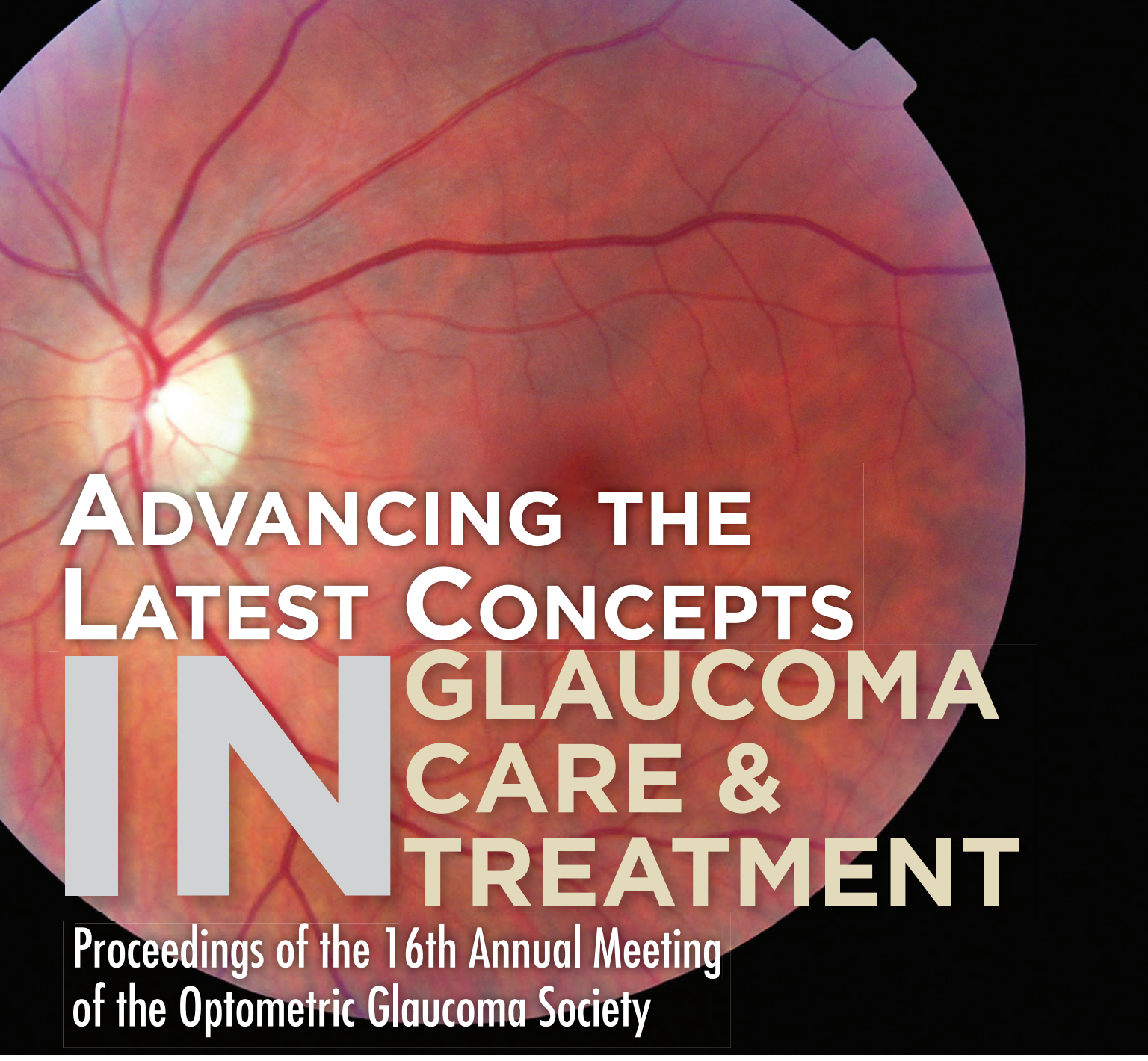


Advancing the Latest Concepts in Glaucoma Care & Treatment

Proceedings of the 16th Annual Meeting of the Optometric Glaucoma Society

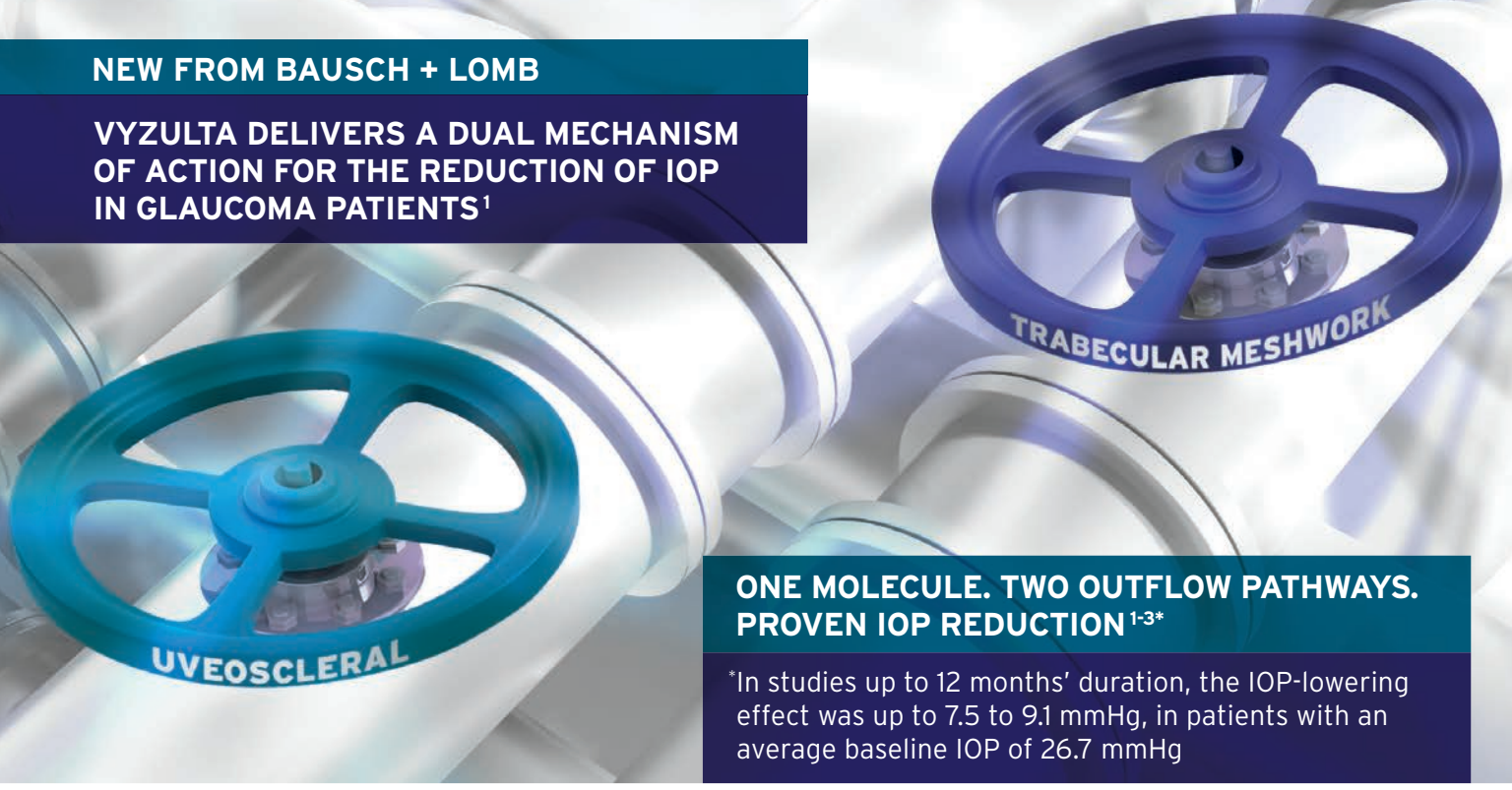
INSIDE:

- Big Glaucoma Clinical Trials and Their Key Lessons
- Intracranial Pressure in Glaucoma
- Ocular Surface Disease and Topical Glaucoma Therapy
- Minimally Invasive Glaucoma Surgery
- Glaucoma in Developing Countries

Supplement to
REVIEW® OF OPTOMETRY
MARCH 2018

NEW FROM BAUSCH + LOMB

VYZULTA DELIVERS A DUAL MECHANISM OF ACTION FOR THE REDUCTION OF IOP IN GLAUCOMA PATIENTS[1]



ONE MOLECULE. TWO OUTFLOW PATHWAYS. PROVEN IOP REDUCTION[1-3*]

*In studies up to 12 months' duration, the IOP-lowering effect was up to 7.5 to 9.1 mmHg, in patients with an average baseline IOP of 26.7 mmHg

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 (CONTINUED)

- 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 next page.

References:

1. VYZULTA Prescribing Information. Bausch & Lomb Incorporated. 2017.
2. Weinreb RN, Sforzolini BS, Vittitow J, Liebmann J. Latanoprostene bunod 0.024% versus timolol maleate 0.5% in subjects with open-angle glaucoma or ocular hypertension: the APOLLO study. *Ophthalmology*. 2016;123(5):965-973.
3. Medeiros FA, Martin KR, Peace J, Sforzolini BS, Vittitow JL, Weinreb RN. Comparison of latanoprostene bunod 0.024% and timolol maleate 0.5% in open-angle glaucoma or ocular hypertension: the LUNAR study. *Am J Ophthalmol*. 2016;168:250-259.

For more information about VYZULTA and how it works, visit vyzultanow.com

VYZULTA™
(latanoprostene bunod ophthalmic solution), 0.024%

BAUSCH + LOMB

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.

Distributed by:

Bausch + Lomb, a division of

