Suspension and should be closely monitored for corneal health. Postmarketing experience with topical NSAIDs suggests that patients with complicated ocular surgeries, corneal denervation, corneal epithelial defects, diabetes mellitus, ocular surface diseases (e.g., dry eye syndrome), rheumatoid arthritis, or repeat ocular surgeries within a short period of time may be at increased risk for corneal adverse events which may become sight threatening. Topical NSAIDs should be used with caution in these patients.

Postmarketing experience with topical NSAIDs also suggests that use more than 1 day prior to surgery or use beyond 14 days post surgery may increase patient risk and severity of corneal adverse events.

Contact Lens Wear
ILEVRO™ Suspension should not be administered while using contact lenses.

ADVERSE REACTIONS
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 the rates in the clinical studies of another drug and may not reflect the rates observed in practice.

Ocular Adverse Reactions
The most frequently reported ocular adverse reactions following cataract surgery were capsular opacity, decreased visual acuity, foreign body sensation, increased intraocular pressure, and sticky sensation. These events occurred in approximately 5 to 10% of patients.

Other ocular adverse reactions occurring at an incidence of approximately 1 to 5% included conjunctival edema, corneal edema, dry eye, lid margin crusting, ocular discomfort, ocular hyperemia, ocular pain, ocular pruritus, photophobia, tearing and vitreous detachment.

Some of these events may be the consequence of the cataract surgical procedure.

Non-Ocular Adverse Reactions
Non-ocular adverse reactions reported at an incidence of 1 to 4% included headache, hypertension, nausea/vomiting, and sinusitis.

USE IN SPECIFIC POPULATIONS
Pregnancy
Teratogenic Effects.
Pregnancy Category C: Reproduction studies performed with nepafenac in rabbits and rats at oral doses up to 10 mg/kg/day have revealed no evidence of teratogenicity due to nepafenac, despite the induction of maternal toxicity. At this dose, the animal plasma exposure to nepafenac and amfenac was approximately 70 and 630 times human plasma exposure at the recommended human topical ophthalmic dose for rats and 20 and 180 times human plasma exposure for rabbits, respectively. In rats, maternally toxic doses ≥10 mg/kg were associated with dystocia, increased post-implantation loss, reduced fetal weights and growth, and reduced fetal survival.

Nepafenac has been shown to cross the placental barrier in rats. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, ILEVRO™ Suspension should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Non-teratogenic Effects.
Because of the known effects of prostaglandin biosynthesis inhibiting drugs on the fetal cardiovascular system (closure of the ductus arteriosus), the use of ILEVRO™ Suspension during late pregnancy should be avoided.

Nursing Mothers
ILEVRO™ Suspension is excreted in the milk of lactating rats. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ILEVRO™ Suspension is administered to a nursing woman.

Pediatric Use
The safety and effectiveness of ILEVRO™ Suspension in pediatric patients below the age of 10 years have not been established.

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

NONCLINICAL TOXICOLOGY
Carcinogenesis, Mutagenesis, Impairment of Fertility
Nepafenac has not been evaluated in long-term carcinogenicity studies. Increased chromosomal aberrations were observed in Chinese hamster ovary cells exposed *in vitro* to nepafenac suspension. Nepafenac was not mutagenic in the Ames assay or in the mouse lymphoma forward mutation assay. Oral doses up to 5,000 mg/kg did not result in an increase in the formation of micronucleated polychromatic erythrocytes *in vivo* in the mouse micronucleus assay in the bone marrow of mice. Nepafenac did not impair fertility when administered orally to male and female rats at 3 mg/kg.

PATIENT COUNSELING INFORMATION
Slow or Delayed Healing
Patients should be informed of the possibility that slow or delayed healing may occur while using nonsteroidal anti-inflammatory drugs (NSAIDs).

Avoiding Contamination of the Product
Patients should be instructed to avoid allowing the tip of the dispensing container to contact the eye or surrounding structures because this could cause the tip to become contaminated by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions.

Use of the same bottle for both eyes is not recommended with topical eye drops that are used in association with surgery.

Contact Lens Wear
ILEVRO™ Suspension should not be administered while wearing contact lenses.

Intercurrent Ocular Conditions
Patients should be advised that if they develop an intercurrent ocular condition (e.g., trauma, or infection) or have ocular surgery, they should immediately seek their physician's advice concerning the continued use of the multi-dose container.

Concomitant Topical Ocular Therapy
If more than one topical ophthalmic medication is being used, the medicines must be administered at least 5 minutes apart.

Shake Well Before Use
Patients should be instructed to shake well before each use. U.S. Patent Nos. 5,475,034; 6,403,609; and 7,169,767.

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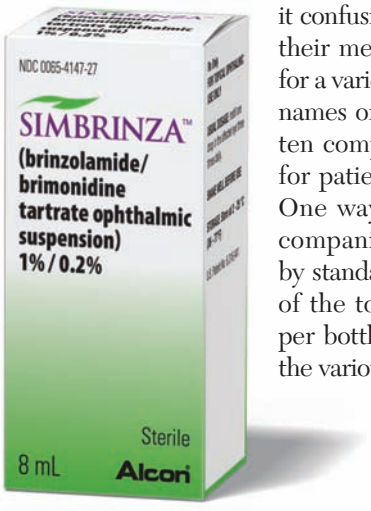
multiple chronic conditions, such as diabetes and high blood pressure, that also require ongoing medication," says Dr. Olivier. "With rising co-payment costs, patients are obliged to request generics whenever possible in order to try to be compliant. I have a number of patients getting their medications from Canada because the prices are more affordable. Not all generics go through the rigorous testing that brand-name drugs do. We run into situations where a number of different companies offer formulations of a certain generic, and one will do a much better job of controlling pressure than the others."



Newly approved Simbrinza (Alcon) pairs brinzolamide 1% and brimonidine 0.2%. It is the only combination drug on the U.S. market that does not contain timolol, a beta-blocker.

Steven Vold, MD, in private practice in Fayetteville, Ark., agrees, noting that the use of generic glaucoma medication has grown dramatically in recent years with the availability of generic latanoprost. "However, the efficacy of generic beta-blockers does not seem to be quite as good as the branded beta-blockers," he says. "The reduced costs associated with generic medication are often the driving force for many clinicians in their selection of these drugs for their patients."

Dr. Stiles agrees that generics may not be as efficacious as their brand-name counterparts. "There is concern about equal bioavailability of the active ingredient and equal clinical efficacy in generic medications," he says. "For instance, generic latanoprost is produced by several companies, and comparative studies between Xalatan and latanoprost have shown reduced clinical efficacy with the generic version. In addition to not always being as efficacious, in some cases, these drugs have a higher side effect profile. Cost is the only reason to consider a generic medication."

Another reason for non-compliance among patients is confusion about the medications, Dr. Olivier explains: "Glaucoma patients can find it confusing to comply with their medication regimens for a variety of reasons. The names of the drops are often complicated and hard for patients to remember. One way pharmaceutical companies are helping is by standardizing the colors of the tops of their dropper bottles to differentiate the various classes of drugs. Now, when a patient comes to the doctor and talks about taking the 'colored top' drops, we know which class of medication it is. But even this is not perfect and may still confuse many patients."

New Medications

A variety of new medications are in various stages of development. Rescula (unoprostone, Sucampo Pharmaceuticals) has been re-released. "It may have a slightly different mechanism of action than other prostaglandins and may improve ocular blood flow," Dr. Vold says. "However, Rescula requires twice-a-day dosing and doesn't lower pressure as well as other prostaglandins, making it a tough sell to many clinicians."

Dr. Olivier notes that the growing availability of preservative-free glaucoma medications is an encouraging development. "They tend to be friendlier to a patient's ocular surface," she says. "Such medications appeal to physicians because they offer us a new dimension for treating patients with low tolerance to preservatives, and they may be more appealing to younger patients with this chronic disease. Timoptic Ocudose, Cosopt PF and Zioptan are examples of these medications. Reformulations or decreased drug concentrations have also hit the market. Our ultimate goal would be a drug that has a low side effect profile, minimal dosing and high efficacy."

A new product that was just approved by the Food and Drug Administration is Simbrinza (Alcon), which is a combination medication composed of brinzolamide 1% and brimonidine 0.2%. "This drug lowers intraocular pressure 22 percent to 35 percent depending on the time of day," Dr. Vold says. "It clearly works better than each of these drugs used individually. This is the only combination drug on the market that does not have timolol, a beta-blocker. Patients with chronic obstructive pulmonary disease or cardiac arrhythmia will almost certainly benefit from this new glaucoma treatment option."

A recent double-masked, randomized study compared the efficacy and safety of the combination drug with each agent alone in 650 patients with open-angle glaucoma or ocular hypertension. *(Whitson J, et al. Phase 3 Randomized 3-month Trial with an Ongoing 3-month Safety Extension of Fixed Combination Brinzolamide 1%/brimonidine 0.2%. Abstract #91. Presented at the 23rd Annual Meeting of the American Glaucoma Society, 2013).*

After the initiation of treatment, patients were evaluated at two weeks, six weeks and three months. During each visit, their IOPs were checked at four times: 8 a.m., 10 a.m., 3 p.m. and 5 p.m. The study found that the combination medication was significantly more effective for lowering IOP than either of the medications alone. All patients experienced significant reductions in IOP at three months,

and those in the combination group benefited most. Because Simbrinza doesn't contain a beta-blocker, it may be a good alternative for patients with asthma or depression.

Bausch + Lomb is also studying a new medication (BOL 303259-X). Phase II results were presented at the AGS meeting. *(Weinreb R, et al. A Prospective Randomized, Multicenter, Single-masked, Parallel, Dose Ranging (VOYAGER) Study to Compare the Safety and Efficacy of BOL-303259-X to Latanoprost in Subjects with Open Angle Glaucoma or Ocular Hypertension. Presented at the 23rd Annual Meeting of the American Glaucoma Society, 2013).* The study included 413 patients with open-angle glaucoma or ocular hypertension who were assigned to one of five treatment groups: once-daily BOL 303259-X 0.006%, 0.012%, 0.024% or 0.040%, or once-daily latanoprost. All patients were evaluated at seven visits over the 28 days of treatment and on the day after treatment ended.

On day 28 (the last day of treatment), the mean diurnal IOP reduction was 9 mmHg with BOL 303259-X 0.024% and 7.8 mmHg with latanoprost, and there were no significant differences in adverse effects between the two groups. On the day after treatment ended, the mean diurnal IOP reduction was still greater in the BOL 303259-X 0.024% group than in the latanoprost group (7.2 vs. 6.25 mmHg).

Additionally, a new class of glaucoma medications with a unique approach to lowering IOP is being developed. Rho kinase inhibitors will act specifically on the trabecular meshwork to enhance aqueous humor outflow. Rho kinase inhibitors have been shown to reduce cellular stiffness and enhance outflow through the trabecular meshwork, thereby reducing IOP.

New Drug Delivery Systems

Because the biggest issue with topical medications is compliance, companies are investigating new ways to deliver the drugs that could improve compliance. "Punctal plugs that slowly release medication into the tear film are under investigation, eliminating compliance issues," Dr. Stiles explains. "Biodegradable implants could be placed under the conjunctiva and slowly release medication."

Dr. Vold notes that both Ocular Therapeutix and ForSight Labs Vision 5 are developing promising new drug delivery systems. "Allergan is

(continued on page 80)

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*United States Census Bureau, *"2010 Census Briefs – Age and Sex Composition: 2010, Table 2"* (2011).


AIR Presents a True Diagnostic Challenge

The clinical features of automimmune retinopathy overlap with a number of other retinal degenerative disorders.

By Landon Grange, Monica Dalal, MD, and H. Nida Sen, MD, MHs, Washington, D.C.

Autoimmune retinopathy (AIR) is an inflammatory mediated retinopathy characterized by vision loss, scotomas, visual field deficits, photoreceptor dysfunction and the presence of circulating antiretinal autoantibodies (ARAs). The *sine qua non* of AIR is the presence of circulating ARAs, which target retinal antigens and are believed to be responsible for the photoreceptor damage, though the precise mechanisms are not entirely understood.[1-2] AIR can be studied in two groups: paraneoplastic and non-paraneoplastic (npAIR), with paraneoplastic further subdivided into cancer-associated retinopathy and melanoma-associated retinopathy. Paraneoplastic AIR was first described in 1976 and the term "paraneoplastic retinopathy" was coined in 1984.[3-4]

Evidence suggests that paraneoplastic AIR may be triggered by molecular mimicry between tumor antigens and retinal proteins. Similarly, npAIR may be triggered by molecular mimicry between retinal proteins and presumed viral or bacterial proteins. Multiple retinal proteins have been found to be antigenic; some of these are retina-specific (e.g., recoverin) and others can be found in non-retinal tissues as well (e.g., enolase). While recoverin and enolase are the most widely studied antigens in AIR, associations with autoantibodies against carbonic anhydrase, arrestin, transducin-β, TULP1, neurofilament protein, heat shock protein-70, photoreceptor-cell-specific nuclear receptor, Müller-cell-specific antigen, transient receptor potential cation channel, subfamily M, member 1 (TRPM1) and some yet-unidentified antigens have been reported.[5-6] Recoverin is most commonly associated with cancer-associated retinopathy but has also been found in npAIR as well.[7] These ARAs can target any retinal cell type, including photoreceptor cells, ganglion cells or bipolar cells. However, the presence of ARAs alone is not sufficient for the diagnosis of this ocular disorder, as ARAs can also be found in the serum of healthy controls.[8-10]

Although it is believed to be rare, the prevalence of AIR is currently unknown. The overlap of clinical features with other degenerative retinal disorders and the lack of standardized diagnostic criteria, clinical and laboratory, may be contributing to the underestimation of its prevalence.

Signs and Symptoms

Patients with npAIR typically present with subacute vision loss, scotomas, photopsias, nyctalopia or photoaversion and dyschromatopsia. Visual acuity can be deceivingly good in the early stages. On examination, the fundus may appear unremarkable. Common clinical features in AIR patients include retinal vascular attenuation, diffuse retinal atrophy, retinal pigment epithelial changes and waxy disc pallor. AIR is usually bilateral but it can be asymmetric. Typically there are minimal or no intraocular inflammatory cells.[11-14] Visual field testing shows constriction and central or paracentral scotomas, and ERG can show abnormalities in rods, cones or bipolar cell responses or a combination of these. Although rare, there may be retinal vascular leakage on angiography or cystoid macular edema on optical coherence tomography.[11-12] Recent advances in imaging technology are promising.

