Managing Vision Disorders in Children, p. 32

REVIEW® OF OPTOMETRY

July 15, 2019

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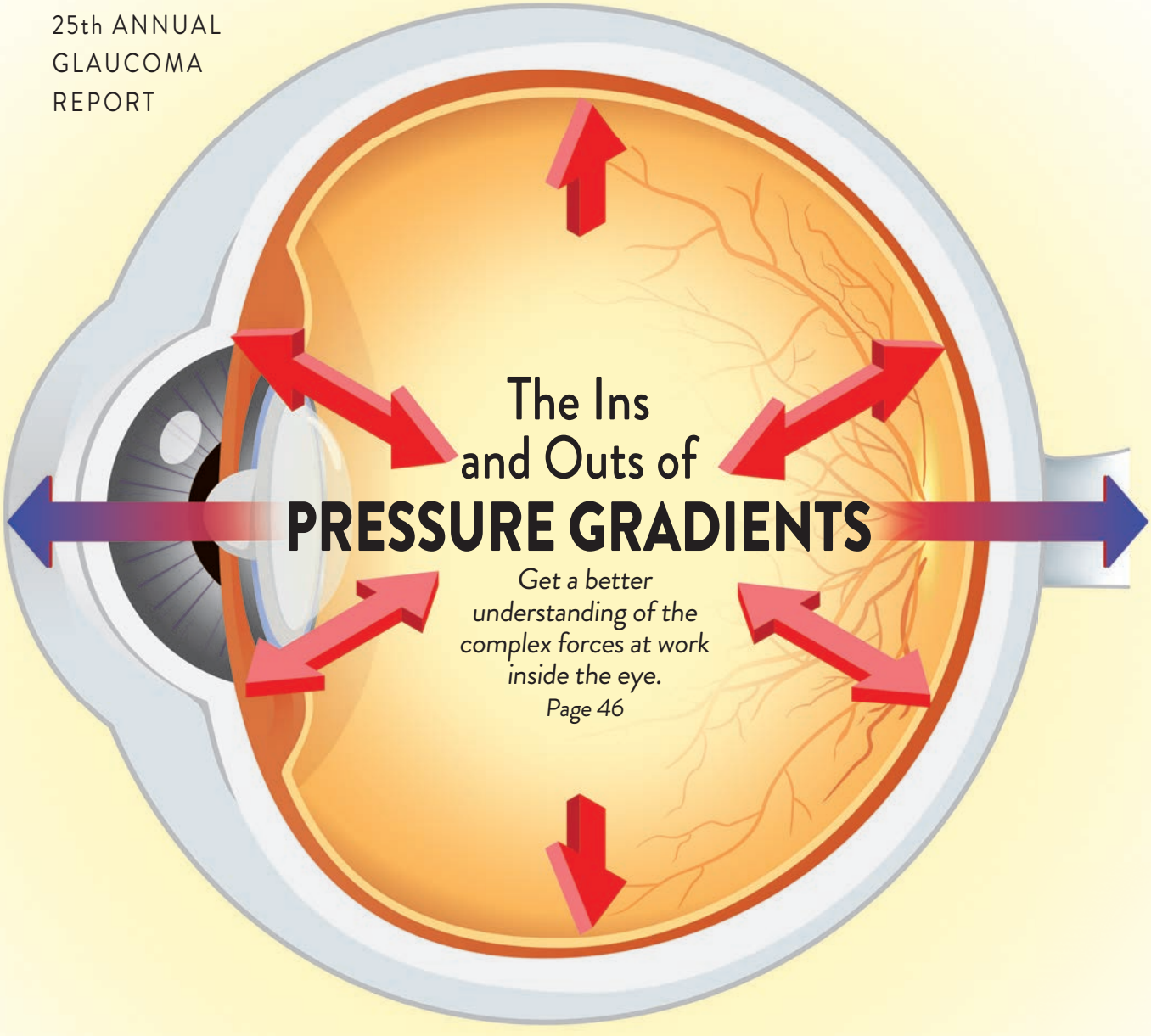

The Ins and Outs of PRESSURE GRADIENTS

Get a better understanding of the complex forces at work inside the eye.

Page 46

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*These statements have not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease.

†For patients with moderate to advanced age-related macular degeneration.

Reference: 1. Age-Related Eye Disease Study 2 (AREDS2) Research Group. Lutein + zeaxanthin and omega-3 fatty acids for age-related macular degeneration: the Age-Related Eye Disease Study 2 (AREDS2) randomized clinical trial. *JAMA*. 2013;309(10):2005-2015.

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VOL. 156 NO. 7 ■ JULY 15, 2019

IN THE NEWS

One 10mL drop of lissamine green is sufficient when assessing lid wiper epitheliopathy (LWE) and waiting three to five minutes before inspecting the staining will garner better results than checking after one minute. Researchers found that drop dosage and time were significant because of the change in minimum intensity that occurred over time and the difference in minimum intensity that existed overall between the specific staining conditions.

Lievens C, Norgett Y, Briggs N, Vianya-Estopa M. Intensity of lid wiper epitheliopathy staining with alterations of dye amounts and timing of observation. ARVO 2019. Abstract 6763.

Researchers found that **high cholesterol may have a role in early AMD development**. The study included records of 194 men evaluated in the 1960s and again between 2005 and 2012. Those who developed intermediate or late AMD by the recent exam had significantly higher total cholesterol (TC) in their first exam. Those with high TC in the original exam also had the largest drusen size (≥125µm) compared with the other subjects.

Kananen F, Strandberg T, Loukovaara S, et al. Early middle-age cholesterol levels and the risk of age-related maculopathy. ARVO 2019. Abstract 1158.

A new study shows that **patients taking lipid-lowering drugs before their Type 2 diabetes diagnosis were significantly less likely to progress to diabetic retinopathy (DR)**. Approximately 6% of patients already taking lipid-lowering drugs eventually were diagnosed with nonproliferative DR, proliferative DR or diabetic macular edema. Of those not taking lipid-lowering medications, 6.5% had one of those diabetic eye diseases.

Vail D, Callaway N, Ludwig C, et al. Lipid-lowering medications are associated with lower risk of retinopathy and ophthalmolic interventions among U.S. patients with diabetes. Am J Ophthalmol. June 10, 2019. [Epub ahead of print].

Cosmetics Affect Contact Lens Parameters

Makeup removers and mascara are the two biggest offenders. **By Rebecca Hepp, Managing Editor**

Cosmetics are a way of life for many patients, yet they can cause significant ocular issues. Even when used appropriately, they can be toxic to the ocular surface and can interfere with safe contact lens wear.[1,2] Silicone-based lenses in particular, given their lipophilic nature, are more prone to absorb waterproof cosmetics that often contain oil-based or silicone-based film-forming agents.[3] And no matter how careful patients are, many still get cosmetic products on their lenses, which can alter the parameters, new research shows.[4]

Researchers recently studied cosmetics' impact on the physical dimension and optical properties of three monthly replacement silicone hydrogel contact lenses.[4]

They coated three lens types—Acuvue Vita (Johnson & Johnson Vision), Ultra (Bausch+Lomb) and Air Optix plus Hydraglyde (Alcon)—with three hand creams, three makeup removers and three mascaras, followed by a one-hour soak in phosphate-buffered saline. They created six replicates for each lens-cosmetic combination and assessed the lenses for diameter, sagittal depth, base curve, lens power and optical quality.[4]

Compared with uncoated control lenses, the test lenses coated with mascara or makeup remover were affected, while those coated with the hand creams were not. All of the parameter changes were dependent on the lens type and the specific cosmetic tested. For two of the lenses, one of the makeup removers led to a diameter increase of 0.26mm, while another remover showed a 0.35mm increase—both removers decreased the diameter of the third lens by 0.01mm. Mascara impacted sagittal depth the most, with one product increasing the sagittal depth in the three lenses by 0.16±0.06mm, 0.24±0.22 and 0.26±0.09mm. Base curve changed by as much as 0.35mm when coated with two of the three mascaras.[4]

The researchers note that the Acuvue Vita had a surprising power change of –1.18±0.65D (more minus) when exposed to one of the mascaras.[4]

"Makeup removers and mascaras changed the lens parameters to varying degrees, which may affect the fit and overall performance of the lens," they concluded.[4]

1. Chen X, Sullivan DA, Sullivan AG, et al. Toxicity of cosmetic preservatives on human ocular surface and adnexal cells. Exp Eye Res. 2018;170:188-97.
2. Tsukiyama J, Miyamoto Y, Fukuda M, et al. Influence of eye cosmetics and cleansing products on contact lenses. J Jpn CL Soc. 2010:52:101-7.
3. Carney FP, Nash WL, Sentell KB. The Absorption of major tear film lipids in vivo to various silicone hydrogels over time. Invest Ophthalmol Vis Sci. 2008 Jan;49(1):120-4.
4. Luensmann D, van Doorn K, May C, et al. The impact of cosmetics on the physical dimension and optical performance of contemporary silicone hydrogel contact lenses. Eye Contact Lens. June 19, 2019. Epub ahead of print].

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PEDs May Signal Choroidal Nevi

Serous pigment epithelial defects are often an incidental finding during a retinal exam, but clinicians should take notice, since they may point to choroidal neovascularization, researchers from the Jules Stein Eye Institute report.

Their study, presented at the 2019 ARVO meeting, enrolled 360 eyes with choroidal nevi, including 19 eyes associated with serous pigment epithelial defects, detected with OCT.

The study reported nine of those 19 eyes (47%) had no change in OCT imaging over the approximate three-year follow-up. In three of the 19 eyes (16%), serous pigment epithelial defects overlying choroidal nevi were associated with choroidal neovascularization.

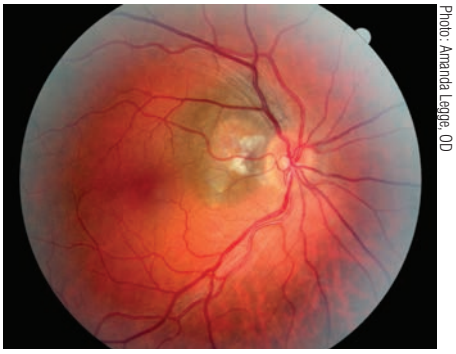


Photo: Amanda Legge, OD

A choroidal nevus, as seen here, may be accompanied by serous pigment epithelial defects, according to new research.

These patients were treated with anti-VEGF therapy (one prior to evaluation and two during routine follow-up).

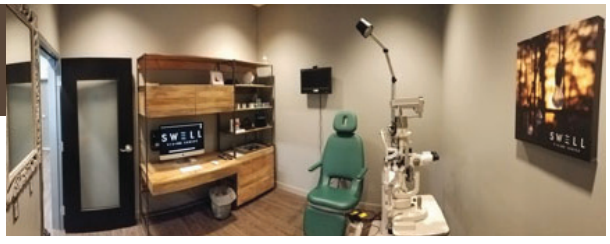
The study also found one of the 19 eyes developed associated subretinal fluid and orange pigment that was subsequently treated with plaque radiotherapy for presumed malignant transformation.

An additional four eyes with serous pigment epithelial defects had associated subretinal fluid without shaggy photoreceptors or obvious orange pigment and were stable without signs of progression to choroidal malignant melanoma by B-scan ultrasound and fundus photos.

Serous pigment epithelial defects are a rare finding associated with choroidal nevi and can often be mistaken for subretinal fluid during a clinical exam, but it is rarely a sign of malignancy, researchers added.

Hou KK, Soberón V, McCannel TA. Serous pigment epithelial detachments associated with choroidal nevi. ARVO 2019. Abstract 724 - B0202.

2019 Office Design Contest
Call for Entries



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Endophthalmitis Under the Microscope

Two new studies shed light on the best prophylactic approach to avoid endophthalmitis, a rare but serious adverse event, and when a culture might be worth it when it does present.

Moxifloxacin Most Successful

Patients with open-globe injuries routinely receive fluoroquinolone prophylaxis to prevent infectious endophthalmitis. However, there's a dearth of clinical trials evaluating optimal prophylactic dosing, given the rarity of this infection.[1]

To address this knowledge gap, researchers in Canada did a risk assessment study to identify the antibiotic dosing options that optimize prophylactic treatment success against common bacterial pathogens implicated in post-traumatic endophthalmitis. They found that moxifloxacin 400mg PO daily had the highest likelihood of reaching the target concentration ratios in the vitreous humor necessary to prevent post-traumatic endophthalmitis. The study also found this dosing option was superior to the ciprofloxacin and levofloxacin dosing options currently endorsed by expert opinion.[1]

The team used data from published studies to evaluate five fluoroquinolone dosing options to determine which performed best. Moxifloxacin 400mg PO daily led the pack with a 72% probability of achieving the target response, followed by levofloxacin, which was successful between 54% and 63% of the time. Ciprofloxacin's cumulative fraction of response was between 28% and 35%.[1]

Culture Predicts Outcomes

After assessing whether vitreous culture results affect the clinical management of patients with acute endophthalmitis after intravitreal anti-VEGF injection, researchers from Philadelphia's Wills Eye Hospital found that vitreous culture data may help anticipate visual outcomes but appear to have a limited effect on clinical management.[2]

This single-center, retrospective case series evaluated patients who developed endophthalmitis after intravitreal anti-VEGF injection. Of 204,986 anti-VEGF injections performed, the team identified 60 cases of endophthalmitis (0.0293%), of which 18 were culture-positive. Three of 18 culture-positive cases (17%) had a change in clinical management, while another three of 42 culture-negative cases (7%) also underwent a management change.[2]

The study authors changed their management strategy based on either declining vision or worsening clinical exam, and did not perform any additional interventions based on positive-culture results. Comparing vision loss from baseline by culture result at final follow-up, they note that oral flora-associated culture-positive cases lost 17.5 lines, non-oral flora-associated culture-positive cases lost 9.1 lines and culture-negative cases lost 2.5 lines of vision.[2]

1. Peragine C, Walker SAN, Walker S, et al. Fluoroquinolone antibiotic prophylaxis to prevent post-traumatic bacterial infectious endophthalmitis: using Monte Carlo simulation to evaluate the probability of success. J Ocul Pharm Thera. May 8, 2019. [Epub ahead of print].
2. Patel SN, Storey PP, Pancholy M, et al. Changes in management based on vitreous culture in endophthalmitis after intravitreal anti-vascular endothelial growth factor injection. Am J Ophthalmol. June 13, 2019. [Epub ahead of print]

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Diabetes Impacts Young Eyes

Among American youths, diabetes is growing—and fast.[1] From 2002 to 2012, newly diagnosed cases of Type 2 diabetes in patients younger than age 19 jumped by 7.1% annually.[1] No wonder, then, patients in their mid-20s are seeing serious impact to their eye health.

Previously, investigators used data collected as part of the Treatment Options for Type 2 Diabetes in Adolescents and Youth study, looking at 699 newly diagnosed Type 2 diabetic adolescents aged 10 to 17 from 2004 to 2011.

A recent follow-up—the Longitudinal Outcomes in Youth With Type 2 Diabetes study—enrolled 517 of those original participants, now in their mid-20s. On average, they saw increases in body mass index and HbA1c. Their eyes were worse for the wear, too, as investigators noted significant diabetic retinopathy progression.[2] Of the 370 returning participants with diabetes who had their fundus photos taken in 2011 and again in 2018, 22% had developed mild nonproliferative diabetic retinopathy (NPDR).[2] In 2011, only 14% has mild NPDR. Additionally, 4% developed macular edema, up from none in 2011.

Altogether, 142 adjudicated eye events were seen, including NPDR, proliferative diabetic retinopathy, macular edema, cataracts and glaucoma—equal to 15.5 eye disease events per 1,000 patients per year.[3] Of particular note, diabetic retinopathy was more prevalent among those who did not maintain glycemic control.[3]

1. Mayers- Davis E, Lawrence J, Dabelea D, et al. Incidence trends of Type 1 and Type 2 diabetes among youths, 2002–2012. New Eng J Med. 2017;376:1419-29.
2. Zeitler P, Hirst K. Treatment options for Type 2 diabetes in adolescents and youth (TODAY). Clin trials. https://clinicaltrials.gov/ct2/show/record/NCT00081328. May 2019. Accessed June 14, 2019.
3. Busko M. Alarming complications in 20-year-olds with Type 2 diabetes. Medscape. June 14, 2019.

Vitreolysis Patients Unhappy With Results

Studies investigating the structural and functional effects of Nd:YAG laser vitreolysis with objective outcome measures are slim to none. However, researchers have recently turned that around, founding that patients who had vitreolysis for vitreous floaters had a less dense vitreous than untreated controls. Unfortunately, they still had similar visual function.

This retrospective, comparative study evaluated 132 eyes of 132 subjects—35 healthy controls, 59 untreated controls and 38 subjects with vitreous floaters who underwent laser treatment. The team used an NEI visual function questionnaire (VFQ-39) to assess visual well-being, quantitative ultrasonography to measure vitreous structure and best-corrected visual acuity (BCVA) and contrast sensitivity function to evaluate vision.

Compared with healthy controls, the study authors observed that untreated subjects reported worse VFQ-39 scores and had 57% greater vitreous echodensity and significant contrast sensitivity function degradation (130%). Compared with untreated eyes, they note that vitreolysis eyes had 23% less vitreous echodensity but no differences in VFQ-39 score, BCVA or contrast sensitivity function.

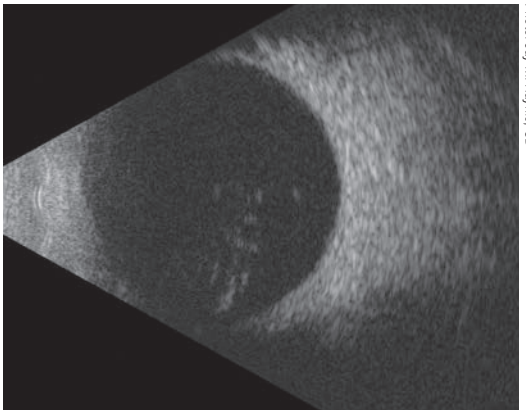

Photo: Jay M. Haynie, OD

An ultrasound of symptomatic vitreous floaters in a patient considering surgical management.

They also discovered that 25 of the vitreolysis patients were unhappy with the results and sought vitrectomy, while 13 were satisfied with observation only. They add that subjects seeking vitrectomy had 24% greater vitreous echodensity and 52% worse contrast sensitivity function.

Since some treated eyes had a less dense vitreous and better visual function than untreated eyes, the researchers suggest the next step is conducting a prospective, randomized study of Nd:YAG laser treatment of the vitreous using uniform laser treatment parameters and objective quantitative outcome measures. ■

Nguyen JH, Nguyen-Cuu J, Yu F, et al. Real-world assessment of vitreous structure and visual function after Nd:YAG laser vitreolysis. Ophthalmology. June 21, 2019. [Epub ahead of print].

BRIEF SUMMARY OF PRESCRIBING INFORMATION

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

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

Initial U.S. Approval: 2017

1 INDICATIONS AND USAGE

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

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Pigmentation

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

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

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

5.2 Eyelash Changes

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

5.3 Intraocular Inflammation

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

5.4 Macular Edema

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

5.5 Bacterial Keratitis

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

5.6 Use with Contact Lens

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

6 ADVERSE REACTIONS

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

6.1 Clinical Trials Experience

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

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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

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

The background risk of major birth defects and miscarriage for the indicated population is unknown. However, the background risk in the U.S. general population of major birth defects is 2 to 4%, and of miscarriage is 15 to 20%, of clinically recognized pregnancies.

Data

Animal Data

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

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

8.2 Lactation

Risk Summary

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

8.4 Pediatric Use

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

8.5 Geriatric Use

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

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

13.2 Animal Toxicology and/or Pharmacology

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

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

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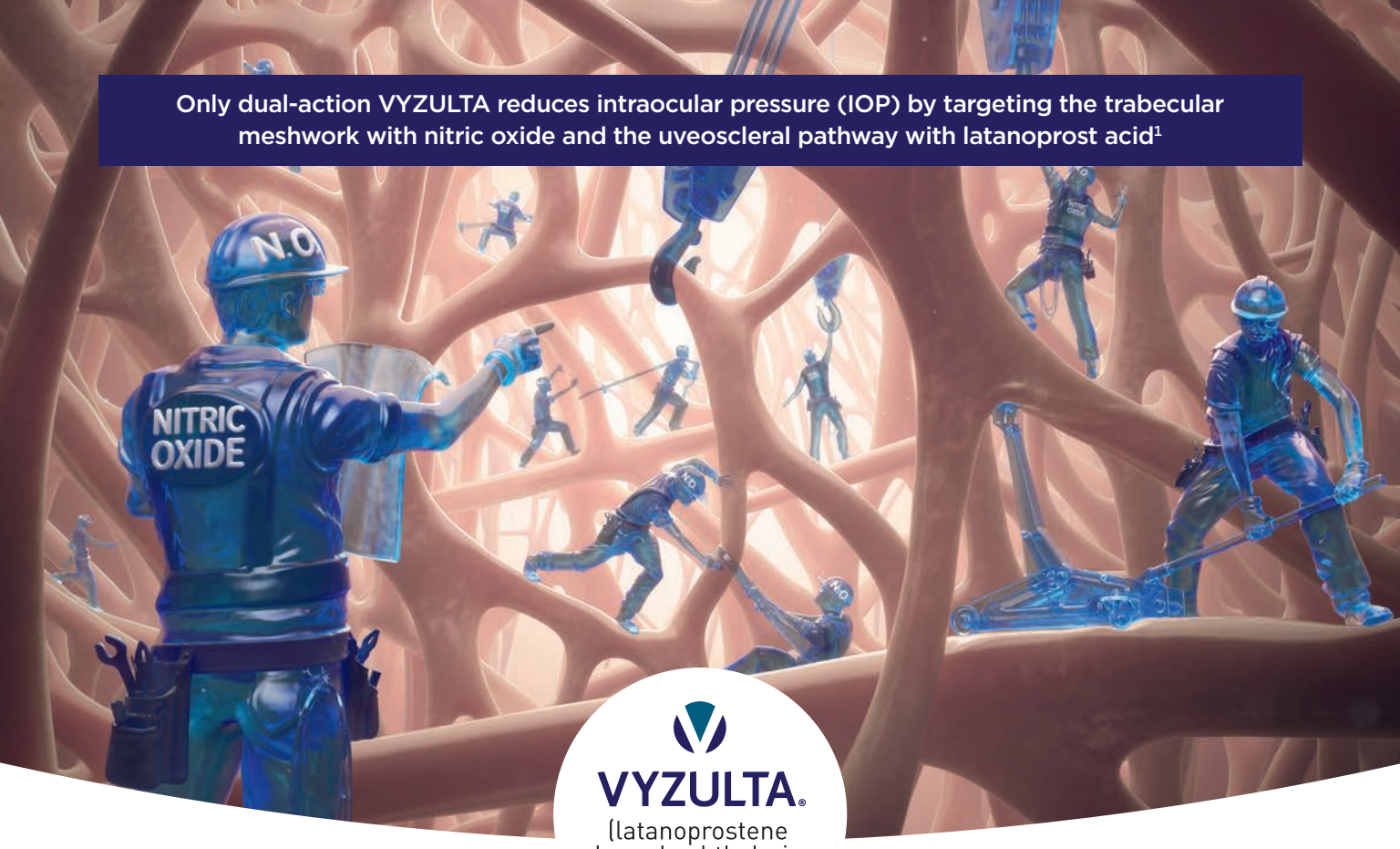

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VYZULTA achieved significant and sustained long-term IOP reductions vs Timolol 0.5% in pivotal trials[7]

P<0.001 vs baseline at all pre-specified visits over 12 months in a pooled analysis of APOLLO and LUNAR clinical trials (N=831)

VYZULTA demonstrated safety profile in clinical trials

Only 6 out of 811 patients discontinued due to ocular adverse events in APOLLO and LUNAR clinical trials[1,8,9]

Visit VYZULTANOW.com to see our efficacy results

INDICATION

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

IMPORTANT SAFETY INFORMATION

- Increased pigmentation of the iris and periorbital tissue (eyelid) can occur. Iris pigmentation is likely to be permanent
- Gradual changes to eyelashes, including increased length, increased thickness, and number of eyelashes, may occur. These changes are usually reversible upon treatment discontinuation
- Use with caution in patients with a history of intraocular inflammation (iritis/uveitis). VYZULTA should generally not be used in patients with active intraocular inflammation
- Macular edema, including cystoid macular edema, has been reported during treatment with prostaglandin analogs. Use with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema

IMPORTANT SAFETY INFORMATION cont'd

- There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products that were inadvertently contaminated by patients
- Contact lenses should be removed prior to the administration of VYZULTA and may be reinserted 15 minutes after administration
- Most common ocular adverse reactions with incidence ≥2% are conjunctival hyperemia (6%), eye irritation (4%), eye pain (3%), and instillation site pain (2%)

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

References: 1. VYZULTA Prescribing Information. Bausch & Lomb Incorporated. **2.** Cavet ME. *J Ocul Pharmacol Ther*. 2018;34(1):52-60. DOI:10.1089/jop.2016.0188. **3.** Wareham LK. *Nitric Oxide*. 2018;77:75-87. DOI:10.1016/j.niox.2018.04.010. **4.** Stamer DW. *Curr Opin Ophthalmol*. 2012;23:135-143. DOI:10.1097/ICU.0b013e32834ff23e. **5.** Cavet ME. *Invest Ophthalmol Vis Sci*. 2015;56(6):4108-4116. **6.** Kaufman PL. *Exp Eye Research*. 2008;861:3-17. DOI:10.1016/j.exer.2007.10.007. **7.** Weinreb RN. *J Glaucoma*. 2018;27:7-15. **8.** Weinreb RN. *Ophthalmology*. 2016;123(5):965-973. **9.** Medeiros FA. *Am J Ophthalmol*. 2016;168:250-259.