Valeant Pharmaceuticals North America LLC

Bridgewater, NJ 08807 USA

U.S. Patent Numbers: 6,211,233; 7,273,946; 7,629,345; 7,910,767; 8,058,467.

Based on 9464800 11/2017 VYZ.0055.USA.16 Issued: 11/2017

TABLE OF CONTENTS

4
INTRODUCTORY REMARKS
Highlights From the Annual Scientific Meeting
BY MURRAY FINGERET, OD

6
PRESIDENT'S LECTURE
Big Glaucoma Clinical Trials and Their Key Lessons
DAVID S. FRIEDMAN, MD, MPH, PHD

9
INTRACRANIAL PRESSURE
Intracranial Pressure in Glaucoma
JOHN BERDAHL, MD

14
OGS HONOREE LECTURE
Ocular Surface Disease and Topical Glaucoma Therapy
ROBERT D. FECHTNER, MD

17
MIGS
Minimally Invasive Glaucoma Surgery
JOHN BERDAHL, MD

19
OUTREACH
Glaucoma in Developing Countries
ROBERT D. FECHTNER, MD

22
About the Optometric Glaucoma Society

INTRODUCTORY REMARKS

The 16th Annual Scientific Meeting of the Optometric Glaucoma Society (OGS), held Oct. 9-11, 2017, in Chicago, brought together preeminent researchers and clinicians who are thought leaders in the field of glaucoma. These trailblazers shared seminal findings from clinical investigations affecting the way we practice.

Kicking off the President's Lecture, David S. Friedman, MD, PhD, MPH, highlighted key discoveries from clinical trials that are translating into best practices for glaucoma care. In particular, we've learned from one of the pivotal investigations that cataract removal is an important treatment option related to the management of angle-closure glaucoma.

Moving onto glaucoma and eye pressure, though the field widely accepts the idea that glaucoma is centered around intraocular pressure (IOP), John Berdahl, MD, shattered that core belief. His research and the work of other teams have convinced him that glaucoma is a balance between IOP and intracranial pressure.