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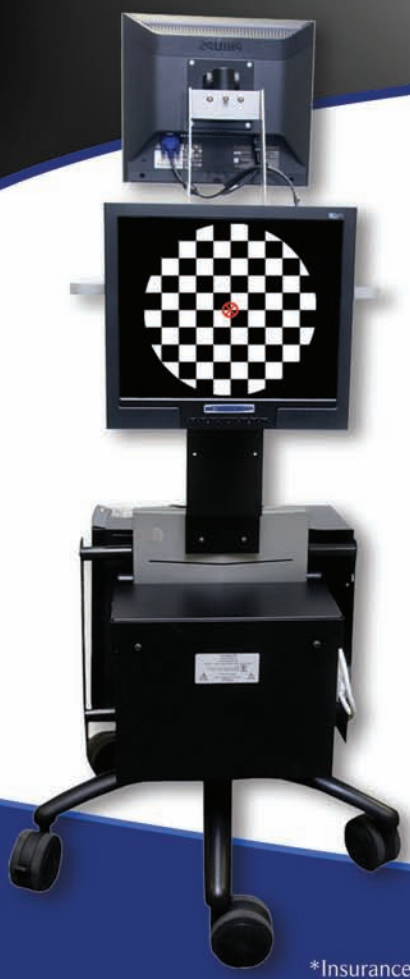

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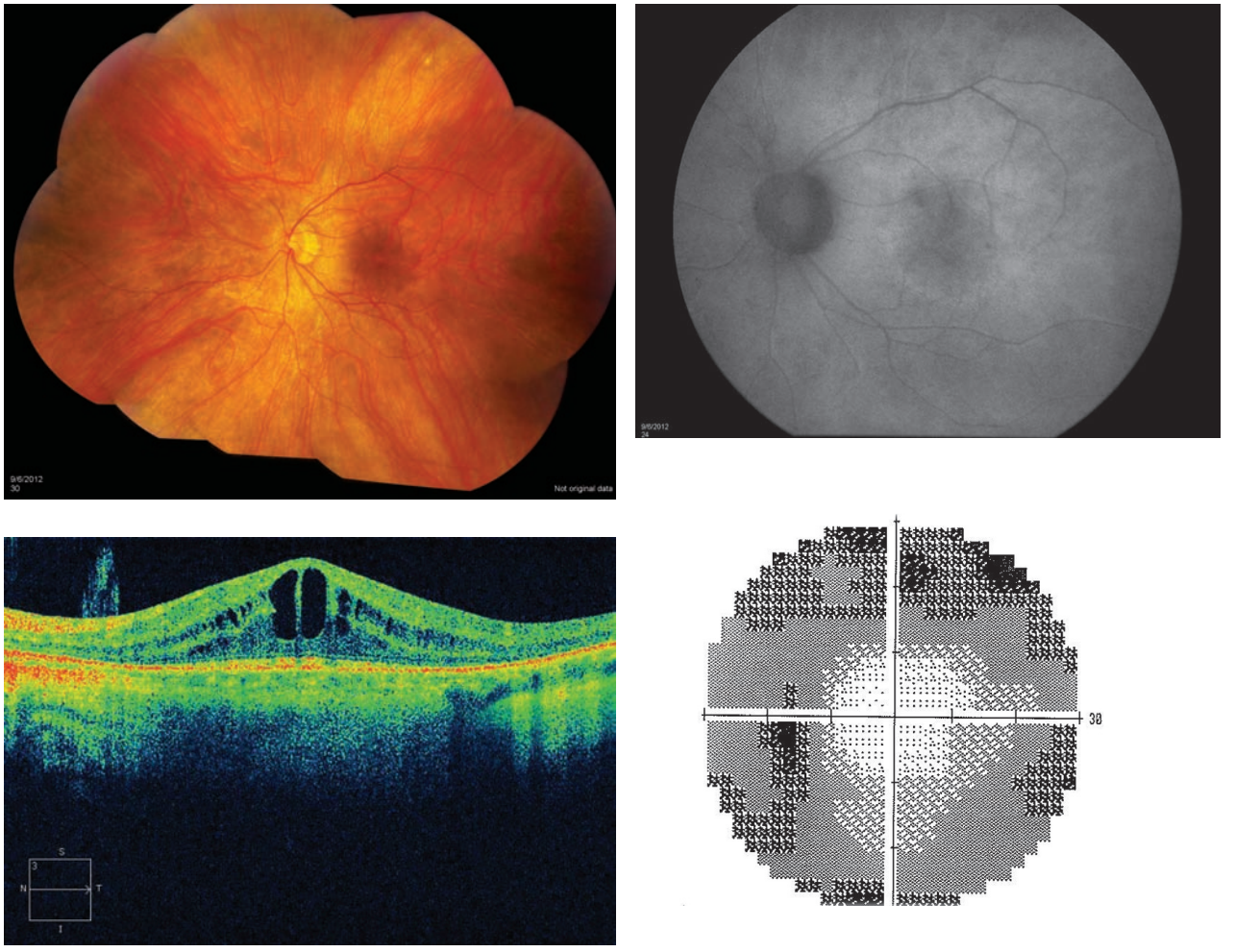

Figure 1. A non-paraneoplastic automimmune retinopathy patient with 20/20 vision. Top left: Fundus photo demonstrates a poor foveal reflex, with an otherwise normal-appearing fundus. Top right: Fundus autofluorescence reveals a ring of outer hyperautofluorescence. Bottom left: Spectral domain optical coherence tomography of the macula demonstrates loss of IS-OS junction and cystic intraretinal fluid. Bottom right: Humphrey visual field 30-2 with marked peripheral loss out of proportion to the clinical picture.

For instance, OCT and fundus autofluorescence are being investigated as tools to aid in the diagnosis of AIR, to understand its pathogenesis and to monitor disease progression.[15-16]

Among npAIR patients, there is a female predominance (63 to 66 percent), and a history of autoimmune disease is common.[11,12,14,17] The typical patient would be an adult female in her fifth to sixth decade with no history of visual problems prior to the onset of photopsias, presence of scotomas, and no family history of retinitis pigmentosa. If these features and the circulating ARAs are present, and if there is no malignancy at presentation or following a thorough investigation, a tentative diagnosis of npAIR can usually be made.

As might be expected for an entity with no consensus in diagnosis, retrospective studies in patients with npAIR showed that clinical features vary considerably. In one study, diffuse retinal atrophy was seen in the majority of patients (83 percent) and pigment deposits in only a small proportion (13 percent), and macular edema was present in approximately half of the cases. In another study pigmentary changes were seen in approximately half of the patients and macular edema was present in only 24 percent.[9,11,12,14]

Differential Diagnosis

Due to the lack of definitive or standardized diagnostic criteria, the diagnosis of npAIR is difficult. Currently, the diagnosis is made based on the presence of clinical manifestations and the demonstration of serum ARAs. ARAs can be detected using Western blot, immunohistochemistry or enzyme-linked immunosorbent assay, and the majority of AIR patients may have more than one antibody.

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Diagnosis is made more difficult due to the fact that the mere presence of ARAs is not diagnostic. ARAs can be found in other systemic autoimmune diseases as well as retinal degenerations, uveitis and in normal controls.[18-21]

Differential diagnosis of npAIR includes paraneoplastic AIR (e.g., cancer- or melanoma-associated retinopathy), white-dot syndrome spectrum disorders (particularly acute zonal occult outer retinopathy), retinal degenerative disorders (such as RP and cone-rod dystrophy), and non-infectious and infectious uveitis syndromes. RP patients can have very similar clinical features to AIR, and approximately 10 to 37 percent of patients with RP may have circulating ARAs, which makes differentiating these two entities with overlapping features very difficult.[22-23] It is unclear if the antibodies in RP patients precede the onset of retinopathy or are a consequence of retinal damage. Some uveitis syndromes such as Vogt-Koyanagi Harada syndrome and sympathetic ophthalmia[13,24] can also demonstrate ARAs but most of these syndromes have typical fundus findings that help differentiate them from AIR.

Because of significant implications, it is important to differentiate paraneoplastic AIR from npAIR, and an extensive investigation to rule out any malignancy should be undertaken in any patient who presents with signs and symptoms suggestive of AIR. This should include a thorough physical exam and basic laboratory investigations accompanied by an age- and gender-appropriate workup, best performed by the primary-care physician with clear communication between the ophthalmologist and primary medical team so appropriate investigations can be undertaken. Imaging with CT, MRI or PET scan should be guided by the review of systems and the patient's individual risk factors.

Paraneoplastic retinopathies, similar to npAIR, are characterized by vision loss, photopsias, nyctalopia and scotomas with a more rapid decline. Cancer-associated retinopathy is typically associated with antirecoverin antibody, and most commonly associated with small-cell carcinoma of the lung and ERG shows involvement of cone responses.[7,25-26] Melanoma-associated retinopathy occurs most commonly in patients with cutaneous melanoma and is characterized by a negative waveform on standardized full-field ERG due to reduction in b-wave amplitudes. CAR can precede the diagnosis of cancer, whereas MAR typically presents after the diagnosis of melanoma.[13]

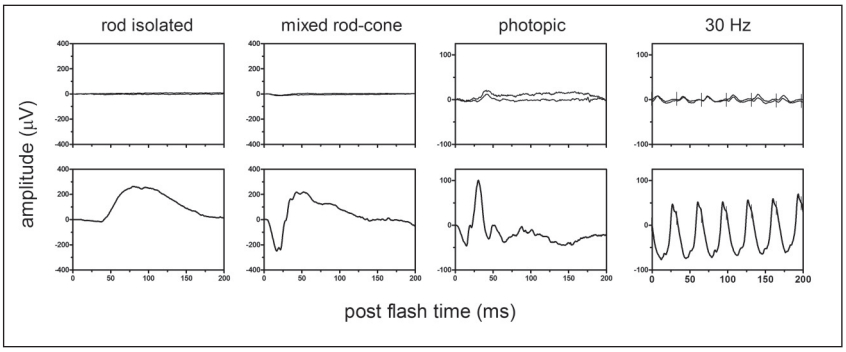

Figure 2. Full-field electroretinogram responses from the same patient as shown earlier (top row) and a control subject (bottom row). Rod responses are absent from the patient. Photopic and 30 Hz tests reveal cone responses that are extremely reduced and delayed.

Acute zonal occult outer retinopathy (AZOOR) can present with symptoms, visual fields and ERG findings similar to AIR. It is typically bilateral but asymmetric and the majority of patients either stabilize or show partial recovery without treatment. Multiple evanescent white dot syndrome (MEWDS), despite having similar symptoms, is a unilateral retinopathy that is characterized by an afferent pupillary defect, optic nerve swelling and spontaneous recovery, and hence is more readily differentiated from AIR. Both AZOOR and MEWDS may show an enlarged blind spot on visual fields. In addition, the majority of eyes affected by AZOOR may show characteristic and striking fundus autofluorescence abnormalities, which has not been observed in AIR.[17,27-28] FA and ICG in AIR are often unrevealing, while in MEWDS FA frequently demonstrates early hyperfluorescence with late staining and ICG may show hypofluorescent lesions throughout the posterior pole more numerous than apparent on clinic examination. OCT in AZOOR and MEWDS may demonstrate loss of the retinal photoreceptor inner and outer segments similar to AIR, although in MEWDS it may return to a more normal appearance after the acute episode. Given the overlap and often nonspecific imaging findings, correlation with the clinical history and exam is needed to differentiate AIR.

ARAs have also been found in patients with retinal vasculitis, uveitis patients with VKH, Behçet's disease and sympathetic ophthalmia. In patients with VKH, antibody reactivity to photoreceptors correlated with disease activity. All these syndromes are characterized by significant intraocular inflammation in addition to their unique fundus findings, making the differentiation rather unproblematic. Other rare cases of retinopathies associated with ARAs include onchocerciasis and ocular toxoplasmosis. Antibodies to retinal pigment epithelium, neural retina or photoreceptor layer have been described in these infectious retinopathies.[24,29,30] Typical fundus findings in these

Table 1. Diagnostic Criteria for Non-paraneoplastic Autoimmune Retinopathy

Essential Criteria:	Supportive Criteria:
No evidence of malignancy	Photopsias
No evidence of RP	Scotomas
(+) serum anti-retinal antibodies	Dyschromatopsia
ERG abnormality or visual field abnormality	Nyctalopia or Photoaversion

entities are helpful in differentiating them from AIR. In all of the aforementioned diseases, it is unclear if the antibodies preceded the retinal disease or if the immune reactivity is simply a consequence of the retinal degenerative process.

Treatment

Because of the presumed autoimmune nature of AIR, various forms of immunomodulatory approaches have been tried. However, the ambiguity in diagnosis creates an enormous challenge in the management of AIR. Immunomodulatory therapy can be considered empiric. For paraneoplastic retinopathies, decreasing tumor burden using surgery, chemotherapy or radiation, as applicable, is the best approach. Common approaches to both para- and non-paraneoplastic AIR include systemic or local corticosteroids, intravenous immunoglobulin or plasmapheresis. Additionally for npAIR, antimetabolites such as mycophenolate mofetil, azathioprine and T-cell inhibitors such as cyclosporine have been used.[11-12] Less frequently, targeted B-cell therapy, such as anti-CD20 monoclonal antibody (Rituximab), has also been used in the treatment of npAIR.[31-32] Therapy is not helpful once widespread retinal degeneration occurs.[11,12,22,33]

In a cohort of 24 nonparaneoplastic AIR patients who received therapy with various combinations of prednisone, cyclosporine, azathioprine, mycophenolate mofetil, periocular or intravitreal steroid injections, 15 of the 24 showed varying degrees of improvement in visual acuity or visual field, and CME improved in almost half of the patients. Decrease in ARAs following treatment may be seen in some cases,[11,24,33] however clinical significance of this finding is unclear.

In summary, there are currently no clear parameters to guide treatment and no clear indicators for prognosis. Whether changes in autoantibody levels correlate with clinical improvement is still unclear. The response to treatment is very variable, with more favorable results achieved in paraneoplastic retinopathy, particularly CAR, with a combination of chemotherapy and immunosuppression. Whether an earlier attempt to treat with immunosuppression in npAIR would be more beneficial is not known. Early treatment attempts are limited by lack of sensitive and specific assays and more definitive clinical criteria. Additional studies are needed to identify the specificity and pathogenicity of ARAs and the appropriate treatment. REVIEW

Table 2. Proteins Targeted by Antiretinal Antibodies

CAR	Recoverin (23 kD), Alpha-Enolase (46 kD), Tubby-like protein 1 (TULP-1) (65 kD), Heat shock protein 70 (HSC 70) (70 kD), Unknown Proteins (34, 40, 46, 60, 70 kD)
MAR	Transducin (35 kD), Arrestin (S-Antigen) (48 kD)
npAIR	Recoverin, Alpha-Enolase, Arrestin (S-Antigen), Interphotoreceptor binding protein (IRBP) (141 kD), Unknown Proteins (22, 34, 35, 37, 40, 68 kD)

Antibodies against the listed proteins were identified in the serum of patients with AIR or AIR-like clinical findings. CAR, cancer-associated retinopathy; MAR, melanoma-associated retinopathy; npAIR, non-paraneoplastic autoimmune retinopathy. (*Modified from Retina, 5th Ed, Ryan et al., Vol. 2, Section 2, Ch. 77)*

Mr. Grange is a medical student at the University of California, San Diego, who, as a participant in the National Institutes of Health Medical Research Scholars Program, is conducting clinical research with the Ocular Immunology Laboratory of the National Eye Institute. Dr. Dalal is a uveitis and ocular immunology fellow at the NEI. Dr. Sen is the director of the Uveitis and Ocular Immunology Fellowship Program at the NEI with a joint appointment as associate clinical professor with the Department of Ophthalmology at the George Washington University. Correspondence should be addressed to Dr. Sen at: senh@nei.nih.gov.