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Contents

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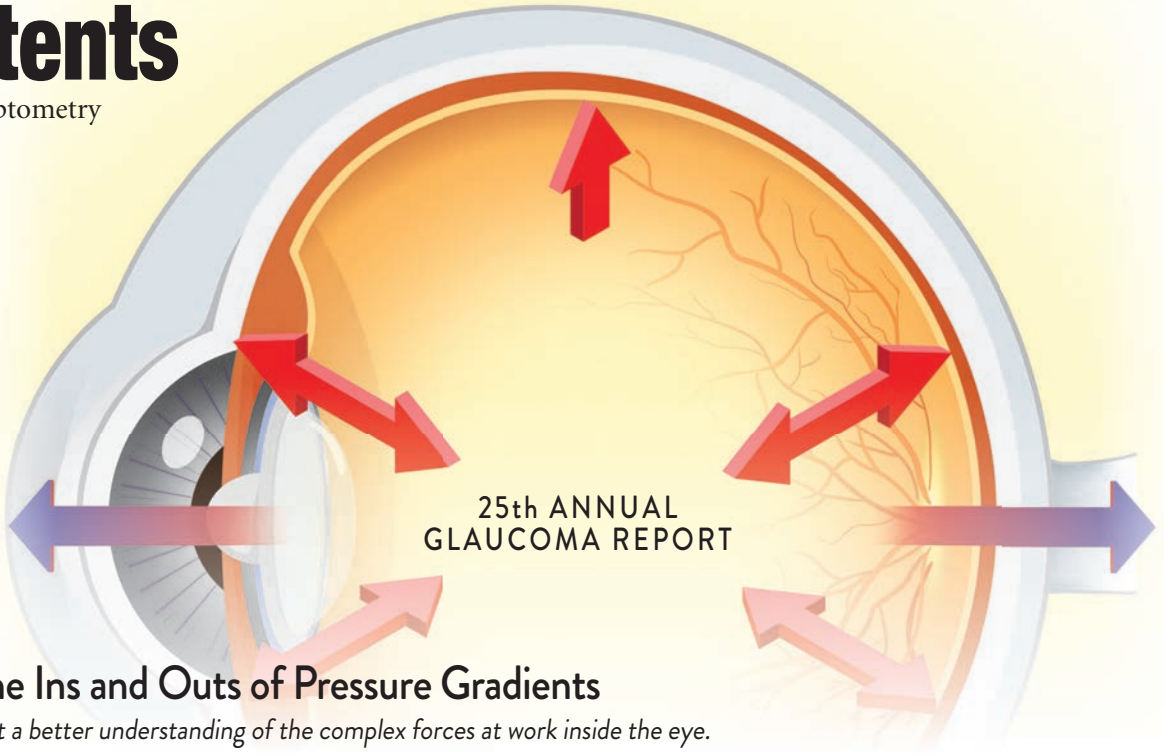
July 15, 2019



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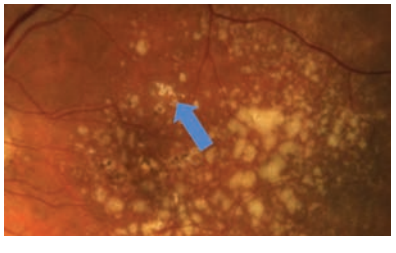

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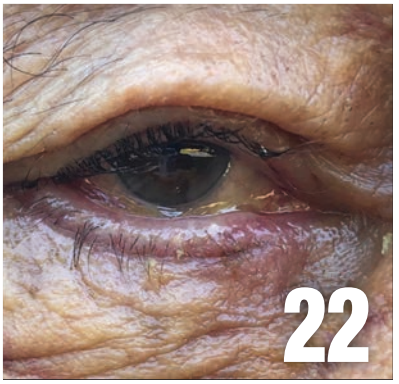

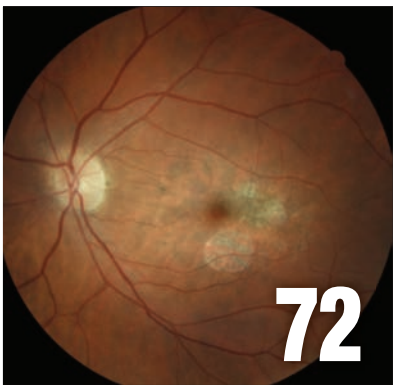

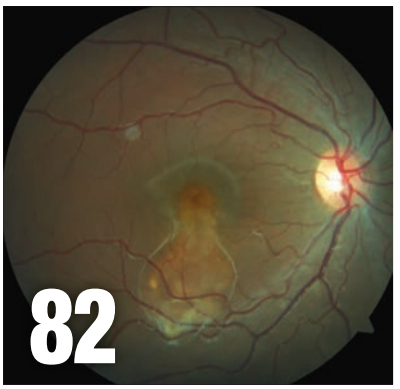

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References:

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

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

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

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

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

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

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

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

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

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

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

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

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Outlook

By Jack Persico, Editor-in-Chief

Optometry on Trial—Again

The public may get to make the call on a contested scope expansion bill. Will it be another PR nightmare?

Consider this commentary on your profession: "There are many conscientious and skilled optometrists; men who will frankly admit their limitations when they see that the eye conditions of their visitors are beyond their abilities and training. But there are many optometrists—far too many—who blithely undertake problems beyond their training. To consult one of these, when you have serious eye trouble, may be worse than useless."

Aside from the sexism (not all ODs are men, by a long shot), that could have been published today. But it dates back to 1937, the year *Reader's Digest*, of all publications, attacked the still-young profession of optometry in a scathing, exposé-style article called "Optometry on Trial." You can read all about it in our 125th anniversary issue from July 2016, but the gist is that *Reader's Digest* took it upon itself to have people pose as patients and sent them for optometric exams in hopes of uncovering widespread ineptitude.

That article and the ensuing scandal stymied optometry's progress for years. Now, a group called the Safe Surgery Coalition is hoping to do the same, using a video testimonial by a woman who experienced complications (IOL pitting) from an optometrist's capsulotomy to gin up support for a letter-writing campaign aimed at stopping scope expansion bills that push for minor surgical procedures.

The patient's suffering is legitimate and shouldn't be marginalized. But complications do happen, no matter who's sitting behind the laser. Studies show IOL pitting occurs in 10% to 20% of cases. Are we to believe these were all done by ODs? I find it odd that the medical lobby—usually so straight-laced about adhering to the tenets of evidence-based medicine—would rely almost entirely on a single report to support its argument. Since when does n=1 indicate strong evidence of anything?

Anyway, such was the opening gambit in the group's bid to undo the recent bill that gave Arkansas ODs the right to do laser procedures. The MDs have called for a referendum on the bill to be added to the November 2020 ballot. If they get the requisite signatures by July 23, optometry's fate suddenly will be decided in the court of public opinion.

So be it. This isn't the '30s. Today's educational institutions and professional standards are radically better. If we're about to embark on a year and a half of public bickering over qualifications, optometry has plenty to tout, first and foremost 20 years of successful outcomes in Oklahoma. Also, the AOA is publicizing a study projecting a $4.6 billion savings to be had from widespread scope expansion and a survey showing strong public support for optometric care. A new OD group called Arkansans for Healthy Eyes is already working hard to cut through the disinformation campaign in that state. We're ready.

"The article contains some truth," *Review*'s editor wearily wrote back in 1937, "but it also contains some half-truths, a good deal of exaggeration and generalization, some statements that are manifestly unfair and some that are positively silly." Brace yourself for more of the same. ■

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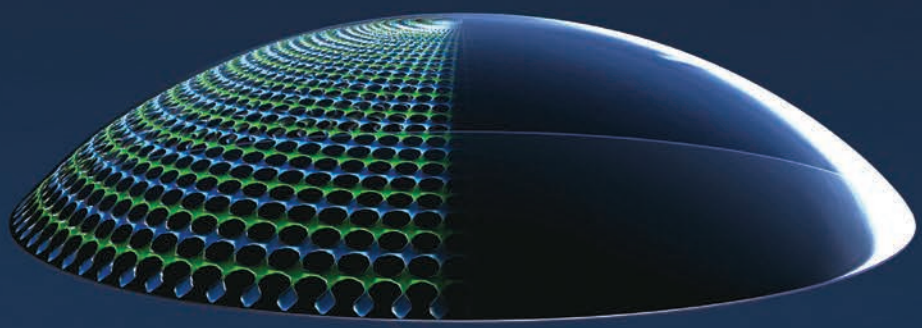

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Glaucoma on the Surface

Comorbidities are inevitable, and we need to consciously look for them in every glaucoma patient. **By Paul M. Karpecki, OD, Chief Clinical Editor**

We are all guilty at one point or another of getting into a silo when we categorize a patient, especially if that patient has a chronic, progressive disease such as glaucoma. I myself, a cornea specialist, tend to ignore ocular surface considerations when first treating a glaucoma patient. However, these are co-existing diseases and often require concurrent care.

Double Trouble

Research shows glaucoma patients on long-term preserved drops have a significant increase in ocular surface disease (OSD).[1] One study found that at least three years of therapy increased the odds ratio of OSD by more than 5x, which jumps to 100x with at least 2,000mcg of benzalkonium chloride (BAK) exposure.[1]

Another team of researchers found glaucoma patients experiencing ocular side effects had far more progression in the first 2.5 years after diagnosis compared with those who did not report ocular side effects—a 3.3x greater relative risk of progression.[2]

This is significant, considering one study of more than 20,500 glaucoma patients found those with OSD had 12x the rate of symptoms such as foreign body sensation and ocular pain and 4x the rate of blurred vision and photophobia compared with patients without OSD.[3]

Save the Surface

We are always hesitant to add another medication to a glaucoma patient's regimen, but sometimes it is necessary. When it is, be selective and consider different glaucoma medications. Preservative-free therapeutics to treat the inflammation include Xiidra (lifitegrast, Shire), Restasis (cyclosporine, Allergan) or, in the near future, Cequa (cyclosporine, Sun Pharma).

If the patient has blepharitis or meibomian gland disease, consider in-office blepharoexfoliation with Blephex (Rysurg), thermal pulsation with LipiFlow (TearScience), iLux (Alcon) or TearCare (Sight Sciences), or intense pulsed light therapy (Lombart EyeLight or Lumenis) followed by a daily hydrating compress (e.g., Bruder Medibeads).

For glaucoma, consider preservative-free drops such as Zioptan (Akorn) and Cosopt PF (Akorn) or drops with non-BAK preservatives. A single agent that has the most IOP-lowering effect such as Vyzulta (Bausch + Lomb) or Rocklatan (Aerie) can help to avoid adding more drops to the regimen. Preservative-free compounded drops, such as the Imprimis triple or quad drops, may also be helpful options.

If the OSD is significant, selective laser trabeculoplasty or a minimally invasive glaucoma surgery at the time of cataract surgery can help to reduce or even eliminate the patient's glaucoma medications. New research shows that more than 80% of patients previously using a single glaucoma therapy were medication-free three years after a Hydrus microstent (Ivantis) was inserted.[4,5]

It's time to start looking at comorbidities such as OSD as the reason for failures and frustrations in glaucoma. Manage these, and your success will rise significantly. ■

Note: Dr. Karpecki consults for companies with products and services relevant to this topic.

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Compliance Concerns

The pain upon instillation and blurred vision glaucoma medications can often lead to poor drop adherence, which is a significant reason for disease progression. However, patients often resume their glaucoma drops a week or a few days before a scheduled follow-up. One study found patients over-estimated their adherence to their glaucoma medications by 95%, and patient adherence peaked just prior to an appointment and then lapsed soon after the exam, confounding long-term IOP assessments.[1] The resultant increase in IOP leads us practitioners to think the glaucoma medication regimen needs a shakeup when in fact it's patient adherence that's the issue.

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Step Away From the Donuts

Office snacking is all about making healthy choices—and hiding your stash of the good stuff. **By Montgomery Vickers, OD**

Optometry makes me hungry—not for fame and fortune, but for food. The problem with this is that, even though thinking hard is estimated to burn around 20% of the calories we intake every day, the other 80% resides in my waistline.

It's OK… bread, pasta and donuts were invented by God for us to enjoy, and I tried to keep my employees on a sugar buzz throughout my career. This exponentially increases energy levels, speeds up their work and makes every second much more productive. Unfortunately, the improvement only lasts for about 10 minutes before the donut coma sets in.

The Snack Drawer

After 20 years, 25 pounds and a couple of crushed office chairs, I got the picture and changed the food groups I lovingly provided.

My staff members were thrilled with the fresh fruit, vegetable trays, fine cheeses and sparkling waters. And by "thrilled" I mean "confused and disappointed." I lost weight, but they started stealing drawer space for candy bars, cookies and, of course, donuts.

My spread of fine cheeses became a bacteriological research project. I had to make one of the most important decisions of my career. After much prayer, I started hoarding my own cookie drawer. I couldn't let my wife/office manager find out, as that could be more dangerous than any sleepy staff member by far.

Our sugar buzz mojo was back and stuff started to get done again. The staff members secretly shared their treats, and I secretly threw them some cash from time to time to reload. I gained back that weight and had a hard time convincing my wife/office manager that this eating plan was a powerful tax deduction and instrumental to our ability to put our kids through college.

However, I did feel guilty that I, a licensed health care provider, was contributing to not only my own future heart attack but also to that of my wonderful, loving staff members. I needed to reduce the potential for diabetes and heart disease in my office—and my guilt—so, I downsized and fired most of them. This reduced my snack collateral damage from eight people to two, and I slept better at night.

Redirect Your Taste Buds

Now, as the new junior associate in two practices in Texas, I have no power over the snack table. I love the lack of responsibility. However, every strip mall in Dallas has three things in common: (1) a reflexology center, (2) a dentist and (3) a donut shop.

I'm a sucker for two of the three (my daughter and her husband are dentists and my son is an oral surgeon). But I dream of someone working over my feet while I gorge on donuts. No wonder everyone is moving to Texas.

Based on the state of unlimited tamales and brisket, my new staff understands me well. I can say "no" to pecan pie far more easily if a bowl of keto-friendly burnt barbecue ends is readily available. I decided to drop 20 pounds and, thanks to my new choices, I'm only 35 pounds away.

Actually, I have lost 15 pounds and I feel quite spry. And now I avoid the donuts, opting instead for the obviously more healthy choice of 10 or 12 donut holes once every 90 days. This reminds me… another quarter has passed, so I am off to treat my feet and eat my treat. ■

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Turning Inward

Brush up on the treatment options for involution entropion.

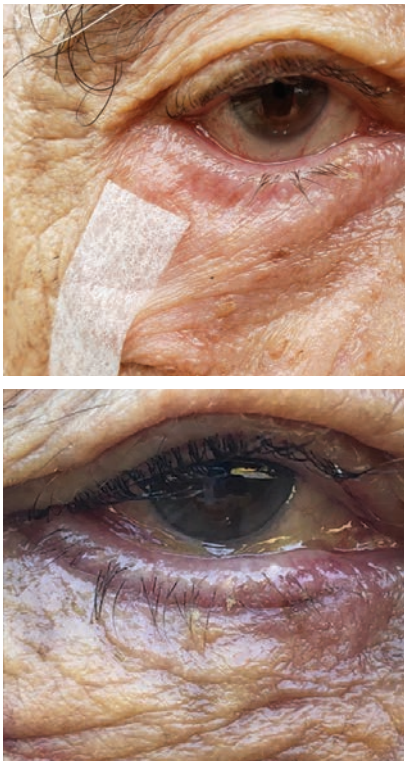
Edited by Paul C. Ajamian, OD

Q I have a patient with significant entropion and lashes contacting the globe that are causing a great deal of discomfort. Artificial tears aren't helping. What are some short- and long-term solutions?

A There are a number of causes of a lower lid that turns inward. Involutional entropion is established after ruling out cicatricial or mechanical causes, according to Brent Murphy, MD, of Atlanta Oculofacial Plastic Surgeons. "Check the conjunctiva for scarring that is pulling the eyelid inward," Dr. Murphy says. "Entities such as ocular cicatricial pemphigoid or prior chemical burn can cause this." Get a good external view of the lids and lashes and gently pull the lower lid down to compare the normal position of the lid with the inverted configuration.

"The short-term solutions you can offer patients with involutional entropion are lubricating ointment and what I like to call 'the tape trick,'" Dr. Murphy says. Apply a small piece of paper tape vertically on the patient's cheek to pull the lower lid down enough so that it does not turn in. Apply the tape about a centimeter from the lid margin on the lateral third of the lid. Then apply mild inferolateral tension and secure the tape to the cheek.

"This is a very useful temporary fix that can keep the patient out of trouble while awaiting the definitive fix, which is often surgical," Dr. Murphy says. "It's also simple for the patient to reapply at home after getting the tape wet during a shower."



Taping the lid back to its normal position (top) can help resolve an entropion.

Involutional entropion is common in people over the age of 60. It is the result of a dehiscence of the lower eyelid retractors and horizontal laxity in the lower eyelid, which causes the lower lid to roll in. When this happens, it can be extremely uncomfortable, and the lashes rubbing the eye can put the cornea at risk of scarring or infection. Lubrication and the tape trick help avoid these problems.

Surgical Options

Surgical repair involves a fairly brief outpatient surgery that corrects the two underlying causes. Dr. Murphy uses the carbon dioxide laser to make an incision in the subciliary crease. Through that incision, the dehisced lower lid retractors can be reattached to the base of the tarsal plate, and a horizontal tightening can be done by full thickness excision of the lateral lid. The lid can then be reattached to Whitnall's tubercle. The incision is closed with dissolving sutures.

The postoperative course is relatively straightforward, says Dr. Murphy. Cold compresses are used the first three days while the patient is awake, and antibiotic ointment is used on the stitches until they are gone, usually by 10 days. Bruising and swelling dissipate over the first two weeks. Rarely do patients report pain, although the lateral canthal area remains tender for four to six weeks.

"During this time, as well as preoperatively, it is good for the optometrist to monitor the health of the corneal surface," Dr. Murphy says. Rarely does entropion lead to significant corneal abrasions or ulcerations. "I'll usually have the patient return four to six weeks after surgery for a final evaluation of the lid," Dr. Murphy notes.

This surgery provides a long-term fix for entropion, and complications are rare. The most common complication is wound dehiscence in the lateral canthus. "A complete eye examination three to four months after surgery ensures that no refractive changes have occurred from the lid tightening and that the eye is healing as desired," Dr. Murphy says. ■

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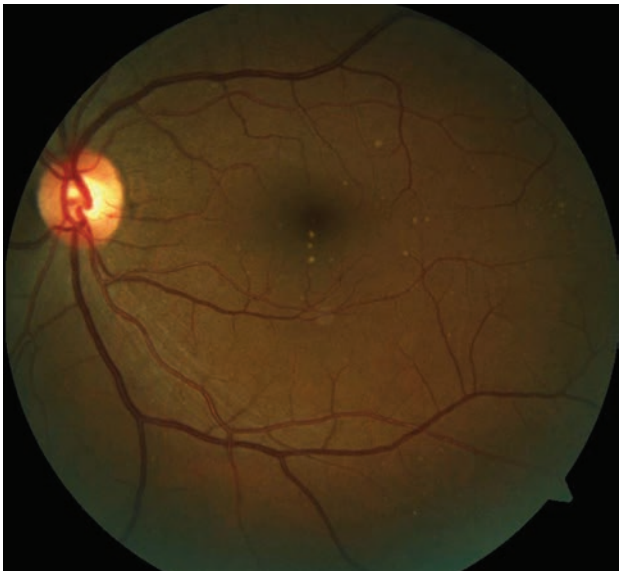
Crusin' for Drusen

These clinical findings are more elusive than you might think, and they don't always indicate macular degeneration. **By Bisant A. Labib, OD**

Drusen, along with pigment mottling, are the earliest clinical signs and a characteristic hallmark of age-related macular degeneration (AMD).[1,2] This is an important clinical finding, as AMD ranks globally as the third leading cause of blindness after cataracts and glaucoma.[2] Since AMD is chronic and progressive, early identification is imperative in delaying the course of the disease and referring for prompt treatment when necessary to preserve visual integrity.[2]



This patient has subretinal drusen deposits in the macular region.

However, drusen are also known to occur in younger eyes without AMD. This discussion of the unique pathophysiology and histological changes in AMD, and how it differs from healthy, non-pathological drusen deposition, can help you differentiate the two.

Debris Buildup

Drusen are extracellular deposits of debris and waste products that accumulate at the level of Bruch's membrane below the retinal pigment epithelium (RPE).[1] Clinically, they appear as focal, whitish yellow excrescences beneath the retina, often of variable size and number.[3] Despite significant advancement within the past several years in understanding the exact pathogenesis of AMD, the mechanism of drusen formation is not yet fully defined.[1]

Drusen deposits are made up of various proteins, polysaccharides, glycosaminoglycans and lipid, amyloid and complement factors that arise from inflammatory and immune responses to RPE cell damage.[1,2] This damage is made evident as a result of continuous light exposure at the RPE/Bruch's membrane interface and subsequent formation of reactive oxygen formation and oxidative stress.

Drusen may also become deposited from the choroidal vasculature and systemic circulation.[1] The accumulation of RPE waste products, among other types of cellular debris, results in the thickening of Bruch's membrane and decreased permeability. This influences the diffusion of nutrients and waste products between the RPE and choroidal bloodstream, leading to dysfunction.[1,3] Later in the disease, this dysfunction is made visible clinically as drusen.[2,3]

Drusen are also found in the periphery of normal eyes without AMD, with a few modifications in its makeup compared with degenerative macular drusen. While both are made up of several types of proteins, research shows crystallins are more abundant in AMD.[1] Histologically, hard drusen are amorphous, eosinophilic structures that are PAS positive and are much more compact than soft drusen. They are also associated with overlying RPE defects, whereas soft drusen are not. However, they may exhibit overlying RPE pigmentary changes.

Compared with the peripheral retina, the macula contains a greater number and density of photoreceptors and RPE cells, which contributes to the sharp visual acuity in that region. With normal aging, macular rod density declines by up to 30% while the number of photoreceptors, with the exception of severe AMD cases, remains stable. Light exposure over time and the accumulation of oxidative damage leads to reactive oxygen species formation and the impairment of outer

segment phagocytosis in this area by the RPE cells. Waste products then accumulate within the RPE and lead to deteriorating vision.

Drusen also attract increased inflammatory and vasoactive stimuli that can lead to progressive and more advanced signs of AMD, such as hemorrhaging and neovascular formation.[3]

Consistency is Key

Two main clinical classifications of drusen exist: hard and soft.

Hard drusen are smaller in size, nodular and appear clinically as discrete yellow spots.[1,2] Hard drusen are found in different ages and populations and generally are not a risk factor for AMD.[1,2,4] In fact, small, yellow lesions with sharply distinct margins are common in younger adults and reportedly a highly hereditary trait.[5]

Soft drusen are larger and more diffuse. It is the presence of numerous and confluent soft drusen that is considered a major risk factor in the development and progression of AMD.

Imaging Add-ons

Diagnosis of drusen is most commonly made through clinical exam and often with the help of color fundus photography. More recently, optical coherence tomography (OCT) has been helpful in the diagnosis and progression of drusen and additional changes related to AMD. Both hard and soft drusen appear as RPE elevations that are homogenous and convex structures. Progression is observed on OCT through changes in size as well as overlying pigment. It is also helpful in identifying additional AMD-related conditions, such as the presence of choroidal neovascularization, hemorrhage or pigment epithelial detachments.[6]

A Moving Target

In addition to variable mechanisms of formation and consistency, drusen can come and go. They are not always a steady clinical finding, as one study found between 20% and 34% of drusen disappear within a five to seven year span.[7] Researchers speculate growing drusen indicate a functioning RPE capable of secreting debris. Once the drusen are large enough, however, the RPE cells either migrate or die, cutting off the drusen's supply. This allows the clearing process to catch up, causing the drusen to disappear.[8] The variable presentation from visit to visit this process creates can lead to significant diagnostic confusion.

The pathological mechanisms for AMD are multifactorial and complex in nature, despite intense progress in research. As AMD is a leading cause of vision loss with limited treatment options, it is important for clinicians to identify the clinical risk factors for the development and progression of the disease as early as possible. Certain interventions, such as vitamin supplements, are beneficial only in earlier stages of the disease, warranting careful monitoring to reduce risk of debilitating vision loss. ■

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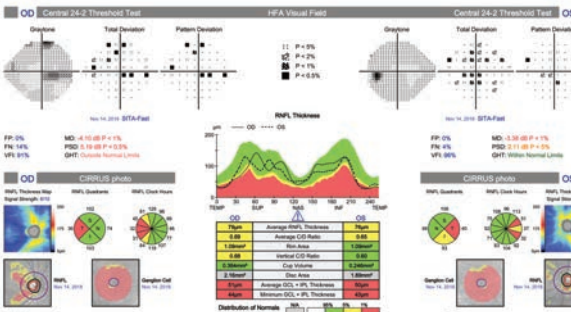
Don't Let Debilitation Progress

Suspect MS when patients present with optic nerve pallor and neuritis.

By Michael Trottini, OD, and Michael DelGiodice, OD, PhD, and Kaitlyn Kolzow, BS

A 38-year-old Caucasian female presented for a second opinion regarding progressive blurred vision (OU) and possible optic nerve pallor with moderate cup-to-disc ratio. Investigative historical findings elicited chronic malaise and progressive, bilateral visual decline over the course of 12 months. Further questioning revealed pronounced muscular fatigue, unsteady gait and visual decline following exercise.



Reduced NFL and GCC consistent with bitemporal pallor and VF loss can point to MS as the possible culprit.

Best-corrected visual acuity was 20/100 OU. The patient had pronounced horizontal jerk-type nystagmus in far lateral right and left gaze positions with noted oscillopsia. Horizontal saccades revealed a decrease in both accuracy and velocity. A dilated fundus examination revealed moderate neuroretinal rim thickness and poor perfusion of the temporal rim in each eye.

The finding of bitemporal pallor of the optic nerve prompted us to order spectral domain optical coherence tomography (SD-OCT) of the nerve fiber layer (NFL), ganglion cell complex (GCC) and formal visual fields (Humphrey 30-2). NFL and GCC were abnormally reduced in thickness bilaterally. Formal visual fields yielded a cecocentral scotoma in the right eye and scattered shallow point depressions in the left.

Evaluation

Given the above findings, the differential diagnosis included space-occupying lesion, demyelinating disease, nutritional optic neuropathy and autoimmune-related optic neuropathy. Consequently, we scheduled her for magnetic resonance imaging (MRI) of the brain and orbits with and without contrast and fat suppression. Imaging studies revealed multiple periventricular white matter (PWM) lesions.

Causes of PWM lesions are extensive but most commonly include normal (age-related) senescent changes, hypertension, focal cerebrovascular accidents, demyelination, migraine, vitamin B6 (pyridoxine) deficiency and infectious or inflammatory vasculitis.[1] All ordered serologies were within normal range.

Accordingly, we referred the patient to neurology for evaluation. An additional MRI of the neck and spine was unremarkable. A lumbar puncture revealed increased levels of lymphocytes and supernumerary oligoclonal bands. Given the patient's age, segmental pattern of optic nerve pallor, saccadic dysmetria, PWM lesions and increased levels of lymphocytes and supernumerary oligoclonal bands, she was diagnosed with primary progressive multiple sclerosis (MS) and started on Ocrevus (ocrelizumab, Genentech).

A low vision evaluation was ordered to address her specific visual needs. She was scheduled for visual evoked potential (VEP) and she will be seen bi-annually for SD-OCT of the NFL and GCC and HVF 24-2. Although the VEP was not performed during the initial consultations, we would expect a delay in latency from demyelination.

Discussion

MS is the most common debilitating neurological disease found in young adults.[2] The disease occurs because of an autoimmune reaction against the fatty insulation of the neurons of the central nervous system, the myelin sheath.[2] During the inflammatory process, the myelin is attacked and damaged, leaving behind plaques (or lesions) detectable on MRI imaging that may or may not result in a variety of symptoms.[2] While the etiology of the immune response is unknown, immunological characteristics include involvement of type 1 helper T and interleukin-17 cells which may be multifactorial.[2,3,4]

Practitioners should keep several ocular symptoms in mind when working with suspected MS, such as transient or chronic visual decline with or without pain, unsteady gait,

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bowel or bladder changes, numbness or muscular pain and trouble with speech or swallowing. Uhthoff's phenomenon, a specific finding in demyelinating diseases, was present in our patient. Uhthoff's phenomenon describes worsening of neurologic symptoms in MS and other demyelinating conditions when the body becomes overheated. The most common symptoms consist of transient visual blur, muscular fatigue and a feeling of light-headedness.[5]

MS has a highly variable course and may result in minor to major disability, depending on the sub-type present.[2] There are four categories, distinguished by the disease's course:

Relapsing-remitting MS is the most common and is characterized by flare-ups of symptoms followed by remission, during which the symptoms may improve or disappear.[3,6]

Secondary-progressive MS is characterized by a worsening of the disease with or without remission or plateaus of severity. This type of MS may even develop in patients with the relapsing-remitting form of the disease.[5]

Primary-progressive MS is characterized by symptoms that gradually worsen from the disease's onset with no periods of remission (although there may be plateaus) and is typically more resistant to drug therapy.[6]

The last, and most rare, form of MS is the *progressive-relapsing* form, in which the disease progresses from the start with intermittent flare-ups of worsening symptoms—there are no periods of remission.[6]

Atypical presentations of MS-related optic nerve dysfunction include extensive bilateral optic pallor with moderate-severe bilateral vision loss.[7]

In our case, the patient presented with the previously-mentioned criteria, which warranted further imaging of the spine and neck and a lumbar puncture to discount neuromyelitis optica (NMO) as well as alternative infectious and inflammatory conditions. It is crucial to distinguish between MS and NMO, since the latter may respond negatively to some treatments typically indicated for MS.[8] One strong characteristic of NMO is the length of spinal cord lesions on MRI.