The OGS Honoree Lecture from Robert D. Fechtner, MD, confirmed many suspicions we already had about the relationship between ocular surface disease (OSD) and glaucoma therapy. Dr. Fechtner discussed findings from DEWS II and studies associating OSD with the ophthalmic preservative benzalkonium chloride, found in many glaucoma medications. He reaffirmed: If you are caring for patients with glaucoma, you must constantly be on guard for, and ready to treat and manage, OSD.

Dr. Berdahl gave an overview on minimally invasive glaucoma surgery (MIGS) devices and the role they can play in lowering IOP for glaucoma patients. MIGS are filling a gap in a clinical landscape burdened by issues of patient medication compliance and the limits of traditional glaucoma surgery.

Rounding out the series, Dr. Fechtner educated us on the unique struggles that developing countries face in providing glaucoma care. International efforts by the World Glaucoma Association and other groups, along with the innovative thinking of researchers, are breaking down barriers for patients in these financially strained regions of the world. Dr. Fechtner challenged us to consider whether there is anything we can do to help in the battle against glaucoma in developing areas of the globe. Perhaps we can all reach out a little further.

This supplement, developed by *Review of Optometry*, was made possible with generous support from Bausch + Lomb.

Please visit the OGS website (www.optometricglaucomasociety.org) and consider signing up for our free, quarterly e-journal to keep up with the group's latest happenings, and developments in glaucoma diagnosis, treatment and management.

Murray Fingeret, OD
Founding Member and Past President, Optometric Glaucoma Society

TIMOPTIC® in OCUDOSE®

(TIMOLOL MALEATE 0.5% OPHTHALMIC SOLUTION)

(DISPENSER)

Istalol®

(timolol maleate ophthalmic solution) 0.5%

BAUSCH + LOMB

President's Lecture

Big Glaucoma Clinical Trials and Their Key Lessons

David S. Friedman, MD, PhD, MPH

The field of glaucoma care has changed dramatically over the last two decades—largely due to a growing-body of research about patient outcomes in clinical trials. Findings from these studies help guide decision-making in day-to-day clinical practice when caring for our patients. This information has also translated into our increasing ability to individualize care—a mission-critical imperative for arresting a chronic and progressive disease such as glaucoma.

Results from well-managed clinical trials have transformed the way we approach glaucoma, specifically from the standpoint of: intraocular pressure (IOP) and patient risk; which disease types presage severe glaucoma; how older treatments such as laser trabeculoplasty affect progression; the benefits and risks of invasive surgical procedures (e,g., 'trabs vs. tubes'); evidence-based therapies to halt angle-closure glaucoma; and how practice might change in the future.

Considerations for Lowering IOP

Lowering IOP remains the only proven therapeutic intervention for glaucomatous optic neuropathy, thus making IOP reduction the first-line treatment for open-angle glaucoma (OAG) patients and those at high risk of OAG.[1]

The Ocular Hypertension Treatment Study (OHTS) was a well-designed randomized clinical trial comparing no treatment with topical ocular hypotensive medication to lower IOP in patients with OHT.[2] A total of 1,636 participants ages 40 to 80 without glaucoma, with IOPs between 24 mmHg and 32 mmHg in one eye and 21 mmHg and 32 mmHg in the other eye, were randomized to observation or treatment. At 60 months, the cumulative probability of developing POAG was 4.4% in the treatment group compared with 9.5% in the observation group (p<0.0001).

This study highlighted the fact that focusing on a cutoff of 21 mmHg for glaucoma risk was misguided because the risk of patients with higher IOP developing glaucoma was low. It also confirmed that medical treatments aimed at lowering eye pressure were beneficial in reducing the likelihood of progressing to glaucoma.

Only 10% of the untreated group developed glaucoma after five years, so the OHTS showed us that some individuals were at much higher risk than others; in particular, those with higher IOP, larger optic nerve cups and thinner corneas.[3]

Furthermore, as OHTS monitored individuals beyond five years, the probability of manifesting glaucoma increased, so our treatment decisions need to account for life expectancy. The OHTS calculator can help determine a person's five-year risk for glaucoma development.[4]

OHTS & Probability of Progression to POAG[2]

The OHTS sought to determine the safety and efficacy of topical ocular hypotensive medication in delaying or preventing the onset of POAG.[2]

- A total of 1,636 participants, ages 40 to 80 years, with no evidence of glaucomatous damage—with an IOP between 24 mmHg and 32 mmHg in one eye, and between 21 mm Hg and 32 mm Hg in the other eye—were randomized to observation or treatment with commercially available topical ocular hypotensive medication. The goal in the medication group was to reduce the IOP by 20% or more and reach 24 mmHg or less.
- The primary outcome was the development of reproducible visual field (VF) abnormality or reproducible optic disc deterioration attributed to POAG.
- At 60 months, the cumulative probability of developing POAG was 4.4% in the treatment group compared with 9.5% in the observation group (p<0.0001).
- Researchers concluded that topical ocular hypotensive medication was effective in delaying or preventing the onset of POAG in individuals with elevated IOP. They added that, although the findings did not imply that all patients with borderline or elevated IOP should receive medication, clinicians should consider initiating treatment for individuals with ocular hypertension who are at moderate or high risk for developing POAG.

Glaucoma Progression Risk Factors

Clinical trials continue to show us that not all glaucoma types are created equal, as certain factors are associated with more rapid deterioration and greater likelihood of advanced disease.