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Alternative Therapy: Good, Bad or TBD?

Natural therapies may have some benefit for patients, but it pays to be aware of what can go wrong, as well.

Mark B. Abelson, MD, CM, FRCSC, FARVO, and James McLaughlin, PhD, Andover, Mass.

Perhaps we're imagining things, but there seems to be a correlation between the information overload of our increasingly wired world and the burgeoning popularity of complementary and alternative medicines, or CAM. Like it or not, filtering through the case reports, testimonials and even controlled studies on non-traditional therapies has become a necessary part of ophthalmology. Even if we never prescribe a single herbal extract, patients are employing them at an ever-increasing rate so, at a minimum, we need to be aware of the adverse effects and potential interactions between these CAM treatments and conventional therapies.

Ginkgo biloba extract is a mainstay of alternative therapy.

The subject of alternative pharmacotherapy elicits strong emotions and opinions from both its proponents and its skeptics. While much of the literature supporting use of alternative medicines doesn't meet the standard of evidence-based medicine we have come to expect, these treatments cannot simply be ignored as modern equivalents of snake oil. In this month's column, we'll consider examples of the alternative treatments recommended for ocular disorders. In many cases we find good scientific rationale (if not proof of efficacy) behind their indication. In addition, we'll look at examples of alternative therapies with ocular side effects. While the data is incomplete or inconclusive in many cases, we hope to show that traditional therapeutic principles can be applied equally to both atropine sulfate and *Atropa belladonna*.

The Natural Pharmacopeia

The NIH classification of CAM includes mind-body interventions, energy therapies and biological-based treatments.[1] This last group includes herbs, vitamins, minerals and nutrition-based approaches. All of these therapies are regulated under the Dietary Supplement and Health Education Act of 1994. The most significant effect of this law is the requirement of natural products to state, "This product and its claims have not been evaluated by the FDA. This product is not intended to diagnose, treat, cure or prevent any disease. Consult a health-care professional before using this or any product if you are pregnant or have a serious medical condition." While this statement represents the primary oversight of the production and sale of CAM therapies, there is an increasing pressure for more rigorous, controlled clinical testing of herbal-based and nutriceutical medicines.

Vitamins and dietary supplements

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are an important part of CAM ocular therapies. The AREDS study reflects a naturopathic approach to AMD, and has established that either a combination of antioxidants, zinc supplements or both can reduce age-related macular degeneration progression by 17 to 25 percent.[2] Several other studies examined other dietary approaches, including β-carotene, vitamin E, or α-tocopherol, but none of these treatments showed a significant effect against AMD progression. Antioxidants, multivitamins and individual vitamins A, C and E have all been screened in large cohort, observational studies such as the Beaver Dam Eye Study, the Women's Health Initiative and the Blue Mountains Eye Study.[3] Some of these studies reported modest effects of these various treatments on AMD progression, cataract formation or progression of diabetic retinopathy, but there was no clear consensus. There is evidence, however, from several cohort studies showing a protective effect of the B vitamins (niacin, riboflavin) in reducing cataract progression.[4]

One of the most-often recommended herbal treatments for ocular disease is *Ginkgo biloba*; extracts of this plant are suggested as therapies for degenerative retinal diseases including AMD and glaucoma.[5] The extracts have been shown to inhibit platelet activation and enhance blood flow, and several small studies have suggested that *Ginkgo* extract treatments may have protective effects on visual field changes in normal tension glaucoma.[5] Other examples of herbal remedies suggested for glaucoma include the Chinese wolfberry (*Lycium barbarum*), *Coleus forskohlii* and bilberry.[3] Lycium is known as an "anti-aging" herb in Chinese medicine, and studies demonstrating its neuroprotective properties have recently been published;[6] whether these can be translated to an effective treatment for retinal degeneration is unknown. *Coleus* species are the source of the diterpene forskolin, a compound used experimentally as an activator of adenylate cyclases. This action would be comparable to that of a non-selective beta-adrenergic agonist, and so would have mixed effects on ocular hypertension. It has been reported that the extracts of this plant elicit a mild, transient decrease in ocular pressure.[7] Also, stories traced to British pilots during World War II have given the bilberry (as well as the carrot) a claim to enhanced visual function, especially night vision. Although both plants have well-established antioxidant constituents, there are no clinical studies that support these assertions.[3]

There are fewer herbal treatments described for ocular surface diseases. Several Chinese herbs or herb mixtures have been suggested as treatments for dry eye,[8] and a recent study described properties of *Atropa acuminata* extracts as treatments for several conditions including ocular inflammation.[9] Clinical studies of omega-3 and omega-6 fats, including those found in sea buckthorn extracts,[10] support a therapeutic benefit of herbs containing these ingredients for individuals with dry eye.

Beyond the use of herbal extracts, many CAM advocates also encourage the use of various elemental salts and colloidal preparations. Such treatments date to the historical use of mercurous chloride solutions (Calomel), both topically and in elixirs, for the treatment of diverse conditions, including infections. Obviously, mercury salts are no longer used, but other elemental preparations including chromium, selenium and silver are commonly employed. Chromium is CAM therapy for diabetes,[11] selenium is a treatment for hypothyroidism (but has also been associated with cataract formation)[12] and silver solutions, including silver nitrate or Argyrol, are still considered appropriate therapy for *ophthalmia neonatorum*, even though they've been replaced, at least in the United States, by erythromycin for this indication.[13]

When Herbs Go Bad

Many advocates of CAM therapies seem to make the *a priori* assumption that herbal therapies have no side effects—only drugs have side effects, right? In fact many herbs and other natural products can evoke significant adverse effects, and many of these impact visual function directly or indirectly.[14] Patients with this erroneous preconception are left with a false sense of security that can lead to overdosing or delays in responding to harmful reactions.

Examples of adverse ocular effects include those seen with topical use of *Echinacea* and *Chamomile*, plants commonly used for systemic treatments of conditions including colds, fevers, burns and inflammation.[14] Operating with the idea of "no adverse effects," patients have used extracts of both plants topically to treat ocular inflammation, which has resulted in a severe conjunctivitis characterized by hyperemia, itching and excessive watering.

The therapeutic effect of *Ginkgo*, the inhibition of platelet function, also leads to dose-dependent adverse effects such as subarachnoid and retinal hemorrhage. It's clearly important to be aware of a patient's use of *Ginkgo*, especially if he is also using other platelet inhibitors such as Coumadin or aspirin.[14]

A second compound with significant ocular side effects is niacin. High doses of this vitamin have been recommended by naturopaths as a treatment for diabetes, atherosclerosis and hypertension, but there is also clear evidence of risk of cystoid macular edema in patients taking greater than 1.5 g niacin per day.[14]

While most therapies espoused by supporters of alternative medicine are

generally safe, the dearth of reliable studies leaves open the questions of efficacy and safety. In such an informational vacuum, it's possible that misinterpretation of the few available studies can lead to adoption of unsubstantiated speculation as fact. The reported connection between silver and glaucoma is just such a case.

The Strange Silver Saga

Silver salts have been used at deliveries as both ocular antiseptics and to chemically cauterize the newborn umbilicus. Silver sulfadiazine is a useful topical antibacterial, especially for burn infection. The traditional antiseptic Argyrol was an essential part of any physician's black bag before the advent of modern antibiotics, and today silver still has important application in dental reconstructions, implants, catheters and some contact lens storage devices. These devices take advantage of the bacteriostatic characteristics silver imparts to their exposed surfaces.[15]

In contrast to its mainstream topical use, the systemic use of silver colloidal suspensions has become a mainstay of many naturopathic practitioners, and is purported to treat conditions including arthritis, cancer and infectious diseases including HIV. According to the National Institute for Complementary and Alternative Medicines, "Scientific evidence does not support the use of colloidal silver to treat any disease, and serious, irreversible side effects can result from its use."[16]

The side effect referred to in relation to colloidal silver is argyria, a permanent bluing of the skin that results from silver deposition in the dermis. The ocular version of this condition, argyrosis, was common in silversmiths and others who routinely worked with silver in industrial settings. What is surprising, however, is that beyond this discoloration there is no evidence that systemic silver has any other significant toxicities.

Several isolated reports have linked silver to glaucoma, in part because of the deposition of silver in ocular tissues that accompanies argyrosis. The most recent study suggested a potential relationship between glaucoma and argyrosis.[17] With precise instrumentation, the authors analyzed *in vivo* silver deposition in a single patient exhibiting ocular hypertension and corneal opacity. This patient also suffered asthma secondary to 30 years of exposure to silver salts in his work as a jeweler. Confocal microscopy examination confirmed silver deposits throughout the stroma, in Descemet's membrane and in Bowman's membrane, and showed pigmentation of the trabecular meshwork. The authors referenced earlier work[18] and stated, "A possible link between argyrosis and glaucoma has also been attributed to thickening of the trabecular endothelial basement membrane, obstruction of the trabecular meshwork by small silver granules and by unknown factors." Surprisingly, the cited reference makes no such link, but simply provides an analysis of how different types of silver exposure (occupational, topical or ingested) can affect the location and extent of silver accumulation in ocular tissues. In addition, the researchers explicitly state that no silver deposition was observed in the trabecular meshwork. Despite this, other publications have cited the study when suggesting a link between argyrosis and glaucoma, when neither this report nor any other study provides evidence for such a link.[19,20]

This case of this non-existent link between silver toxicity and glaucoma reminds us of the importance of fully vetting the peer-reviewed literature, particularly when we are making treatment decisions based upon it. This holds equally for both drugs developed by the pharmaceutical industry and for CAM therapeutics. Even with a mountain of medical literature at our fingertips, establishing valid therapeutic guidelines still comes down to blending our experience with a thoughtful consideration of individual trials and reports. REVIEW

Dr. Abelson is a clinical professor of ophthalmology at Harvard Medical School. Dr. McLaughlin is a medical writer at Ora Inc.

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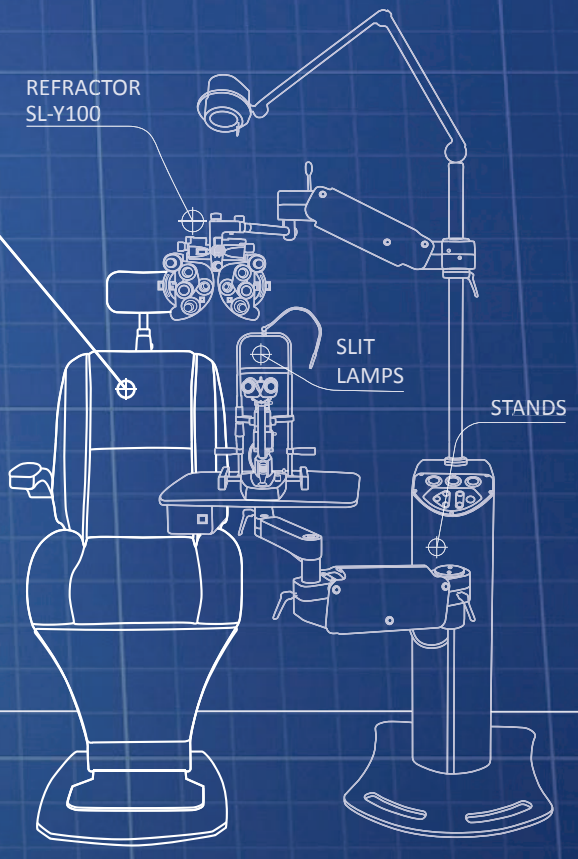

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Managing Periocular Capillary Hemangioma

Though benign, these lesions can have significant systemic and ocular consequences and require early intervention.

Jonathan H. Salvin, MD, Wilmington, Del.

Infantile hemangiomas are the most common tumor of infancy. These benign vascular tumors are usually not apparent at birth, but appear soon after in the first several weeks of life. They generally are associated with a growth phase characterized by rapid enlargement and reach 80 percent of their full size by 5 months of age. This is followed by what was previously thought to be a plateau phase of no growth. Recent evidence, however, has shown it is more a period of slowed growth.[1] This is then followed by a regression stage, resulting in gradual decrease in the size of the lesion. Involution occurs at a rate of 10 percent per year with approximately 50 percent of lesions completely resolved by 5 years old, and by 9 to 10 years old, 90 percent completely regress.[2] Overall, 85 percent of lesions regress without the need for treatment.

These lesions can be superficial (50 to 60 percent), subcutaneous (15 percent), or mixed (25 to 35 percent). Superficial hemangiomas, also known as "strawberry angiomas" are generally well-demarcated, red-purple, smooth lesions with a firm consistency *(See Figure 1)*. Deep hemangiomas, also known as "cavernous hemangiomas," are well-defined protruding masses covered by normal-appearing skin with a deeper blue-purple color *(See Figure 2)*. Deep hemangiomas can mimic subcutaneous lymphangiomas or orbital dermoids, and neuroimaging is often necessary to determine the lesion's extent. Hemangiomas can also be classified as localized or segmental.

Systemic, Ocular Complications

Anatomic location and size dictate potential morbidity from these otherwise benign lesions. Any of the skin lesions may be disfiguring and potentially leave fibrovascular scarring after involution. Large facial hemangiomas can be associated with PHACES syndrome (posterior fossa malformations, hemangioma, arterial anomalies, cardiac defects, eye abnormalities, sternal clefting). Lower face and neck hemangiomas have been associated with concomitant airway hemangiomas that may cause significant bleeding during anesthesia. Lesions overlying the lumbosacral spine have been associated with tethered cords and other genitourinary abnormalities.

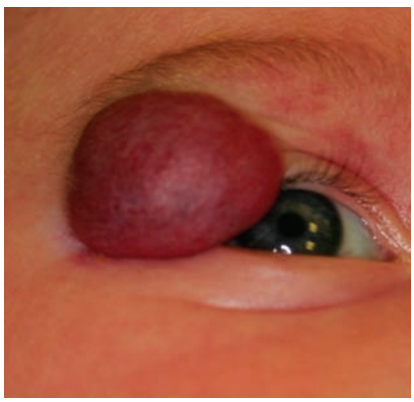

Figure 1. Superficial hemangiomas are generally well-demarcated, red-purple, smooth lesions with a firm consistency.