Spinal cord lesions in NMO can span three or more continuous vertebrae, where lesions from MS are smaller and typically do not extend past two segments.[9] Brain lesions in NMO often appear later and are clinically asymptomatic (with the exception of brainstem lesions), as opposed to MS where lesions occur early in the disease and serve as a piece of diagnostic criteria.[9]

Treatment

Numerous treatments are available for MS; however, we will focus on the two newest additions. The first FDA-approved orally administered treatment for MS is Gilenya (fingolimod, Novartis). In patients with relapsing forms of MS, fingolimod may reduce the number of relapses a patient will experience and delay disability progression.[10] The mechanism is currently unknown; however, researchers believe that fingolimod reduces lymphocyte migration into the central nervous system.[11]

Ocrevus is the first FDA-approved drug for the treatment of primary progressive MS.[12] This drug is administered via intravenous infusion.[13] The drug is proposed to work by binding to CD-20-expressing B-cells in the immune system, initiating cellular and complement mediated lysis.[13]

MS is a complicated disease and frequent medication review is crucial for the optometrist as a member of the MS care team. The patient in this case is currently receiving Ocrevus and has been responding well to her treatments.

Suspect demyelinating disease in patients presenting with cardinal signs and symptoms such as optic nerve pallor, saccadic dysmetria, peripheral limb weakness and paresthesia. These symptoms are highly consistent with white matter lesions within the brain and/or spinal cord. Order pre- and post-contrast MRI with fluid-attenuated inverse recovery and fat suppression to substantiate demyelination.

Rapid, accurate diagnosis of MS will allow the patient to quickly receive the appropriate treatments and have the greatest chance at maintaining a high quality of life. In the setting of primary progressive MS, we recommend biannual follow-up with SD-OCT to assess the NFL and GCC as well as a HVF 24-2 and VEP. ■

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Glaucoma Coding in Five Steps

Use your toolbox wisely to protect you and your patients.

By John Rumpakis, OD, MBA, Clinical Coding Editor

With today's technological advances, we can diagnose glaucoma earlier and treat it more effectively than ever before. However, for many, diagnostic testing protocols for glaucoma often consist of many more tests than are called for in the American Optometric Association's (AOA) Clinical Practice Guidelines and the American Academy of Ophthalmology's (AAO) Preferred Practice Patterns.[1,2]

A protocol is nothing more than a toolbox of clinical tests, not all of which are necessary for each and every patient. Rather, you must selectively use the tools that are most appropriate for each presentation. These easy steps will keep you at the cutting edge of diagnostic prowess and keep you and your practice safe.

1. Establish Medical Necessity

Your medical record must clearly state why each test ordered and performed meets the requirement for being medically necessary. Tests are not deemed necessary just because they are part of a protocol or because they garner additional, confirmatory information.

Additionally, each of your contracted medical carriers may have a specific clinical policy they have approved for appropriate clinical care. If a required test is not covered by the carrier's medical policies, follow the appropriate rules to complete an ABN form with the patient prior to the test to preserve your rights of compensation.

2. Complete the I/R

Diagnostic tests are not billable until their interpretation and report (I/R) is complete. You cannot create a "master" I/R for all diagnostic tests; rather, each test and I/R needs to stand on its own, and the record should reflect this. An I/R should contain the clinical findings, test reliability, comparative data (if applicable) and clinical management.

3. Respect the CCI Edits

Correct coding initiative (CCI) edits are a set of federal rules carriers follow that stipulate what CPT codes can be performed and coded for on the same date of service. They exist to preserve standards of care and help with coding consistency nationwide for specific disease states.

If you are going to violate a CCI rule, your medical record should demonstrate that it was imperative to do so, and you must use appropriate CPT modifiers to further define the clinical situation that forced you to violate a rule.

Often, I see scenarios where a clinician performs two tests that are not allowed to be performed on the same day, and they choose to not code for or charge for one of the services provided. This is not an acceptable practice and puts you and your practice at risk.

4. Use ICD Properly

The ICD-10 rules are rather unforgiving. As with your insurance provider agreements, they stipulate that you must code to the highest level of specificity of a disease state that the individual patient has. Fudging a diagnosis to get a test covered could easily be construed as fraud. Make the time to learn the ICD-10 rules—they are far more important beyond getting paid for your clinical care.

5. Embrace Technology, But Know Its Limits

Much of the newer technology introduced for faster, easier and more accurate diagnosis may not be included in the AOA or AAO clinical protocols and may not be included in your carriers' covered testing policies. In addition, many CPT coding changes within the last few years have changed the definitions of some tests, as well as the category of CPT codes, all of which can affect your coding accuracy and subsequent reimbursement.

By following these five steps, you will provide the appropriate care on the appropriate date of service, and you won't perform the same battery of tests on every individual with the same ICD-10 diagnosis. The more discerning you are and the more detailed your medical record, the greater chance you will be properly paid and safe from audit. ■

Send your coding questions to rocodingconnection@gmail.com.

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As a practitioner who wears contact lenses while volunteering for mission work in remote areas around the world, I understand that sometimes, life's adventures require a contact lens that can keep up with a wearer's demanding life. That's why, when I'm backpacking through (or to) an area with no electricity and questionable water purity, it's a blessing to wear AIR OPTIX® NIGHT & DAY AQUA contact lenses continuously, even while sleeping, for up to 30 days and nights.

Life may not always be adventurous, but it can pose challenges to healthy contact lens wear. My eye care practice in southern Oregon focuses on medical eye issues and contact lenses, so we serve a wide range of patients with varied needs and symptoms—including normal daily challenges that could impact healthy lens wear. For example, many nurses, EMS techs, and new moms keep long hours, and often nap during downtime while still needing clear vision the moment they awaken. Sometimes vacationers—such as those going on long flights or going camping for a weekend—would prefer to leave their replacement contact lenses or lens care solutions at home. And, young adults—juggling school, sports and social lives—sometimes eschew lens care and replacement recommendations.

Patient health and satisfaction are my top priorities, so when I suspect that a patient is sleeping in their lenses, or not replacing them according to the manufacturer-recommended schedule, it's something to investigate. Asking about patients' careers and lifestyles helps uncover their true needs, so we can discuss healthy options like AIR OPTIX® NIGHT & DAY® AQUA contact lenses. It's often a surprise—and great relief—for my patients to learn that these lenses are FDA-approved for 30 days and nights of continuous wear—a convenient and comfortable[1] option, even for wearing during sleep. And, to make sure my patients get the most out of their AIR OPTIX® NIGHT & DAY® AQUA contact lenses, I also recommend overnight cleaning with CLEAR CARE® PLUS with HydraGlyde® whenever possible.

AIR OPTIX® is the #1 prescribed* monthly replacement lens brand in the US,[2] the lens family I trust for many wearers, including astigmats, presbyopes, cosmetic lens wearers, and myself! Like all AIR OPTIX® brand lenses, AIR OPTIX® NIGHT & DAY® AQUA lenses feature SmartShield® Technology, which provides a smooth,[3] wettable[4,5] lens surface that effectively helps resist lipid deposits[6,7] for excellent moisture and comfort.[1,4,5] They are made from lotrafilcon A material with an established safety profile,[8] and feature the highest oxygen transmissibility on the market.[9-11†] For these reasons and many others, AIR OPTIX® NIGHT & DAY® AQUA lenses are a trusted part of my life—my go-to lenses for wearers (including myself) whose demanding lifestyles require a high-performance contact lens. Help your patients see, look and feel their best with AIR OPTIX® NIGHT & DAY® AQUA contact lenses!

* Based on a ProVoice Survey of ECPs through October 2018.
† Dk/t = 175 @ -3.00D. Other factors may impact eye health.

Important information for AIR OPTIX® NIGHT & DAY® AQUA (lotrafilcon A) contact lenses: Indicated for vision correction for daily wear (worn only while awake) or extended wear (worn while awake and asleep) for up to 30 nights. **Relevant Warnings:** A corneal ulcer may develop rapidly and cause eye pain, redness or blurry vision as it progresses. If left untreated, a scar, and in rare cases loss of vision, may result. The risk of serious problems is greater for extended wear vs. daily wear and smoking increases this risk. A one-year post-market study found 0.18% (18 out of 10,000) of wearers developed a severe corneal infection, with 0.04% (4 out of 10,000) of wearers experiencing a permanent reduction in vision by two or more rows of letters on an eye chart. **Relevant Precautions:** Not everyone can wear for 30 nights. Approximately 80% of wearers can wear the lenses for extended wear. About two-thirds of wearers achieve the full 30 nights continuous wear. **Side Effects:** In clinical trials, approximately 3-5% of wearers experience at least one episode of infiltrative keratitis, a localized inflammation of the cornea which may be accompanied by mild to severe pain and may require the use of antibiotic eye drops for up to one week. Other less serious side effects were conjunctivitis, lid irritation or lens discomfort including dryness, mild burning or stinging. **Contraindications:** Contact lenses should not be worn if you have: eye infection or inflammation (redness and/ or swelling); eye disease, injury or dryness that interferes with contact lens wear; systemic disease that may be affected by or impact lens wear; certain allergic conditions or using certain medications (ex. some eye medications). **Additional Information:** Lenses should be replaced every month. If removed before then, lenses should be cleaned and disinfected before wearing again. Always follow the eye care professional's recommended lens wear, care and replacement schedule. Consult package insert for complete information, available without charge by calling **(800) 241-5999** or go to **myalcon.com**.

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PEER • REVIEWED PRA ARTICLE

Managing Vision Disorders in Children

These tips can help you avoid misdiagnosis and maintain their eyesight.

By Breanne McGhee, OD

The visual system develops throughout different milestone periods in early childhood; however, not everyone is able to acquire or master complex visual skills.[1-3] Research shows that 25% of grade school children have vision problems that are often undiagnosed.[2,3] Children who struggle with vision disorders may encounter challenges in the classroom, recreational play or sporting activities.

Because of the high prevalence and incidence of vision disorders, primary care optometrists and other healthcare professionals should address this area of concern appropriately. Early intervention is critical because vision problems can develop in adulthood if they are not addressed sooner.[1-3] This article briefly reviews some common pediatric vision disorders and discusses possible diagnostic, treatment and management strategies.

Use the NSUCO oculomotor test to assess pursuit eye movements.

Oculomotor Dysfunction

This common visual disorder is characterized by an anomaly in fixation, saccades or pursuit eye movements.[3,4] Symptoms might include a reader losing their place on a page, skipping words or lines of content, re-reading words or reading one word slowly at a time.[3,5-7] These disruptions interfere with fluency development and academic motivation.[3,6-8] If these deficits are not properly assessed and treated, they may interfere with educational learning, depth perception and sports participation.[2,7-9] Over time, patients may develop compensatory habits, such as moving their head or using their finger as a guide during reading, to avoid visual symptoms.[1,2,7,8]

Different methods exist to assess oculomotor function.[3,4,10] The Northeastern State University College of Optometry (NSUCO) oculomotor test is a quick and effective test to check gross oculomotor function.[10] It is based on four parameters: ability (how long the child stays with the task), accuracy (saccadic intrusions, refixations for pursuits and by over- or undershoots for saccades), head movement and body movement (ability to control motor overflow).[10]

To test pursuits, instruct the patient to follow a near rotating target without taking their eyes off of it.[10] With saccades, use two different targets and have the patient alternate viewing between each one only when instructed to do so.[10] For pediatric patients, bright, and colorful targets help to maintain good visual attention.[3,4]

Other diagnostic oculomotor tests include the Developmental Eye Movement (DEM) and the King-Devick, which subjectively evaluate linear visuomotor skills, rapid automated naming skills and visual processing speed.[6,9,11-13] Specifically, the DEM differentiates automaticity and oculomotor deficits, while the King-Devick

test cannot differentiate the two. Objectively, the visagraph (Bernell) and readalyzer (Bernell) use videooculography to analyze microocular movements and estimate an approximate reading grade level.[14] With each test, carefully observe for compensatory head movements or finger guides without giving prior instructions on head and hand positioning.[4,11,14]

Vision therapy is the treatment of choice for oculomotor dysfunction (*Table 1*).[3,4,7] Use sequential techniques that train both gross and fine oculomotor movements properly.[3,4,7] To make these tasks more challenging, consider loading each technique with items such as a metronome or balance board.[3,4,7]

Amblyopia

There are three types of amblyopia: visual deprivation, refractive error and strabismus.[15-17] With visual deprivation amblyopia, there is a structural obstruction of the eye that prevents light to enter, resulting in a failed visual response being sent to the brain.[16] Several conditions cause visual deprivation amblyopia, such as congenital cataracts, eyelid ptosis and corneal opacities.[15-17] Treat the incriminating factor first to eliminate the obstruction prior to addressing this type of amblyopia with therapy.[15-17]

Uncorrected refractive error causing amblyopia occurs because the visual information sent to the brain is blurred due to larger refractive errors.[15-17] The higher the refractive error, the greater the risk of amblyopia.[15-17]

While examining the patient, look for clues that may suggest amblyopia. During visual acuity testing, they may slowly read the letters on the chart, try to peek around the photoper or remove the occluder, allowing the sound eye to see. Optical correction can improve visual acuity in the amblyopic eye.[15-17] Light or flexible frames are a good recommendation for children. Head straps or temple cables can also optimize an appropriate fit. Impact resistant polycarbonate lenses should be recommended to all pediatric patients.

Patching is another effective treatment approach in amblyopia, as it forces the brain to receive and process visual information from the amblyopic eye.[18-21] Studies show that patching for two hours a day is as effective as longer patching times.[15,17] Adhesive patches can be used to ensure patients are receiving effective treatment. Previously, studies recommended near activities during patching hours; however, more recent research shows that patients performing distance activities while patching are as effective in visual recovery.[15,17]

An alternative to patching is pharmacological penalization with cycloplegic agents, which forces the patient to use visual input from their amblyopic eye for near tasks.[15-17] Atropine 1% is commonly used in practice and has yielded positive results.[21,22] Clinical studies reveal that pharmacological penalization results are similar to patching alone.[16,17,21,22] One advantage to this type of therapy is that it increases compliance due to easy installation. It is also good for milder degrees of amblyopia.[16,17] Advise patients on possible symptoms of decreased visual acuities in the non-amblyopic eye and increased photosensitivity secondary to mydriasis.[16,17]

Optical penalization can also be used to blur the spectacle prescription in the good eye while maximizing the prescription in

Table 1. Vision Therapy Techniques for Oculomotor Dysfunction

Pursuits	Saccades
• Pegboard rotator • Flashlight chase • Space fixator	• Pencil saccades • Hart charts • Wall saccades • Ann Arbor letter tracking • Monocular prism jumps • Marsden Ball

Table 2. Types of Vergence Disorders With Common Associated Clinical Findings[1]

Vergence Disorder	Clinical Findings
Convergence insufficiency (CI)	• Greater exophoria at near • Low AC/A ratio • Receded near point of convergence • Reduced fusional convergence
Convergence excess (CE)	• Greater esophoria at near • High AC/A ratio
Divergence insufficiency (DI)	• Greater esophoria/tropia at distance • Low AC/A ratio • High tonic esophoria
Divergence excess (DE)	• Equal esophoria at distance and near • Normal AC/A ratio
Basic esophoria (BE)	• Equal esophoria at distance and near • Normal AC/A ratio
Basic exophoria (BX)	• Equal esophoria at distance and near • Normal AC/A ratio
Vergence insufficiency	• Normal AC/A ratio • Restricted fusional vergence amplitudes • Steep fixation disparity curve
Vertical phorias	• Comitant deviations • Non-comitant deviations

Table 3. Vision Therapy Techniques for Accommodative and Vergence Dysfunction

Accommodative	Vergence
• Monocular/binocular with +/-2.00 D flippers • Push up/push away activities • Minus/plus lens activities • Monocular lens clearing • Monocular lens sorting • Hart chart near-distance rock • Accommodative rock	• Pencil Pushups • Brock string • Vectograms • Tranaglyphs • Lifesaver Cards • Aperture Rule • Computer Orthoptics • Eccentric Circles • Wheatstone Mirror Stereoscope

the amblyopic eye.[16,17] Bangerter filters are also options where a translucent filter is placed over the lens of the nonamblyopic eye to cause blur.[15-17] Cosmetically, they are less noticeable than an eye patch, making them a good option for patients who are conscience of the appearance. For these therapies to work, the patient has to wear their glasses.[15-17]

Dichoptic treatment is also available, in which patients receive more visual stimulation through higher contrast and brighter images in the amblyopic eye.[16,23,24]

Regular follow-ups are important to assess whether the amblyopic eye is strengthening. Improvement with therapies can take weeks to reveal any progress, and compliance can be difficult. While most children show improvements with these therapeutic approaches, not all pediatric patients respond.[16,23,24] In my practice, we treat amblyopia first before undergoing strabismic strategy if heterotropic or hypotropic deviations are present.[16,23,24]

Strabismus

According to the American Association for Pediatric Ophthalmology and Strabismus, this condition affects a little more than 3% of children in the US population.[25] Some causes of strabismus include large uncorrected refractive error, paretic extraocular muscles, genetic developmental disorders and trauma.[25,26]

Depending on the degree of misalignment, patients may present with symptoms of diplopia, blurred vision, headaches, eye fatigue, difficulties with reading and eye strain.[1,6] However, some strabismic patients are asymptomatic due to visual suppression of the weaker eye and preferential use of the dominant, or clearer, eye.[25] Traditionally, strabismus amblyopia patients have this type of visual profile.[25,26]

Many clinical techniques can assess strabismus.[25,26] Use a transilluminator or near fixating target and observe eye movements in all nine cardinal directions to ensure the proper function of all extraocular muscles and that both eyes are working with each other simultaneously.[25,26] While some large angle deviations are obvious, other subtle misalignments may be difficult to pick up.[18,25,26]

Use cover tests to identify phorias and tropias.[26] A unilateral cover test (cover-uncover test) will reveal the presence of a tropia if the clinician looks at the eye not being covered.[6] During the unilateral cover test, the strabismic eye will attempt to correct itself either by moving inward (exotropia) or outward (esotropia).[26] The alternating cover test (cross-cover test) is used to break fusion to detect a phoria when the clinician observes the eye after it is uncovered.[26] Use prism bars or loose prisms to measure the magnitude of the deviation during the test. Titrate the necessary amount of prism until no movement is seen as the occluder is alternately switched from eye to eye.[26]

The Hirschberg test is another useful clinical tool that detects misalignment using the direct ophthalmoscope or transilluminator.[26] During this test, look at the corneal reflex and compare its position to the underlying pupil. Normally, the corneal reflex should lie exactly over the pupil. For every millimeter that the corneal reflex is off-center, it is equivalent to 22 prism diopters of deviation.[26]

The first visual corrective option for any strabismic patient should be spectacles to improve visual acuity, stereopsis and ocular alignment.[26] Plus lenses in accommodative esotropia cases may aid with focusing and visual discomfort symptoms.[25-27] Other treatment options include prisms, vision therapy and patching.[18,26]

If spectacle or prism correction do not improve the misalignment, surgical intervention is available to correct the deviation.[26] The Infantile Esotropia Observation Study showed that infants who had surgery at six months experienced better stereoscopic outcomes at four years of age compared with infants who underwent surgery after six months.[27,28]

Early intervention is required in constant deviations that do not improve with spectacles or other noninvasive treatment options.[26,27] Only then should you consider surgery to correct the deviation and improve stereopsis ability.[25,26]

Accommodative & Vergence Disorders

School-aged patients, especially third and fourth graders who have reading difficulties, diagnosed learning disabilities or poor academic performance should

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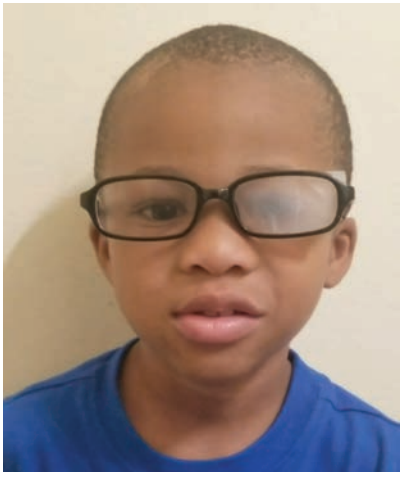
have a comprehensive vision exam to evaluate for underlying accommodative and vergence problems. These conditions can have a significant impact on the increased near viewing demand and workload.[1-3,7]

Ratios below and above the normal convergence induced by accommodation per unit of accommodation (AC/A) ratio, 4:1, have been implicated in binocular vision problems *(Table 2)*.[1,3,7] Incorporate accommodative testing into the phoropter routine by adding plus or minus lenses until the patient first notices unresolved blur.[3] Monocular estimate method (MEM) retinoscopy is a binocular test performed behind the phoropter using a reading card that can attach to the face of the retinoscope. Similar to standard retinoscopy, neutralize the "with" (lag of accommodation) or "against" (lead of accommodation) motion with the appropriate lenses until no movement is observed.[1,3,7] Other dynamic retinoscopy (e.g., Nott) tests can check accommodation abilities.[1,3,7]

Convergence insufficiency is the most common vergence disorder affecting the ability to maintain proper binocular eye alignment on near targets, resulting in visual discomfort at near.[3,7] Assess vergence skills in office with techniques such as near point convergence and fusional divergence and convergence tests to assess the efficiency abilities of this system.

Recommend corrective lenses, vision therapy (*Table 3*) or orthoptics as treatment options to improve deficient accommodative and vergence skills.[1,3,4] Specifically, add a plus lens for accommodative dysfunction to improve the patient's focusing skills.[1,3,4] Vision therapy techniques can be loaded with increasing plus/minus lenses



Optical penalization can be used to treat amblyopia.

or prism amounts.[4] Carefully monitor for suppression during vergence therapy techniques.[1,3,4]

If children present with any of these vision disorders, they may experience challenges when reading, writing and computer use, ultimately lowering their educational potential.

As primary eye care providers, we have a duty to advocate for our younger patients. We must recommend comprehensive eye exams with careful assessments for the presence of vision disorders. If present, we must offer the appropriate treatments and advise regular follow-ups. ■

Dr. McGhee practices at Chiasson Eye Center and Bond Wroten Eye Clinic in Louisiana.

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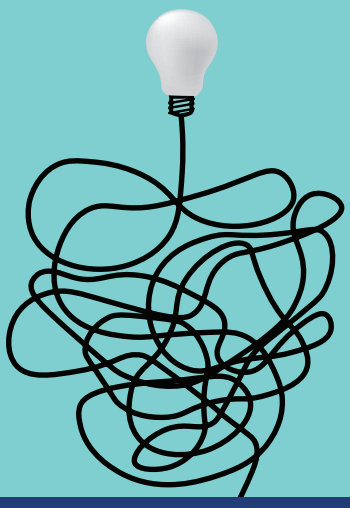

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PEER • REVIEWED PRA ARTICLE

My Patient Has AMD… Now What?

The first clinical steps are crucial to setting patient expectations and initiating the right management plan. **By Mohammad Rafieetary, OD, Jessica Haynes, OD, and Roya Attar, OD**

As the leading cause of vision loss in adults older than age 60 in the United States, age-related macular degeneration (AMD) is unavoidable in optometric practice.[1] The initial diagnosis, which can be alarming for many patients, requires significant patient education, baseline evaluation and correspondence with other healthcare providers. Here, we discuss a strategy for addressing these first-visit obligations.

About this Series

To help optometrists strengthen their protocols for managing conditions that require ongoing—perhaps life-long—care, this series explains the steps to take after confirming a diagnosis, from day one through long-term management. Each installment in the five-part "Now What?" series will cover a different chronic condition:

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April—RCE
May—diabetic retinopathy
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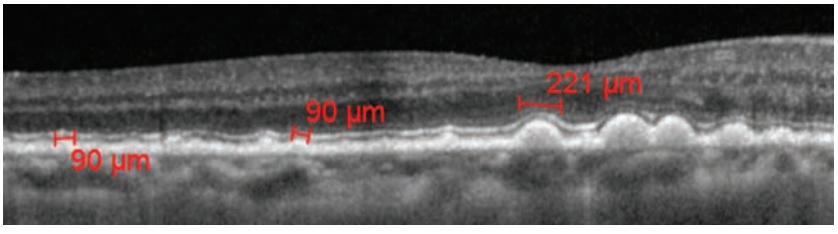

Fig. 1. Drusen size measured with calibers on OCT.

Patient Education

As is true of many ocular conditions, patients may or may not know anything about AMD upon diagnosis—making patient education just as individualized as the management plan. Many are completely unfamiliar with the condition, and even those who do know about AMD may have inaccurate information. In addition, some who have family members affected by AMD may have increased anxiety about suffering vision loss themselves. Thus, patient education at the initial diagnosis can require a significant amount of chair time, as you should address these topics with the patient and their family members:

What is AMD? Macular degeneration is a degenerative condition of the retina that specifically affects the macula. The macula is responsible for central, detailed vision and is required for tasks such as reading or driving. Macular degeneration is the most common cause of vision loss in patients older than 60, but not all patients with the condition will suffer from significant vision loss. Furthermore, contrary to many laymen's notion, AMD does not typically cause "total blindness," a point that needs to be emphasized during initial patient education.

What does dry vs. wet AMD mean? All patients with AMD begin with the non-neovascular, or dry, form. This may go undetected or undiagnosed. According to a recent study, 33% of patients who have AMD may go undiagnosed

during an eye examination.[1] About 10% of patients with dry AMD will develop subretinal or choroidal neovascular membrane (CNVM), a secondary complication where blood vessels grow from underneath the retina, leaking fluid and possibly bleeding. This complication can cause sudden and dramatic visual decline.

CNVM is associated with other macular diseases and is not unique to AMD. However, because of the fluid leakage, this neovascular stage of AMD is commonly known as "wet" or "exudative" AMD. CNVM often requires treatment by a retina specialist. The sooner wet AMD is detected, the better the visual outcome can be. Although past data reported that 90% of patients with wet AMD had significant vision loss, today's treatments can help many patients with wet AMD maintain reasonably good central vision. Currently no treatments exist for dry AMD, and 10% of patients are at risk for significant vision loss due to geographic atrophy (GA), a process in which the retinal pigment epithelium and photoreceptors essential for vision are lost due to degeneration.[2]

What are the risk factors and what can I do to change them? Tobacco use is the number one modifiable risk factor, as smoking increases both the risk of developing AMD and the risk for progression of the disease.[3,4] Sunlight exposure over a lifetime contributes to the development of AMD, and appropriate protection with sunglasses and hats can limit the exposure.[5] In addition, a healthy, balanced diet high in brightly colored fruits and vegetables and green leafy vegetables may delay the progress of AMD.[6]

The overall health of the body is important for the health of the eyes, as research links regular exercise to a lower risk of AMD development and progression, and conditions such as high cholesterol, hypertension and obesity can all contribute to AMD.[7-10] Clinicians can recommend vitamins high in antioxidants and pigments important for the health of the macula for patients at certain stages of macular degeneration.[11] Patients under medical care and taking multiple medications should discuss supplementation and any dietary modifications with their primary care physicians.