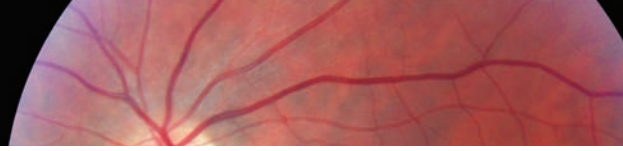
The Early Manifest Glaucoma Trial (EMGT) enrolled 255 patients, ages 50 to 80, with early glaucoma, VF defects and a mean IOP of 20 mmHg.[5] These subjects were older with relatively low baseline pressures and a mean deviation of -4.5 dB (less than 10% had exfoliation). Over six years, 62% of untreated eyes and 45% randomized to receive laser trabeculoplasty and betaxolol hydrochloride had worsening of glaucoma (p=0.007). Control subjects maintained the same IOP throughout the study, while the treatment arm had IOP lowered by an average of 20% from baseline. Multivariable analyses determined that each mmHg of IOP lowering yielded a 10% reduction of risk of having glaucoma advance.[6]

Factors associated with more rapid deterioration included high IOP, worse disease and involvement of both eyes at baseline, and older age. Importantly, pseudoexfoliation was a significant risk factor leading to more rapid decline.[5] This trial highlighted important predictors of glaucoma and the need for vigilance with conditions such as pseudoexfoliation.

Relying on Medication to Slow Progression

In the past, we may have wrongly assumed that using medication to lower IOP was sufficient to prevent glaucoma from getting worse. Recent clinical trials show that this is not necessarily the case.

The Collaborative Normal-Tension Glaucoma Study (CNTGS) assessed whether IOP lowering was effective in preventing normal-tension glaucoma from progressing. Mean entry IOP was 16 mmHg with pressures as high as 24 mmHg.[7] Subject eyes were randomized to be untreated or have IOP lowered 30% from baseline using medication, trabeculoplasty



or incisional surgery. Researchers found that 40% of participants required trabeculectomy to achieve a 30% reduction in IOP. Nearly 60% of subjects did not worsen over three or more years of follow-up and were never enrolled in the trial, and the main publication concluded that IOP lowering was successful in slowing the rate of glaucoma. However, an intention-to-treat analysis of the CNTGS found no treatment benefit after censoring for patients who had also undergone cataract surgery.[8] Further, a meta-analysis of randomized clinical trials found no clear advantage to lowering IOP using medications or surgery in patients presenting with low IOP.[9]

The Collaborative Initial Glaucoma Treatment Study (CIGTS)—a randomized, controlled clinical trial assessing whether newly diagnosed OAG (primary, pigmentary or pseudoexfoliative) patients were better off with first-line medications or filtration surgery—found that surgery and medicines were both good at slowing glaucoma, although a follow-up publication reported that those with more advanced disease had better VF outcomes when first treated with surgery.[10,11] At the same time, CIGTS conclusively determined that trabeculectomy was associated with cataract development. Still, the follow-up report affirms that it is reasonable to consider early surgery, even with all its potential harms, in later-stage patients.

Low-Uptake Laser Trabeculoplasty

When looking at more established therapies to reduce IOP, laser trabeculoplasty (LTP)—a procedure in which laser energy is applied to melanin-containing cells in the trabecular meshwork (TM) to prompt chemical and biological changes that help remove obstructive proteins and improve aqueous humor (AH) outflow—has been around since the 1970s. Several clinical trials conclude that the procedure is safe and effective. A more recent approach to LTP, selective laser trabeculoplasty (SLT), appears to have similar results to the traditional method. Despite its effectiveness, I have found that only about 10% of glaucoma patients undergo LTP.

The Glaucoma Laser Trial—one of the first NIH-funded, multicenter trials—compared LTP with medication. Investigators randomized one eye to medication first (MF) and the other eye to laser first (LF) groups, and used masked evaluation of optic disc photos and automated VFs to interpret results.[12] At the end of two years, 89% of people in the LF group had their glaucoma controlled on one or fewer medications (vs. 66% of the MF group), with 44% on no medication and IOP roughly 2 mmHg lower in the LF group. At 42 months, 21% in the LF group had confirmed deterioration of VFs compared with 28% of the MF group, and all other outcome measures, including the cup-to-disc ratio, were slightly better in the LF group.

Also looking at laser surgery, the Advanced Glaucoma Intervention Study examined how argon laser trabeculoplasty (ALT) and trabeculectomy impacted the relationship between IOP and VF damage progression over six or more years.[13] Eyes were randomly assigned to one of two sequences of glaucoma surgery—beginning with ALT or trabeculectomy. Seventy percent of black subjects and 65% of white participants who underwent ALT did not need additional surgery at five years.[14]

More recently, researchers randomized subjects to SLT- or medicine-first cohorts.[15] IOP reduction was similar in both arms after nine- to 12-months of follow-up, although more treatment steps were necessary to maintain target IOP with medication.

So why was LTP so much more effective than medication in these cases? Medication adherence is a major problem. Many patients do not take their drops as prescribed, so they have more fluctuations in vision. As such, these findings support wider use of LTP. However, some patients are not good candidates including younger individuals and those with uveitic or congenital glaucoma. The lesson here: If you administer a laser early, patients have a greater likelihood of maintaining lower, more stable eye pressures.

Trabeculectomies: The Good, The Bad & The Ugly

While trabeculectomy often can effectively lower IOP, the surgery has associated risks. As one example, the investigation on CIGTS' baseline mean deviation determined that patients who underwent trabeculectomies had a nearly 25% chance of needing cataract surgery at five years.[11] Similar results came out of a large clinical trial in Singapore.[16]

Thus, it is wise to convey to patients that traditional IOP-lowering surgeries will likely lead to the need for cataract surgery in the following 10 years and often within five. Other key issues with a trabeculectomy are that it doesn't always work, and some patients will develop harmful side effects, particularly hypotony.

One randomized clinical trial compared the safety and efficacy of another IOP-lowering procedure, tube shunt surgery, with trabeculectomy with mitomycin in eyes that had previous cataracts and/or failed glaucoma surgeries.[17] Researchers found that both procedures yielded similar IOP reductions at one year, but post-trabeculectomy subjects required less supplemental medical therapy.[17] Yet, the incidence of postoperative complications was higher after trabeculectomy, although serious issues associated with vision loss or reoperation rates were comparable after both procedures. Overall failure rates defined by the researchers were much higher in the trabeculectomy group.