Generally, an ophthalmologist should be concerned for PHACES syndrome when a hemangioma is segmental and over 5 cm. The workup includes a cardiac echocardiogram to rule out contraindications for propranolol, and an MRI/MRA of the head and neck. Children with PHACES syndrome are more likely to develop migraine headaches, seizures, developmental delays, speech delays and, very rarely, ischemic strokes. The Dandy-Walker malformation is the most common developmental abnormality

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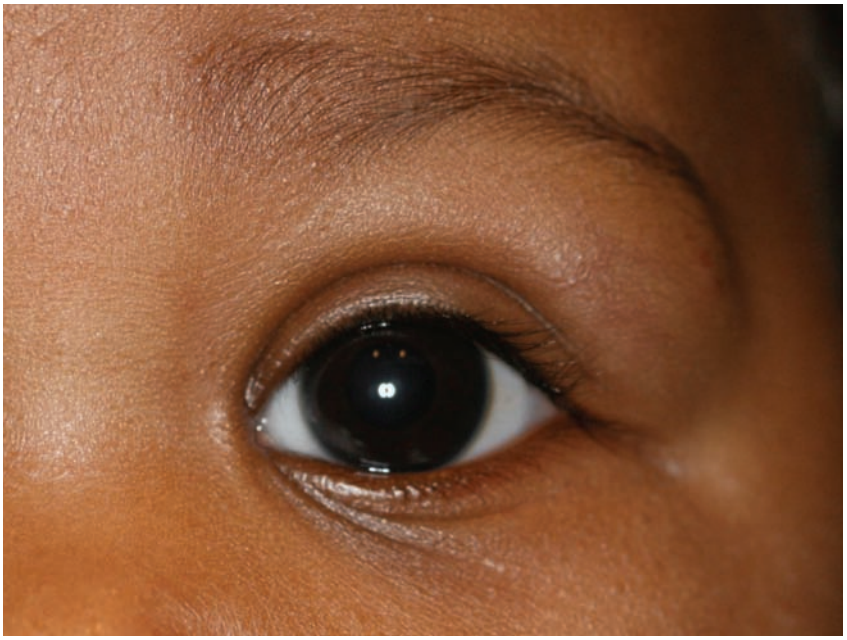

Figure 2. Deep or "cavernous" hemangiomas are covered by normal-appearing skin with a deeper blue-purple color.

of the brain and is found in approximately one-third of PHACES patients. They may also have cardiac anomalies such as coarctation of the aorta, other aortic arch abnormalities and vascular anomalies. Aneurysms, anomalous branches of the internal carotid artery and arterial stenosis are common associations. PHACES patients also have a significant risk for permanent cosmetic deformity, since their hemangiomas are often extensive. Ocular abnormalities that have been reported with PHACES syndrome include ipsilateral Horner's syndrome; strabismus; retinal vascular dilation and tortuosity; optic atrophy; iris vessel hypertrophy; iris hypoplasia; optic nerve hypoplasia; congenital cataracts; sclerocornea; lens coloboma; proptosis; congenital third nerve palsy; and oculomotor apraxia.

Periorbital and orbital hemangiomas can be associated with vision loss from several etiologies. Eyelid lesions can cause ptosis and occlusive amblyopia. They may also be associated with induced astigmatic error causing refractive amblyopia that may not resolve with hemangioma treatment alone. Orbital hemangiomas are associated with proptosis and secondary exposure keratopathy, ocular motility restrictions and optic nerve compromise if the posterior orbit is involved. With the new appreciation that these lesions reach full size by 5 months, early referral and evaluation for ocular complications is encouraged for early treatment consideration.

Treatment Options

Treatment is indicated to prevent life-threatening complications (with airway or liver involvement), to prevent functional impairment (vision loss/amblyopia), and to prevent or improve ulceration and pain with potential long-term scarring and disfigurement.[3] Observation alone is a very reasonable choice for lesions that do not seem to be interfering with vision, causing significant deformity or threatening life.

• ***Corticosteroids.*** Until recently, both intralesional and systemic corticosteroids have been considered the mainstay of treatment when observation combined with amblyopia therapy fails. Systemic steroids of varying doses can be used with a reasonable response in many cases. Systemic steroids carry potentially significant risks, especially in the infant population, including adrenal suppression, growth retardation and immunosuppression. Possible local eye complications from systemic steroids include steroid induced glaucoma and cataract formation. Intralesional injections of steroids are also an option, but have also been reported to have side effects of localized fat atrophy, cutaneous pigmentary changes, and rarely, central retinal artery occlusion. Steroid therapy needs to be closely monitored by the pediatrician and the ophthalmologist throughout the treatment course.

• ***Laser.*** Pulse-dye laser has been used for hemangiomas with some improvement. Generally this has been advocated during the early proliferative phase or the late regression phases when the lesion is flatter.

• ***Surgical excision.*** Well-circumscribed superficial lesions can be surgically excised with good results. Surgery tends to more successful in the early phases when the lesions are smaller and more confined. Because these are vascular tumors, intraoperative bleeding is a risk factor. Surgical excision in the late involuted phases may be of value to remove unsightly residual lesions.

• ***Oral propranolol.*** Propranolol is a non-selective beta-blocker used in children for several decades for cardiac, neurologic and endocrine diseases with a good safety and tolerance record. In 2008, Christine Leaute-Labreze, MD, and colleagues described two cases of resolution of capillary hemangiomas when the patients were started on oral propranolol for cardiac disease. They subsequently treated nine additional children without cardiac disease with oral propranolol for capillary hemangioma. All patients had changes in the hemangioma within 24 hours and had resolution of the lesions

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over the course of treatment without significant systemic side effects from the medication.[4]

Propranolol is a non-selective beta-blocker and inhibits the action of epinephrine and norepinephrine on β1 and β2 receptors. It is commonly used in children for hypertension, tachycardia, migraine headaches, tremors and performance anxiety. The mechanism of action for its effects on hemangiomas, however, remains unclear. Possible mechanisms include vasoconstriction of the intralesional blood vessels, down-regulation of growth factors including vascular endothelial growth factor (VEGF) and fibroblast growth factor, and triggering apoptosis.[5]

Since this initial report, multiple reports have emerged using oral propranolol as a primary treatment with excellent results. These reports have also helped to define a safe and effective protocol for its use. Reported side effects from treatment include bradycardia, hypotension, hypoglycemia, allergic reaction to the medication and gastrointestinal upset. Unfortunately, not all lesions respond. Some regress within weeks of starting propranolol; others continue to grow unfettered.

Pre-treatment clearance by the pediatrician for baseline vital signs including heart rate and blood pressure and finger stick glucose testing are necessary. Electrocardiogram is indicated prior to starting treatment and if found to be irregular, then subsequent cardiology evaluation and echocardiogram are indicated.

Current dose recommendations are to initiate treatment at 0.5 mg/kg/day divided in two to three doses and to taper up to 2.0 mg/kg/day divided into two to three doses over the course of the first several days of treatment.[5-7] Many providers initiate therapy in the inpatient setting to closely monitor for cardiac and respiratory side effects, followed by periodic outpatient evaluation by the primary care physician. Kathryn M. Haider, MD, and colleagues recently reported safe initiation of treatment entirely in the outpatient setting with close monitoring by the parents and the pediatrician.[7] Parents must be instructed to administer the medication with meals and avoid pre-bedtime doses to avoid nocturnal hypoglycemia.

Multiple reports have emerged using oral propranolol as a primary treatment with excellent results.

Treatment is continued throughout the proliferative phase and can be tapered and stopped when sufficient regression has been achieved. In their study, Patrizia Vassallo, MD, and colleagues reported complete resolution of hemangiomas in four months of treatment in patients under 1 year old.[6] In their older patients, longer treatment did not yield greater results, likely because these lesions were already out of the proliferative phase. Recurrence of the lesions requiring restarting therapy was reported infrequently.

- ***Topical timolol.*** Recently, investigators have begun to study the effects of topical beta blockers on small, well-defined hemangiomas.[8,9] Timolol maleate is a non-selective beta blocker similar to propranolol and historically used to treat glaucoma. Several authors have shown a regression response in hemangiomas treated with topical solution. Christopher Chambers, MD, and colleagues showed good response using timolol maleate gel 0.25% twice a day for superficial and mixed type hemangiomas. The one deep lesion in their study did not respond to topical therapy. They reported no adverse ocular or systemic side effects.

Infantile hemangiomas are benign lesions histopathologically, but may carry significant systemic and ocular morbidity and potential mortality. Early intervention for these high-risk lesions should be taken to avoid irreversible complications and also to provide improved cosmetic results as these children get older. PHACES syndrome should be considered in patients with segmental lesions over 5 cm, and workup should be completed before considering systemic treatment. Treatment considerations include systemic propranolol, surgical excision, systemic or injected corticosteroids, pulse-dye laser and topical timolol. Propranolol therapy has been shown to be safe and effective in reducing the size of these lesions and promoting rapid and permanent regression. Topical beta-blocker therapy is emerging as promising therapy for smaller, less aggressive lesions. REVIEW

Dr. Salvin practices in the Division of Ophthalmology at Nemours/A.I. DuPont Hospital for Children, and the Department of Ophthalmology and Pediatrics at Jefferson Medical College/ Wills Eye Institute.

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Ahmed, Baerveldt or Something Else?

Data comparing the popular glaucoma shunts continues to come in—and new surgical options show promise as well.

Ike K. Ahmed, MD, FRCSC, and Panos G. Christakis, MD, Toronto, Ontario

Surgical options for managing glaucoma have become increasingly varied in recent years. Innovation has offered new hope to patients suffering from the disease, but has also forced surgeons to make difficult decisions regarding treatment options. In particular, surgeons must critically evaluate each patient's disease and treatment goals to determine which surgical option would best suit their needs.

Glaucoma drainage devices have become more frequently used to treat glaucoma that's refractory to maximum tolerated medical therapy. This is following the results of the Tube Versus Trabeculectomy study, which reported better success at five years with Baerveldt implantation than with trabeculectomy with mitomycin-C in patients who had undergone previous surgery. A follow-up Primary Tube Versus Trabeculectomy study is under way to assess the efficacy of Baerveldt implantation in patients without previous surgery. In addition, two major trials are comparing the two most commonly used glaucoma drainage devices (the Ahmed and Baerveldt implants): the Ahmed Versus Baerveldt study (which we are involved in) and the Ahmed Baerveldt Comparison study.

AVB at Year Three

Last November we presented the three-year results of the Ahmed Versus Baerveldt study, an international, multicenter, randomized trial of 238 patients with uncontrolled or high-risk glaucoma, at the American Academy of Ophthalmology Annual Meeting. Enrolled patients had failed to achieve target pressures despite maximum medical therapy, and many had already failed trabeculectomy and/or trabeculoplasty. Mean preoperative IOP was 31.4 ±10.8 mmHg on 3.1 ±1.0 glaucoma medications with a median Snellen visual acuity of 20/100.

One hundred twenty four patients received an Ahmed-FP7 valve implant and 114 patients received a Baerveldt-350 implant. The primary outcome was failure (defined as an intraocular pressure not falling between 5 and 18 mmHg, or not achieving at least a 20-percent reduction from baseline), recorded at two consecutive visits after a three-month period. Other criteria for failure included vision-threatening complications, the need for additional glaucoma procedures and loss of light perception.

In brief, the three year data showed that:

- Both devices were effective in reducing IOP and the need for glaucoma medications.
- The cumulative probability of failure was significantly greater in the Ahmed group (51 percent, vs. 34 percent in the Baerveldt group; p=0.03).
- Mean IOPs at three years were not significantly different, although there was a trend toward a lower IOP in the Baerveldt group (14.4 ±5.1 mmHg vs. 15.7 ±4.8 in the Ahmed group, p=0.09).
- Fewer medications were required in the Baerveldt group (1.1 ±1.3 vs. 1.8 ±1.4 in the Ahmed group; p=0.002).
- Complication rates were not significantly different, but the Baerveldt group had a higher rate of hypotony-related, vision-threatening complications (6 percent vs. 0 percent in the Ahmed group; p=0.005). Also,

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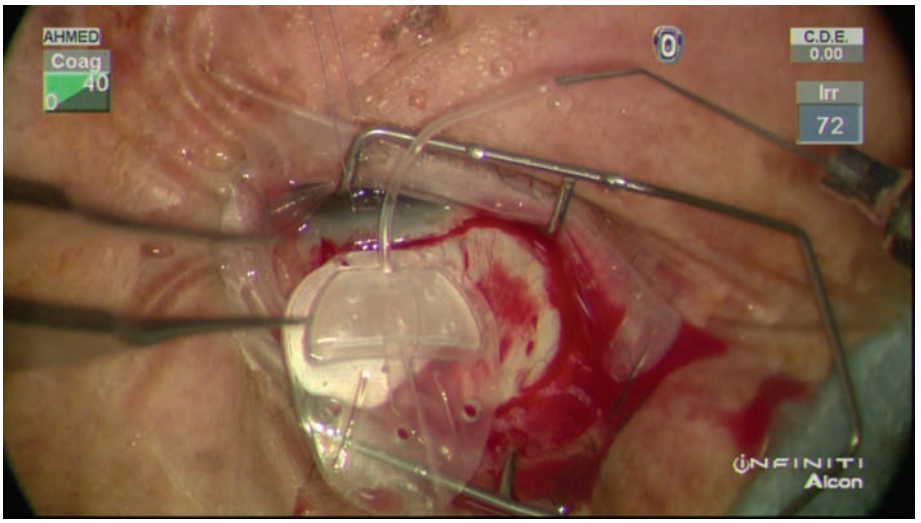


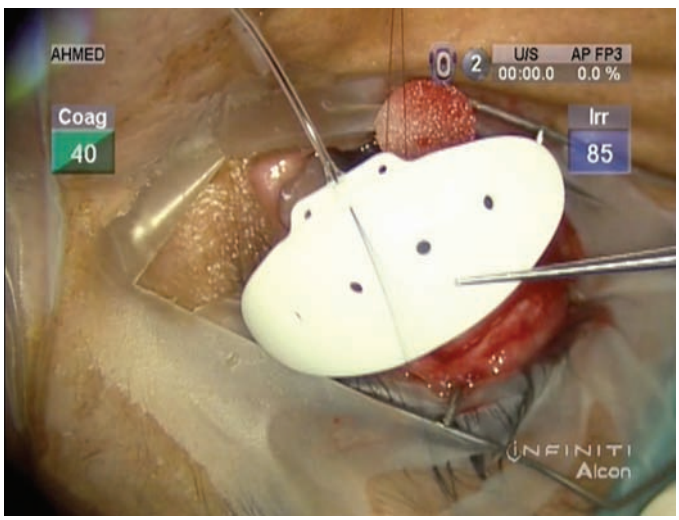
The Ahmed shunt has a built-in valve mechanism that allows immediate postoperative flow and prevents hypotony; however, studies suggest that use of the Ahmed valve may leave the patient needing more glaucoma medications in the long term than use of the Baerveldt.

there was a trend towards more interventions being required in the Baerveldt group, although most interventions were only slit-lamp procedures. Both groups had a moderate decrease in visual acuity.