Should I tell my children and siblings? In addition to modifiable environmental factors, research has identified many genes in association with AMD. Because an inheritance tendency exists for AMD, family members may benefit from lifestyle modifications and routine eye examination.[12] Genetic testing for patients with AMD and those at risk remains controversial.[13] Although commercially available genetic testing is marketed to tailor vitamin supplementation to a patient's genome, contradicting study results have thwarted any consensus on whether or not genetic profile alters response to vitamin supplementation.[14-17]

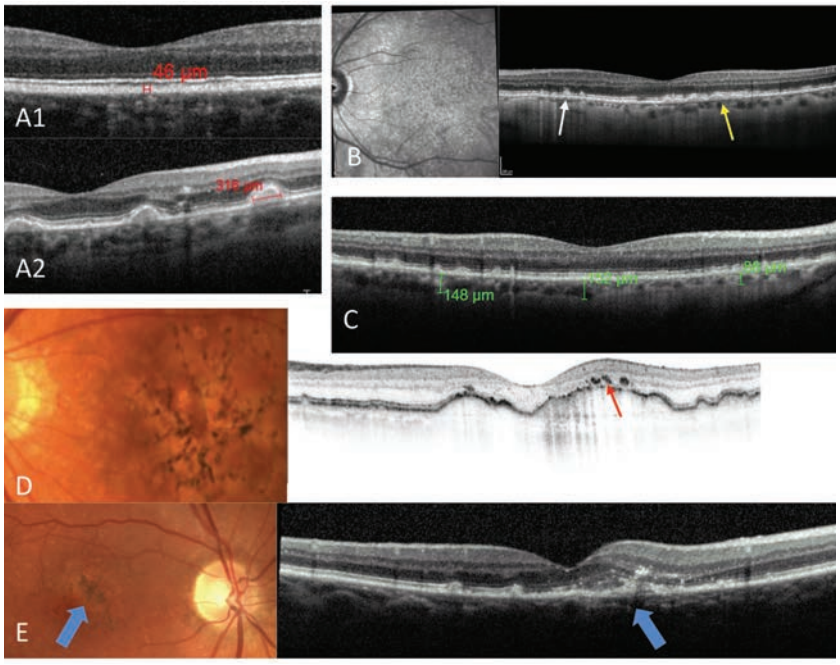

Fig. 2. Possible OCT findings in AMD: small drusen (A1), large drusen (A2), presence of both typical sub-RPE drusen (yellow arrow) and RPD, with lipofuscin deposits above the RPE (white arrow) and the pattern of RPD discernable on the infrared photo (B). Thinner than average choroidal thickness consistent with AMD (C). Pigmentary changes over large pigment epithelial detachments (red arrow) (D). Early detection of CNV (blue arrows) (E).

Table 1. AMD Staging Criteria[19]

No AMD	Early AMD	Intermediate AMD	Advanced AMD
No drusen or few small drusen	Several small drusen or a few medium-sized drusen	Several medium-sized drusen or presence of large drusen or pigmentary changes	Presence of GA or CNV

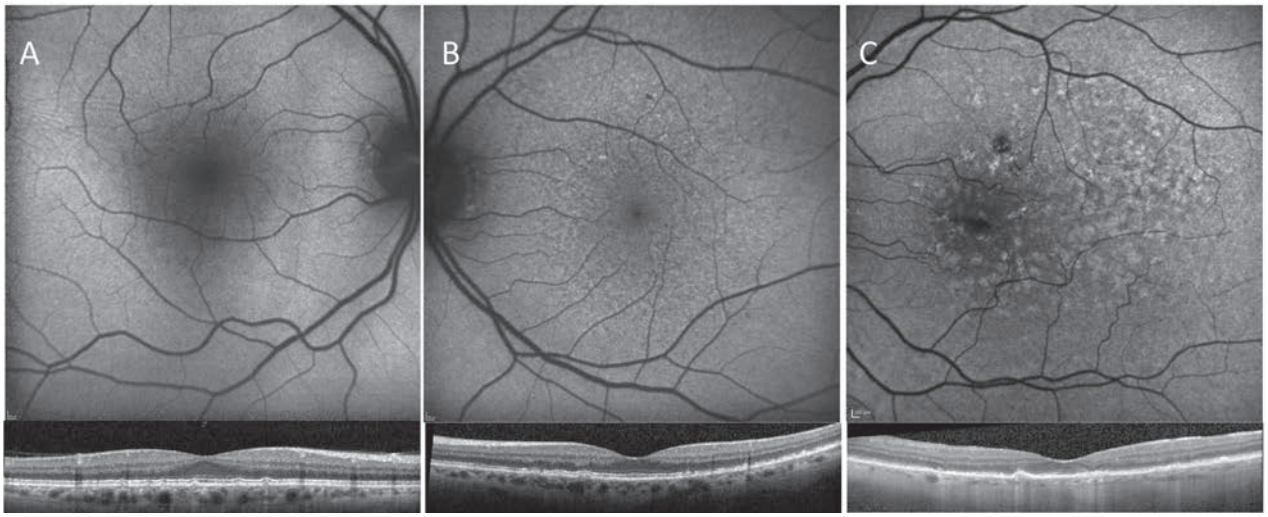

Fig. 3. The top FAF images correspond with the OCT B-scans below. With OCT imaging, all of these patients have presence of intermediate sized drusen; however, patient A has much less disruption of the autofluorescent signal than patients B and C, suggesting the overall health of the RPE in patient A is better than that of B and C.

How can macular degeneration affect my vision? AMD can lead to varying levels of vision loss including legal, but not total, blindness. The disease affects the central vision, therefore reducing our ability to read, drive or perform other tasks requiring detailed central acuity. In addition, patients with AMD may notice that they do not adapt as quickly to sudden changes in lighting conditions, as delayed dark adaptation is one of the earliest functional symptoms of AMD.[18] Therefore, it may take more time for patients to adjust to both bright and dim illuminations. They may require more light for reading and seeing detail, as well as increased contrast in reading materials.

Not all patients with AMD have significant vision loss. While central vision is important for detailed tasks, the peripheral vision remains intact in patients with AMD. Therefore, most patients will not require assistance for most of their daily living activities.[7] Still, it's important to remind all AMD patients, even those with only mild visual impairment, that low vision interventions can help improve their visual performance both now and as the disease progresses, if they so desire.

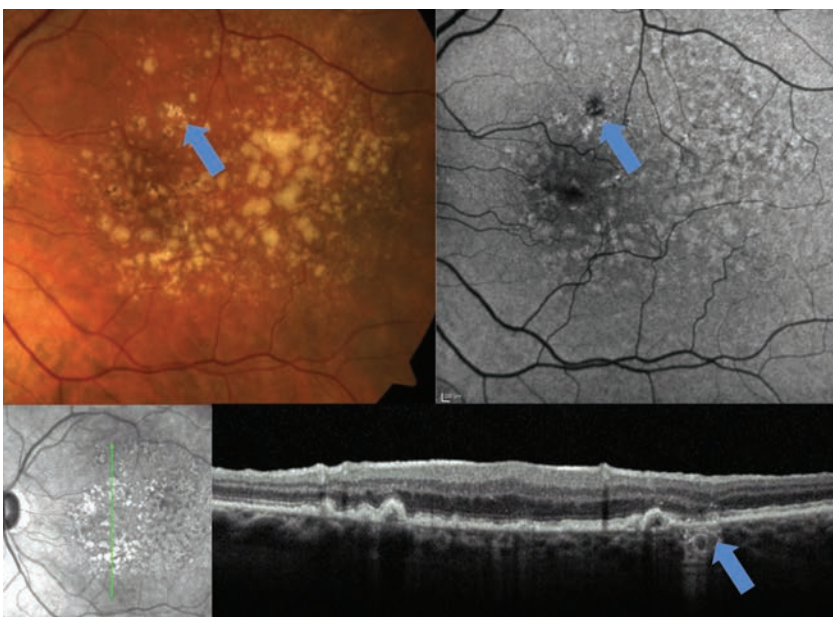

Fig. 4. This early area of GA, identified with FAF and OCT, would be difficult to detect on fundus examination.

Day One Responsibilities

Clinicians should complete a careful patient history at the initial visit to identify modifiable risk factors such as tobacco use, poor diet, significant sunlight exposure and systemic factors such as hyperlipidemia, hypertension and obesity. Communication and comanagement with the primary care physician improves outcomes by addressing concerns such as tobacco cessation, dietary modifications and control of contributing systemic disease.

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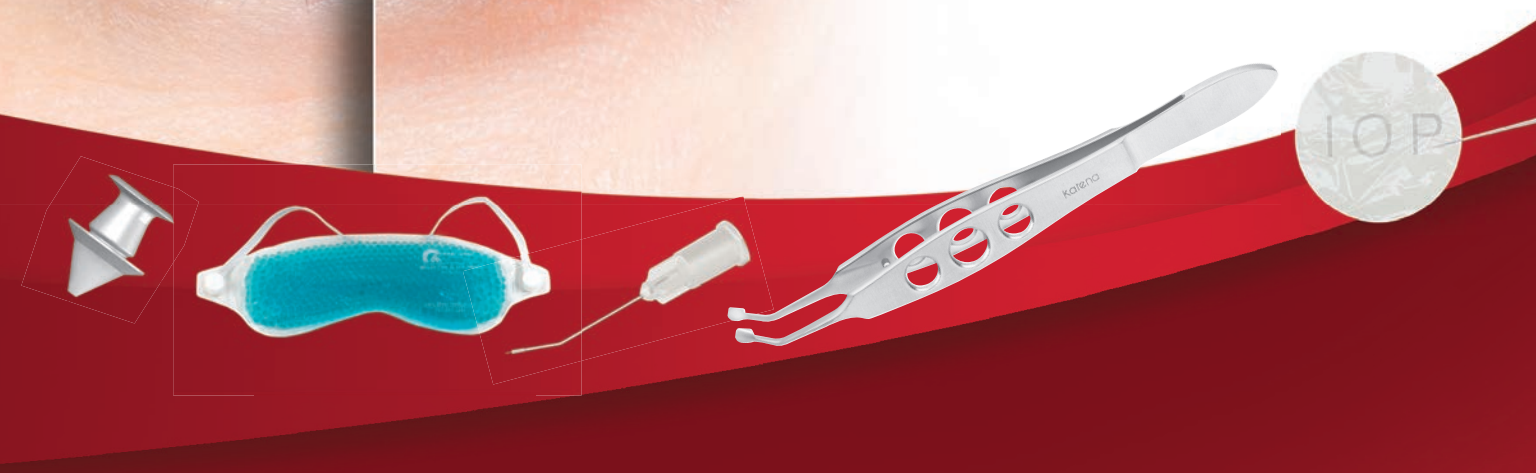

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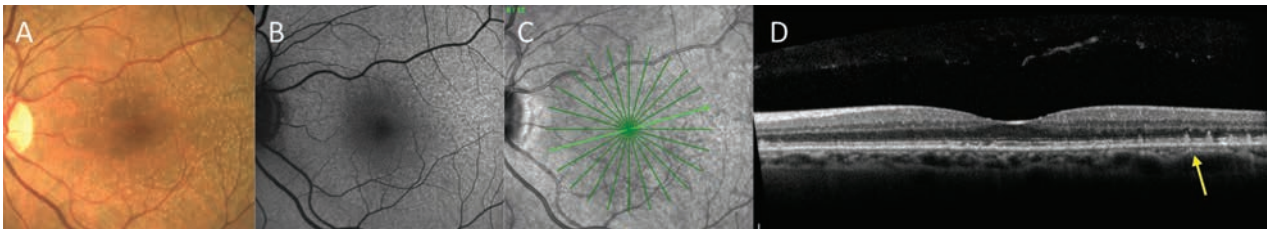


Fig. 5. Fundus photo (A), FAF (B), infrared image (C), and OCT (D) of a patient with small to intermediate size drusen on clinical examination. No pigmenatry changes or large drusen are present, suggesting the risk for progression to advanced stages is low. However, FAF and OCT reveal the presence of RPD, which is known to carry increased risk of advanced AMD.

The first clinical steps after the initial diagnosis include determining the stage of the condition, identifying any retinal findings that increase the risk of progression to advanced stages and ruling out the presence of CNVM.

Staging. This is key because the Age-Related Eye Disease Studies (AREDS1 and AREDS2) found that those with intermediate AMD benefited from vitamin supplementation.[11] Generally accepted staging data, simplified from the AREDS, categorize small drusen as ≤63µm, medium drusen as >63µm but ≤125µm and large drusen as ≥125µm (*Table 1*).[19] The caliber of large retina veins near the optic disc is approximately 125µm, which can be used as a reference to estimate the size of drusen.[20] But more practically, small drusen are difficult to detect clinically; thus, easily discernible drusen can be considered intermediate, and quite obvious drusen can be considered large. Fundus findings of large soft drusen and pigmentary changes also increase the risk of progression to advanced stages and should be noted.

Data from AREDS1 and 2 provide a simple dry-to-wet AMD risk assessment tool that assigns a point for each finding of large drusen and pigmentary changes per eye (*Table 2*).[21] The risk is calculated based on the patient's point score (0 points = 0.5% risk of conversion to advanced AMD in five years, 1 point = 3.0% risk of conversion, etc.). Optical coherence tomography (OCT), among other instruments, can also be a useful tool for determining drusen size (*Figure 1*).

Progression and CNVM assessment. Fundus and additional diagnostic examination should also be performed to carefully evaluate for signs of CNVM. During the fundus examination, the presence or absence of subretinal fluid, hemorrhage or both should be documented, as these signs may indicate the presence of CNVM.

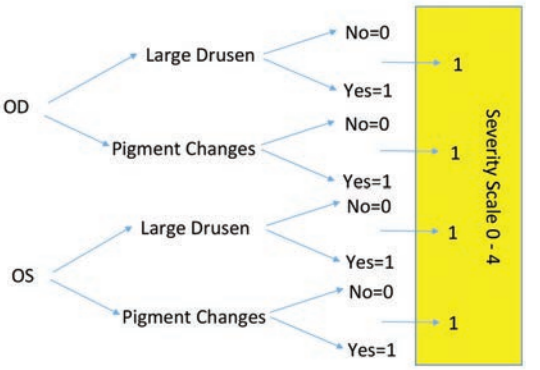
Diagnostic imaging with OCT and fundus autofluorescence (FAF) should be considered at the initial visit to more thoroughly evaluate both the risk of progression and the presence of CNVM. It can also help establish a visual baseline of the disease state, thereby serving as a valuable resource to monitor a patient's progression or efficacy of treatment.

In addition to evaluating drusen size, OCT scans can also help determine choroidal thickness (patients with AMD tend to have thinner than average choroids); pigmentary changes; presence of reticular pseudodrusen (RPD), which carries increased risk of progression to advanced stages; and presence of sub- or intraretinal fluid and CNVM (*Figure 2*).[22-25]

FAF can assist in the detection of RPD and early GA and can reflect the general status of the retinal pigment epithelium (*Figures 3-5*).[26] The additional information gleaned by OCT and FAF provides a more complete clinical picture than fundus evaluation alone as to the overall risk of progression to advanced stages.

Additional testing such as OCT angiography (OCT-A), intravenous fluorescein angiography (IVFA), or indocyanine green angiography (ICGA) may be necessary if there

Table 2. AREDS Risk Assessment Tool[21]



Score	Chance to progress to advanced AMD in five years (%)
0	0.5
1	3.0
2	12.0
3	25.0
4	50.0

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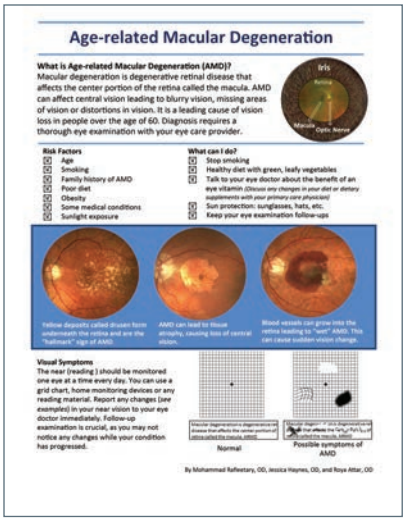
is suspicion of CNVM with fundus evaluation or OCT imaging.[27] Patients with evidence or suspicion of CNVM require prompt referral to a retina specialist for additional imaging and possible anti-vascular endothelial growth factor treatment (*Figure 6*). Because exudative AMD is a chronic disease in most cases, conversion to this stage often requires continued care and comanagement between the referring doctor and the retina specialist.

Assigning Homework

With all of the clinical testing out of the way, patients should be counseled on the importance of at-home monocular vision monitoring, as it can lead to earlier detection of CNVM and better visual outcomes.[28] Clinicians should demonstrate tools such as the Amsler grid, or other visual target, with specific instructions on daily vison monitoring, including what changes to look for and steps to take if the patient detects a change. In addition, remote home monitoring devices are now available that can detect early visual changes that may be associated with AMD progression.



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Follow-up

Patients with AMD should be followed at reasonable intervals to monitor for formation of CNVM (*Table 3*).[29,30] Follow-up schedules can range from every four to 12 months, depending on the clinical picture, and any changes on home monitoring would warrant prompt examination.[29,30] Depending on the clinical picture, follow-up visits may include fundus photography, Amsler grid, OCT, FAF, OCT-A or IVFA.[29,30]

Patients' visual limitations and complaints will worsen over time, and clinicians should address those issues optically or with additional devices such as magnifiers, telescopes, electronic visual aids and rehabilitative care to make the most of their remaining visual function. Consider a formal low vision evaluation or consultation if these services cannot be provided in your clinic. In addition, clinicians should address the patient's legal driving status.

Table 3. Recommended Follow-up for AMD[29,30]

Type of Patient	Frequency of Examination	Management Plan	Testing
Patient with two or more risk factors for AMD, older than age 55	Annual examination if asymptomatic or prompt examination if new symptoms	• Recommend UVR protection, proper diet and exercise, smoking cessation and weekly home Amsler or comparable monocular near vision self-monitoring	• Consider baseline testing: fundus photos, FAF, OCT
Patient with early AMD	Six to 12 months, depending on risk	• Recommend UVR protection, proper diet and exercise, smoking cessation and daily home Amsler or comparable monocular near vision self-monitoring	• Consider baseline testing: fundus photos, FAF, OCT • OCT and FAF imaging to evaluate for high risk characteristics such as reticular pseudodrusen • OCT, OCT-A, IVFA to rule out any suspicion of CNVM, if necessary
Patient with intermediate AMD	Six to 12 months, depending on risk	• Recommend UVR protection, proper diet and exercise, smoking cessation and daily home Amsler or comparable monocular near vision self-monitoring	
Patient at high risk with soft confluent drusen, granular pigmentary degeneration or reticular pseudodrusen	Four to six months	• Recommend UVR protection, proper diet and exercise, smoking cessation and daily home Amsler or comparable monocular near vision self-monitoring • Recommend vitamin supplementation with AREDS 2 formulation	
Patient with geographic atrophy	Six to 12 months	• Recommend UVR protection, proper diet and exercise, smoking cessation and daily home Amsler or comparable monocular near vision self-monitoring • Recommend vitamin supplementation with AREDS 2 formulation • Consider low vision consult	

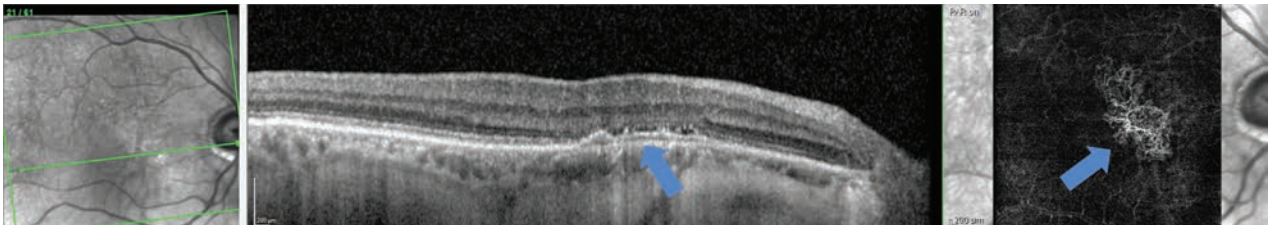
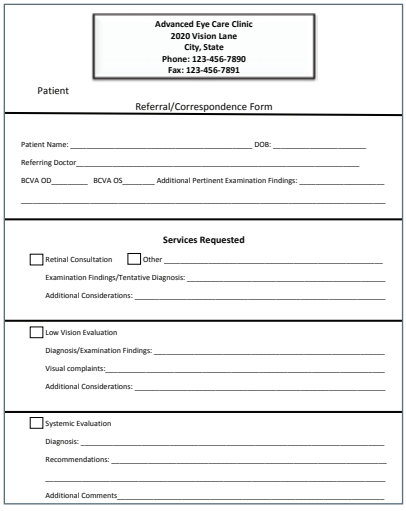


Fig. 6. Type 1 sub-RPE choroidal neovascular membrane with minimal evidence of exudation on OCT but evidence of neovascular net in the avascular region on OCT-A.

Communications

Patients with AMD often require referral and communication with a variety of healthcare providers, whether at the initial visit or at some point in their follow-up care. Clinicians should use a succinct, yet thorough, patient referral form when referring patients with AMD to other healthcare providers. The form should include basic patient information, your pertinent clinical findings, diagnosis, the services you are recommending, and any additional comments that could help the other provider best care for the patient.

The initial diagnosis of AMD carries significant responsibility for the diagnosing physician who must address patient concerns, manage progression risk factors, thoroughly evaluate the condition's stage, determine follow up and communicate with other medical professionals. Balancing all of these during the initial visit is crucial to ensure the patient is prepared for the management road ahead. ■



Advanced Eye Care Clinic
2020 Vision Lane
City, State
Phone: 123-456-7890
Fax: 123-456-7891

Patient

Referral/Correspondence Form

Patient Name: _____ DOB: _____

Referring Doctor_____

BCVA OD_____ BCVA OS_____ Additional Pertinent Examination Findings: _____

_____

Services Requested

☐ Retinal Consultation ☐ Other _____

Examination Findings/Tentative Diagnosis: _____

Additional Considerations: _____

☐ Low Vision Evaluation

Diagnosis/Examination Findings: _____

Visual complaints:_____

Additional Considerations: _____

☐ Systemic Evaluation

Diagnosis: _____

Recommendations: _____

_____

Additional Comments_____

For a full-size downloadable version of this referral sheet, read this article online at www.reviewofoptometry.com.

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25th Annual Glaucoma Report

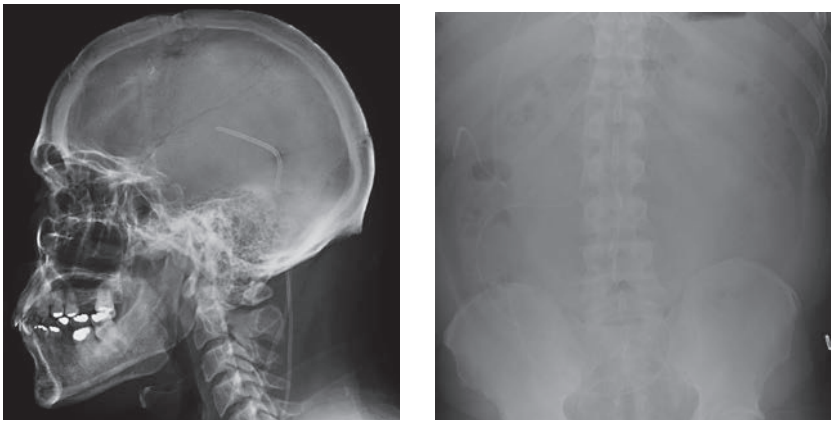
The Ins and Outs of Pressure Gradients

Get a better understanding of the complex forces at work inside the eye.

By Jennifer Sanderson, OD, Andrew Rixon, OD, and James Williamson, OD

Historically, intraocular pressure (IOP) and its role in glaucoma boiled down to a simple equation: high pressure equals glaucoma diagnosis. Although IOP remains the most important and only modifiable risk factor in glaucoma care, modern research indicates that the historical formula is more complex than initially understood.

At present, a number of recognizable forces influence the retinal ganglion cells and optic nerve head (ONH). These include IOP, cerebrospinal fluid pressure (CSFP) and ocular perfusion pressure (OPP). The interrelations between these forces are complicated, and our understanding of each of their roles is constantly evolving.



These scans show skull and abdomen radiographs of a patient who is post-ventriculoperitoneal shunt placement for pathological increase in CSF.

Pressure Differences

IOP—taken with conventional Goldmann applanation tonometry (GAT)—is often interpreted as an accurate representation of the pressure within the eye. However, what is measured by conventional force tonometry is the transcorneal pressure difference (where force applied outside the eye is equal to force inside the eye, as measured across the cornea) and not truly representative of IOP.[1,2] In fact the absolute pressure in the eye involves atmospheric pressure and is calculated as the sum of transcorneal pressure and atmospheric pressure (standard atmospheric pressure at sea level is 760mm Hg).

For example, if an eye is measured at 15mm Hg using GAT, the actual pressure is 775mm Hg (760mm Hg +15mm Hg). For an eye measuring 30mm Hg by GAT, it is 790mm Hg (760mm Hg + 30mm Hg). Some may infer that if an eye's GAT pressure measures 30mm Hg it is twice as great as one measured at 15mm Hg. However, in this example, on an absolute level the pressure difference is only 2.5%.[2]

To further advance this notion of absolute pressure and its effect on the eye, consider that no evidence shows that scuba divers exposed to increased atmospheric pressures experience acutely increased eye pressure leading to glaucoma, nor that mountain climbers at decreased

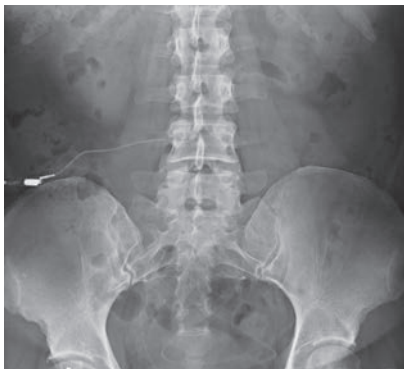
atmospheric pressure are protected from the disease. The transcorneal pressure does not change under either of the above circumstances.[2] This knowledge led to the proposal that glaucoma is not influenced only by pressure in the eye, but rather by other relative systemic pressure imbalances.[3]

What this all means is that transcorneal pressure difference (TCPD) may not be the most critical metric in glaucoma. ONH damage may be most dependent upon the *translaminar* pressure difference (TLPD). However, the TCPD may be able to function as a surrogate for TLPD, which is currently difficult to directly assess.[1] The lamina cribrosa (LC) also contains fenestrations that transmit optic nerve axons and is thought to be the primary site of glaucomatous damage.[4] Thus, the pressure gradient across the LC is of significant interest.

To understand the TLPD and its proposed role in ONH pathology, first understand that the LC functions as an anatomical barrier between the intraocular and retrolaminar (subarachnoid) spaces.[2,5] IOP in the intraocular space and intracranial pressure (ICP) in the retrolaminar space are interrelated and exist as relatively independent pressurized systems, maintaining equilibrium through their respective aqueous and cerebral spinal fluid (CSF) circulations.[6] In its function as a barrier, it has been proposed that the LC may prevent leakage of aqueous humor from the intravitreal space into the retrobulbar CSF surrounding the retrobulbar portion of the optic nerve, and vice versa.[2]

Translaminar Pressure

The average TCPD by GAT is 10mm Hg to 21mm Hg, and normal CSFP is 5mm Hg to 15mm Hg. In general, a mean positive pressure



This anteroposterior radiograph shows the lumbosacral region of a 43-year-old patient with a history of intractable IIH having undergone lumboperitoneal shunt placement. Had this case occurred presently, this patient may have undergone transverse sinus stenting.

difference of 4mm Hg is directed posteriorly across the LC.[3,7] This is known as the translaminar pressure gradient (TPG). The TPG depends on the TLPD and the distance between the intraocular and retrobulbar space, with this distance between the compartments highly dependent on axial thickness of the LC.[7] Under normal conditions, there is continuous ortho and retrograde axoplasmic transport of small and large molecules within the ONH. Any imbalance in this normal pressure gradient may result in constriction of axoplasmic flow, LC deformation, altered blood flow and subsequent damage to ONH axons.[6,7]

The role of TPG and ICP in the development of glaucoma is the focus of recent research.[7] A 2015 meta-analysis shows that patients with normal tension glaucoma (NTG) and high tension glaucoma (HTG) have an abnormally high TPD compared with healthy subjects, presumably due to lower CSFP specifically in the NTG group.[6] Another study reviewing medical records from patients undergoing lumbar puncture shows a substantial reduction in CSFP beginning in the sixth decade of life. Given that the prevalence of glaucoma increases with age while the CSFP decreases, researchers hypothesize that lower CSFP has a deleterious effect on the ONH.[8] Conversely, an abnormally high CSFP exists in patients with ocular hypertension (OHT), resulting in a normal TPG in spite of higher IOP.[9,10] Accordingly, the pressure differential at the LC may be protective in OHT, but detrimental in NTG and HTG.