Despite the moderately superior findings for tube shunts, clinicians should not rush into this procedure, given the troubling potential side effects. For example, double vision is known to occur in about 5% of patients, and corneal edema can emerge as late as five to 10 years later. Though tube shunts could be considered a reasonable approach for primary surgery, complications make the decision more nuanced.

Taking Aim at Angle-Closure Glaucoma

Unlike OAG, angle-closure glaucoma (ACG) is less common and often accompanied by higher eye pressure. Recent studies have found that cataract surgery can significantly reduce IOP in and, in some cases, control this

more severe form of glaucoma, as well as produce fewer complications.

One randomized trial out of Hong Kong evaluated phacoemulsification (phaco) alone vs. phacotrabeculectomy with adjunctive mitomycin C (MMC) in medically uncontrolled chronic ACG eyes with coexisting cataract.[18] Phacotrabeculectomy with MMC yielded a lower postoperative mean IOP over 18 months than phaco alone. At 18 months, IOP in phacotrabeculectomy-with-MMC eyes was 13.6 mmHg vs. 15.9 mmHg in phaco alone (p=0.01), and resulted in 1.25 fewer topical glaucoma drugs (p<0.001) in the 24-month postoperative period.

A similar trial in Singapore compared the two-year efficacy of phaco/IOL implants with laser peripheral iridotomy (LPI) in managing APAC.[19] A total of 18 patients were randomized to LPI and 19 to phaco/IOL. The post-treatment mean IOP was 14.5 mmHg ± 6.9 mmHg, and the two-year cumulative survival was 89.5% for the phaco/IOL and 61.1% for the LPI group (p=0.034). Phaco/IOL subjects only reported one postoperative complication vs. four noted in the LPI group (p=0.180) in that time. We learn that if you do phacoemulsification and IOL implants, waiting a few weeks before taking the lens out, the patient is going to do better than with LPI over two years.

Glaucoma Surgery	Lens extraction N=208	Laser PI N=211
Lens Extraction*		16
Trabeculectomy	1	6
i-Stent		1
Ahmed tube		1
TOTAL	**1**	**24**
*Cataract surgery for reduced vision	n/a	12

FIGURE 2. ADDITIONAL GLAUCOMA SURGERY NEEDED POST-LPI
EAGLE researchers found that only one individual in the lens extraction group needed further surgery post-procedure, while 24 people undergoing LPI went on to have other procedures, including 16 cataract surgeries.
Image: David S. Friedman, MD, MPH, PhD

Another transformative study is the EAGLE Trial.[20] Subjects with primary angle closure glaucoma (PACG), or angle closure and high IOP were randomly assigned to receive clear-lens extraction, or standard care with LPI and topical medical treatment. Similar to cataract surgery in execution, clear lens extraction is intended as a glaucoma treatment rather than a vision restoration therapy. Eligible participants were ages 50 or older, did not have cataracts and had newly diagnosed PAC with baseline 30 mmHg-or-greater IOP. Participants needed at least 180 degrees of angle closure, and most exhibited significant synechiae. They were older because researchers didn't want to create presbyopia as well as aphakia because the randomization was essentially cataract surgery. As well, severe cases and very small eyes were ineligible as a precaution. On average, pressure was fairly high.

The primary outcome was a quality-of-life questionnaire. While the lens extraction group stayed the same, the LPI cohort deteriorated and participants' quality of life went down. The lens extraction group's IOP ended in the 16 mmHg to 18 mmHg range—lower than the LPI group. At 36 months, 60% of these individuals had an average pressure of 16.6 mmHg on no medication. Only one person in the group needed further surgery, while 24 people undergoing LPI went on to have other interventions, including 16 cataract surgeries and several glaucoma surgeries.

To recap, these individuals had ACG, or angle closure and high IOP and a large amount of synechial closure before lens removal. Afterward, their pressures dropped by 10 mmHg to 12 mmHg, which is substantial; the procedure notably reduced the burden of medical care for these patients. As with most surgeries, lens extraction carried risks. Three individuals suffered complications such as posterior capsule rupture and visual loss, but overall vision loss of three or more lines was less common in the clear lens extraction arm. Researchers concluded that clear-lens extraction yielded greater efficacy and cost-effectiveness than LPI, and recommended it be considered for first-line treatment. However, the study has been published for more than a year and adoption is still low.

So we glean several key points from EAGLE, namely that lens extraction surgery is a glaucoma operation for people with angle closure and very high eye pressures, or established glaucoma. To apply these results to other glaucoma groups would be extrapolating from uncertain data.

Future Studies & Glaucoma Care

Evolving glaucoma clinical trials include one promising to have seminal findings for the field. The Zhongshan Angle Closure Prevention study—a collaborative project between the Zhongshan Ophthalmic Center, Moorfields Eye Hospital/University College London and the Wilmer Eye Institute at Johns Hopkins University—is a prospective, randomized, controlled trial evaluating the efficacy and safety of LPI in preventing the development of synechiae, elevated pressures and acute ACG. The fellow eye was left untreated, so the patient was his or her own control. The study was conducted in Guangzhou in South China and screened more than 10,000 people, enrolling 850-plus subjects. ANALIS is a similar trial in Singapore.

Stay tuned for the findings from these investigations, which are expected to add important insights on glaucoma treatment and management to our knowledge-base.

What we have learned about glaucoma from the aforementioned clinical trials is that the lens is significant. How we approach IOP reduction, treat and manage glaucoma, and decide whether to remove a patient's lens to control pressure should be balanced by a confluence of factors and

information, including the latest reported outcomes offering wisdom about best practices to reduce the disease burden on our patients.

David S. Friedman, MD, MPH, PhD, is director of the Dana Center for Preventive Ophthalmology, and the Alfred Sommer Professor of Ophthalmology at the Wilmer Eye Institute of Johns Hopkins University School of Medicine.