Overall, both of these devices were effective treatment options, even in this population of challenging patients. The Baerveldt had a higher success rate and required fewer medications, but had a higher rate of serious hypotony-related complications. These results are not entirely surprising; the ABC study reported similar findings.

Choosing a Shunt

Selecting a device involves balancing many factors, including a patient's age, glaucoma subtype and treatment goals. For example, although the Baerveldt may yield a lower long-term pressure (note that the difference was not significant in our trial), there is often pressure volatility in the early postop period that may not be amenable to patients with severe disease. Because the Baerveldt tube is occluded during the first four to six weeks after surgery while the bleb forms around the plate, it often requires manipulation and intervention. However, this appears to have a long-term beneficial effect on the bleb; it's not exposed to early postop aqueous that may cause inflammation and bleb remodeling. Eventually, when the tube occlusion dissolves or is removed, flow begins. That can cause the pressure to drop quickly and may result in hypotony-related complications, the major risk associated with this device. In contrast, the Ahmed has a built-in valve mechanism that allows immediate postoperative flow and prevents hypotony, but may require more glaucoma medications in the long term.



The Baerveldt's tube is occluded during the first four to six weeks after surgery. This appears to have a beneficial effect on the bleb, but may increase the need for manipulation and increases the risk of hypotony related complications when the tube occlusion is removed or dissolves.

Some people might interpret our results to mean that the Baerveldt is a better device than the Ahmed, but which device is "better" depends on the situation. Treating glaucoma is about individualizing patient care by using your clinical acumen to determine treatment goals.

For example, if I need to get a patient's pressure as low as possible to prevent progression, I might choose a Baerveldt device. If I'm trying to treat somebody with a higher target pressure or with neovascular glaucoma and I just want to get the pressure down to a more normal level, then I might choose an Ahmed valve because the risk to the patient is less. If I have a patient younger than 50 years old, which would make me concerned about healing and bleb encapsulation, then I'd probably choose the Baerveldt. If a patient is over 75 and just had surgery, I'd prefer the Ahmed for safety reasons, and perhaps because of life expectancy. If a patient has had a failed trabeculectomy and we've needled the bleb and it's

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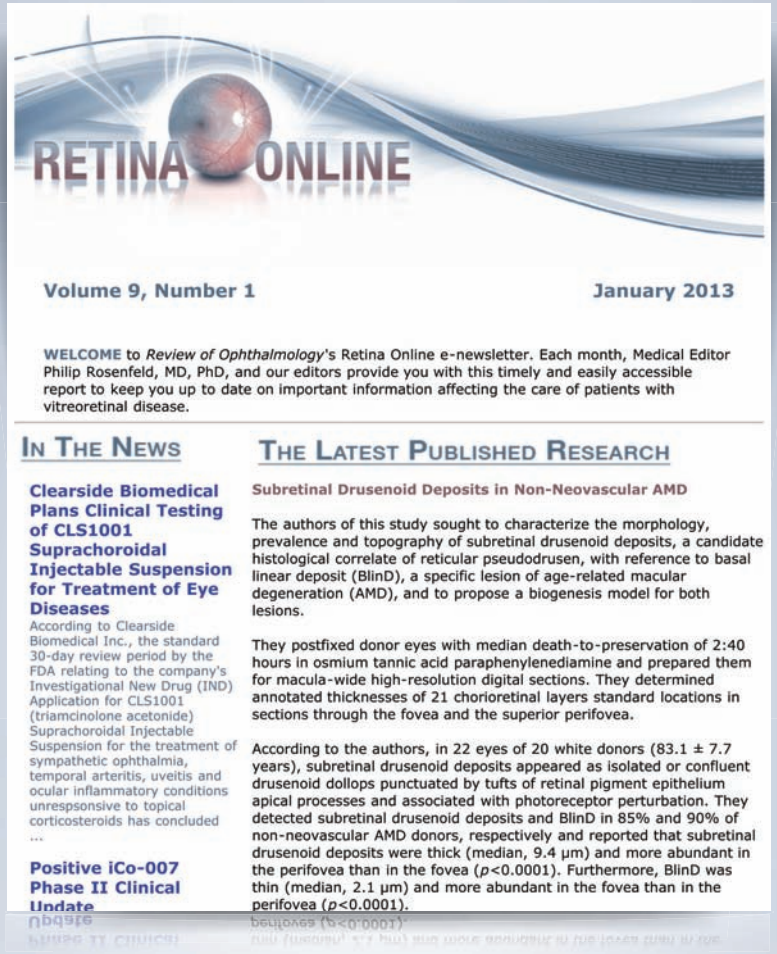

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WELCOME to *Review of Ophthalmology*'s Retina Online e-newsletter. Each month, Medical Editor Philip Rosenfeld, MD, PhD, and our editors provide you with this timely and easily accessible report to keep you up to date on important information affecting the care of patients with vitreoretinal disease.

IN THE NEWS

Clearside Biomedical Plans Clinical Testing of CLS1001 Suprachoroidal Injectable Suspension for Treatment of Eye Diseases

According to Clearside Biomedical Inc., the standard 30-day review period by the FDA relating to the company's Investigational New Drug (IND) Application for CLS1001 (triamcinolone acetonide) Suprachoroidal Injectable Suspension for the treatment of sympathetic ophthalmia, temporal arteritis, uveitis and ocular inflammatory conditions unrespsonsive to topical corticosteroids has concluded ...

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The authors of this study sought to characterize the morphology, prevalence and topography of subretinal drusenoid deposits, a candidate histological correlate of reticular pseudodrusen, with reference to basal linear deposit (BlinD), a specific lesion of age-related macular degeneration (AMD), and to propose a biogenesis model for both lesions.

They postfixed donor eyes with median death-to-preservation of 2:40 hours in osmium tannic acid paraphenylenediamine and prepared them for macula-wide high-resolution digital sections. They determined annotated thicknesses of 21 chorioretinal layers standard locations in sections through the fovea and the superior perifovea.

According to the authors, in 22 eyes of 20 white donors (83.1 ± 7.7 years), subretinal drusenoid deposits appeared as isolated or confluent drusenoid dollops punctuated by tufts of retinal pigment epithelium apical processes and associated with photoreceptor perturbation. They detected subretinal drusenoid deposits and BlinD in 85% and 90% of non-neovascular AMD donors, respectively and reported that subretinal drusenoid deposits were thick (median, 9.4 µm) and more abundant in the perifovea than in the fovea ($p<0.0001$). Furthermore, BlinD was thin (median, 2.1 µm) and more abundant in the fovea than in the perifovea ($p<0.0001$).

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scarred down, and the conjunctiva isn't in great health, I'd probably consider a Baerveldt.

Sadly, we've seen very little innovation in the area of glaucoma drainage devices. There are a few alternatives to the Ahmed and Baerveldt devices such as the Molteno 3 device and the Krupin device, but they're not new and they're not used as often. A device with some sort of flow control would be excellent, but that hasn't appeared yet. However, many new devices are allowing us to increase drainage into other spaces, including Schlemm's canal and the choroidal space. Many of the procedures surrounding those devices are less invasive and easier to accomplish.

Turning to MIGS?

That raises the issue of the increasingly popular minimally invasive glaucoma surgeries, including placement of the iStent in Schlemm's canal. This may not seem like a fair comparison, because generally these procedures are thought of as treatments for mild to moderate glaucoma. Typically, the patients who undergo these procedures have healthier eyes, and these procedures are more often combined with cataract surgery. In contrast, the glaucoma drainage devices are generally reserved for more advanced patients with sick eyes and multiple risk factors; they're less often combined with phaco and may involve multiple surgeries with a complicated postoperative course.

Nevertheless, the idea of using some of these devices to treat more advanced patients is gaining credibility, at least in my experience. For example, I recently had a challenging monocular 70-year-old patient with a failed trabeculectomy. We had done needling, but his pressure was still at 24 mmHg on four medications. And, he had a cataract. Many surgeons would have opted for a tube or a second trab, and the TVT study might have inclined the surgeons to choose a Baerveldt.

Sadly, we've seen very little innovation in the area of glaucoma drainage devices.... However, many new devices are allowing us to increase drainage into other spaces, including Schlemm's canal and the choroidal space. Many of the procedures surrounding those devices are less invasive and easier to accomplish.

However, in this case I was very concerned about the risks. I talked with the patient extensively, and we eventually agreed to try doing phaco with the implantation of multiple iStents (with the option of going to a tube later, if required). We felt that there was a chance this might work, and if it did, it would save the patient from having to undergo a riskier procedure. To maximize the odds of a good outcome, when it came time to do the surgery we used our "targeted" approach, in which we place the iStents in areas of high capacity, near aqueous veins.

The patient is currently four months out. To our amazement, his pressure is now hovering around 13 mmHg—on no glaucoma medications. That's a home run, which we don't always manage to achieve. But if we can reach that level of success with this kind of patient, then MIGS may have more potential than many surgeons currently believe. We definitely need to learn more about these devices and procedures and how to use them most effectively.

I think that all surgeons are capable of performing the MIGS procedures. However, these procedures are highly technical. I've been doing them for six years now, and it's taken me that long to feel that I know their nuances, including the technical planning and patient indications. As a result, I'm definitely hitting more home runs with these procedures today than I did early on.

I'm really excited about these procedures, and I'm looking forward to seeing their role expanded. I believe these procedures will eventually be chosen for some of the patients who currently are seen as candidates primarily for tubes or trabs. *(For more on the MIGS procedures, see "MIGS and the General Ophthalmologist" on p. 34.)*

Whether you choose to resort to a trabeculectomy, a tube or one of the newer MIGS procedures when faced with a challenging case, there's no question that it's an exciting time to be a glaucoma surgeon. Technological innovation and research are thriving in the field. We hope that this will translate into better outcomes for our patients. REVIEW

Dr. Ahmed is an assistant professor at the University of Toronto in Ontario. (He is not the creator of the Ahmed valve and has no financial interest in it.) Dr. Christakis is an ophthalmology resident at the University of Toronto.

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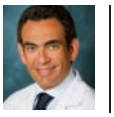


ASCRS Surgeons Sidestep Ectasia

The results of the 2012 ASCRS Refractive Surgery Survey show a marked decrease in ectasia cases.

Walter Bethke, Managing Editor

For years following the approval of LASIK in the United States, the specter of ectasia hung over surgeons and their procedures, becoming one of the procedure's most feared complications. Ophthalmologists concentrated on the problem, however, and figured out ways to select patients properly and minimize their risk, and this year's ASCRS refractive surgery survey shows the fruits of their labor: 78 percent of ASCRS surgeons have never seen a case of ectasia in any of their refractive surgery patients. In addition to this happy news about ectasia, this year's survey also reveals other trends in such areas as astigmatism management, surgical volumes and simultaneous intraocular surgeries.

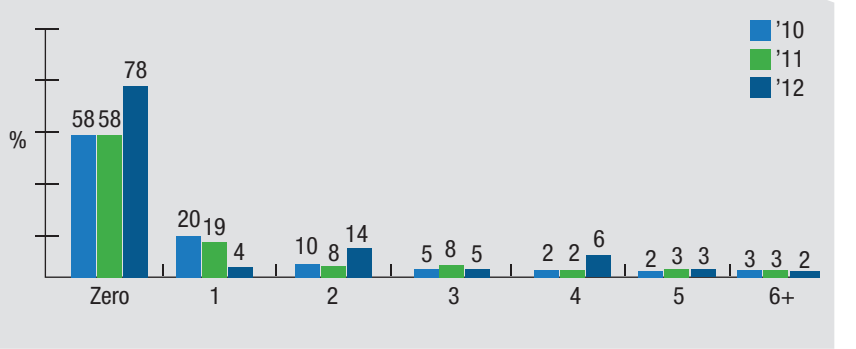
The survey was emailed to 4,142 U.S. members of ASCRS, and 11 percent, or 452 surgeons, responded. Here's a look at the highlights.

Ectasia Rates

Mobile, Ala., ophthalmologist Richard Duffey, who administers the survey each year with Palm Springs, Calif., ophthalmologist David Leaming, finds the ectasia results significant and encouraging. "It's really important," he says. "Seventy-eight percent of surgeons haven't seen a case of ectasia of their own. This is because as newer, younger surgeons come in and adopt our more conservative approach to surgery and better diagnostic testing, they're not operating on patients who have a greater likelihood of developing ectasia, just like more experienced surgeons won't. I also think we'll see the number of ectasia cases drop further and further as time goes by because of our improved diagnostic skills and more conservative thinking regarding such factors as the residual stromal bed."

Part of the post-LASIK ectasia equation consists of such factors as corneal and residual stromal bed thicknesses, which the survey also inquired about. "Looking at the results from the survey's question on the minimum corneal thickness a surgeon would operate on, 58 percent of the respondents would operate on corneas 480 µm thick or less," Dr. Duffey says. "This tells me that corneal thickness in and of itself isn't the biggest parameter. Topographic changes in the cornea, the residual stromal bed thickness and other factors are probably more important to all of us."