The current challenge with measuring a patient's ICP is the invasiveness of conventional measuring techniques.[6] Newer studies suggest alternative noninvasive methods for measuring ICP, such as two-depth transcranial doppler ultrasound.[6] Although exciting, such techniques are not yet commercially available. In addition to CSFP being difficult to directly measure and inaccurate to estimate, we currently do not have good therapy to increase CSFP as a treatment for glaucoma.

Fortunately, research continues to improve our understanding of CSF dynamics, and treatment may be on the horizon. Ongoing safety trials are evaluating pressurized goggles (Multipressure Dial, Equinox) whose goal is to restore balance in the pressure differential between IOP and CSFP in patients with ONH diseases pathologically affected by known or presumed imbalance.[11] These goggles are designed to create a negative pressure over the eye to decrease IOP and restore normal IOP/CSFP balance.

Elevated CSFP

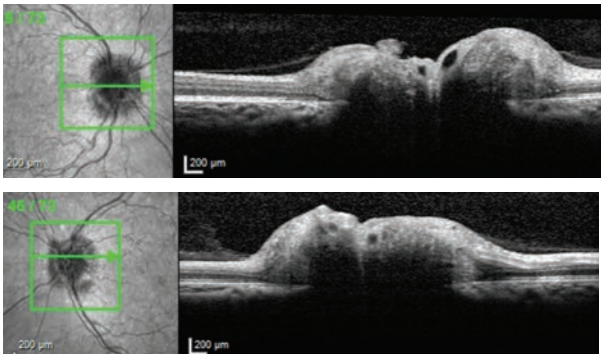
In situations when the CSFP is abnormally high, the TPG is pathologically altered, with forces into the eye exceeding those going out, producing anterograde axoplasmic stasis and subsequent ONH edema.[12]

This is seen in cases of idiopathic intracranial hypertension (IIH), where bilateral ONH edema may result in axonal loss, optic atrophy and subsequent permanent vision loss with reduced quality of life.[13]

IIH is most prevalent in women of childbearing age who are obese. Obesity increases the risk of developing IIH 20-fold.[14] The pathogenesis of IIH is unknown, with multiple proposed theories, including CSF hypersecretion, obstruction of outflow and decreased CSF reabsorption and increased venous pressure.

Venous studies show IIH patients often have stenosis along the transverse-sigmoid sinus junction, either bilaterally or involving the dominant sinus. It is unknown whether this stenosis is intrinsically due to sinus wall abnormalities or extrinsically a result of compression due to increased CSF. Regardless, both can result in reduced CSF absorption and subsequent significant patient symptoms.[13] Although this association between IIH and venous sinus stenosis does not prove a causal link, it has provided an additional treatment method for patients with intractable disease.

Optimal management is based on treating the underlying disease, protecting vision and minimizing disabling headaches.[15] Unless vision loss is imminent, medical management and weight loss prevail as initial therapies.



Cross-sectional OCT slices through ONHs of 38-year-old patient with IIH and opening CSF pressure 38cm H_2O.

Corneal Hysteresis

A major confounder in the use of TCPD as a surrogate for TLPD is that conventional Goldmann tonometry is limited by capturing only force applied and not corneal dynamics.[16] Goldmann was aware that corneal thickness and elastic properties might influence readings, but the ability to record these measurements only became available recently. It is accepted that thin corneas can lead to underestimation of IOP and thick corneas to overestimation.[17]

Although central corneal thickness (CCT) is a corneal dimension, it is not a biomechanical property that limits its utility.[18] The viscoelastic cornea can be more accurately characterized by hysteresis.[19] This is a measurement capturing how a material or system adapts to the loading and unloading of a force applied to it.[19] Corneal hysteresis (CH) reflects the cornea's ability to absorb and release energy created by applanation forces during measurement.[19,20]

Similarly, glaucoma may involve the biomechanical properties of the ONH, specifically the LC, scleral canal wall and peripapillary sclera.[21] Researchers propose that corneal biomechanics might reflect the constitution of the extracellular matrix (ECM). Given that the cornea, sclera, peripapillary ring and LC are essentially derived from the same ECM, it is reasonable to postulate that their biomechanical properties are similar.[22] Accordingly, CH could reflect the ONH's ability to resist deformation from the various confounding pressures. A high CH would thus confer a protective effect whereas a low CH would increase susceptibility to damage.[23]

Research suggests a lower CH in glaucoma patients vs. glaucoma suspects and normals.[24] Low CH is also associated with progression of glaucoma and an increased rate of progression.[25-29] Furthermore, that association is more powerful than the association with CCT.[25-29] Used in isolation, one report found a CH average of 7.5mm Hg±1.4mm Hg in progressors versus 9.0mm Hg±1.8mm Hg with stable disease.[28] Research shows that for every 1mm Hg decrease in CH from baseline there was an associated 0.25% per year increased rate of visual field index decline.

Like other measurements, CH suffers from measurement noise and is directly influenced by CCT.[23] It is also inversely influenced by IOP.[23] Thus, both influences should be considered when interpreting CH. One study evaluated the relationship in a study of patients with primary open-angle glaucoma (POAG) and OHT. They found that, as CCT increases, so does CH. Specifically, patients with POAG and thinner corneas maintained lower CH levels than those with intermediate and thicker corneas.

The authors interpreted these findings as suggestive that CH in isolation, without consideration of CCT, could erroneously suggest or mask glaucoma risk. Combining the two improves the sensitivity of diagnosis beyond either individually.[23]

As with IOP, CH can change over time. Studies suggest an inverse relationship: CH is lower as IOP increases, and can become higher as IOP lowers.[19] All this information

Table 1. Drugs That Lower IOP

Category	Mechanism of Action	Brand (Generic)
Rho kinase (ROCK) inhibitors	Increase outflow + decrease aqueous production + decrease episcleral venous pressure	• Rhopressa (netarsudil)
Prostaglandin analog (PGA)	Increase uveoscleral outflow	• Lumigan (bimatoprost) • Travatan, Travatan Z (travoprost) • Vyzulta (latanoprostene bunod) • Xalatan (latanoprost) • Xelpros (latanoprost) • Zioptan (tafluprost single use, preservative-free)
Beta-blocker (BB)	Increase uveoscleral outflow	• Betagan (levobunolol) • Betimol (tilolol hemihydrate) • Betoptic-S (betaxolol) • Istalol (timolol) • Optipranolol (metipranolol) • Timoptic, Timoptic-XE (timolol)
Carbonic anhydrase inhibitor (CAI)	Decrease aqueous production	• Azopt (brinzolamide) • Diamox (dorzolamide oral) • Neptazane (methazolamide oral) • Trusopt (dorzolamide)
Alpha adrenergic agonist (AA)	Decrease aqueous production + increase uveoscleral outflow	• Alphagan P (brimonidine) • Iopidine (apraclonidine)
Cholinergic	Increase trabecular meshwork outflow	• Carpine (pilocarpine) • Pilocar (Isopto)
CAI + BB	Fixed-combination	• Cosopt, Cosopt PF (preservative-free)
AA + BB	Fixed-combination	• Combigan
CAI + AA	Fixed-combination	• Simbrinza
ROCK + PGA	Fixed-combination	• Rocklatan

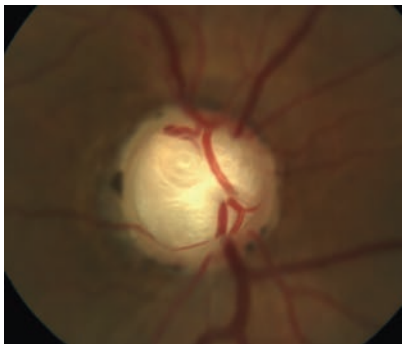
underscores the realization that reliance on the TCPD alone is insufficient in risk assessment.

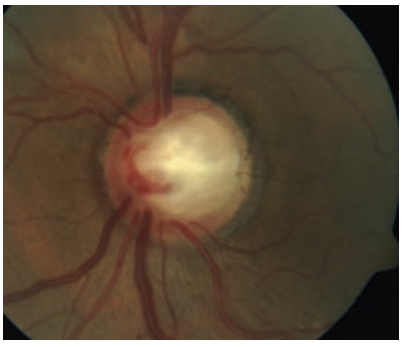
At present, the Ocular Response Analyzer (Reichert Technologies) is the only commercially available product that can capture corneal hysteresis in office.[30,31]

What Causes IOP to Rise?

In a normal eye, aqueous humor (AH) flow against resistance generates the IOP. IOP increases with either overproduction of AH or a compromised outflow. Two pathways exist for AH drainage: Conventional/pressure-sensitive (major) and unconventional/pressure-insensitive (minor). The conventional pathway consists of the trabecular meshwork, Schlemm's canal and collector channels. Interestingly, the discovery of AH atherosclerotic plaque markers in glaucoma patients supports the view that the anterior chamber is a specialized vessel where corneal and trabecular endothelial cells form the walls and whose "blood" is the AH.[32]

The second, unconventional, pathway—frequently referred to as uveoscleral outflow—represents nontrabecular clearance of AH and is composed of the uveal meshwork





Deep laminar cupping can be seen in this 70-year-old patient whose in-office IOPs never exceeded 19mm Hg. Lower CSFP with subsequent alteration to the TLPD may have resulted in the substantial excavation in this NTG case.

and anterior face of the ciliary muscle.[33] Thus, this pathway lacks recognizable channels and vessels.

Pressure Fluctuations

IOP is a dynamic parameter that varies spontaneously over time. As such, it is subject to short- and long-term diurnal and nyctohemeral fluctuation.[43] IOP regulation is complicated. It can be influenced by activity, body positioning (supine vs. standing, or sitting), nocturnal elevation, hypo- or hyper-response to medications and other factors.[35,36] IOP fluctuation, peak IOP or the combination of the two play a prominent role in the development and progression of glaucomatous damage, with more recent studies suggesting peak IOP to be the best predictive factor.[37-42]

Understanding and accounting for these dynamics becomes important when regulating IOP with commerically available drugs (*Table 1*).

Ocular Perfusion Pressure

Several studies have suggested associations between vascular factors and glaucoma.[43] OPP refers to the pressure available to move blood through ocular vasculature, with lower OPP presumably resulting in less blood flow to the ONH and subsequent ischemic damage.

Perfusion pressure of an organ is the pressure difference between its arterial and venous supply. This does not necessarily hold true for the eye, as there are other factors at play. Historically, the simple calculation of blood pressure (BP) minus IOP has been employed to reflect OPP.[43] Recent research suggests this calculation should be abandoned, as it may oversimplify OPP's complexity.[44]

Studies show a correlation between glaucoma and both low and fluctuating OPP, where the greater the fluctuation or the lower the OPP the greater risk of damage.[45-47] One study specifically shows a diastolic perfusion pressure (diastolic BP minus IOP) of 56mm Hg or lower to be a useful threshold to help clinically identify patients at risk for progressive glaucomatous optic neuropathy.[45-47]

Conversely, a 2015 study found that although there appears to be a relationship between TLPD and optic nerve damage, there was no support for the notion that OPP plays a major role in the pathogenesis of optic neuropathy. The authors calculated OPP as follows:[45]

$OPP = {}^{2}/_{3}\,[diastolic\ BP + {}^{1}/_{3}\,(systolic\ BP - diastolic\ BP)] - IOP$

Undoubtedly, dynamics within and between the different interrelated measurements (CSF pressure, IOP and TLPD) provide uncertainty when attempting to calculate and implement OPP. Pulse-related issues can increase the CSF in relation to IOP, so that TLPD decreases. If, for a brief moment, the orbital CSF pressure becomes higher than IOP, than TLPD becomes reversed. This can result in a change in the undulation of the TLPD, with consequences for axoplasmic flow entering the eye.[45]

In addition to pulse-related changes, both IOP and CSF pressure change in relationship to body position.[45] Circadian variations in OPP change as BP dips during sleep while IOP is at its peak. This places the ONH in a potentially more vulnerable state. Ambulatory BP monitoring can help identify patients who are "dippers" and at a higher theoretical risk from advancing glaucomatous damage.[48] A recent publication demonstrated that the extent of the dip in diastolic BP is a significant predictor of subsequent visual field progression in patients with NTG.[49]

Another consideration is the effect of systemic or topical medication when attempting to determine OPP. It decreases when systemic BP is lower or when IOP is higher. Attempts to modify either of these conditions with medication affect the overall equation. Ultimately, a team approach with the patient's primary care physician is advisable when managing patients with BP issues and glaucoma.[48]

Undoubtedly, the eye is exposed to many forces, creating a complex relationship that, when imbalanced, can result in glaucomatous optic neuropathy. Increased knowledge and awareness of these various pressures will only increase our capacity to provide more customized management of our patients. ■

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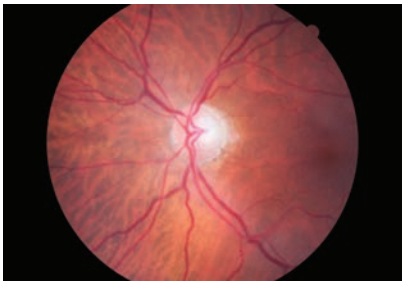
25th Annual Glaucoma Report

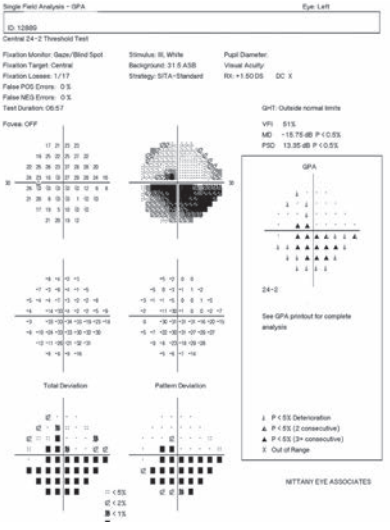
Is it Glaucoma, a Comorbidity or Both?

To care for patients with this sight-stealing disease, be aware of additional ocular or systemic issues. By Michael Cymbor, OD, and Jenae Stiles, OD

As an eager, young practitioner, I (Dr. Cymbor) can recall seeing a patient for the first time. A man, approximately 70 years old, presented with a previous diagnosis of glaucoma. His visual field showed an inferior arcuate in the right eye and scattered nonspecific defects in the left eye. His intraocular pressures (IOPs) were in the high teens on topical medications. Even though his nerves showed minimal cupping, his diagnosis of glaucoma seemed reasonable, and I continued his topical meds. One year later, his fields and nerves were unchanged.

Upon further scrutinizing his nerves, I noticed his right eye had a small amount of pallor corresponding to the field defect and the other eye had a somewhat crowded disc. Further questioning revealed he had suffered an episode of a sudden change of vision in his right eye 10 years prior but never had it checked. One year after that event, he was diagnosed with glaucoma. Based on this new history and stable fields and nerves, I changed his diagnosis





Figs 1 and 2. Visible in this patient's optic disc is a temporal pallor with numerous arterial constrictions and a/v nicking. At right is her visual fields.

to non-arteritic ischemic optic neuropathy, stopped the drops and he has been stable ever since.

Reflecting on this case, I should have questioned the diagnosis of glaucoma. I might have saved him the burden of a year of unnecessary treatment.

Not every patient with a reduced OCT and visual field actually has glaucoma. Non-glaucomatous disorders may mimic glaucoma. Comorbidities may also influence the management of glaucoma. Patients with glaucoma have a higher risk of systemic and retinal disease. One study found that 50.5% of patients with glaucoma also had hypertension and more than 30% had hyperlipidemia or diabetes.[1] A meta-analysis also found that patients with glaucoma had higher mean triglyceride levels.[2] Patients with these diseases have a higher risk of non-glaucomatous optic neuropathies. Patients with glaucoma are at a higher risk of retinal disease, such as diabetic retinopathy (DR) and age-related macular degeneration (AMD).[3]

In other words, patients with

glaucoma have a higher risk of non-glaucomatous eye disease and patients with non-glaucomatous eye disease have a higher risk of glaucoma.

Hypertension and IOP

A relationship exists between systolic and diastolic BP and IOP. A 10mm Hg increase in systolic blood pressure is associated with a 0.26mm Hg increase in IOP and a 5mm Hg increase in diastolic BP is associated with a 0.17mm Hg increase in IOP.[5]

Patients with hypertension and hypertensive retinopathy have an increased risk of retinal artery occlusion, retinal vein occlusion (RVO), retinal arteriole macroaneurysn, BP, anterior ischemic optic neuropathy (AION), AMD, arteriolar emboli, epiretinal membrane, cystoid macular edema and glaucoma.[6] Because of these associations, be careful to distinguish when fundus, field and nerve changes originate from glaucoma from other pathologies.

While RVOs must be monitored for secondary neovascular glaucoma, the later stages of RVOs can also manifest as possible glaucomatous damage to the optic nerve head upon first glance. If a sclerotic or "ghost" vessel is present, ODs can infer ischemic damage if corresponding with a similar area of retina and disc. This would be even more reassuring of a diagnosis in the setting of chronic diseases, such as hypertension, diabetes and hypercholesterolemia. It is when the vessel re-perfuses that confusion can arise.

Optic disc pallor has been found in 20% of those with major branch retinal vein occlusion (BRVO).[7] Research shows RNFL thinning of the BRVO-affected area in both ischemic and non-ischemic vein occlusions.[8]

When Comorbidities Collide

An 83-year-old woman came to the office for her yearly evaluation. She had an ocular history of a non-arteritic ischemic optic neuropathy (NAION) OS, which occurred within a few days of cataract surgery six years prior due to a transient IOP spike. She also had a history of dry eye. Her systemic history was significant for longstanding hypercholesterolemia and hypertension. Her best-corrected visual acuity (BCVA) was 20/25 OD and 20/70 OS. IOPs were typically in the mid-teens, but had climbed to 33mm Hg OD and OS at this visit. Central corneal thicknesses (CCT) were 543µm OD and 541µm OS with corneal hysteresis (CH) of 11.7mm Hg and 11.0mm Hg. This lower CH may put the left eye more at risk for glaucoma conversion/progression. Her blood pressure (BP) was 139/85 RAS. The optic disc of the left eye showed temporal pallor with numerous arterial constrictions and a/v nicking (*Figure 1*). Her visual field showed a dense inferior defect (*Figure 2*). An OCT image showed a reduced paramacular ganglion cell complex (GCC) with supratemporal atrophy of the retinal nerve fiber layer (RNFL) (*Figure 3*).

This case illustrates the complexity of managing glaucoma with multiple comorbidities. The patient has a previous diagnosis of NAION in the left eye, hypertensive retinopathy in the right and, now, ocular hypertension OU.

Although her right eye's visual field and OCT images were unremarkable, her recently increased IOPs were a major concern, especially in the right eye because of an increased risk of an ischemic event due to the NAION in her left eye. A topical beta-blocker may not be the best option because of her hypercholesterolemia, as beta-blockers may worsen the condition.[4] We started her on a preservative-free prostaglandin, which lowered her IOP by approximately 30% to 20mm Hg OS and 21mm HG OD. After several months she reported difficulty with drop insertion, so we performed bilateral selective laser trabeculoplasty (SLT). Her IOPs have since been consistently in the high teens.

Nonglaucoma Neuropathies

AION is the most common acute optic neuropathy among patients older than 50 and it may be the most easily confused with glaucoma.[9] Both produce nerve fiber bundle field defects and nerve fiber layer atrophy. After initial axonal swelling, nerve fiber atrophy occurs and may continue for up to six months before stabilizing.[10] OCT images of the GCC show a strong correlation with visual field because GCC thinning from AION occurs prior to nerve fiber layer thinning.[11,12]

Arteritic anterior ischemic optic neuropathy (AAION) represents inflammation and a vascular occlusion of the posterior ciliary arteries, which originate from the ophthalmic artery, resulting in optic nerve infarction.[13] AAION accounts for only 5% to 10% of all AION cases, but half of them develop optic disc cupping.[14,15] Patients may experience a rapid onset of unilateral vision loss with a devastating reduction in visual acuity and color vision. Altitudinal visual field defects and relative afferent pupillary defects are common.[16] History is key as patients may describe symptoms of jaw claudication, scalp tenderness, fatigue, weight loss and headache. AAION without symptoms—occult AAION—occurs in 20% of cases.[17]

Nonarteritic anterior ischemic optic neuropathy (NAION) occurs from a small-vessel infarction of the anterior optic nerve in the posterior ciliary arteries. NAION accounts for 90% to 95% of all AION cases and typically affects patients between ages 50 and 70.[9,18] Symptoms typically are painless, unilateral and occur immediately or evolve over several hours to days. Visual acuity varies from 20/20 to

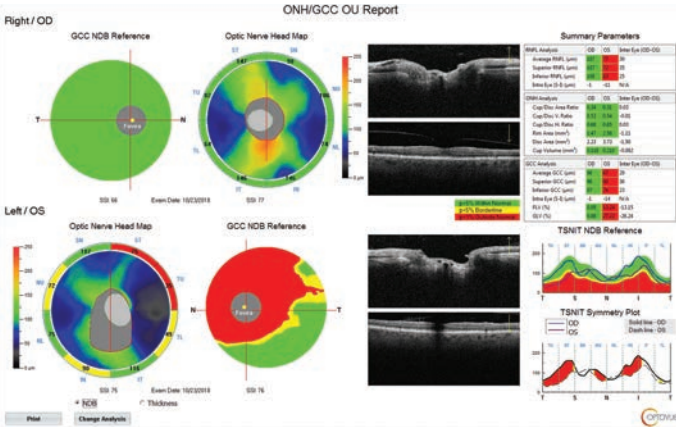


Fig. 3. Using OCT technology, we can see the patient from page 54 also has a reduced paramacular ganglion cell complex with supratemporal atrophy of the RNFL.

no light perception but stays better than 20/200 around two-thirds of the time.[9] For these patients, color vision is reduced, and a relative afferent pupillary defect will occur in unilateral cases. An altitudinal defect is often seen, but an arcuate defect may also occur, making it more difficult to differentiate from glaucoma. Optic nerve cupping is uncommon in NAION. The non-affected eye often has a crowded disc with the absence of a cup. OCT angiography (OCT-A) may help differentiate between NAION and glaucoma.[19]

Except for acute angle closure, glaucoma rarely presents with sudden vision loss. AION patients, however, often experience sudden vision loss when waking up. Acute AION patients often have optic nerve edema while nerve edema does not occur with glaucoma. Pallor is another way to differentiate the two pathologies.

In general, glaucomatous eyes have larger and deeper cups, with less rim volume.[13] Glaucomatous rim tissue remains pink late into the disease state.

Neuropathy Etiology

When considering possible causes of optic neuropathy, think about the demyelinating processes that can contribute to these findings. Multiple sclerosis (MS), perhaps the most well-known demyelinating disease, is classically associated with optic neuritis and can occur in up to half of all MS patients.[20] This swelling of the optic nerve can result in optic atrophy and pallor with a resultant abnormal OCT six to eight weeks following onset.[21]

Visual field defects can be unpredictable with this disease. Partial arcuate, paracentral and arcuate nerve fiber bundle defects are the most common defect patterns post inflammation in both the affected and fellow eyes.[22] When considering the possible diagnosis of glaucoma in a patient without a known history of MS, carefully assess the history for concurrent neurological symptoms. Peripapillary RNFL thickness is thinner in MS patients.[23]

Tumors

Various other brain malignancies can cause optic neuropathies that mimic that of glaucomatous damage. In these cases, doctors must consider all aspects of the visual pathway.

While vision loss with primary open angle glaucoma is typically gradual and painless, so is that of vision loss associated with optic pathway gliomas. In general, this type of benign tumor typically affects children, but malignant glioblastomas occur in adult males and carry a very poor prognosis.

Approximately 10% of optic pathway tumors occur within the optic nerve and, when labeled as an optic nerve glioma, typically present with unilateral proptosis and afferent pupillary defect.[24] Unilateral papillitis will be seen initially, but then leaves the optic nerve atrophic with pallor disproportionate to what would be seen with end-stage glaucomatous cupping.[24]

When considering the pattern of RNFL loss contributing to increased cupping seen in compressive optic neuropathy, typically more nasal and temporal loss is noted, but any type of cupping is quite rare.[23] This is different to what is commonly seen in glaucoma as supra-temporal and infratemporal RNFL loss.

Meningioma is the most common type of tumor of the head and typically affects women as they age.[25] This tumor can occur in any area of the brain and accounts for the second most common primary optic nerve tumor. This type of tumor also presents with gradual and painless vision loss, typically unilateral. A pathognomonic feature of this tumor is the formation of optociliary shunt vessels that result from chronic retinal venous outflow resistance.[26] While optic disc swelling may also be seen, most often secondary pallor will be noticed.

Blood flow abnormalities must also be considered with optic neuropathies where glaucoma is only one of the differential diagnoses. Along the 50mm course of the optic nerve, direct compression by aneurysm occurs from branches of the internal carotid artery, which maintains the vascular supply to the anterior optic pathway within the circle of Willis. Rupture of the aneurysm can cause ischemia to the tissue it supplies, also leading to atrophy.[27] While follow-up radiologic studies assessing blood flow would be

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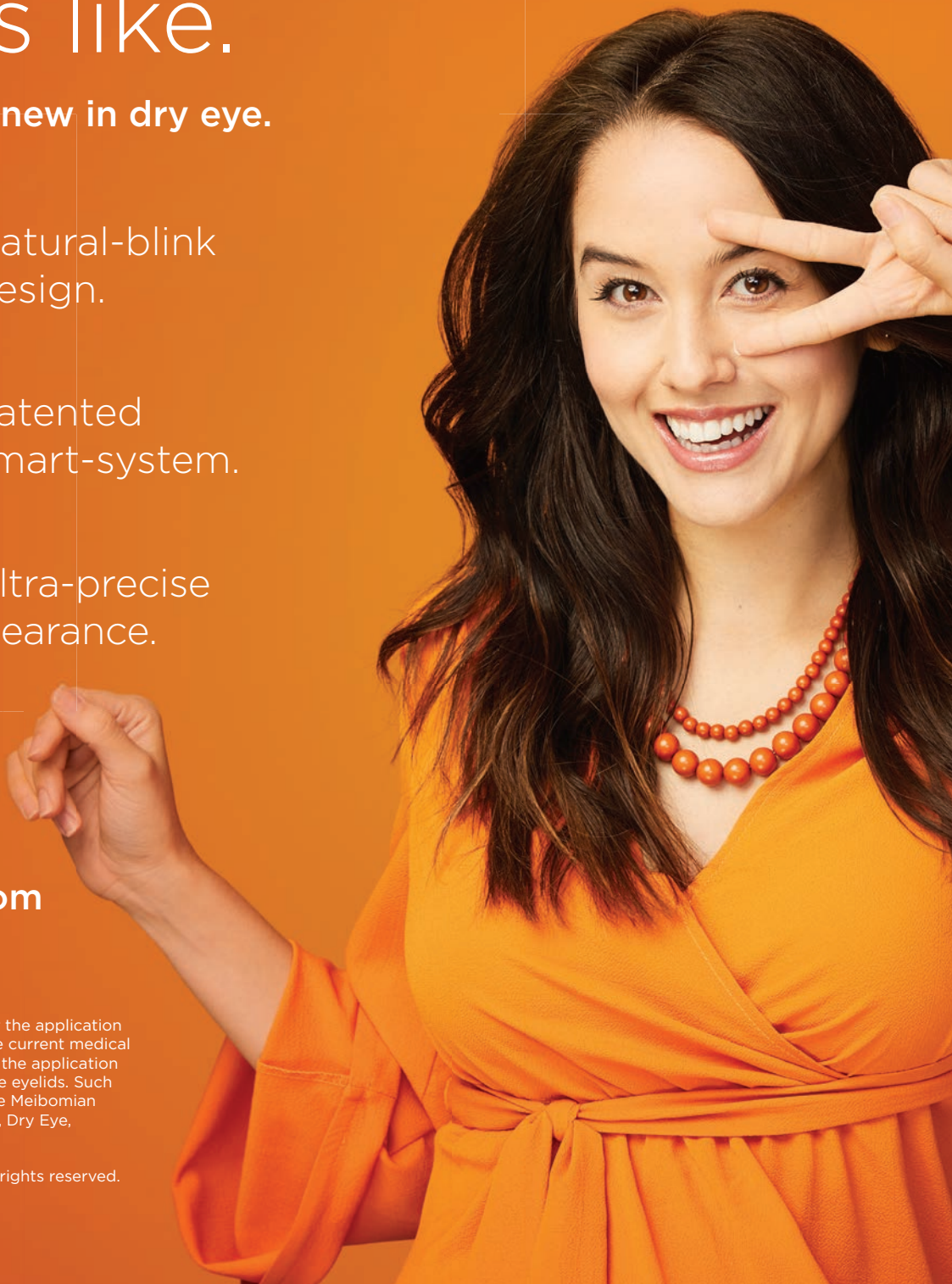

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Neuro-sarcoidosis and NFL Defects

A 48-year-old black female with a history of sarcoidosis was first diagnosed in 2004. Her most recent angiotensin converting enzyme reading in mid-2018 was normal and her last pulmonary function test around the same time showed mild obstructive lung defects with normal volumes and diffusion capacity. Her first comprehensive eye exam was in 2010 and since that time, her highest measured IOP had been 19mm Hg in both eyes. In 2017, fundus photography showed a superior temporal RNFL defect with corresponding pallor (*Figure 4*). This NFL damage was further confirmed with OCT (*Figure 5*). A full glaucoma work-up was completed at that time with normal gonioscopic findings and thin pachymetry (510µm/495µm). RNFL values have remained stable since that time. 24-2 visual field showed central defects in the right eye corresponding on 10-2.