1. Sambhara D, Aref AA. Glaucoma management: Relative value and place in therapy of available drug treatments. Ther Adv Chronic Dis. 2014 Jan;5(1):30-43.
2.Kass MA, Heuer DK, Higginbotham EJ, et al. The Ocular Hypertension Treatment Study: a randomized trial determines that topical ocular hypotensive medication delays or prevents the onset of primary open-angle glaucoma. Arch Ophthalmol. 2002 Jun;120(6):701-13; discussion 829-30.
3. Shih CY, Graff Zivin JS, Trokel SL, et al. Clinical significance of central corneal thickness in the management of glaucoma. Arch Ophthalmol. 2004;122(9):1270-5.
4. Point System for Estimating 5-Year Risk of Developing POAG. Available at: https://ohts.wustl.edu/wp-content/uploads/2017/02/Points-System.pdf (last accessed Dec. 11, 2017).
5. Leske MC, Heijl A, Hyman L, et al. Early Manifest Glaucoma Trial: design and baseline data. Ophthalmology. 1999 Nov;106(11):2144-53.
6. Heijl, A, Leske, MC, Bengtsson, B, et al. Reduction of intraocular pressure and glaucoma progression: Results from the Early Manifest Glaucoma Trial. Arch Ophthalmol. 2002;120(10):1268-79.
7. Collaborative Normal-Tension Glaucoma Study Group. Comparison of glaucomatous progression between untreated patients with normal-tension glaucoma and patients with therapeutically reduced intraocular pressures. Am J Ophthalmol, 1998;126(4):487-97.
8. Collaborative Normal-Tension Glaucoma Study Group. The effectiveness of intraocular pressure reduction in the treatment of normal-tension glaucoma. Am J Ophthalmol. 1998 Oct;126(4):498-505.
9. Sycha T, Vass C, Findl O, et al. Interventions for normal tension glaucoma. Cochrane Database Syst Rev. 2003;(4):CD002222.
10. Musch DC, Lichter PR, Guire KE, et al. The collaborative initial glaucoma treatment study. Ophthalmology 1999;106(4): 653-62.
11. Musch DC, Gillespie BW, Lichter PR, et al. Visual field progression in the Collaborative Initial Glaucoma Treatment Study the impact of treatment and other baseline factors. Ophthalmology. 2009;116(2):200-7.
12. Spaeth GL. The Glaucoma Laser Trial (GLT). Ophthalmic Surg 1985;16(4):227-8.
13. Ederer F, Gaasterland DE, Sullivan EK, et al. The Advanced Glaucoma Intervention Study (AGIS): 1. Study design and methods and baseline characteristics of study patients. Control Clin Trials. 1994;15(4):299-325.
14. AGIS Investigators. The Advanced Glaucoma Intervention Study (AGIS): 9. Comparison of glaucoma outcomes in black and white patients within treatment groups. Am J Ophthalmol. 2001 Sep;132(3):311-20.
15. Katz LJ, Steinmann WC, Kabir A, et al. Selective laser trabeculoplasty versus medical therapy as initial treatment of glaucoma: a prospective, randomized trial. J Glaucoma. 2012 Sep;21(7):460-8.
16. Wong TT, Khaw PT, Aung T, et al. The singapore 5-Fluorouracil trabeculectomy study: Effects on intraocular pressure control and disease progression at 3 years. Ophthalmology. 2009 Feb;116(2):175-84.
17. Gedde SJ. the Tube Versus Trabeculectomy Study Group. Results from the tube versus trabeculectomy study. Middle East Afr J Ophthalmol 2009; 16(3):107-11.
18. Tham CC, Kwong YY, Leung DY, et al. Phacoemulsification versus combined phacotrabeculectomy in medically uncontrolled chronic angle closure glaucoma with cataracts. Ophthalmology. 2009 Apr;116(4):725-31.
19. Husain R, Gazzard G, Aung T, et al. Initial management of acute primary angle closure: A randomized trial comparing phacoemulsification with laser peripheral iridotomy. Ophthalmology. 2012 Nov;119(11):2274-81.
20. Azuara-Blanco A, Burr J, Ramsay C, et al. Effectiveness of early lens extraction for the treatment of primary angle-closure glaucoma (EAGLE): a randomised controlled trial. Lancet 2016;1;388(10052):1389-97.

Intracranial Pressure

Intracranial Pressure in Glaucoma

John Berdahl, MD

For years, the field of glaucoma care has accepted certain ideas regarding glaucoma without question. One core belief is that that the disease is centered around intraocular pressure (IOP). However, having been involved with research examining the role of eye pressure in glaucoma, I am convinced that glaucoma is a "two-pressure disease"—a balance between IOP and intracranial pressure (ICP), also known as cerebrospinal fluid (CSF) pressure.

A Misnomer

The word "intraocular"—with its prefix "intra" meaning within in Latin—has incorrectly led many individuals to view IOP as the pressure inside the eyeball. But when we measure IOP, we are actually measuring the pressure difference across the cornea. And yet, glaucoma occurs at the optic nerve head, not in the cornea.

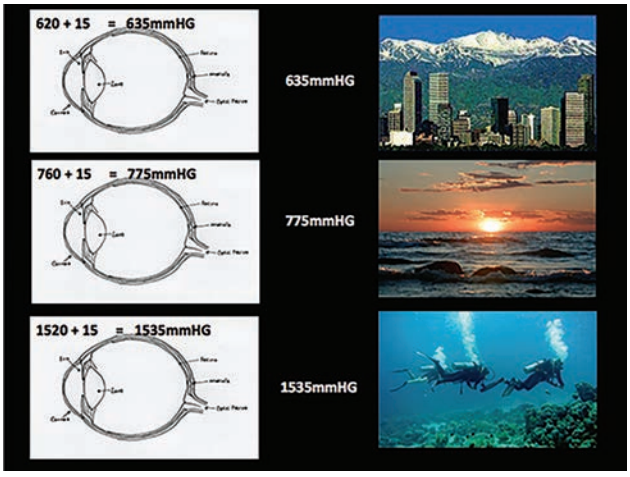


FIGURE 1. PRESSURE DIFFERENTIAL
Absolute pressure in our eyeball varies widely and may not be as important to the progression of glaucoma as the pressure differential across the cornea and optic nerve head.
Images: John Berdahl, MD

One way I have tried to reconcile the role of eye pressure in glaucoma is to look at pressure changes occurring in the eye at lower and higher elevations. When scuba diving 30 feet below sea level, an individual's eye pressure can rise to 1,535 mmHg as a result of 760 mmHg pushing on the body. Yet, if a person goes to Colorado where elevation is higher and only 620 mmHg of atmospheric weight is bearing down on the eye, the absolute pressure inside the eye can drop to 635 mmHg. However, there is no research to suggest that people who scuba dive have a higher incidence of glaucoma or that those who live in low atmospheric pressure zones have a reduced rate of disease.