Total Cases of LASIK Ectasia (as the Primary Surgeon)



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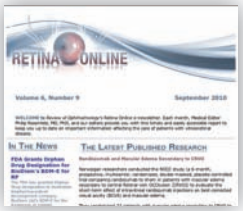

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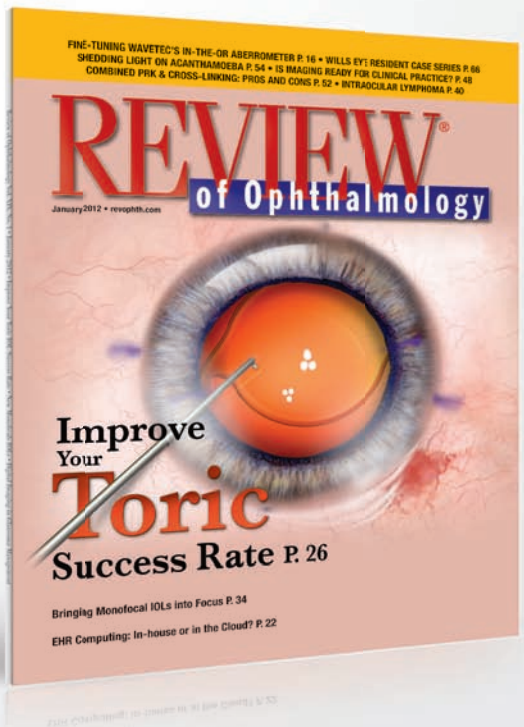

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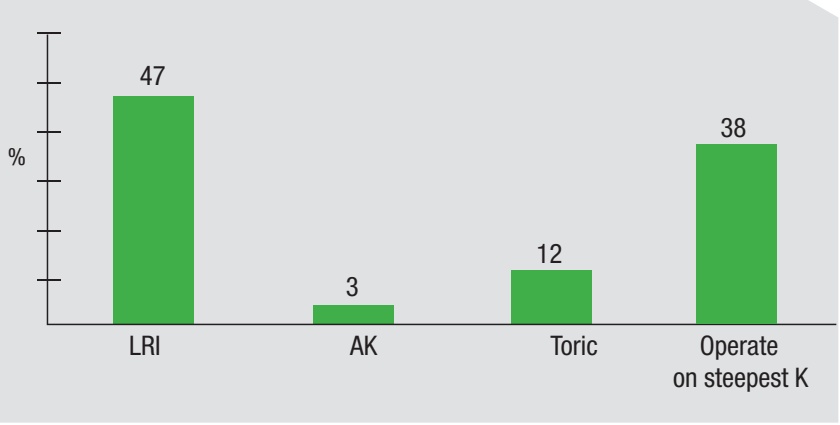

Managing Astigmatism

This year's survey revealed that surgeons are pretty aggressive in terms of when they offer to correct astigmatism.

Forty-seven percent of surgeons will offer to correct a patient's astigmatism when it reaches 0.75 D, and 78 percent offer to correct it when it's at 1 D or higher. "I think we're better at correcting astigmatism now," says Dr. Duffey, suggesting a reason for the propensity of surgeons to offer astigmatism correction. "We can do limbal relaxing incisions and astigmatic keratotomy incisions better than we ever could before, and the presence of toric lenses makes surgeons feel more comfortable with managing astigmatism, as well. Also, the fact that you can be reimbursed by the patient for managing the astigmatism gives surgeons an incentive to get better at astigmatic correction and offer it to patients if it's something that's important to them."

In terms of the astigmatic procedures surgeons prefer for low levels of astigmatism (0.5 to 1 D), 47 percent like LRIs, 38 percent prefer to operate on the steep meridian, 12 percent use toric lenses and 3 percent prefer AK. For moderate astigmatism (1.12 to 2 D), the percentage of toric IOL backers jumps to 74 percent, with 22 percent preferring LRIs. For astigmatism greater than 2 D, 94 percent of surgeons say they prefer toric lenses.

Procedure Preferences

Dr. Duffey points out that, even though LVC volumes are going down, PRK remains a popular option.

"We're on a downward slide for LVC but, as a ratio, PRK is a fifth of all LVC, which is up from 12 percent in 2005," Dr. Duffey says. "The reason for this is simple: If we have any doubt regarding the risk of ectasia or complications, we're going to fall back more on PRK than on LASIK. I see this in my own practice. For patients on whom I would have done LASIK five years ago, if I see something out of the ordinary—even if it's minimal like a 475-µm cornea or a very high myope whose postop stromal bed would be a little thinner than 300 µm—I'll do PRK on that patient.

"Also, with the use of mitomycin-C, we almost never see corneal haze anymore," Dr. Duffey continues. "I prophylactically use mitomycin-C for every patient on whom I operate with PRK. I know that many surgeons use it more sparingly, but I think that when you realize you won't have an issue with corneal haze with PRK when you use mitomycin-C, it becomes a very safe alternative for you."

The survey is also beginning to show that there's a percentage of surgeons who are tolerant of other surgeons' decision to perform bilateral, simultaneous intraocular surgery, which has historically been taboo. When asked if they've performed such a procedure, 24 percent say they have with phakic intraocular lenses, but only 9 percent say the same regarding refractive lens exchange. Seventeen percent have done it for corneal inlays. "This is not to say that these surgeons do these procedures routinely," says Dr. Duffey. "They're basically saying that they won't protest if a surgeon thought it was the right way to do it. The higher rate for phakic IOLs is because they're less invasive than refractive lens exchange. In P-IOL surgery, you're not removing the patient's crystalline lens, so there's less risk of macular edema and retinal detachment, though there's no less risk of infection. So there's a little bit less of a risk with a phakic IOL implantation than there is when you're removing the lens and placing an implant."

Though procedure volumes are down, Dr. Duffey takes comfort in knowing that refractive surgeons still believe in refractive surgery procedures, based on how many have had it themselves. A quarter of the respondents have had refractive surgery, 56 percent say their siblings have had it and 28 percent of the surgeons say their spouses have had LVC. "When you see these rates, which have consistently stayed high, it tells you that we who know the most about the procedures, refractive surgeons and our families, have had them done at a higher rate than the general population," notes Dr. Duffey. "It's kind of an index of satisfaction. If you saw that, suddenly, no surgeons we're having it done on their own eyes, then there would have to be a better alternative. Right now, though, there's no better alternative than LVC." REVIEW

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Reading Speed in RVO After Ranibizumab

New research published Online First in *JAMA Ophthalmology* suggests that patients with macular edema after retinal vein occlusion who are treated monthly with ranibizumab are more likely to have improvements in reading speed of the affected eyes through six months compared with sham treatment. These results demonstrate that visual acuity improvements translate into measurable improvements in visual function.

There were 789 participants in the two multicenter, double-masked, Phase III clinical trials in which participants with macular edema secondary to branch RVO (BRAVO trial) or central RVO (CRUISE trial) were randomized 1:1:1 to monthly sham (n=132 in BRAVO, 130 in CRUISE), ranibizumab 0.3 mg (n=134 in BRAVO, 132 in CRUISE) or ranibizumab 0.5 mg (n=131 in BRAVO, 130 in CRUISE) for six months. Patients were able to receive macular laser after three months if they met prespecified criteria. The main study outcome was reading speed, which in the study eye was measured with enlarged text (letter size equivalent to approximately 20/1500 at the test distance) at baseline and one, three and six months. The number of correctly read words per minute was reported. The reading speed test required a sixth-grade reading level and did not account for literacy or cognitive state.

In patients with branch RVO, the mean gain for the 0.5-mg group was 31.3 wpm compared with 15 wpm in sham-treated eyes (difference, 16.3 wpm; p=0.007) at six months. In patients with central RVO, the mean gain for the 0.5-mg group was 20.5 wpm compared with 8.1 wpm in sham-treated eyes (difference, 12.4 wpm; p=0.01) at six months. A gain of 15 or more letters of BCVA letter score corresponded to an increase in reading speed of 12.3 wpm and 15.8 wpm in patients with branch and central RVO, respectively.

JAMA Ophthalmology 2013;():1-6 doi:10.1001/jamaophthalmol.2013.114.

Suñer I, Bressler N, Varma R, Lee P, et al.

Myocardial Infarction After Treatment with VEGF Inhibitors

Whole-population data suggests that although adverse events are rare, patients treated with VEGF inhibitors are significantly more likely to experience myocardial infarction. It is unknown if this risk is related to the underlying age-related macular degeneration or the use of VEGF inhibitors.

Hospital and death records were examined for 1,267 patients treated with VEGF inhibitors and 399 patients treated with photodynamic therapy attending Western Australia eye clinics from 2002 to 2008, and 1,763 community controls, aged ≥50 years. Hospital records from 1995 to 2009 were analyzed for history of MI, stroke and gastrointestinal bleeding before treatment. Records were searched for evidence of these events in the 12 months after treatment.

The 12-month MI rate was higher for anti-VEGF patients than photodynamic therapy patients and the community group (1.9/100 vs. 0.8 and 0.7). No differences were observed between patients treated with bevacizumab and ranibizumab. The adjusted MI rate was 2.3 times greater than the community (95 percent CI, 1.2-4.5) and photodynamic therapy group (95 percent CI, 0.7-7.7). The 12-month MI risk did not increase with the number of injections administered, nor did stroke and gastrointestinal bleeding differ between any exposure groups.

Retina 2013;33:920-927.

Kemp A, Preen D, Morlet N, Clark F, et al.

LASIK with Next Gen Cyclotorsion Controlled Excimer Laser

New research supports laser-assisted *in situ* keratomileusis for primary high mixed astigmatism using optimized aspherical profiles and a fast-repetition-rate excimer laser with cyclotorsion control as a safe, effective and predictable procedure.

Fifty-two eyes of 36 patients with primary mixed astigmatism over 3 D underwent LASIK surgery using the sixth-generation excimer laser Amaris with cyclotorsion control and a

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femtosecond platform for flap creation. Visual, refractive, corneal topographic and aberrometric outcomes were measured during a three-month follow-up. Refractive astigmatic changes were measured by Alpins method.

A reduction of refractive sphere and cylinder was observed three months postop (p=0.001), with an associated improvement of uncorrected distance visual acuity (p=0.001). Best-corrected distance visual acuity remained unchanged in 31 eyes (59.6 percent), while three eyes (5.76 percent) lost two lines of BCDVA. Fourteen eyes (26.9 percent) had spherical equivalent within ±0.5 D of emmetropia and 34 (65.3 percent) had SE within ±1.0 D of emmetropia. Comparing surgically induced and target astigmatism showed no significant difference. A significant induction of higher-order aberration attributable to increase of spherical aberration was found (p=0.003) and seven eyes (13.4 percent) required retreatment.

Am J Ophthalmol 2013;155:829-826.
Alio J, Pachkoria K, Aswad A, Plaza-Puche A.

Anti-VEGF Therapy to Treat Corneal Neovascularization

A systemic review and meta-analysis of literature to evaluate the therapeutic effect of bevacizumab on corneal neovascularization suggests that topical and subconjunctival bevacizumab achieve significant reduction in the area of the neovascularization.

Seven eligible clinical human studies and 18 eligible experimental animal studies were identified through a PubMed search and included in the meta-analysis. The random-effects model (of DerSimonian and Laird) was used to combine the results from selected studies. Heterogeneity was explored using available data and publication bias was assessed.

A significant reduction of corneal NV was seen in clinical human studies, with a pooled reduction of 36 percent overall (95 percent CI, 18 to 54 percent), 32 percent for subconjunctival anti-vascular endothelial growth factor injections (95 percent CI, 10 to 54 percent) and 48 percent for topical treatment (95 percent CI, 32 to 65 percent). Pooled mean change in best-corrected visual acuity showed an improvement in BCVA by 0.04. The summary standardized mean difference in animal studies indicated a statistically significant reduction in the area of corneal NV when treated with bevacizumab compared with the control group by -1.71 (95 percent CI, -2.12 to -1.30). The subtotal pooled standardized mean differences were -1.83 for subconjunctival anti-VEGF injections (95 percent CI, -2.38 to -1.28) and -1.50 for topical treatment (95 percent CI, -1.88 to -1.12).

Cornea 2013;32:535-444.
Papathanassiou M, Theodoropoulou S, Analitis A, Tzonou A, et al.

Additive Risks for Ganglion Cell Dysfunction and Glaucoma

A rat study from University of Melbourne researchers shows that both ω-3 polyunsaturated fatty acid deficiency and repeat acute intraocular pressure cause retinal ganglion cell dysfunction. The combination of these factors results in a cumulative effect that may have implications for glaucoma management. The researchers' data indicates that sufficient dietary ω-3 PUFA improves RGC, making it less susceptible to IOP insult.

Female Sprague-Dawley rats were fed either ω-3 PUFA sufficient (ω-3+, n=15) or deficient (ω-3-, n=16) diets five weeks before conception, with pups subsequently weaned onto their mothers' diets. At 20 weeks of age, acute IOP elevation was induced repeatedly through anterior chamber cannulation to 70 mmHg for one hour on three separate occasions, separated by one week. Electro-retinograms were recorded one week after each IOP elevation to assay the photoreceptors (PIN), ON-bipolar cells (PH) and ganglion/amacrine cells (STR).

Researchers say repeat IOP insults result in a specific RGC dysfunction (pSTR -14.5 percent, p=0.035) as does ω-3 deficiency (-26.4 percent, p<0.01). The combination causes a larger RGC functional loss (-40.1 percent, p<0.001) than either does in isolation (p<0.001).

J Glaucoma 2013;22:269-277.
Nguygen C, Vingrys A, Bui, B.

Risks of Bleb-Related Complications in Trabeculectomy

Data collected from a randomized, multicenter clinical trial indicates a low five-year risk of endophthalmitis (1.1 percent) and other bleb-related complications in the trabeculectomy cohort of the Collaborative Initial Glaucoma Treatment Study.

Long-term postoperative complications in the 300 patients randomized to trabeculectomy in the CIGTS were tabulated and Kaplan-Meier analyses were used to estimate the time-related probabilities of blebitis, hypotony and endophthalmitis. After accounting for declining treatment assignment and other early events, 285 patients were included in the final trabeculectomy cohort, and were followed for an average of 7.2 years.

Of the 247 patients with five-plus years of follow-up, 50 required further treatment for glaucoma, 57 required cataract extraction and 40 required bleb revision at least once. Bleb-related complications included bleb leak (n=15), blebitis (n=8) and hypotony (n=4). While 163 patients (57 percent) received 5-fluorouracil during surgery, the occurrences of blebitis, hypotony or endophthalmitis were not significantly associated with its use. The calculated risks of blebitis and hypotony at five years were both 1.5 percent, whereas the risk of endophthalmitis was 1.1 percent.

Am J Ophthalmol 2013;155:174-180.
Zahid S, Musch D, Niziol L and Lichter P.

FDA Approval for Alcon, B + L Drugs

Last month, the Food and Drug Adminstration approved Alcon's Simbrinza Suspension, indicated for the reduction of elevated intraocular pressure in patients with primary open-angle glaucoma or ocular hypertension. Simbrinza is a fixed-dose combination medication that offers a wide range of treatment possibilities due to its strong efficacy and ability to decrease elevated IOP by 21 to 35 percent, according to Alcon. In addition, it is the only available, fixed-dose combination therapy for glaucoma in the United States without a beta blocker.

Simbrinza is a fixed-dose combination of a carbonic anhydrase inhibitor (brinzolamide 1.0%) and an alpha 2 adrenergic receptor agonist (brimonidine tartrate 0.2%). It combines the two drugs into one multi-dose bottle, helping to reduce the medication burden for glaucoma patients. Patients are to administer one drop of Simbrinza into the affected eye(s), three times per day.