This patient is being closely followed for neuro-sarcoidosis due to possible involvement of the optic nerve. Neuro-sarcoidosis affects 5% to 15% of those with sarcoidosis and commonly manifests with Bell's palsy, auditory impairment, seizures, memory loss, hallucinations and pituitary abnormalities.

National Institute of Neurological Disorders and Stroke. Neurosyphilis. www.ninds.nih.gov/Disorders/All-Disorders/Neurosyphilis-Information-Page. March 3, 2019. Accessed June 1, 2019.

warranted, a history of worsening headaches could hint at this lesion.

Several toxins may contribute to optic neuropathy that can resemble glaucomatous RNFL pattern deficits in the setting of a seemingly normal work-up. Typically painless, progressive and bilateral in nature, toxic optic neuropathy can have devastating and irreversible effects. Other common findings include color vision abnormalities, sluggish pupils, temporal optic nerve head pallor and central scotoma. Suspected etiology is that of impaired vascular supply and metabolism due to toxin accumulation within the unique configuration of the blood supply of the optic nerve head.[28] Alcohol (methanol), antibiotics, antiarrhythmic, anticancer, heavy metals and carbon monoxide are all possible etiologies of toxic optic neuropathy and lab work (CBC, urinanalysis, metal screening, B12) should be ordered. Neuroimaging is often needed to rule out other causes of optic nerve head pallor. Vitamin B deficiency can amplify the effects of these toxins and contribute to nutritional optic neuropathy, commonly seen in alcoholic patients.[29]

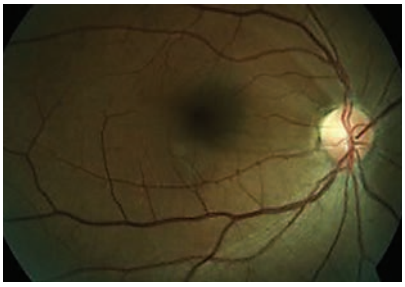

Fig 4. This fundus photo shows a 48-year-old female's superior temporal RNFL defect with corresponding pallor.

If presenting at the time of injury, traumatic optic neuropathy could be a straightforward diagnosis. Patients who present years after the event require an extensive history. While, most likely, decreased visual acuity or visual field defects bring these patients into your clinic, objective signs on examination often include optic atrophy due to decreased color vision and afferent pupillary defect testing.

The full glaucoma work-up including gonioscopy is necessary in those patients for whom past ocular trauma is suspected to rule out angle recession glaucoma as a contributor to the impaired optic nerve function. The International Optic Nerve Trauma Study found that 85% of patients with indirect traumatic optic neuropathy were male, with the most common injury etiology being that of motor vehicle accidents. Optic atrophy can take three to six weeks after initial trauma to present, so close follow up is a requirement.[30]

Infections

Sexually transmitted diseases (STDs) can cause systemic issues within every organ system. Syphilis is known as the "great imitator" as its sequelae can present in any part of the eye and often cause devastating consequences if left untreated. This spirochete infection does not commonly involve the optic nerve (estimated at about 20% of cases), but can be bilateral or unilateral in presentation. Papillitis is commonly noted at initial presentation, which can make the diagnosis difficult if this has cleared and left the nerve atrophic with pallor.[31] A history of intravenous drug use, past STDs, or multiple sexual partners can aid in ordering lab work to rule this out.

Rapid plasma reagin typically is used to detect active infection (rule in) while treponemal tests, such as fluorescent treponemal antibody absorption, are ordered to detect if infection has ever occurred, indicating a past exposure.[32] Argyll Robertson pupil is a sign of late-stage syphilis where small, bilateral pupils are present that constrict more to a near object than to bright light.[31]

Congenital Conditions

Several inherited conditions exist that can result in longstanding or progressive optic atrophy that could leave the clinician with an initial lengthy list of differential diagnoses. Leber's hereditary optic neuropathy is one of these conditions in which the patient can initially present with a seemingly normal

posterior pole. As an example, a 21-year-old Caucasian male presented to the clinic with bilateral blurry vision for the past month. No improvement was shown on refraction with BCVA of 20/100 in each eye. Upon further questioning, the patient stated that his mother and maternal grandfather have never had good vision as well as his male cousin, while his female cousin has been deemed a Leber's carrier.

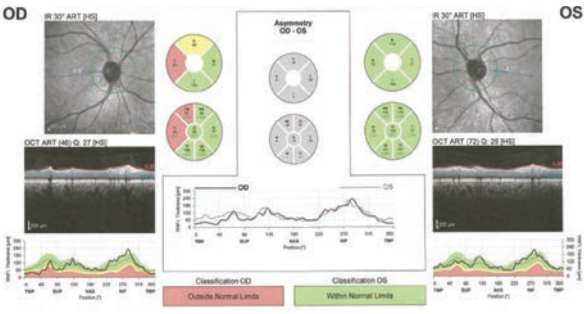

Fig. 5. This OCT reading of the same patient from page 58 confirms her RNFL damage.

Due to the pathology of this optic neuropathy inherited as a mitochondrial disorder, males are disproportionately affected along the maternal lineage. The symmetric and bilateral nature of this patient's case led to a lack of afferent pupillary defect, but this can occur if asymmetric at presentation. While extensive testing could still be needed to rule out other causes of optic neuropathy and severe vision loss, specifically questioning the ocular history of the patient's maternal lineage can greatly aid in the diagnosis.

Recent study has focused on the effects of degenerative neurological diseases on the retina, specifically in using OCT to detect early changes indicative of Alzheimer's disease. Decreased RNFL thickness, increased cupping and vascular tortuosity have all been associated with Alzheimer's.[23] The literature suggests that certain ophthalmologic conditions (AMD, glaucoma and DR) may serve as precursors to Alzheimer's disease and exist in the same neurodegenerative pathway. One large study found that in those recently diagnosed with glaucoma, a 46% higher risk of Alzheimer disease risk was found.[33] This diagnosis should be kept in mind for those showing RNFL changes and possible dementia symptoms.

Mimickers of glaucomatous optic atrophy and RNFL loss can be tricky, especially in the setting of mildly elevated IOP and positive family history of glaucoma. When evaluating a patient where the clinical findings may lead to another diagnosis, one must consider all aspects of past history and current behavior when deciding upon further diagnostic evaluation. While glaucoma could be playing a role in the patient's optic nerve head appearance and visual field loss, there could be more contributing factors that warrant further treatment for best visual outcome. ■

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25th Annual Glaucoma Report

GLAUCOMA MEDICATIONS: WHEN GOOD DRUGS DO BAD THINGS

IOP-lowering agents, like all other medicines, have the potential to produce both clinical benefits and harmful effects. **By Bruce E. Onofrey, OD, RPh**

In the late 1800s, the medical management of glaucoma was simple. The one and only choice of treatment was topical pilocarpine, a miracle drug at the time. Over the many decades of its use, patients have certainly enjoyed pilocarpine's clinical benefits but have also suffered its side effects.

Today, our choices of glaucoma medications are significantly greater. We have multiple drugs that work well as monotherapy, along with many that we can add to improve the clinical outcome with combination drug approaches. Unfortunately—perhaps inevitably—these drugs carry side effects of their own.

This article discusses the concept of rational drug selection and specifically identifies the side effects and adverse events of medications designed to treat the various forms of glaucoma (*Table 1*).

First, let's review some basic pharmacology concepts and terms. The pharmacology of any drug includes the drug's mechanism of action, indications, side effects, adverse events, dosages, dosage forms and warnings.[1] A brief definition of each of these terms is warranted:

Pharmacokinetics: The movement of medicine into, through and out of the body—the progression of its absorption, bioavailability, distribution, metabolism and excretion.

Mechanism of action: How the drug interacts with the patient's physiology and alters it to cure or control a certain disease state.

Release Date: July 15, 2019
Expiration Date: July 15, 2022
Estimated Time to Complete Activity: 2 hours

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Educational Objectives: After completing this activity, the participant should be better able to:

- Identify the side effects, ocular and systemic, of all types of glaucoma medications, new and old.
- Determine treatment options based on factors of efficacy, safety, risk and compliance.
- Evaluate the benefits and risks of additive/adjunctive medication.
- Incorporate strategies to prevent, reduce, or reverse medication side effects in glaucoma patients.

Target Audience: This activity is intended for optometrists engaged in the care of patients with glaucoma.

Accreditation Statement: In support of improving patient care, this activity has been planned and implemented by the Postgraduate Institute for Medicine and Review Education Group. Postgraduate Institute for Medicine is jointly accredited by the Accreditation Council for Continuing Medical Education, the Accreditation Council for Pharmacy Education, and the American Nurses Credentialing Center, to provide continuing education for the healthcare team. Postgraduate Institute for Medicine is accredited by COPE to provide continuing education to optometrists.

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Indication: The condition for which the US Food and Drug Administration has approved the drug to be safe and effective to treat.

Contraindication: Pre-existing condition in which a drug is not safe or effective in a given individual.

Side effects: Undesirable effects of a drug that are predictable by the drug's mechanism of action.

Adverse events: Undesirable effects of a drug that are not predictable by the drug's mechanism of action. They can be dose-dependent (toxic drug effects) or non-dose-dependent (allergic reactions).

Dosages: The calculated amount of safe and effective drug that can be administered to a patient. This calculation can be based on age, weight and renal and hepatic function.

Dosage forms: These include topical solutions, suspensions, emulsions and ointments as well as systemic tablets, suppositories, capsules and injectable forms.

Warnings: Patient counseling that includes significant symptoms that may indicate toxic undesirable effects of a drug. Symptoms can be annoying but non-life-threatening and tolerable, or may indicate a potential life-threatening condition that requires the immediate discontinuation of the drug.

Rational Prescribing

In pharmacology there is a singular truth: drugs have the potential to produce clinical benefits and the potential to produce harm, otherwise known as the risk/benefit ratio.[1] It's up to the clinician to select the right drug for the right disease for the right patient:

1. For any disease, the clinician should choose the most effective drug or drug combination that provides the best chance to control or cure the condition (i.e., benefit).

2. The clinician, after performing a thorough medical interview with the patient—including their medical, social, surgical and ocular histories—can then determine the best drug/dose to treat the given condition while attempting to minimize adverse events/side effects (i.e., risk).

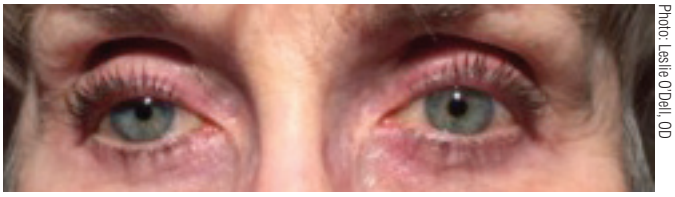


Photo: Leslie O'Dell, OD

This patient has prostaglandin-associated periorbitopathy with deepened sulci bilaterally due to periorbital fat atrophy and ptosis. After topical treatment with a PGA for more than 10 years, she also has a relative endophthalmos with a sunken globe appearance.

Weighing benefits vs. risks requires a thorough knowledge of the pharmacology of the drug, the pathophysiology of the condition and the medical history of the patient.[1]

Special Populations

Within the general population, certain patients have pre-existing conditions that could potentially predispose them to increased side effects or adverse events due to their condition (*Table 2*).

Treatment Goals

The goal of the pharmaceutical management of glaucoma is to select a drug or group of drugs that safely lowers the patient's intraocular pressure (IOP) while minimizing clinically significant undesirable effects. The concept of combining two or more drugs that produce an effect that is greater than the sum of their separate effects is known as synergy. It is based on the selection of drugs that do the same thing (i.e., lower IOP) but use different mechanisms of action. By this process, one drug enhances instead of interferes with or inhibits the other drug(s).

Additionally, we now know that glaucoma risk is not simply based on IOP—alterations in cardiovascular dynamics (which include blood pressure and pulse), diurnal fluctuations of IOP and use of concurrent systemic cardiovascular agents all can limit the drugs that a patient can safely use to treat their form of glaucoma.[2]

Currently, the only way to lower the risk of glaucoma progression is by reducing IOP. Depending on the selected agent, this is accomplished by: (1) decreasing aqueous production; (2) increasing trabecular outflow; (3) increasing extra-trabecular outflow; or (4) reducing episcleral venous pressure.

We select medications that maximize each individual factor to increase efficacy, and we avoid drugs that, in each patient, may increase their risk of significant, undesirable clinical effects. Most importantly, we attempt to maximize compliance of therapy by minimizing cost and side effects and maximizing convenience.

Aqueous Physiology

All current glaucoma drugs manage the disease by some alteration of aqueous dynamics.

The aqueous is produced by the ciliary body via ultra-filtration, secretion and diffusion. It is formed by the ciliary processes, each of which is composed of a double layer of epithelium. Within each ciliary process, the apical surface of the outer pigmented layer faces the apical surface of the inner non-pigmented layer, and they're joined by tight junctions. Sandwiched between these two layers is stromal tissue, along with a system of fenestrated capillaries. The inner non-pigmented epithelial cells produce the aqueous.

The production of aqueous humor is controlled by factors that include the enzyme carbonic anhydrase along with blood flow to the ciliary processes.[3] This is an important com-

ponent of the blood-aqueous barrier. The autonomic nervous system, in controlling the afferent blood flow (to the process) and efferent blood flow (from the process), has a significant impact on aqueous production, which is normally approximately 2µL/minute.[3] About 90% of aqueous outflow is through the trabecular meshwork, with the remaining 10% through extra-trabecular outflow mechanisms.[4]

Episcleral venous pressure is now recognized as a new parameter that can be pharmacologically manipulated. It is inversely related to trabecular outflow, and lowering episcleral venous pressure enhances trabecular outflow (assuming the angle is open).[5]

Glaucoma Drugs

Here is a look at each class of medication, inlcuding the ocular and systemic effects:

Cholinergics. The discovery of the autonomic nervous system, neurotransmitters and receptor physiology led to the development of many of the modern drugs used today. Because these receptors are located on every organ of the body, this class of drugs allows for the significant manipulation—and as a result, significant systemic side effects—that are associated with the parasympathetic component of the autonomic nervous system.

Cholinergic drugs mimic the effects of the neurotransmitter acetylcholine. When released from the postganglionic terminals, acetylcholine binds to parasympathetic receptors producing a local response. The enzyme acetylcholinesterase then neutralizes the neurotransmitter and stops the parasympathetic activity.

The physiology of this process is important in predicting the side effects produced by cholinergic glaucoma drugs. These drugs fall into two major categories: direct- and indirect-acting cholinergic agents. The direct-acting agents mimic acetylcholine and directly stimulate the parasympathetic receptors. Indirect (or mixed-acting) agents block the enzyme acetylcholinesterase that deactivates acetylcholine. The indirect agents have the same side effects as the direct-acting agents.[6]

The mechanism of action of these drugs and their side effects are intimately related.[7] They reduce IOP by physically producing contraction of the ciliary body, which increases trabecular outflow. Along with increased trabecular outflow, patients may get other undesirable effects.

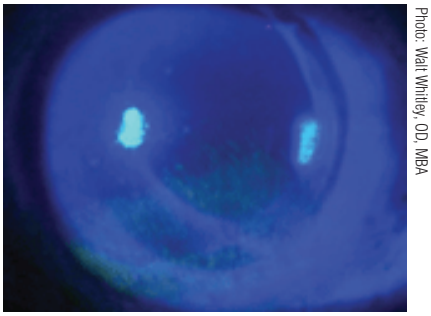
Potential ocular side effects:

- Stinging, burning and redness
- Headache/brow ache
- Miosis
- Increased accommodation
- Ciliary spasm
- Induced myopia
- Reduced acuity
- Posterior synechiae
- Retinal detachment (rare)

Contraction of the ciliary body is responsible for many of these undesirable effects.[7] Miosis can be problematic in individuals with lens opacities. Certainly, in the presence of intraocular inflammation, miosis increases the risk of posterior synechia and the development of pupil block. For these reasons, cholinergics are contraindicated in patients with intraocular inflammation or angle-closure glaucoma.

The worst of the cholinergics are the indirect-acting agents with long half-lives, such as the phosphorylating agent Phospholine Iodide (echothiophate iodide, Pfizer).[7] A major concern in the use of these agents is a potential interaction with succinylcholine, a drug used to paralyze muscles during general surgery. Use of these agents must be discontinued three weeks prior to the use of general anesthesia to prevent a risk of increased apnea in the operated patient.[8]

Potential systemic side effects:



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Superficial punctate keratitis is a possible finding associated with CAIs.

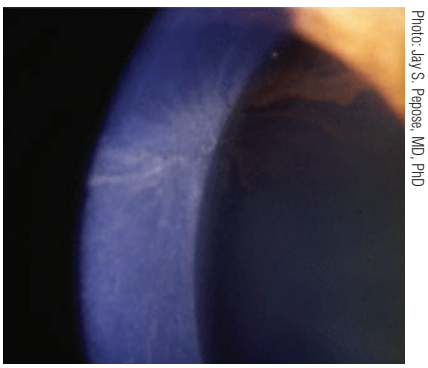


Photo: Jay S. Pepose, MD, PhD

Corneal verticillata may be a common side effect of rho-kinase inhibitor use.

- Bronchospasm in asthmatics
- Nausea, vomiting and diarrhea associated with increased GI motility
- Bradycardia via stimulation of the vagus nerve (CN X)
- Salivation and sweating via stimulation of exocrine glands
- Central nervous system depression

Alpha-2 agonists. While alpha-1 receptors tend to produce vasoconstriction and raise blood pressure, alpha-2 receptors tend to inhibit alpha-1 activity. As a result, stimulation of alpha-2 receptors leads to decreased blood pressure, sedation and aqueous production reduction.[9]

The original alpha-2 agonist was clonidine, which is most commonly used systemically to control blood pressure.[10] The current glaucoma medications apraclonidine and brimonidine are derivatives of clonidine. Again, these drugs do not affect aqueous outflow, but do reduce

aqueous production. The side effects of these drugs are closely tied to clonidine and its alpha-2 activity and partial alpha-1 activity.[11]

Potential ocular side effects:

- Conjunctival blanching
- Lid retraction
- Mydriasis/miosis
- Significant incidence of ocular allergy (apraclonidine 36% within 90 days and brimonidine 10% within one year)
- Follicular conjunctivitis

Potential systemic side effects:

- Dry mouth
- Sedation
- Hypotension
- Reduced optic nerve perfusion (due to drop in blood pressure)

Beta-blockers. Drugs that block sympathetic beta-1 and beta-2 receptors were discovered in 1958. The original non-selective (B1 and B2) blocker is propranolol.[12] It was designed to treat elevated blood pressure, cardiac arrhythmias and angina. When researchers discovered that this drug could also lower IOP by reducing aqueous production, the search for a useful topical agent began. Propranolol proved to be unacceptable because of its corneal side effects, including profound dry eye, corneal anesthesia and subconjunctival scarring.

Eventually, the non-selective beta-blocker timolol revolutionized glaucoma management in 1978.[13] Although ocular side effects are

Table 1. Glaucoma Medications: Mechanisms, Dosing and Precautions

Brand	Generic	Mechanism of Action	Dosage/Avg. % Reduction
CHOLINERGIC AGENTS			
Direct			
Pilocarpine (generic)	Pilocarpine 1%, 2%, 4%	Increases trabecular outflow	BID-QID/15-25%
Indirect			
Phospholine Iodide (Pfizer)	Echothiophate iodide 0.125%	Increases trabecular outflow	QD-BID/15-25%
ALPHA-2 AGONISTS			
Alphagan P (Allergan)	Brimonidine tartrate 0.1%, 0.15% with Purite preservative	Decreases aqueous production, increases uveoscleral outflow	BID-TID/up to 26%
Brimonidine tartrate (generic)	Brimonidine tartrate 0.15%, 0.2%	Same as above	Same as above
Iopidine (Novartis)	Apraclonidine 0.5%	Decreases aqueous production	BID-TID/up to 25%
BETA-BLOCKERS			
Non-selective			
Betagan (Allergan)	Levobunolol 0.25%, 0.5%	Decreases aqueous production	QD-BID/20-30%
Betimol (Akorn)	Timolol hemihydrate 0.25%, 0.5%	Same as above	QD-BID/20-30%
Carteolol (generic)	Carteolol 1%	Same as above	QD-BID/20-30%
Istalol (Bausch + Lomb)	Timolol maleate 0.5%	Same as above	QD/20-30%
Optipranolol (Bausch Health)	Metipranolol 0.3%	Same as above	BID/20-30%
Timoptic (Bausch Health)	Timolol maleate 0.25%, 0.5%	Same as above	QD-BID/20-30%
Timoptic XE (Bausch Health)	Timolol maleate gel-forming solution 0.25%, 0.5%	Same as above	QD/20-30%
Selective			
Betoptic S (Novartis)	Betaxolol 0.25%	Same as above	BID/15-20%
CARBONIC ANHYDRASE INHIBITORS			
Topical			
Azopt (Novartis)	Brinzolamide 1%	Decreases aqueous production	BID-TID/15-20%
Trusopt (Merck)	Dorzolamide 2%	Same as above	BID-TID/15-20%
Oral			
Acetazolamide (generic)	Acetazolamide	Same as above	BID-QID/15-20%
Methazolamide (generic)	Methazolamide	Same as above	BID-TID/15-20%
HYPEROSMOTIC AGENTS			
glycerine (oral)	50%	Decreases vitreous volume, increases anterior chamber depth	1-1.5gm/kg
mannitol (IV)	5%, 10%, 15%, 20%	Same as above	1.5gm/kg
PROSTAGLANDINS			
bimataprost (generic)	bimataprost 0.03%	Increases uveoscleral outflow	QHS/27-33%
Lumigan (Allergan)	bimataprost 0.01%	Same as above	QHS/27-33%
Travatan Z (Novartis)	travaprost 0.004%	Same as above	QHS/25-32%
Xalatan (Pfizer)	latanaprost 0.005%	Same as above	QHS/25-32%
Xelpros (Sun Ophthalmics)	latanoprost emulsion 0.005%; BAK-free	Same as above	QHS/25-32%
Zioptan (Akorn)	tafluprost 0.0015%; preservative-free	Same as above	QHS/25-32%
PROSTAGLANDIN/NITRIC OXIDE PRODUCER			
Vyzulta (Bausch + Lomb)	latanoprostene bunod 0.024%	Increases uveoscleral and trabecular outflow	QD/34.6%
RHO-KINASE INHIBITORS			
Rhopressa (Aerie)	netarsudil 0.02%	Increases trabecular outflow, decreases episcleral venous pressure and aqueous production	QD/25-30%
COMBINATION AGENTS			
Combigan (Allergan)	timolol 0.5%/brimonidine 0.2%	Decreases aqueous production	BID
Cosopt (Akorn)	timolol 0.5%/dorzolamide 2%	Decreases aqueous production	BID
Rocklatan (Aerie)	netarsudil 0.02%/latanaprost 0.005%	Increases trabecular outflow and extra-trabecular outflow, decreases aqueous production and episcleral venous pressure	QHS/20-40%
Simbrinza (Novartis)	brinzolamide 1%/brimonidine 0.2%	Decreases aqueous production	BID

generally mild, the non-selective beta-blockers are notorious for cardiac and pulmonary side effects. The identification of beta-1 selective agents improved the safety of this group in those with chronic obstructive pulmonary disease (COPD) and asthma.[13]

Potential ocular side effects:

- Dry eye
- Ptosis
- Conjunctival hyperemia
- Corneal anesthesia
- Blurred vision
- Cicatricial ocular pemphigoid (timolol)

Potential systemic side effects:

- Cardiovascular
- Bradycardia (less with carteolol)
- Systemic hypotension
- Arrhythmia
- Angina
- Heart attack
- Heart block
- Death (anaphylaxis reversal)
- Pulmonary (less with betaxolol)
- Bronchospasm
- Wheezing
- Dyspnea
- Cough
- Central nervous system
- Depression
- Sedation
- Fatigue
- Confusion
- Inhibits SSRIs
- Memory loss
- Metabolic side effects
- Increased cardiac risk

	Product Sizes	Side Effects	Warnings
	15ml	Headache, blurred vision, myopia, retinal detachment, bronchiole constriction, narrowing of angle	Angle closure, shortness of breath, retinal detachment
	5ml	Same as above plus cataractogenic iris cysts in children, pupillary block, increased paralysis with succinylcholine	Same as above, plus avoid prior to any general anesthetic procedure
	5ml, 10ml, 15ml	Dry mouth, hypotension, bradycardia, follicular conjunctivitis, ocular irritation, pruritus, dermatitis, conjunctival blanching, eyelid retraction, mydriasis, drug allergy	Monitor for shortness of breath, dizziness, ocular redness and itching, fatigue
	5ml, 10ml	Same as above	Same as above
	5ml, 10ml	Same as above but higher drug allergy (40%)	Same as above
	5ml, 10ml, 15ml	Bronchospasm, bradycardia, hypotension, elevated triglycerides and decreased HDL = increased CV risk, CNS confusion, lethargy, depression, impotence, masked hypoglycemia, exacerbates myasthenia gravis	Monitor for shortness of breath, hypoglycemia, altered blood lipids, angina, dizziness
	5ml, 10ml	Same as above	Same as above
	5ml, 10ml, 15ml	Same as above, but less bradycardia	Same as above
	2.5ml, 5ml	Same as levobunolol	Same as above
	5ml, 10ml	Same as levobunolol	Same as above
	5ml, 10ml, 15ml	Same as levobunolol	Same as above
	5ml	Same as levobunolol	Same as above
	5ml, 10ml, 15ml	Same as levobunolol, but fewer pulmonary side effects	Same as above
	10ml, 15ml	Slight risk of parasthesia, metallic taste, nausea, malaise, depression, loss of libido, hypokalemia, aplastic anemia, metabolic acidosis, kidney stones, sulfonamide sensitivity	Avoid in sulfonamide allergies, sickle cell and renal disease
	10ml	Same as above	Same as above
	125mg, 250mg, 500mg	Same as topicals, but more common	Same as above
	25mg, 50mg	Same as above	Same as above
		Headache, back pain, diuresis, angina, pulmonary edema, heart failure, seizures, sub-arachnoid hemorrhage, nausea, vomiting	Shortness of breath, chest pain; administer drug slowly over ice
		Same as above	Shortness of breath, chest pain
	2.5ml, 5ml, 7.5ml	Hyperemia, iris pigment, hypertrichosis, conjunctival injection, keratitis, uveitis, ocular pain, cystoid macula edema	May darken eye color permanently, can induce dry eye symptoms
	2.5ml, 5ml, 7.5ml	Same as above	Same as above
	5ml	Same as above	Same as above
	2.5ml	Same as above	Same as above
	5ml	Same as above	Same as above
	0.3 ml unit-dose	Same as above	Same as above
	5ml	Hyperemia, eye pain, hypertrichosis	No systemic effects
	2.5ml	Hyperemia, conjunctival hemorrhage, corneal verticillata	Significant red eye, no systemic effects
	5ml, 10ml, 15ml	See timolol and brimonidine	See timolol and brimonidine
	10ml	See timolol and dorzolamide	See timolol and dorzolamide
	2.5ml	See netarsudil and latanaprost	See netarsudil and latanaprost
	8ml	See brinzolamide and brimonidine	See brinzolamide and brimonidine

- Decreased high-density lipoproteins
- Elevated serum triglycerides
- Increased risk of coronary heart disease
- Diabetic hypoglycemia

Take note that topical beta-blockers are able to reach significant blood levels. Eighty percent of the drug leaves the eye via the nasolacrimal system, with a large portion of that being directly absorbed through the nasolacrimal mucosa. When a drug is absorbed by this pathway it avoids the first pass effect—that is, it avoids being initially metabolized by the liver.[14] This produces an effect similar to directly injecting the drug into the bloodstream.