Perhaps this tells us that the absolute pressure inside the eye is less relevant to glaucoma than the pressure variance across the cornea. Since disease occurs at the optic nerve head, specifically the lamina cribrosa, I submit that IOP, which would be more accurately called the "transcorneal pressure difference," is a surrogate measurement for the translaminar pressure changes happening across the optic nerve head.

How Anatomy & Physics Play a Role

To gain a more complete picture of eye pressure's role in glaucoma, it is important to not just consider IOP, but also recognize CSF pressure's close anatomical relationship with glaucoma. In one histology study, researchers assessed enucleated glaucomatous and nonglaucomatous eyes, and observed anatomic differences in the intraocular and CSF spaces of diseased eyes.[1] In the glaucomatous eyes, they found that more of the optic nerve was immersed in CSF until it entered the posterior eye.[1] So, though we spend a great deal of time discussing nocturnal IOP pressure fluctuations, we neglect to consider the shifts occurring with CSF, another pressurized fluid surrounding the optic nerve, just 500μm away from the optic nerve head.

From a structural perspective, an important factor affecting eye pressure is the optic nerve's tendency to bow backward

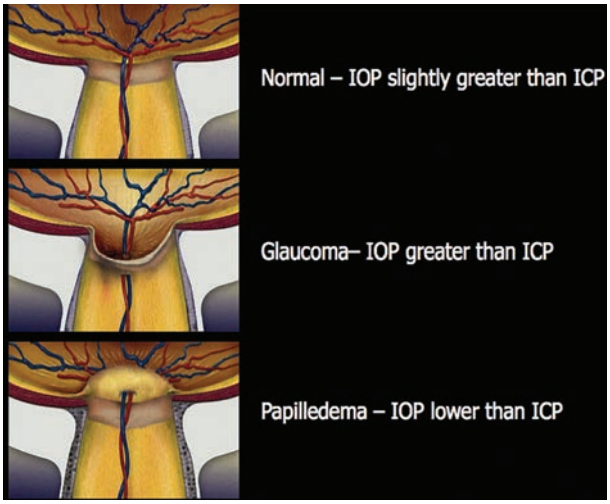


FIGURE 2. NERVE SHIFTS
In glaucoma, which exhibits a high IOP and low CSF pressure, the optic nerve bows backward; in papilledema and hypotony, accompanied by low IOP or high CSF pressures, the optic nerve bows forward—leading to the idea that a pressure differential may be creating the respective movements of the nerve.

in a disease such as glaucoma and forward in conditions such as papilledema. Physics can help elucidate our understanding of why this occurs. Newton's third law of motion, for example, instructs that equal and opposite forces cancel each other out. However, if one force is greater than another, a net force is generated, and "cupping" can occur.

Consider what happens to the eye in early glaucoma. The lamina cribrosa thickens, the peripapillary sclera arcs posteriorly and laminar insertion remodels to a more posterior position. Later in the disease, the lamina thins. These changes contribute to the characteristic cupping seen in glaucoma patients.

Conversely, in idiopathic intracranial hypertension (IIH), which manifests as papilledema, the swollen optic nerve begins to arc forward. A similar phenomenon happens in hypotony.

In IIH and hypotony, chronically elevated CSF pressure—well above IOP—creates edema in the optic nerve, forcing its forward movement. So I would argue that the opposite is likely true in glaucoma, where a persistently high IOP accompanied by a low CSF pressure leads to remodeling of the optic nerve head and lamina cribrosa such that they eventually bow backward.

Rather than the respective high and low pressures precipitating these nerve changes, I believe the pressure differential is the main contributing factor.

Axonal Transport

Another component impacting eye pressure in glaucoma is obstruction in the eye's cellular pathways. The unique features of glaucoma and research tell us the disease is not vascular in nature, but one of axonal transport disruption.

Take a healthy individual without glaucoma: IOP is slightly higher than CSF pressure, and the metabolic needs of the optic nerve are met. But elevate the IOP well above CSF pressure, and axonal transport slows down. If this scenario lasts for years, axonal transport can't catch up. As a result, the optic nerve, which is increasingly starved of its metabolic needs, withers and dies. In the associated process of laminar remodeling, retinal ganglion cell axons are damaged, leading to visual field loss.

Research shows that axonal transport interruptions in glaucoma occur at the optic nerve head, specifically at the level of the lamina cribrosa.[2,3] Harry Quigley and Douglas Anderson experimentally confirmed this phenomenon by injecting a radioactive tracer into the vitreous of primates to label retinal ganglion cells (RGCs) and study axonal transport after short-term IOP elevation.[2] They revealed that the tracer became concentrated at the lamina cribrosa. Gareth Howell and Simon John reaffirmed the findings using genetic axon labeling techniques in a mouse model of pigmentary glaucoma.[3] Investigations have also shown that, even in conditions such as papilledema that yield the opposite pressure imbalance—a high CSF pressure and low IOP—axonal transport still slows at the level of the lamina cribrosa.[4] And eye pressure in glaucoma has been found to be locally reduced at the lamina cribrosa, where less structural support is available to protect the optic nerve head due to the pressure imbalance.[5]

Exactly how changes in eye pressure trigger axonal transport interference is a complex issue and under some speculation. A variety of complicating factors may be to blame. One study found that an overproduction of protein in the subarachnoid space and the cul-de-sac-like anatomy of the optic nerve head might compromise CSF flow in this area.[6]

CSF Pressure's Defensive Position

Given the multiple biologic and metabolic conditions setting the stage for glaucoma, my team wanted to dig further into CSF pressure's involvement.