The FDA approval of Simbrinza is based on data from two pivotal Phase III clinical trials with approximately 1,300 patients. The studies evaluated the safety and efficacy of a fixed-dose combination of brinzolamide 1.0% and brimonidine 0.2%, administered three times daily, compared to separate three-times-per-day dosing of one or the other component. Both studies met their primary endpoint and demonstrated that Simbrinza is statistically superior compared to either component regarding mean IOP at month three for all time points. In both studies, Simbrinza achieved a 5 mmHg to 9 mmHg reduction from baseline to month three. Patients' mean IOP at baseline was 22 mmHg to 36 mmHg.

In the two, three-month clinical trials, the most frequently reported adverse reactions in patients treated with Simbrinza (occurring in approximately 3 to 5 percent of patients in descending order of incidence) were blurred vision, eye irritation, dysgeusia (bad taste), dry mouth and eye allergy. Treatment discontinuation, mainly due to adverse reaction, was reported in 11 percent of Simbrinza patients. The safety profile of Simbrinza is comparable to each of the individual components. Additionally, there were no significant cardiovascular or pulmonary events found with Simbrinza in either clinical study conducted.

For more information, visit alcon.com.

Prolensa, B+L Once-Daily NSAID Approved for Post-Cataract

Bausch + Lomb announced FDA approval of its New Drug Application for Prolensa (bromfenac ophthalmic solution) 0.07 % prescription eye drop, a once-daily nonsteroidal anti-inflammatory drug for the treatment of postoperative inflammation and reduction of ocular pain in patients who have undergone cataract surgery. Prolensa will be available in 1.6 ml and 3 ml bottle sizes.

Prolensa provides powerful and rapid resolution of inflammation and pain by leveraging the unique potency of the bromfenac molecule in a formulation designed to facilitate ocular penetration. The advanced formulation allows for a lower concentration of bromfenac in a once-daily dosing regimen, B+L reports. Prolensa is a solution that does not require shaking to deliver a consistent dose in each drop.

The efficacy of Prolensa was evaluated in two randomized, double-

This article has no commercial sponsorship.

masked, vehicle-controlled studies of patients undergoing cataract surgery. Each randomized patient received Prolensa or vehicle starting with one drop into the surgical eye on the day prior to and the day of surgery, and for 14 days following surgery. The primary efficacy endpoint was complete clearing of ocular inflammation (assessed by the summed ocular inflammation score, SOIS, which includes cells and flare) by day 15. The secondary efficacy endpoint was the number of subjects who were pain-free on day one after surgery.

Results from the pivotal studies demonstrated Prolensa to be superior to vehicle in the treatment of both inflammation and pain following cataract surgery. Twice as many patients as vehicle (46 percent versus 20 percent) demonstrated complete clearance of inflammation (SOIS of 0) at day 15. The difference in the average postoperative inflammation severity between the treatment and vehicle arms was statistically and clinically significant by day eight. Nearly four of five patients treated with Prolensa were pain-free at day one (78.8 percent versus 49.5 percent for vehicle; $p<0.0001$). Patients treated with Prolensa reported a lower incidence of foreign body sensation and photophobia and had less redness than those treated with vehicle. For information, visit bausch.com.

Oasis Debuts Diamond-Like Feather Keratome

Oasis Medical has announced the availability of the diamond-like Feather keratome. Feather utilizes proprietary manufacturing technology that produces an ultra-sharp, low-friction blade performance that rivals diamonds, the company says. It can be used multiple times, which helps to manage cost per case while maintaining compliance with Center for Medicare & Medicaid regulations.

The new Feather keratome blades are available in widths of 1.4 mm, 1.6 mm, 1.8 mm, 2.2 mm, 2.4 mm, 2.75 mm, 2.8 mm, 3 mm and 3.2 mm. For information, call 1 (800) 528-9786 or visit oasismedical.com.

Leica, B+L to Partner in Distribution

Leica Microsystems and Bausch + Lomb announced that Bausch + Lomb will distribute Leica ophthalmic surgical microscopes and accessories in select markets across Europe, the United States, India and Latin America beginning in April.

The partnership combines Leica's innovative ophthalmic microscopes with Bausch + Lomb's global commercial infrastructure, while expanding Bausch + Lomb's offerings for ophthalmic surgeons. Bausch + Lomb's current portfolio of products for cataract, refractive and retinal surgery includes intraocular lenses, equipment, instruments, procedure packs and other supplies. Under this agreement,

REVIEW Advertising Index

Bausch + Lomb can now offer Leica Microsystems' ophthalmic portfolio, which ranges from routine cataract microscopes to high-end retinal systems. Among these is the Leica M822 for cataract procedures, which combines LED and halogen lighting for a stable red reflex.

For information, visit leica-microsystems.com or bausch.com.

LEITR Reports First Use of Preloaded, Eye-Bank Cartridge for Corneal Transplant

Lions Eye Institute for Transplant & Research announced that for the first time, EndoGlide (Angiotech Pharmaceuticals) cartridges preloaded by an eye bank have been successfully used in corneal transplantation.

The EndoGlide was selected for initial endothelial keratoplasty transplant procedures using donor endothelial tissue that was pre-cut, trephined and pre-loaded into the device at LEITR in Tampa, Fla. It was then transported to the Massachusetts Eye and Ear Infirmary, where the procedures were performed by Roberto Pineda II, MD, associate professor of ophthalmology at Harvard Medical School.

To date, more than a dozen cases have been performed at Massachusetts Eye & Ear by Dr. Pineda and by Kathryn Colby, MD, PhD, associate professor of ophthalmology at Harvard Medical School. "In published literature, the EndoGlide device has already shown excellent outcomes in endothelial cell protection when loaded by surgeons," says Dr. Pineda. "Tissue preparation and device pre-loading by eye banks simplifies the surgery and may provide increased reproducible outcomes for endothelial keratoplasty." Last year, LEITR reported that eye banks are able to safely prepare and load corneal tissue into the EndoGlide cartridges.

In a pre-clinical study presented at the 2012 Association for Research in Vision and Ophthalmology Annual Meeting, corneal buttons pre-loaded by LEITR sustained an average of 9.07 percent endothelial cell damage, compared to 36.2 percent endothelial cell damage in control group tissue that was loaded into the insertion system on site. The difference in endothelial damage between the preloaded and control buttons was statistically significant (p=0.004).

"Eye banks have proven their ability to change industry practices for the better," said Lewis R. Groden, MD, medical director at LEITR, associate professor of ophthalmology at the University of South Florida, and executive medical director of LasikPlus Vision Center/LCA Vision. "Pre-loading grafts into insertion cartridges prior to transport may be a compelling new innovation for endothelial keratoplasty," he said. REVIEW

(continued from page 44)

currently evaluating a novel method of drug delivery as well," he says. "All of these developments potentially will make a big difference in how glaucoma patients are cared for in the future. The glaucoma treatment paradigm is definitely in rapid evolution, and I do think new innovative surgical interventions are being utilized earlier in the glaucomatous disease process by many physicians. Yet despite these surgical advances, most doctors will still start with medication for the foreseeable future."

Drugs or Surgery?

Because of the downsides associated with topical glaucoma medications, debate continues about whether medication or surgery is better for patient care. The iStent, approved in June 2012, is the first *ab interno* microstent available for clinical use in the United States. "The big question is how does this device impact when ophthalmologists intervene surgically?" Dr. Vold says. "In the past, we would always use medication and laser therapy first, and surgery was more of a last resort. Now, we are thinking about intervening much earlier with surgery. In my mind, more than three or four glaucoma eye drops a day is probably not going to happen with the vast majority of patients. For me, this has become the new maximal medical therapy, and then we are talking about surgery or laser therapy. In some patients, laser trabeculoplasty is actually indicated as first-line therapy because people can't afford medications or don't like the side effects of drops. Currently available *ab interno* microstents and next-generation microstents currently in FDA-approved clinical trials may also potentially evolve to replace medication or laser procedures as first-line therapy."

Dr. Olivier says that she always offers laser surgery in addition to topical anti-glaucoma medications as a first-line therapy option. "A prostaglandin is usually my preferred class of medications if I initiate medical therapy and is still what most patients prefer," she says. "Doctors would love to have something to give patients that would alleviate the problem of compliance or forgetfulness. Individuals are working on other options since being challenged by our retinal colleagues. We are also more aware of the effects of medications on the ocular surface and problems with dry eyes. Finding a system that can allow us to deliver a drug that can last for six months to a year and has very few side effects would be phenomenal. Combining techniques that can be delivered with cataract surgery could be an option for many individuals. I look forward to when these ideas reach prime time." REVIEW

LUMIGAN® 0.01% AND 0.03%
(bimatoprost ophthalmic solution)

Brief Summary—Please see the LUMIGAN® 0.01% and 0.03% package insert for full Prescribing Information.

INDICATIONS AND USAGE

LUMIGAN® 0.01% and 0.03% (bimatoprost ophthalmic solution) is indicated for the reduction of elevated intraocular pressure in patients with open angle glaucoma or ocular hypertension.

CONTRAINDICATIONS

None

WARNINGS AND PRECAUTIONS

Pigmentation: Bimatoprost ophthalmic solution has been reported to cause changes to pigmented tissues. The most frequently reported changes have been increased pigmentation of the iris, periorbital tissue (eyelid) and eyelashes. Pigmentation is expected to increase as long as bimatoprost is administered. The pigmentation change is due to increased melanin content in the melanocytes rather than to an increase in the number of melanocytes. After discontinuation of bimatoprost, pigmentation of the iris is likely to be permanent, while pigmentation of the periorbital tissue and eyelash changes have been reported to be reversible in some patients. Patients who receive treatment should be informed of the possibility of increased pigmentation. The long term effects of increased pigmentation are not known.

Iris color change may not be noticeable for several months to years. Typically, the brown pigmentation around the pupil spreads concentrically towards the periphery of the iris and the entire iris or parts of the iris become more brownish. Neither nevi nor freckles of the iris appear to be affected by treatment. While treatment with **LUMIGAN®** 0.01% and 0.03% (bimatoprost ophthalmic solution) can be continued in patients who develop noticeably increased iris pigmentation, these patients should be examined regularly.

Eyelash Changes: LUMIGAN® 0.01% and 0.03% may gradually change eyelashes and vellus hair in the treated eye. These changes include increased length, thickness, and number of lashes. Eyelash changes are usually reversible upon discontinuation of treatment.

Intraocular Inflammation: LUMIGAN® 0.01% and 0.03% should be used with caution in patients with active intraocular inflammation (e.g., uveitis) because the inflammation may be exacerbated.

Macular Edema: Macular edema, including cystoid macular edema, has been reported during treatment with bimatoprost ophthalmic solution. **LUMIGAN®** 0.01% and 0.03% should be used with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema.

Angle-closure, Inflammatory, or Neovascular Glaucoma: LUMIGAN® 0.01% and 0.03% has not been evaluated for the treatment of angle-closure, inflammatory or neovascular glaucoma.

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

Use With Contact Lenses: Contact lenses should be removed prior to instillation of **LUMIGAN®** 0.01% and 0.03% and may be reinserted 15 minutes following its administration.

ADVERSE REACTIONS

Clinical Studies 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.

In clinical studies with bimatoprost ophthalmic solutions (0.01% or 0.03%) the most common adverse reaction was conjunctival hyperemia (range 25%–45%). Approximately 0.5% to 3% of patients discontinued therapy due to conjunctival hyperemia with 0.01% or 0.03% bimatoprost ophthalmic solutions. Other common reactions (>10%) included growth of eyelashes, and ocular pruritus.

Additional ocular adverse reactions (reported in 1 to 10% of patients) with bimatoprost ophthalmic solutions included ocular dryness, visual disturbance, ocular burning, foreign body sensation, eye pain, pigmentation of the periocular skin, blepharitis, cataract, superficial punctate keratitis, periorbital erythema, ocular irritation, eyelash darkening, eye discharge, tearing, photophobia, allergic conjunctivitis, asthenopia, increases in iris pigmentation, conjunctival edema, conjunctival hemorrhage, and abnormal hair growth. Intraocular inflammation, reported as iritis, was reported in less than 1% of patients.

Systemic adverse reactions reported in approximately 10% of patients with bimatoprost ophthalmic solutions were infections (primarily colds and upper respiratory tract infections). Other systemic adverse reactions (reported in 1 to 5% of patients) included headaches, abnormal liver function tests, and asthenia.

Postmarketing Experience: The following reactions have been identified during postmarketing use of **LUMIGAN®** 0.01% and 0.03% in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. The reactions, which have been chosen for inclusion due to either their seriousness, frequency of reporting, possible causal connection to **LUMIGAN®** or a combination of these factors, include: dizziness, eyelid edema, hypertension, nausea, and periorbital and lid changes associated with a deepening of the eyelid sulcus.

USE IN SPECIFIC POPULATIONS

Pregnancy: Pregnancy Category C

Teratogenic effects: In embryo/fetal developmental studies in pregnant mice and rats, abortion was observed at oral doses of bimatoprost which achieved at least 33 or 97 times, respectively, the maximum intended human exposure based on blood AUC levels.

At doses at least 41 times the maximum intended human exposure based on blood AUC levels, the gestation length was reduced in the dams, the incidence of dead fetuses, late resorptions, peri- and postnatal pup mortality was increased, and pup body weights were reduced.

There are no adequate and well-controlled studies of **LUMIGAN®** 0.01% and 0.03% (bimatoprost ophthalmic solution) administration in pregnant women. Because animal reproductive studies are not always predictive of human response **LUMIGAN®** should be administered during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether **LUMIGAN®** 0.01% and 0.03% is excreted in human milk, although in animal studies, bimatoprost has been shown to be excreted in breast milk. Because many drugs are excreted in human milk, caution should be exercised when **LUMIGAN®** is administered to a nursing woman.

Pediatric Use: Use in pediatric patients below the age of 16 years is not recommended because of potential safety concerns related to increased pigmentation following long-term chronic use.

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

Hepatic Impairment: In patients with a history of liver disease or abnormal ALT, AST and/or bilirubin at baseline, bimatoprost 0.03% had no adverse effect on liver function over 48 months.

OVERDOSAGE

No information is available on overdosage in humans. If overdose with **LUMIGAN®** 0.01% and 0.03% (bimatoprost ophthalmic solution) occurs, treatment should be symptomatic.

In oral (by gavage) mouse and rat studies, doses up to 100 mg/kg/day did not produce any toxicity. This dose expressed as mg/m2 is at least 70 times higher than the accidental dose of one bottle of **LUMIGAN®** 0.03% for a 10 kg child.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility: Bimatoprost was not carcinogenic in either mice or rats when administered by oral gavage at doses of up to 2 mg/kg/day and 1 mg/kg/day respectively (at least 192 and 291 times the recommended human exposure based on blood AUC levels respectively) for 104 weeks.

Bimatoprost was not mutagenic or clastogenic in the Ames test, in the mouse lymphoma test, or in the *in vivo* mouse micronucleus tests.