Due to this first pass effect, topical administration of beta-blockers can lead to autonomic, life-threatening side effects. The most significant cardiopulmonary side effects are bronchiolar constriction and bradycardia. Beta-2 blockade of the lungs produces life-threatening bronchiolar constriction in those with COPD and asthma, and should be avoided in these populations. Beta-1 blockade produces bradycardia, hypotension and a drop in systemic perfusion that can lead to end organ ischemia. Patients who are treated with these agents can have their pulmonary function evaluated very simply with an in-office peak flow test and should have their blood pressure and heart rate checked at each visit.

Beside the cardiovascular and pulmonary side effects seen with beta-blockers, certain individuals with diabetes are at special risk. People with either Type 1 or 2 diabetes can use beta-blockers as long as they aren't prone to significant hypoglycemic events. When blood glucose drops, the body releases epinephrine to stimulate the liver to convert glycogen to glucose (gluconeogenesis). The symptoms of hypoglycemia produced by high levels of epinephrine produce symptoms (tremor, tachycardia, sweating, etc.) that warn the person with diabetes of the risk of going into ketoacidosis from hypoglycemia, which should lead the individual to consume glucose and alter their therapy to avoid coma and death. However, the use of beta-blockers can reduce these warning signs of hypoglycemia, so they should be avoided in any person with diabetes who is prone to hypoglycemia.[15]

Another special situation is when any patient has a significant, life-threatening allergic reaction (anaphylaxis) that requires self-administration of epinephrine (Epipen, Mylan). Beta-blocker use reduces effectiveness of the life-saving epinephrine during an anaphylactic event.[15]

Patients taking antidepressant therapy can expect a significant reduction in the effect of their medication with highly lipid soluble drugs (timolol) and should avoid using it.[15]

Patients taking systemic beta-blockers should avoid the topical form. The oral agent reduces the efficacy of the topical agent, and the sum of the two increases the risk of side effects. So, the two drugs produce little therapeutic benefit but one sees an increase in drug toxicity.[16]

Patients with heart block should definitely avoid these drugs. They can lead to an increase in heart block, including a fatal arrhythmia.[17]

Patients taking calcium channel blockers are particularly prone to bradycardia and/or significant hypertension if used with topical beta-blockers.[18]

Carbonic anhydrase inhibitors (CAIs). The CAIs acetazolamide and methazolamide have been used for decades to manage significant elevation of IOP produced by secondary forms of open-angle glaucoma such as uveitic and hemolytic glaucoma, as well as primary angle-closure glaucoma and, in the past, poorly controlled primary open-angle glaucoma. The systemic side effects of these drugs are significant and certainly limit their use today in the management of primary open-angle glaucoma. The development of topical CAIs in the late 1990s have largely replaced the use of oral agents except in extreme presentations of acute rise in IOP.[19]

As their name implies, CAIs inhibit the enzyme carbonic anhydrase, whose responsibility is the production of bicarbonate ion, important in stabilizing the body's pH, specifically in the kidney. Oral use of the drug must block a substantial amount of carbonic anhydrase activity before it results in a significant reduction in aqueous production. This marked reduction in carbonic anhydrase activity is responsible for the systemic side effects of these drugs and why most primary open-angle glaucoma

Table 2. Special Populations

- Children
- Pregnant and lactating patients
- Patients with a drug allergy
- Patients with cardiac arrhythmia
- Patients with chronic obstructive pulmonary disease
- Patients with congestive heart failure
- Patients with diabetes
- Patients with ocular surface disease
- Patients with preservative sensitivity
- Patients with reduced renal or hepatic function
- Patients with sickle cell disease
- Patients with systemic hypertension

Photo: Bisant A. Labib, OD

Trichomegaly resulting from prolonged use of prostaglandins.

is managed with the topical form of the drug available as dorzolamide and brinzolamide.[19]

Potential ocular side effects (topical drugs):

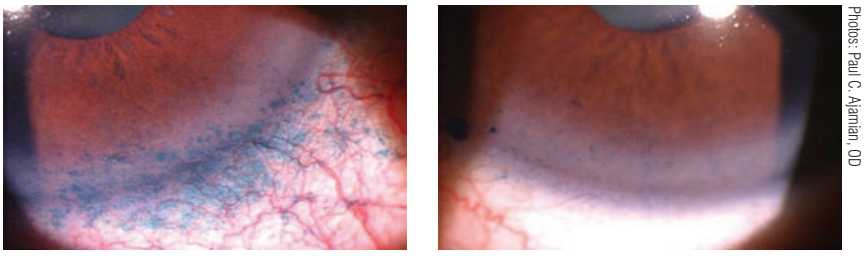
- Burning, stinging and tearing
- Corneal edema (altered endothelial cell function)
- Potential sulfonamide sensitivity (low risk)
- Bitter aftertaste (dysgeusia)
- Allergic reactions of the conjunctiva
- Superficial punctate keratopathy

Potential systemic side effects (oral drugs):

- Metabolic acidosis
- Sickle cell crisis (increased risk of sickling associated with metabolic acidosis)
- Stevens-Johnson syndrome
- Sulfonamide reaction
- Aplastic anemia
- Dysgeusia
- Anorexia
- Weight loss
- Paresthesia
- Malaise
- Fatigue
- Depression
- Hypokalemia

Prostaglandins. The development and use of topical prostaglandin analogs has revolutionized the management of glaucoma. Their high efficacy and relative lack of significant systemic side effects have made them the drug of choice for treating ocular hypertension and glaucoma. Their unique mechanism of action reduces IOP through increased uveoscleral outflow.

Because prostaglandins are highly effective and dosed only once a day, they're an ideal option for a single-drug treatment strategy. When a stronger effect is required, combining a prostaglandin with any other topical hypotensive agent(s) results in a synergistic and potent way to maximize the reduction of IOP.



Photos: Paul C. Ajamian, OD

Lissamine green staining of the conjunctiva and cornea identifies BAK toxicity from a prostaglandin. This patient was switched to a preservative-free prostaglandin analog. His signs and symptoms of dry eye improved over the next three months.

The main side effects of prostaglandins are ocular.[20]

Potential ocular side effects:

- Hyperemia
- Hypertrichosis (increased eyelash growth)
- Darkening of the lids and periocular skin
- Permanent change in iris coloration (darkening)
- Cystoid macular edema

Potential systemic side effects:

- Headache

Nitric oxide generators. The recently approved Vyzulta (latanoprostene bunod, Bausch + Lomb) is a prostaglandin with the addition of bunod. The bunod portion is a nitric oxide (NO) donator that enhances trabecular outflow in addition to the increase in extra-trabecular outflow from the prostaglandin portion of the drug.[21]

The addition of bunod does not add any additional ocular or systemic side effects.

Rho kinase inhibitors. The most recently approved addition to our collection of topical IOP-reducing agents is the rho-kinase inhibiting drug netarsudil, marketed as Rhopressa and as the netarsudil/latanoprost combination drug Rocklatan (both from Aerie Pharmaceuticals).

Netarsudil's mechanism of action and side effect profile are unique to this singular class of anti-glaucoma agents—it's the only drug that has a triple mechanism of action. Netarsudil is able to increase trabecular outflow, reduce aqueous production and decrease episcleral venous pressure.

As unique as the drug is in its mechanism of action, it also displays some significant and unique ocular side effects.[22]

Potential ocular side effects:

- Conjunctival hyperemia
- Corneal verticillata
- Eye pain
- Subconjunctival hemorrhage
- Blurred vision
- Tearing
- Reduced acuity (5% to 10% reported)

Potential systemic side effects:

- None

The main responsibility of primary care providers, like optometrists, is to continuously monitor their patients for adverse events. Some of these adverse events are exacerbated by medications that we prescribe or by those that others prescribe. Continuously updating patients' medical and drug histories, and inquiring about any new symptoms, allows us to detect and prevent the undesirable and sometimes disastrous side effects that certain drugs can produce.

All treatments have both risks and benefits. Choosing the proper treatment requires a thorough knowledge of the patient's histories. Anticipating side effects, excluding patients with allergies or other contraindications, and educating patients on potential adverse events helps to avoid preventable complications. ■

Dr. Onofrey is a clinical professor and the executive director of continuing education programs at the University of Houston.

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OSC QUIZ

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Please check with your state licensing board to see if this approval counts toward your CE requirement for relicensure.

1. Which term refers to a condition that prevents the use of a drug because it isn't safe or effective in a patient?
a. Adverse effect.
b. Contraindication.
c. Side effect.
d. Warning.

2. Weighing the benefits against the risks of prescribing a drug requires a thorough knowledge of:
a. Pharmacology of the drug.
b. Pathophysiology of the condition.
c. Medical history of the patient.
d. All of the above.

3. Approximately how much aqueous outflow normally occurs through the trabecular meshwork?
a. 10%.
b. 30%.
c. 90%.
d. 100%.

4. Which of the following glaucoma drugs is contraindicated in uveitic glaucoma?
a. Brimonidine.
b. Brinzolamide.
c. Pilocarpine.
d. Netarsudil.

5. A direct-acting cholinergic drug:
a. Inhibits acetylcholinesterase.
b. Stimulates sympathetic receptors.
c. Stimulates parasympathetic receptors.
d. Produces mydriasis.

6. Topical pilocarpine generates all of the following effects, *except*:
a. Brow ache.
b. Decreased aqueous production.
c. Increased accommodation.
d. Increased trabecular outflow.

7. The glaucoma drug most likely to produce an ocular allergic reaction is:
a. Travoprost.
b. Brimonidine.
c. Apraclonidine.
d. Both b and c.

8. Which topical glaucoma agent can produce a significant decrease in blood pressure?
a. Brimonidine.
b. Brinzolamide.
c. Latanoprost.
d. Latanoprostene bunod.

9. Taking a drug orally decreases its concentration because it is metabolized before it reaches the bloodstream. This is known as the:
a. First-pass effect.
b. Phase II reaction.
c. Third body effect.
d. Fourth route of administration.

10. Topical beta-blockers can increase:
a. Heart rate.
b. High-density lipoproteins.
c. Serum triglycerides.
d. All of the above.

11. Diabetics should avoid topical beta-blockers if they have:
a. Type 2 diabetes.
b. Type 1 diabetes.
c. Hypoglycemic events.
d. Systemic hypertension.

12. Which class of glaucoma drug should be avoided in patients with life-threatening allergies?
a. Alpha-2 agonists.
b. Non-selective beta-blockers.
c. Prostaglandins.
d. Rho kinase inhibitors.

13. Timolol should not be used in any patient taking:
a. Antibiotics.
b. Antidepressants.
c. Opioids.
d. Steroids.

14. The use of topical beta-blockers with calcium channel blockers can produce:
a. Hypotension.
b. Tachycardia.
c. Bradycardia.
d. All of the above.

15. The oral medication that is classically used to treat angle-closure glaucoma is:
a. Acetazolamide.
b. Acetylsalicylic acid.
c. Ibuprofen.
d. Propranolol.

16. Which of the following drugs is classified as a sulfonamide?
a. Acetazolamide.
b. Brimonidine.
c. Brinzolamide.
d. Both a and c.

17. Oral acetazolamide can produce all of the following side effects, *except*:
a. Metabolic acidosis.
b. Aplastic anemia.
c. Shortness of breath.
d. Sickle cell crisis.

18. The prostaglandins are believed to lower IOP by which mechanism of action?
a. Increased trabecular outflow.
b. Increased uveoscleral outflow.
c. Decreased aqueous production.
d. Decreased episcleral venous pressure.

19. All of the following are side effects of prostaglandins, *except*:
a. Systemic hypotension.
b. Lash growth.
c. Skin darkening.
d. Change in iris coloration.

20. Which drug can produce corneal verticillata and subconjunctival hemorrhages?
a. Betaxolol.
b. Latanoprostene bunod.
c. Netarsudil.
d. Propranolol.

Examination Answer Sheet

Glaucoma Medications: When Good Drugs Do Bad Things

Valid for credit through July 15, 2022

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Answers to CE exam:

1. Ⓐ Ⓑ Ⓒ Ⓓ
2. Ⓐ Ⓑ Ⓒ Ⓓ
3. Ⓐ Ⓑ Ⓒ Ⓓ
4. Ⓐ Ⓑ Ⓒ Ⓓ
5. Ⓐ Ⓑ Ⓒ Ⓓ
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17. Ⓐ Ⓑ Ⓒ Ⓓ
18. Ⓐ Ⓑ Ⓒ Ⓓ
19. Ⓐ Ⓑ Ⓒ Ⓓ
20. Ⓐ Ⓑ Ⓒ Ⓓ

Post-activity evaluation questions:

Rate how well the activity supported your achievement of these learning objectives:
1=Poor, 2=Fair, 3=Neutral, 4=Good, 5=Excellent

21. Identify the side effects, ocular and systemic, of all types of glaucoma medications, new and old. ① ② ③ ④ ⑤
22. Determine treatment options based on factors of efficacy, safety, risk and compliance. ① ② ③ ④ ⑤
23. Evaluate the benefits and risks of additive/adjunctive medication. ① ② ③ ④ ⑤
24. Incorporate strategies to prevent, reduce, or reverse medication side effects in glaucoma patients. ① ② ③ ④ ⑤

25. Based upon your participation in this activity, do you intend to change your practice behavior?
(choose only one of the following options)

Ⓐ I do plan to implement changes in my practice based on the information presented.
Ⓑ My current practice has been reinforced by the information presented.
Ⓒ I need more information before I will change my practice.

26. Thinking about how your participation in this activity will influence your patient care, how many of your patients are likely to benefit? (please use a number): ☐

27. If you plan to change your practice behavior, what type of changes do you plan to implement? (check all that apply)

ⓐ Apply latest guidelines ⓑ Change in pharmaceutical therapy ⓒ Choice of treatment/management approach ⓓ Change in current practice for referral ⓔ Change in non-pharmaceutical therapy ⓕ Change in differential diagnosis ⓖ Change in diagnostic testing ⓗ Other, please specify: _____

28. How confident are you that you will be able to make your intended changes?

ⓐ Very confident ⓑ Somewhat confident ⓒ Unsure ⓓ Not confident

29. Which of the following do you anticipate will be the primary barrier to implementing these changes?

ⓐ Formulary restrictions
ⓑ Time constraints
ⓒ System constraints
ⓓ Insurance/financial issues
ⓔ Lack of interprofessional team support
ⓕ Treatment related adverse events
ⓖ Patient adherence/compliance
ⓗ Other, please specify:

30. Additional comments on this course:

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The following is your: ☐ Home Address ☐ Business Address

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By submitting this answer sheet, I certify that I have read the lesson in its entirety and completed the self-assessment exam personally based on the material presented. I have not obtained the answers to this exam by any fraudulent or improper means.

Signature _____ Date _____

Lesson 118484 RO-OSC-0719

Rate the quality of the material provided:
1=Strongly disagree, 2=Somewhat disagree, 3=Neutral, 4=Somewhat agree, 5=Strongly agree

31. The content was evidence-based. ① ② ③ ④ ⑤
32. The content was balanced and free of bias. ① ② ③ ④ ⑤
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Who Wore it Best?

Several myopia management options exist, but it's important to first select the most suitable candidates for each. **Edited by Joseph P. Shovlin, OD**

Q What myopia control methods are available, and which patients have the best outcomes with each?

A "The putative optical cue for myopia management is myopic defocus—light focused in front of the retina," according to Jeffrey J. Walline, OD, PhD, Associate Dean for Research at Ohio State University College of Optometry. He says two types of contact lenses provide myopic defocus to slow eye growth: multifocal and orthokeratology (ortho-K).

Contact Lens Options

While only center-distance soft multifocal designs have been investigated, Donald Mutti, OD, PhD, also at Ohio State, says center-near designs may also be effective.[1-4] Dr. Walline says patients usually require an extra -0.50D to -0.75D in their distance prescription for optimal vision and myopic defocus.

Ortho-K slows axial elongation, slowing myopia in the process.[5-7] Dr. Walline notes that no specific ortho-K design has been proven superior to another when managing myopia, so practitioners have several options.

Patient Selection

Dr. Walline says soft multifocals and ortho-K have similar success rates with myopia management. He recommends basing your contact lens choice on your patient's personal circumstances and lifestyle needs to give them the best treatment to slow myopia progression at the earliest possible age.

Dr. Mutti says patients who are motivated to wear contact lenses and old enough to care for them are the best candidates for soft multifocals. He notes that patient selection is more complicated for ortho-K, as there is more risk involved in overnight wear. Evidence suggests that the effects of ortho-K are greater in those with larger pupils, steeper corneas and moderate myopia to make for an adequate amount of peripheral myopic defocus.[8]

Dr. Mutti says he considers soft multifocals to be his first choice for any patient who is a good candidate for contact lens wear. He explains that he prefers the safety profile of daily lenses to that of overnight lenses and believes dailies are the most appropriate choice for the long-term wear demands of myopia.

Other Options

Another method of myopia management is atropine.[5,6] Current evidence indicates that 0.05% may be an optimal concentration to provide significant treatment with minimal side effects.[6] Dr. Walline notes that atropine may provide better short-term myopia management than contact lenses. He adds, however, that the mechanism of atropine's myopia management is unknown because it doesn't slow axial elongation as much as contact lenses.

Dr. Mutti adds that combining optical and pharmaceutical approaches is another, more aggressive option. Dr. Walline says there is conflicting evidence about whether combining atropine and ortho-K provides better management than ortho-K alone and a lack of knowledge about combining soft multifocals and atropine. He concludes that combination therapy should be reserved for patients whose myopia is progressing the fastest.

Photo: Jeffrey J. Walline, OD, PhD

Ample communication with young patients helps ensure compliance and allows you to find the option that suits them best.

Today, myopic children are better equipped to deal with their condition than ever before. While one universal method that works just as well for every patient doesn't exist, clinicians have multiple treatment options available. ■

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A Diagnosis Made in a Flash

Visual disturbances can stem from a broad range of etiologies. Learn to tell the urgent apart from the mundane. **By Swati Kumar, OD, and Richard Mangan, OD**

When a patient complains of flashes and floaters, doctors may be wary of what they might find. These ambiguous symptoms may underscore a potentially serious issue.

This column reviews such presentations, what optometrists should look for and what to expect.

The Usual Suspects

As soon as a patient presents with flashes, most ODs will already have four potential diagnoses in mind.

1. ***Ocular migraine with a preceding visual aura.*** This condition can frequently be teased out and confirmed with a thorough case history. For these patients, flashes occur in the form of scintillating lights from the periphery towards the central vision, leading to temporary field loss and subsequent nauseating headaches lasting one to several hours. In most cases, optometrists should dilate to confirm the diagnosis.

2. ***Intraocular lens (IOL) related dysphotopsia.*** This one is tricky because it is often a diagnosis of exclusion. If scleral depression shows the retina is intact, dysphotopsia related to a new IOL may be to blame. Dysphotopsia is the leading cause of dissatisfaction following uncomplicated cataract surgery and is either positive or negative.[1] Positive dysphotopsia manifests as a light in the form of a streak, starburst, flicker, fog or haze. Negative dysphotopsia is seen as a black line or crescent in a patient's far peripheral vision.[1] Researchers believe these visual phenomena are due to the square-edged IOL designs that became popular in the 1990s, or possibly a material with a high index-of-fraction coupled with a lens that has a low radius-of-curvature.[1] Regardless, these patients should be sent back to their cataract surgeon.

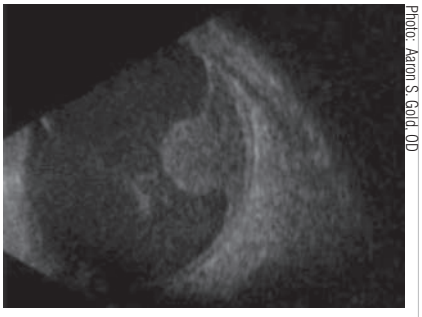

Photo: Aaron S. Gold, OD

This B-scan shows a large mass protruding forward through the retina, causing subsequent sensory detachment.

3. ***Posterior vitreous detachment (PVD).*** This usually develops after the vitreous gel separates from the internal limiting membrane of the retina. In most cases, the posterior hyaloid separation occurs without complication, resulting in a vitreous "floater" that casts a shadow of varying darkness on the retina. Occasionally, however, tractional forces can lead to a full-thickness tear, which could lead to rhegmatogenous retinal detachment.

PVD is, in large part, an age-related event that occurs between the ages of 45 and 65.[2] However, the vitreous may detach earlier in the highly myopic (>6.00D). Patients in their 50s have an expected prevalence of 25% while almost 90% of patients in their 80s will have already had a PVD.

4. ***Retinal break or detachment.*** A 2009 review found that, when patients reported with an acute onset of flashes, floaters or both, a retinal break or tear was present 14% of the time.[3]

In the same review, investigators determined two other predictive factors for retinal tear based on direct clinical examination:

1. Vitreous hemorrhage (62% chance of a tear or detachment).
2. Pigment dusting of the vitreous (88% probability).

Two-thirds of patients presenting with a vitreous hemorrhage had at least one break. A spontaneous vitreous hemorrhage can be a presenting sign or may occur subsequently.

Therefore, in all patients presenting with symptoms of flashes and floaters, a complete dilated examination using binocular indirect ophthalmoscopy with scleral depression, and at times, 3-mirror gonioscopy, is necessary in ruling out a compli-

Table 1. Stages of Posterior Vitreous Detachment

Stage 1	Perifoveal Separation with adhesion of vitreous to the fovea
Stage 2	Complete separation of vitreous from the macula
Stage 3	Extensive vitreous separation with adhesion of vitreous to the disc
Stage 4	Complete posterior vitreous detachment

Note: The proposed staging levels don't always occur in a linear, staged progression

cated PVD with a retinal break, tear or detachment.

With that said, as the following case will illustrate, we cannot forget the "unusual suspects" when confronted with these symptoms.

Examination

A 61-year-old African-American male presented for an urgent care visit. He complained of sudden flashes and floaters upon waking, followed by vision loss in his right eye. He had an established decrease in vision in his left eye since childhood secondary to optic atrophy. He also added that he was recently hospitalized for a "lung infection." He was treated with intravenous antibiotics while admitted and released a few days prior with a course of oral antibiotics.

The patient had an entering uncorrected visual acuity of light perception OD and 2/200 OS with no improvement on pinhole. Extraocular muscle testing was challenging due to an inability to fixate secondary to poor acuity, but was unremarkable with Doll's head maneuver. Pupil testing demonstrated a 3+ APD OD. He was unable to see fingers during confrontation field testing OD and was constricted superior-nasal, inferior-nasal and superior-temporal OS. His anterior chamber angles were ¼:1 with Van Herick on slit lamp exam and demonstrated a closed angle morphology with gonioscopy. B-scan imaging was performed to evaluate retinal integrity since the patient was unable to be dilated at this time.

Discussion

We diagnosed his right eye with an exudative retinal detachment secondary to a choroidal melanoma. He was immediately referred to ocular oncology. The diagnosis was confirmed and found to be a secondary metastasis from primary lung adenocarcinoma.

Table 2. Uveal Melanoma Staging Criteria[7,8]

Size	Prognosis*	Treatment**
Small: ≤3mm	6%, 12%, 20%	• Observation • Laser photocoagulation • Plaque radiation therapy • External beam charged particle radiation therapy • Transpupillary thermotherapy • Location tumor resection • Enucleation
Med: >3mm	14%, 26%, 37%	• Plaque radiation therapy • External beam charged particle radiation therapy • Gamma knife surgery • Enucleation
Large: >8mm	35%, 49%, 67%	

**Prognosis based on metastatic rate within 5, 10 and 20 years, respectively.*
***Treatment can vary largely based on factors other than size. Above are all possible options.*

The most common intraocular malignancies are metastatic in nature.[4] They tend to present within the choroid in the form of choroidal melanoma in 88% of cases.[4] Breast cancer is the most common cause of metastasis in women, and lung cancer in men.[4-6] These conditions generally present with symptoms of flashes and floaters that result in a subsequent decrease in vision shortly after.[4-6] Most metastatic growths are seen within the posterior pole due to its rich blood supply.[4] They often appear as cream-colored lesions with an overlying serous retinal detachment and unilateral presentation.[4-7]

One study shows 66% of these patients had a previous systemic cancer diagnosis, leaving 34% of patients who experienced ocular

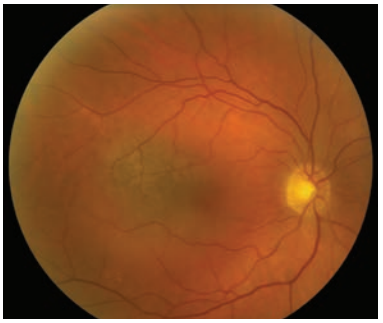

Photo: Julie Rodman, OD and Desiree Wheeler, OD

This fundus photo shows a small, cream-colored choroidal melanoma within the posterior pole without overlying retinal

manifestations initially.[4] This means that, while still rare, these patients are likely walking into primary care optometry offices for initial examination, as was highlighted in this case study. While treatment options for orbital tumors over the years have been promising, it is controversial whether it is worthwhile to begin treatment in cases of metastasis from lung cancer.[4,5] Once choroidal infiltration has occurred, the primary cancer is classed as stage IV.[4] At this stage, a quick progression with poor prognosis is expected. Other sources state external beam radiation therapy or plaque brachytherapy can be advantageous.[5] ■

Dr. Kumar is a resident at Nova Southeastern University.

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Pattern Recognition

Not all gene mutations are benign, especially when they affect the retina.

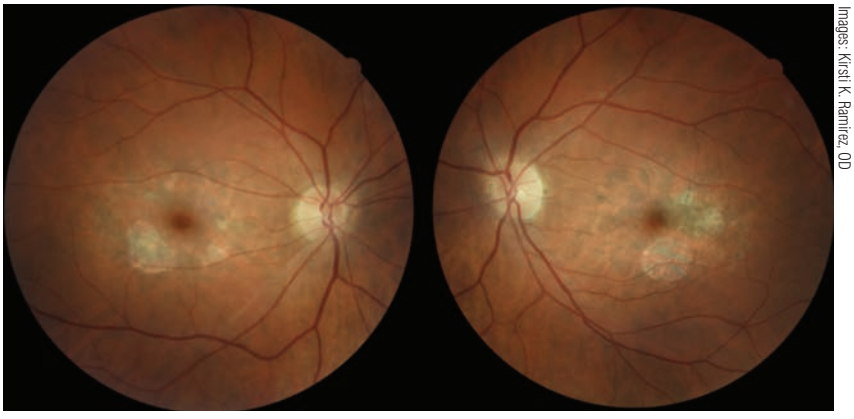
By Carlo Pelino, OD, and Joseph J. Pizzimenti, OD

Genes, which are made up of DNA, are the basic physical and functional units of heredity. The Human Genome Project estimates that humans have between 20,000 and 25,000 genes.[1] The DNA sequence of a gene can be altered in a number of ways, resulting in effects that range from common and benign to rare and debilitating.[1,2]

These gene mutations can be either inherited from a parent and present throughout a person's life in virtually every cell in the body or acquired at some time during a person's life and present only in certain cells. These changes can be caused by environmental factors or can occur if an error is made as DNA copies itself during cell division.[2,3]

Genetic alterations that occur in more than 1% of the population are called polymorphisms.[4] These are responsible for many of the normal differences between people such as hair and eye color and blood type. Although many polymorphisms have no negative effects on a person's health, some may increase the risk of developing certain disorders.[4]

Research continues to reveal the role genes play in many ocular conditions. Some retinal diseases are caused by a single gene, although these tend to be relatively uncommon, such as Best vitelliform macular dystrophy (generally autosomal dominant). Other, more complex, diseases associated with multiple genetic and environmental factors are relatively common, such as age-related macular degeneration (AMD).[4,5]



Images: Kirsti K. Ramirez, OD

Fig. 1. Parafoveal RPE atrophy with scattered deposits in both eyes of a 43-year-old Caucasian female with butterfly pattern dystrophy. Her best-corrected visual acuity is 20/20 in each eye.

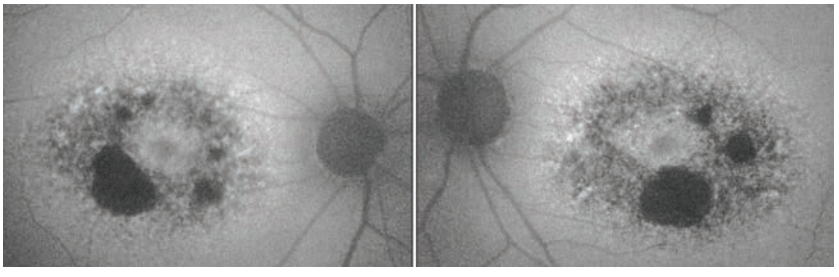


Fig. 2. In the patient's fundus autofluorescence, the dark areas show RPE atrophy, while the surrounding areas of hyper-fluorescence indicate lipofuscin deposits.

Genes and the Retina

In addition to environmental and personal risk factors, research has found that more than 50 gene variants within roughly 35 loci are associated with AMD. The two most extensively studied are complement factor H (CFH) and age-related maculopathy susceptibility 2 (ARMS2).[4,5] The latter gene, which shows the strongest association with AMD, encodes a protein that binds to the cell surface and enhances complement activation. Researchers have also genotyped single nucleotide polymorphisms (SNPs) in the CFH and ARMS2 genes.[5]

The PRPH2 gene, also known as RDS (retinal degeneration slow), encodes a photoreceptor-specific glycoprotein that may play a role in the development and maintenance of photoreceptor outer segment discs. In addition, the gene provides instructions for making the

peripherin 2 retina protein, which is essential for the normal function of photoreceptors. Mutation in this gene could mediate pathogenesis by interfering with the integrity of the photoreceptor membrane. Research has identified more than 100 mutations in the PRPH2 gene, many of which cause autosomal dominant retinitis pigmentosa.[6]

PRPH2 mutations also cause pattern dystrophies of the retinal pigment epithelium (*Table 1*). These dystrophies typically begin in mid-adulthood and are characterized by an abnormal buildup of pigment in cells underlying the retina.[6,7] Examples are adult-onset vitelliform macular dystrophy and butterfly-shaped dystrophy (*Figures 1 and 2*).

Find and Manage Pattern Dystrophies

The phenotypic variation among pattern dystrophies posed a diagnostic challenge. A detailed patient and family history, combined with careful retinal examination, multimodal imaging and genetic testing, should reveal the diagnosis.

All main types of pattern dystrophy have been described in patients with Pseudoxanthoma elasticum. They have also been described in association with myotonic dystrophy, McArdle disease, maternally inherited diabetes, deafness and Crohn's disease.[6,7]

Pattern dystrophies can progress, and fundi of older individuals may exhibit atrophic, depigmented lesions extending into the peripapillary region with markedly reduced visual function. Choroidal neovascularization, while possible, is exceedingly uncommon. In general, patients have normal dark adaptation, color vision and full-field electroretinograms. They have intact peripheral fields and may have deficits on electro-oculography.[6,7]

Cracking the Code

DNA information is stored as a code made of four chemical bases: adenine (A), guanine (G), cytosine (C) and thymine (T). Human DNA consists of about three billion bases, more than 99% of which are the same in everyone. In humans, genes vary in size from a few hundred DNA bases to more than two million bases. The order, or sequence, of these bases determines the information available for building and maintaining an organism, similar to the way letters of the alphabet appear in a certain order to form words and sentences.[3]

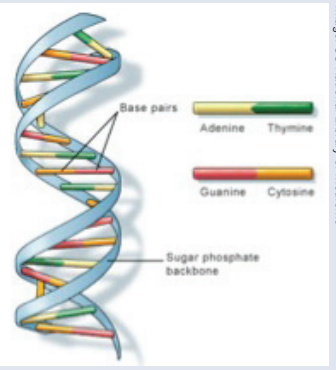


Image: US National Library of Medicine

DNA's double helix consists of base pairs forming the rungs and the sugar and phosphate molecules forming the vertical rails of a ladder-like structure.

DNA bases pair up with each other—A with T and C with G—to form units called base pairs. Each base is also attached to a sugar and a phosphate molecule. Together, a base, sugar and phosphate are called a nucleotide. These are arranged in two long strands that spiral in the iconic DNA double helix. The structure of the double helix is like a ladder, with the base pairs forming the ladder's rungs and the sugar and phosphate molecules forming the vertical rails.[1-3]

One of DNA's crucial properties is its ability to replicate. Each strand of DNA in the double helix can serve as a pattern for duplicating the sequence of bases. This is critical when cells divide, because each new cell must have an exact copy of the DNA present in the old cell.

The central dogma of molecular biology describes the two-step process, transcription and translation, by which the information in genes flows into proteins: DNA → RNA → protein. Transcription is the synthesis of an RNA copy of a segment of DNA.[8]

Alleles are forms of the same gene with small differences in their sequence of DNA bases—the key to each person's unique physical features. In the nucleus of each cell, the DNA molecule is packaged into thread-like structures we know as chromosomes, which contain many genes. A gene mutation is a permanent alteration in a gene's DNA sequence.[1-4] Mutations can affect anywhere from a single DNA base pair to a large segment of a chromosome that includes multiple genes.[4]

Although generally not as debilitating as disorders on the retinitis pigmentosa/cone dystrophy spectrum, pattern dystrophies may not necessarily be visually benign.

Although no treatment for pattern dystrophies exists, clinicians should monitor patients for changes during annual eye exams. In addition, clinicians should recommend genetic testing for patients with pattern dystrophies to help pinpoint the dystrophy and provide genetic counseling to the patient and their family members. ■

Table 1. Pattern Dystrophies of the RPE[6,7]

- Butterfly shaped dystrophy
- Reticular dystrophy
- Multifocal pattern dystrophy, simulating fundus flavimaculatus
- Adult vitelliform dystrophy
- Fundus pulverulentus

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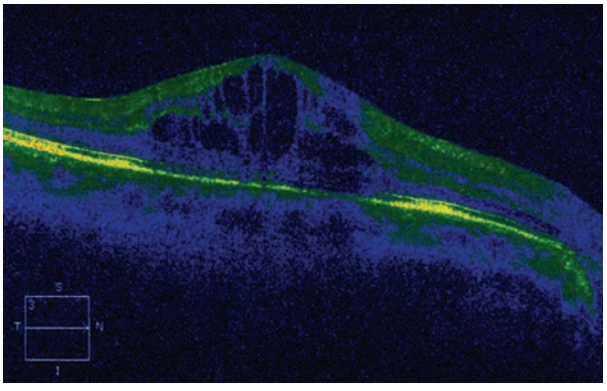
Topical Therapy for a Deep Problem

Medication can help address cystoid macular edema, but won't solve it completely.

By Joseph W. Sowka, OD

A 67-year-old male presented for a glaucoma evaluation due to elevated intraocular pressure (IOP). His history was significant for right eye cataract surgery and astigmatic LASIK correction approximately eight years earlier and laser capsulotomy in his right eye seven years earlier. He reported no complications with any of the surgical procedures. He was diagnosed with primary open-angle glaucoma and, after a discussion of risks and benefits of treatment, was prescribed travoprost 0.004% QHS bilaterally.



This OCT shows medication-induced CME in a glaucoma patient.

Examination

The patient returned four months later and reported that travoprost was well tolerated and that he was adherent. He also reported blurred vision, in his right eye more than the left, beginning soon after the initiation of travoprost. At this time, his corrected visual acuity was 20/50-2 OD. No biomicroscopic changes were noted and no evidence of anterior chamber or vitreal inflammation were present. IOP was reduced to 15mm Hg OU.

Ophthalmoscopically, mild macular thickening appreciated in his right eye with no other apparent changes. Subsequent optical coherence tomography (OCT) analysis revealed significant cystoid macular edema (CME) in the right eye.

Diagnosis

Based upon the history, timing and findings, he was diagnosed with CME in the right eye, presumably from travoprost use. Travoprost was discontinued and replaced with Cosopt (dorzolamide 2%/timolol 0.5% fixed combination, Akorn) BID OU. To address the CME, he was prescribed Pred Forte, (prednisolone acetate 0.1% Allergan) QID and Bromday (bromfenac 0.09%, Bausch + Lomb) BID OD. Over the next several months, the patient's IOP remained stable at 16mm Hg OU with resolution of CME and subsequent improvement in visual acuity. The Bromday and Pred Forte were discontinued.

CME is not a true diagnosis but rather a finding that occurs from numerous causes. These causative factors can include ocular eye drop preservatives, topical prostaglandin analogs and topical beta-blockers.[6-8] After cataract surgery, however, the second most common cause of CME is diabetes.[4]

Monitoring

The predominant symptom caused by CME is visual distortion (metamorphopsia) and reduced acuity. Visual acuity may be minimally or significantly reduced, depending upon the underlying cause of CME. Most patients who have CME detected only by imaging have no visual disturbances.[5]

The ophthalmoscopic appearance of perifoveal retinal thickening is difficult to observe. The true petaloid appearance of CME is best appreciated with fluorescein angiography (FA).[4-6] OCT testing is preferred when possible, as it permits noninvasive observation of the cystic, fluid-filled spaces.[7] Intracellular fluid and Müller cell swelling produce the condition's distinctive hexagonal appearance.[8]

Leaking perifoveal capillaries, subject to the pathophysiology of the underlying cause, go on to create the formation of intraretinal polycystic fluid-filled spaces that disrupt light from reaching the photoreceptors and slow efficient dialogue to the visual pathway.[1,8,9] Exudative or transudative fluid collects in the loosely arranged outer plexiform layer-of-Henle.

The fibers in Henle's layer are horizontally arranged, allowing maximum light transmission. This is what creates the fovea's parabolic shape with the thinnest region being the foveola. This anatomy, along

with the sequential filling of cysts is what fosters the petaloid appearance seen during FA.[5,6]

Various factors and mechanisms are involved in the pathogenesis of CME, including the release of inflammatory mediators such as prostaglandins.[4-6] Light toxicity from the operating microscope and mechanical irritation of the internal ocular tissues are also provocative.[4-6] Inflammatory mediators disrupt the blood-aqueous barrier (and blood-retinal barrier), leading to increased vascular permeability.[4-6] Any disease process that can breakdown these barriers can induce CME.[10,11]

Treatment Options

Topical non-steroidal medications such as Acular (ketorolac tromethamine, Allergan), Nevanac (nepafenac 0.1%, Novartis) and Bromday all show success.[12,13] Topical corticosteroid drops such as Pred Forte, Lotemax (loteprednol etabonate, Bausch + Lomb) and Durezol (difluprednate, Novartis) can be added for more severe cases.[12,13] Common dosing ranges from QID to Q2H. Often, a loading dose of Q2H is initiated and then rapidly dropped to QID after several days. Duration may be several days to months, depending on the CME's severity. Oral carbonic anhydrase inhibitors (CAIs) such as acetazolamide and methazolamide can be helpful in recalcitrant cases.[14]

Significant research supports adjunctive use of topical dorzolamide to manage CME associated with retinitis pigmentosa (RP). Long-term treatment of RP-related CME can improve structure and function with reduced edema and improved acuity.[15-17] CAIs may even reduce outer nuclear layer fluid more effectively than inner nuclear layer fluid due to better access to retinal pigment epithelium basolateral membrane than neurosensory retina.[18] Cosopt also reduces retinal thickness and improves function in CME arising from numerous other causes.[29-33]

Additionally, Cosopt may also have benefits as adjunctive topical therapy for macular edema. Researchers report patients dosed with topical dorzolamide-timolol twice daily and maintained on the same anti-vascular endothelial growth factor drug and same interval between injections saw a significant decrease in macular thickness. They concluded that topical dorzolamide-timolol may have a beneficial anatomical and functional effect in eyes with macular edema secondary to retinal vein occlusion resistant to treatment.[34]

Another study evaluated the effect of topical dorzolamide hydrochloride-timolol maleate on anatomic and functional outcomes in eyes with neovascular age-related macular degeneration (AMD) that had an incomplete response to anti-VEGF therapy. They found that adjunctive topical therapy with Cosopt may reduce central subfield thickness and subretinal fluid in eyes with persistent exudation despite consistent, fixed-interval intravitreous anti-VEGF treatment for neovascular AMD.[35]

While topical therapy for macular edema is inconsistently used, possibly due to the perception that this route of administration has limited success, it appears that there is benefit. Topical dorzolamide and Cosopt especially may have a surprising benefit in managing macular edema arising from many conditions. Combined safety and availability of these agents make for a possibly valuable adjunctive therapy that should be considered. ■

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It'll Grow on Her

A patient reports with a mysterious lesion. Can you use the clues in her history, examination and images to identify it? **By Mark T. Dunbar, OD**

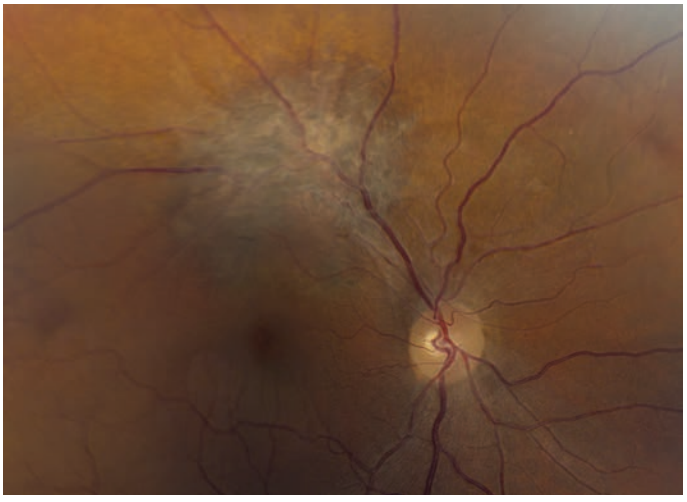
A 53-year-old Caucasian female was referred for a suspicious retinal lesion in her right eye. Her ocular history was significant for a radial keratotomy (RK) performed in her right eye more than 20 years earlier with an excellent visual result. The left eye has always been worse.

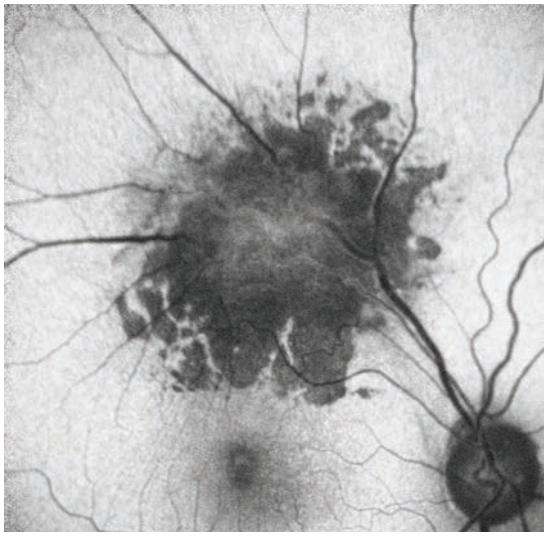
She reports being in good health, though her medical history is significant for allergies. She takes Flonase (fluticasone, GlaxoSmithKline) nasal spray and over the counter Claritin (loratadine, Bayer).

Evaluation

On examination, her uncorrected visual acuity measured 20/20 OD and 20/100 OS. With a hyperopic correction of +3.25 –0.75x090 she corrected to 20/20. Confrontation visual fields were full-to-careful finger counting in both eyes. Her ocular motility testing was normal and her pupils were equally round and reactive without an afferent papillary defect. Her right anterior segment was significant for multiple radial corneal scars consistent with her RK. Her tensions measured 16mm Hg OD and 14mm Hg OS.

On dilated fundus exam, her optic nerves appeared heathy with a small cup and good rim coloration and perfusion OU. Obvious retinal changes were seen in the right eye along the superior temporal arcade (*Figure 1*). Fundus autofluoresence (FAF) and spectral-domain OCT and OCT angiography (OCT-A) were also performed (*Figures 2 and 3*).





Figs. 1 and 2. A widefield (at left) and close up view (below) of the right eye of our patient.

Take the Retina Quiz

1. What is the most likely diagnosis?
a. Eccentric epiretinal membrane.
b. Choroidal melanoma.
c. Combined hamartoma of the retina and retinal pigment epithelial.
d. Astrocytic hamartoma.

2. What are the essential findings on SD-OCT?
a. Epiretinal membrane.
b. Choroidal neovascularization.
c. Complete disorganization of the retinal anatomy.
d. Both a and c.

3. How should this patient be managed?
a. Close observation.
b. Plaque brachytherapy.
c. Enucleation.
d. Pars plana vitrectomy.

4. What is the prognosis?
a. Stability with no effect on visual function.
b. Slow, steady progression and loss of visual function.

c. Will likely develop macular chorioretinal scaring.
d. Will develop cystoid macular edmea or choroidal neovascularization, or both, over time.

Diagnosis

Along the superior temporal arcade in the right eye there is a mildly elevated charcoal gray lesion with an overlying epiretinal membrane (ERM). There is clear tortuosity of the retinal vessels, and retinal striae can be seen extending inferior close to the macula. No exudate or fluid was associated with this lesion. So, what does this represent? The color, thickness and the presence of the ERM suggest that this is a combined hamartoma of the retina and retinal pigment epithelium (CHR-RPE), a rare benign tumor.[1]

Discussion

These rare benign tumors are congenital and most commonly diagnosed in childhood. They are most often located adjacent to the optic nerve but can be seen almost anywhere in the retina, posterior, mid-periphery or periphery. Up to 40% may have reduced acuity and 28% may have strabismus.[1,2] These tumors represent a disorganized amalgamation of glial tissue in addition to retinal and retinal pigment epithelium RPE cells.[2] Variations in the proportions of these components contribute to the variations in clinical appearance.

CHR-RPE are similar to congenital hypertrophy of the RPE (CHRPE), but CHRPE tend to be darker, flatter and have more defined borders. Other differential diagnoses include choroidal melanoma, choroidal hemangioma, osteoma and astrocytic hamartoma. For the most part, the diagnosis is based on the clinical presentation, but ancillary testing such as standardized ultrasound, OCT, fluorescein angiography and FAF may be helpful in establishing a diagnosis.

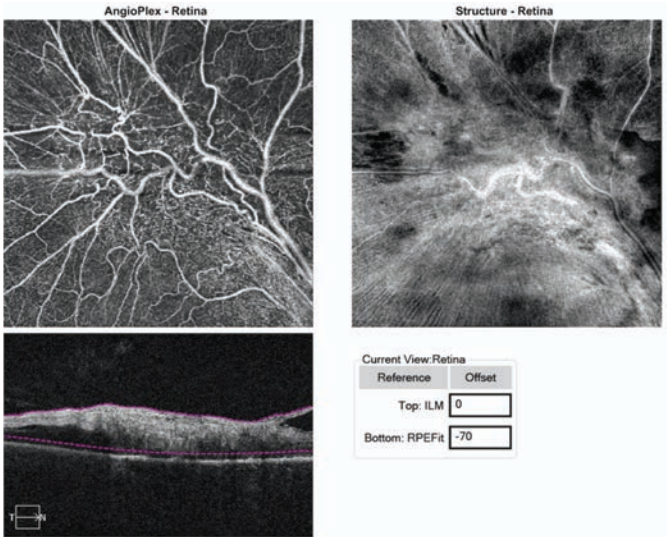


Fig. 3. These images represent 6x6mm OCT-A of the lesion. Note the findings within the sensory retina.

One of the most characteristic features of CHR-RPE is the presence of fibrous tissues and epiretinal membrane on the surface of the tumor. The OCT may be helpful in visualizing the ERM. In a study of 11 patients with CHR-RPE, a distinct ERM was present in 10 patients.[3] Nine of these patients displayed clearly evident retinal folds and striae, and three had significant vitreoretinal traction. All of the patients showed complete retinal anatomic disorganization with an inability to identify the retinal layers.[3]

The SD-OCT and OCT-A images of our patient had very similar features. We saw thickening of the sensory retina and an ERM as well as anatomic disorganization within the sensory retina. It is important to note the clear delineation of the boundary between the RPE and choroid. This is helpful in identifying the anatomic location of this lesion (sensory retina), and it helps rule out choroidal tumors, such as a melanoma or hemangioma. The OCT-A brilliantly highlights the tortuosity of the retinal vessels as well as the clearly visible microvasculature.

An ultrasound confirmed the absence of a choroidal mass, and the FAF showed dramatic hypofluorescence in the area where the hamartoma was located with distinct borders. All of these tests confirmed the diagnosis of CHR-RPE.

The findings were explained to our patient, and she was relieved to learn that it was benign and not likely to have any effect on her visual function, especially considering she functions monocularly. We discussed options for correcting the left eye, including using contact lenses, but she was content to leave it as it is and only wear a prescription for near work. She will continue to be closely followed to make sure it does not change. ■

1. Gass JD. An unusual hamartoma of the pigment epithelium and retina simulating choroidal melanoma and retinoblastoma. Trans Am Ophthalmol Soc. 1973;71:171,83; discussions 184-5.
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Product Review

Contact Lenses

A Multifocal Toric for the Masses

Optometrists interested in same-day fitting of astigmatic presbyopes can now order Bausch + Lomb's Ultra Multifocal for Astigmatism, which is available as a standard offering in the fitting set. The monthly replacement silicone hydrogel lens combines B+L's 3-Zone Progressive multifocal design and its OpticAlign toric design, and incorporates its MoistureSeal technology to ensure sustained comfort throughout the day. The new lens is available in parameters from +4.00D to -6.00D with two add powers and three cylinders of around-the-clock astigmatism correction.

Lid Hygiene

New Allergy Lid Scrub

To encourage long-term allergy relief, clinicians can recommend patients use Ocusoft's new Lid Scrub Allergy wipes. The manufacturer says the scrub removes oil, debris, pollen and other contaminants from the eyelids; it also uses green tea extract, tea tree oil and the lipid phytosphingosine to reduce redness, inflammation and itching. The lipid can help prevent loss of moisture, regulate epidermal cell growth, differentiation and apoptosis, and maintain healthy skin through its bactericidal and anti-inflammatory properties, according to Ocusoft. The product is available through CVS pharmacies and eye care practices, with discounted pricing for doctors.

Antimicrobial Face/Lid Cleanser

The new TheraTears SteriLid Antimicrobial Eyelid Cleanser & Facial Wash from Akorn kills 99.9% of bacteria within 30 seconds, but is pH balanced to be gentle on the lids, according to the manufacturer. The active ingredient is 0.01% hypochlorous acid. Though available as an OTC product, TheraTears SteriLid Antimicrobial is considered a medical device by the FDA, Akorn says. Other OTC lid cleansers are classified as cosmetic products, while medical-grade products had previously only been available by prescription, a company press release explains. The product, supplied as a 2fl. oz. spray bottle, will be available through both retail outlets and doctors' offices.

Dry Eye

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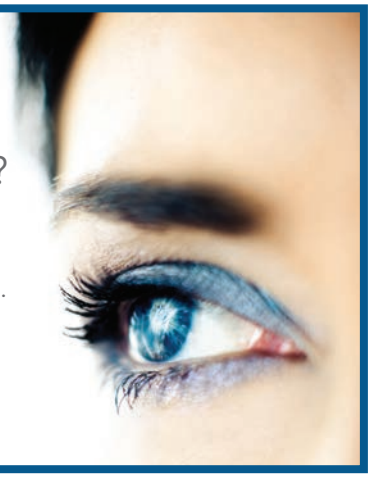

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Diagnostic **Quiz**

Not For the Best

By Andrew S. Gurwood, OD

History

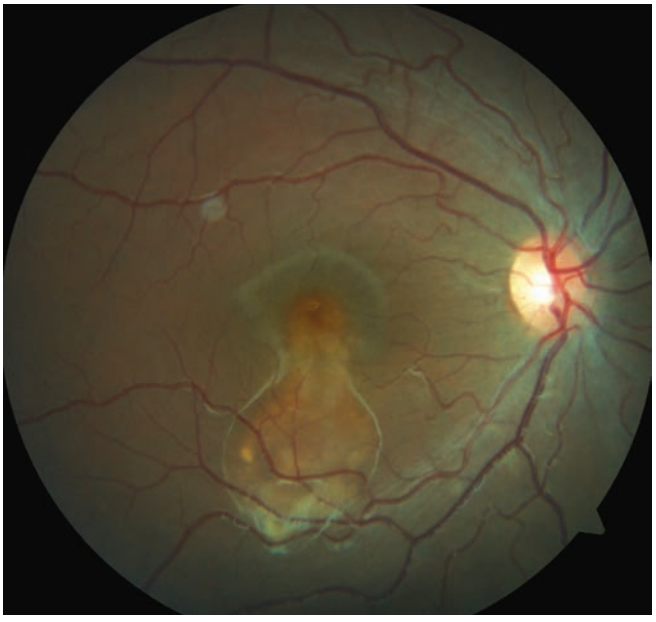
A 16-year-old African-American female presented for a routine eye exam. She had no ocular or systemic history and denied taking medication of any kind. She had no known allergies. She was a foster child, so her family history was unobtainable.

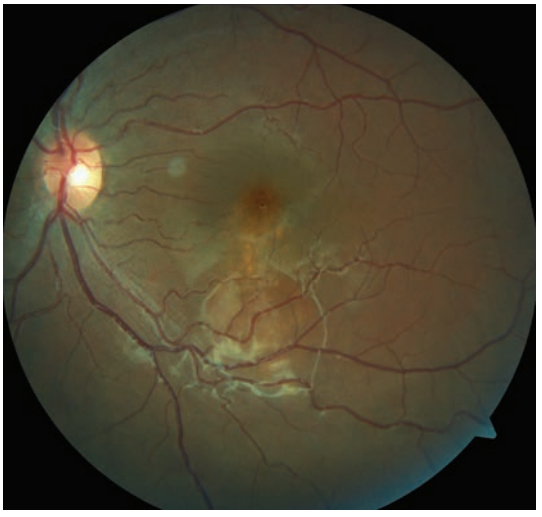
Diagnostic Data

Her entering best-corrected visual acuities were 20/20 OU at distance and near. Her external examination was normal. No evidence of afferent pupil defect was present. Biomicroscopic examination of the anterior segment demonstrated normal tissues with Goldmann applanation pressures measuring 16mm Hg OU. However, her dilated fundus findings did reveal an abnormality.

Your Diagnosis

Does the case presented require any additional tests, history or information? What steps would you take to manage this patient? Based on the information provided, what would be your diagnosis? What is the patient's most likely prognosis? For answers, please visit us online at www.reviewofoptometry.com.





This 16-year-old presented for a routine exam, but an evaluation of her fundus revealed something amiss. Can you identify it?

Retina Quiz Answers *(from page 76):* 1) c; 2) c; 3) a; 4) a.

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