Bimatoprost did not impair fertility in male or female rats up to doses of 0.6 mg/kg/day (at least 103 times the recommended human exposure based on blood AUC levels).

PATIENT COUNSELING INFORMATION

Potential for Pigmentation: Patients should be advised about the potential for increased brown pigmentation of the iris, which may be permanent. Patients should also be informed about the possibility of eyelid skin darkening, which may be reversible after discontinuation of **LUMIGAN®** 0.01% and 0.03% (bimatoprost ophthalmic solution).

Potential for Eyelash Changes: Patients should also be informed of the possibility of eyelash and vellus hair changes in the treated eye during treatment with **LUMIGAN®** 0.01% and 0.03%. These changes may result in a disparity between eyes in length, thickness, pigmentation, number of eyelashes or vellus hairs, and/or direction of eyelash growth. Eyelash changes are usually reversible upon discontinuation of treatment.

Handling the Container: Patients should be instructed to avoid allowing the tip of the dispensing container to contact the eye, surrounding structures, fingers, or any other surface in order to avoid contamination of the solution by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions.

When to Seek Physician Advice: Patients should also be advised that if they develop an intercurrent ocular condition (e.g., trauma or infection), have ocular surgery, or develop any ocular reactions, particularly conjunctivitis and eyelid reactions, they should immediately seek their physician's advice concerning the continued use of **LUMIGAN®** 0.01% and 0.03%.

Use with Contact Lenses: Patients should be advised that **LUMIGAN®** 0.01% and 0.03% contains benzalkonium chloride, which may be absorbed by soft contact lenses. Contact lenses should be removed prior to instillation of **LUMIGAN®** and may be reinserted 15 minutes following its administration.

Use with Other Ophthalmic Drugs: Patients should be advised that if more than one topical ophthalmic drug is being used, the drugs should be administered at least five (5) minutes between applications.

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Before reading on, please see p. 86 for presenting complaint, history and examination.

Diagnosis, Workup and Treatment

The combination of proptosis, central retinal vein occlusion, corkscrew episcleral vessels and elevated intraocular pressure raised concern for obstruction or arterialization of the orbital venous system, with carotid-cavernous sinus fistula being high on the differential diagnosis.

The patient's records were obtained and reviewed. An MRI and MRA were performed during her recent hospitalization, which showed an apparent left enophthalmos with atrophy of the extraocular muscles, and was read as negative for mass, cavernous sinus thrombosis and arteriovenous malformation (AVM). The patient was subsequently referred to the Neuro-Ophthalmology Service at Wills Eye, where orbital Doppler imaging was performed. This showed non-arterialized reversal of flow in the right superior ophthalmic vein (SOV) and absence of flow in the right central retinal vein. Although she lacked the arterialized reversal of flow in the SOV reported in dural AVM, it was felt that she had entered the resolution phase, now at five months after her initial symptoms began.

She was seen by the Retina Service twice prior to her neuro-ophthalmology appointment, given intravitreal bevacizumab at each visit, and had notable improvement of the episcleral engorgement *(See Figure 2a)*, retinal hemorrhages *(See Figure 2b)* and macular edema *(See Figure 2c)*. Intraocular pressure declined to 12 mmHg in the right eye and vision improved to 20/60. Given her clinical improvement and following extensive discussion with the patient regarding the risks and benefits of conventional angiography, close observation with deferral of further imaging was elected.

Discussion

The patient presented with decreased vision secondary to central retinal vein occlusion, along with a questionable diagnosis of scleritis. While both scleritis[1] and CRVO[2] may be caused by vasculitic processes, their coexistence is rare, and generally found with posterior scleritis.[3-7] The lack of history of trauma, negative findings on magnetic resonance angiography and sub-acute presentation made a high-flow carotid-cavernous fistula (CCF) unlikely.

CCF are classified as either direct (high flow) or indirect (low flow), with the latter arising from dural branches of the internal and external carotid arteries.[8] High-flow CCF are most often caused by trauma and exhibit the classic pulsating exophthalmos with an orbital bruit. Conversely, low-flow CCF, also called dural arteriovenous malformations (DAVM), are postulated to occur via localized thrombotic events, with less dramatic presentation.[8] Doppler ultrasound in DAVM classically shows arterialized reversal of flow in the SOV.[9,10]

DAVM most commonly present in females over 50 years old with hypertension, exhibiting exam findings of limbal vascular loops in 25 percent, venous stasis retinopathy via central

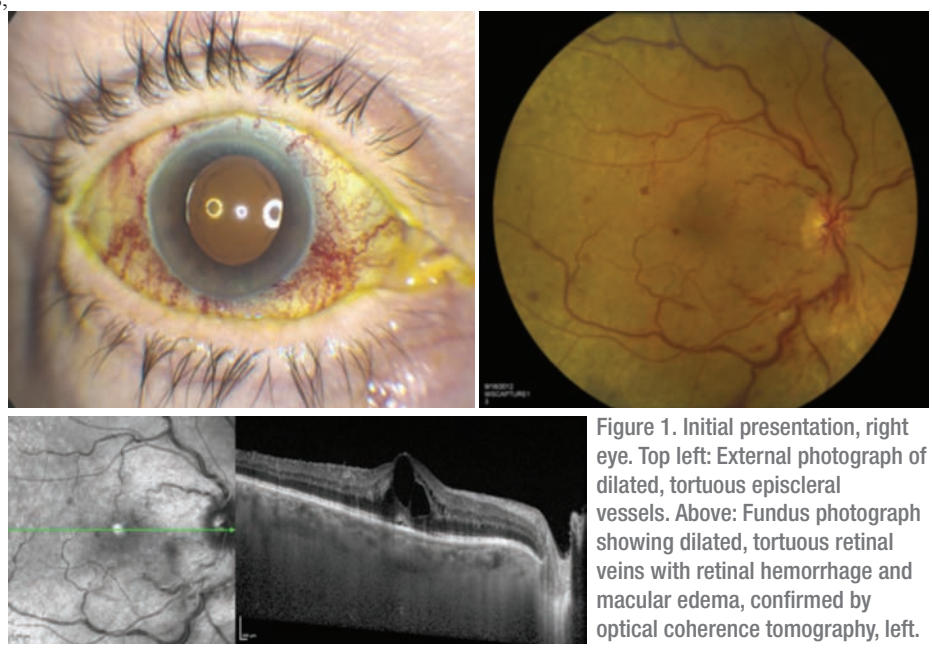

Figure 1. Initial presentation, right eye. Top left: External photograph of dilated, tortuous episcleral vessels. Above: Fundus photograph showing dilated, tortuous retinal veins with retinal hemorrhage and macular edema, confirmed by optical coherence tomography, left.

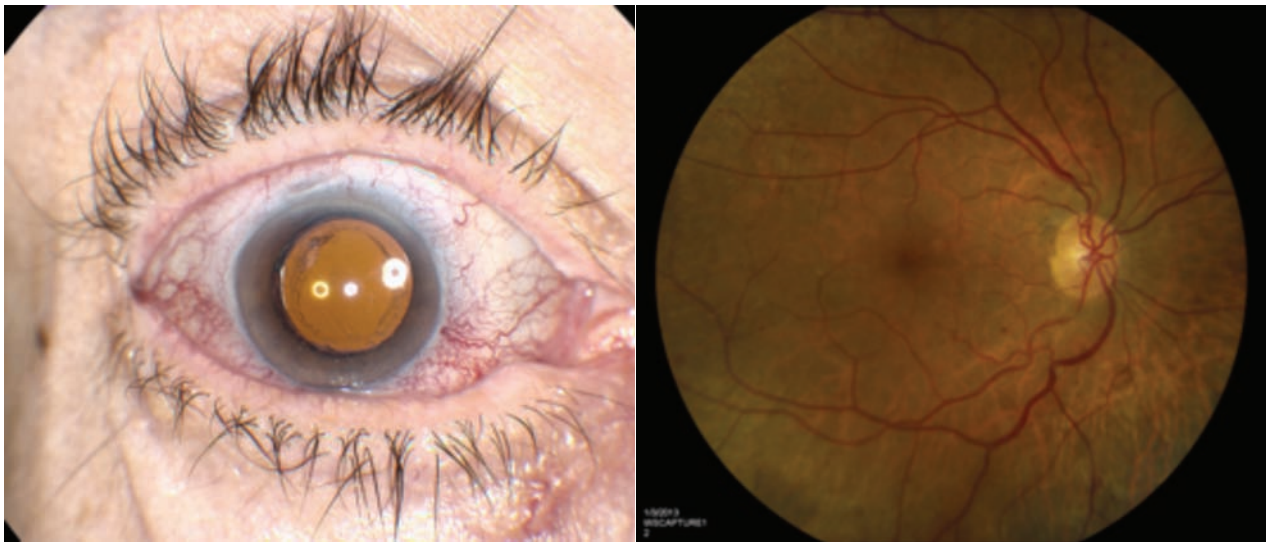

Figure 2. Two and a half month follow-up, right eye. Above: External photograph of partial resolution of episcleral vessel dilation and tortuosity. Top right: Fundus photograph showing nearly resolved hemorrhage. Right: Optical coherence tomography showing minimal residual macular edema.

retinal vein thrombosis in 15 percent and occasionally an orbital bruit.[8] Magnetic resonance or CT angiography may be negative, with definitive diagnosis confirmed by super-selective conventional angiography. Angiography with endovascular treatment however, entails a 2 to 4 percent risk of stroke, vision loss, or other permanent neurologic morbidity.[11,12] Many DAVM will spontaneously resolve, and the decision to pursue conventional angiography must weigh the risks and benefits of the procedure.

DAVM can cause significant ocular morbidity. The most serious complications are from intracerebral hemorrhage with resulting stroke, occurring in 3 percent of patients.[13] These complications occur with deeper venous drainage of the fistula, and attempts have been made to clinically predict the patients who have such drainage patterns. Exam findings predictive of cortical venous drainage include bilateral orbital congestion, post-auricular bruit and CNS dysfunction.[14]

Indications for intervention in DAVM include progressive visual decline, ocular pain, glaucoma, ophthalmoplegia, proptosis and intracranial bleeding.[8] Our patient did not have an indication for intervention, and was showing clinical improvement. After extensive discussion, a plan of close observation was agreed upon. Should she fail to improve further or develop an indication for intervention, treatment options include surgery, trans-arterial or trans-venous embolization and radiosurgery, with the latter two having reported success rates of 90 percent and significantly less morbidity than surgery.[12,15] REVIEW

The author would like to thank John Pitcher, MD, of the Retina Service and Jennifer Hall, MD, and Mark Moster, MD, of the Neuro-Ophthalmology Service at Wills Eye Institute.

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A 'swollen' eye and three-month history of blurred vision precede a patient's visit for a second opinion from the Wills Eye Retina Service.

Brian C. Doyle, MD

Presentation

A 75-year-old Caucasian female presented to the Retina Service at Wills Eye Institute for a second opinion with a red "swollen" right eye associated with blurred vision for the past three months. She had previously been under the care of an outside ophthalmologist who diagnosed her with scleritis of the right eye and anterior uveitis of both eyes.

Her clinical course was notable for resolution of the anterior uveitis after the initiation of difluprednate, but with persistent injection of the right eye despite dosing at four times each day. She also required therapy with aqueous suppressants in both eyes for elevated intraocular pressure. A laboratory workup for scleritis included FTA, ANCA and chest radiograph; all were negative. She endorsed a recent history of shortness of breath, while denying ocular pain, photophobia, diplopia, tinnitus, headache, weakness, paresthesias, arthralgia, diarrhea or bloody stool, facial pain or nasal discharge. She denied any recent trauma.

Medical History

The patient noted a history of strabismus and amblyopia in the left eye, with multiple muscle surgeries as a child. Past medical history was notable for hypertension, hyperlipidemia and hospitalization two weeks prior for deep venous thrombosis with pulmonary embolism severe enough to cause right heart strain. Ocular medications included difluprednate four times a day in the right eye, timolol-dorzolamide twice a day in the right eye, and timolol twice a day in the left eye. Systemic medications included amlodipine, simvastatin and warfarin. She denied any smoking history.

Examination

Ocular examination revealed best corrected visual acuity of 20/80 in the right eye and 20/400 in the left eye. There was no afferent pupillary defect. A comitant left exotropia was noted, with full ocular motility of both eyes. Visual fields were full in both eyes by confrontational testing. Applanation tonometry measured an intraocular pressure of 23 mmHg in the right eye and 17 mmHg in the left eye. Proptosis of the right eye was noted and confirmed by Hertel exophthalmometry that measured 20 mm on the right versus 13 mm on the left with a base of 113 mm. An orbital bruit was not appreciated.

Slit-lamp examination revealed normal adnexa and eyelids. The right eye exhibited diffusely dilated and tortuous episcleral vessels that were noted to have a "corkscrew" appearance. There was no tenderness on palpation of the right globe over a closed eyelid. The conjunctiva, episclera and sclera of the left eye were white and quiet. The anterior chamber of both eyes had trace cell without flare. Posterior chamber intraocular lenses were present in both eyes. Posterior exam of the right eye revealed a mildly edematous optic disc with shunt vessels, dilated and tortuous retinal veins in all four quadrants, flame shaped and dot hemorrhages, and macular edema. The left eye showed a tilted nerve with an otherwise normal-appearing fundus. Optical coherence tomography was performed, showing macular edema in the right eye. Fluorescein angiography of the right eye revealed a delayed arteriovenous phase, late macular and disc leakage and some areas of nonperfusion.

What is your differential diagnosis? What further workup would you pursue? Please turn to p. 84


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For patients starting or changing PGA therapy

Drop IOP.
Keep monotherapy.

Indication: LUMIGAN® (bimatoprost ophthalmic solution) 0.01% is indicated for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

Important Safety Information

Warnings and Precautions: LUMIGAN® causes changes to pigmented tissues, mostly increased pigmentation of the iris, eyelid, and eyelashes as long as LUMIGAN® is administered. Iris color change may not be noticeable for several months to years. After discontinuation of bimatoprost, iris pigmentation is likely to be permanent, while eyelid and eyelash changes have been reported to be reversible in some patients. Patients should be informed of the possibility of increased pigmentation. The long-term effects of increased pigmentation are not known.

LUMIGAN® should be used with caution in patients with active intraocular inflammation (eg, uveitis) because the inflammation may be exacerbated. Macular edema, including cystoid macular edema, has been reported with LUMIGAN®. LUMIGAN® should be used with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema.

Adverse Reactions: The most common (25%-45%) adverse event with LUMIGAN® was conjunctival hyperemia. Approximately 0.5% to 3% of patients discontinued therapy due to conjunctival hyperemia. Other common events (> 10%) included growth of eyelashes and ocular pruritus.

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

Write it RIGHT 0.01%

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(bimatoprost ophthalmic solution) 0.01%