While an intern at the Mayo Clinic, I and my colleagues reviewed 20 years of data on patients determined to have glaucoma via eye exams performed before lumbar punctures, as well as normal individuals and those with ocular hypertension.[7] It turns out that glaucoma participants had a low CSF pressure, and normal-tension glaucoma subjects had an even lower CSF pressure. Ocular hypertensives had high IOP and an elevated CSF pressure with no signs of glaucoma. Zheng Zhang and his team undertook similar research and found comparable results.[8]

We know that most people with ocular hypertension don't get glaucoma. So our findings of elevated CSF pressure in these same individuals led to the hypothesis that CSF pressure might serve a protective role in glaucoma. Perhaps ocular hypertensives who don't progress to disease have elevated CSF pressures that shield them from disease, while those who do advance have lower CSF pressures. So I suggest that lowering normal IOP helps prevent glaucoma because the IOP is getting closer to the patient's CSF pressure.

Another study on CSF pressure changes over time in glau-

coma patients revealed that, of 14,000 data points, CSF pressure started to drop around age 65.[9] Yet, nothing noteworthy happens to IOP at age 65, despite the fact that older age is a known risk factor for glaucoma.[9,10] This could indicate that lower CSF pressure with advancing age might be the circumstance elevating glaucoma risk.

New Model for Pressure-Lowering Therapy

If glaucoma truly is a two-pressure disease, we could potentially alter CSF pressure with new therapeutic options. Or, alternatively, we might locally lower the pressure over the eye to reduce IOP and realign its relationship with CSF pressure. One way to do this would be with goggles that create a vacuum in front of the eye to release atmospheric weight pressing on the eye.

A team of Mayo Clinic investigators, including myself, was able to accomplish this using a device dubbed Equinox in a cadaver model. We dropped the eye pressure by 10 mmHg and held it steady before reducing it another 10 mmHg, for a total of 20 mmHg. The pressure went back up after the experiment.

Our vision for an adjunctive therapeutic solution is to create similar goggles with a pump that independently controls each eye pressure, with technology to remotely monitor patient compliance. The advantage of this strategy is it's non-pharmacologic, non-surgical and predictable. The drawbacks are that patients might not use the device or neglect to wear it long enough. It also remains to be seen whether goggles would be accepted and adopted by doctors, patients or the market in general.

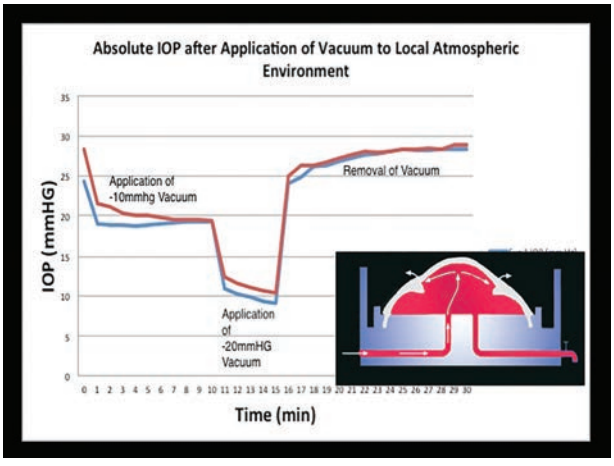


FIGURE 3. USING GOGGLES TO RELIEVE PRESSURE
A team at the Mayo Clinic reduced eye pressure by 20 mmHg in a cadaver model using goggles attached to a vacuum device dubbed Equinox.

The reality of glaucoma in the United States today is, even with evolving medications, drainage devices and surgeries, individuals still go blind from the disease.[11,12] Some ongoing obstacles include a lack of medication adherence, surgery safety and the difficulty of treating normal-tension glaucoma. Exacerbating these issues is an aging worldwide population seeing rising rates of glaucoma, with a projected 79.6 million cases of open-angle and angle-closure glaucoma by 2020—up from 60.5 million in 2010.[13] Given the limitations of today's therapies and a growing number of patients, the field must stay open to additional ways to manage pressure in glaucoma.

Space Travel Applications

Not only would new therapy solutions such as the aforementioned goggles help in the clinical arena, but they might aid in long-term space flight. NASA has found that many astronauts who return from the International Space Station experience diminished vision for years.[14] MRI scans show that pressure changes in the brain caused by weightlessness may be partly to blame.[14]

Vision impairment and intracranial pressure (VIIP), also known as space-associated neuropathy syndrome (SANDS), yields four main side effects: globe flattening, hyperopic shifts, choroidal folds and optic disc edema. As well, low IOP can cause corneal decompensation, accelerated cataract formation, maculopathy and patient discomfort. At zero gravity, IOP is significantly lower than CSF, so over time, many astronauts get papilledema and start to lose vision.

I was selected to serve on the Vision for Mars Challenge, an initiative of the National Space Biomedical Research Institute at Baylor College of Medicine in partnership with NASA, to explore the ophthalmic impact of space travel. Our research centers around the idea of raising IOP to balance the CSF pressure differential, renormalize the pressure gradient and protect astronauts during long-term space flight. The hope is that, once we overcome these hurdles, we might be poised to send astronauts to Mars for extended periods of time—expanding our understanding of that planet and improving our ability to ensure safe human travel for longer space missions.

John Berdahl, MD, is an ophthalmologist at Vance Thompson Vision in Sioux Falls, SD.

1. Jonas JB, Berenshtein E, Holbach L. Anatomic relationship between lamina cribrosa, intraocular space, and cerebrospinal fluid space. Invest Ophthalmol Vis Sci. 2003;44(12):5189-95.
2. Quigley HA, Anderson DR. The dynamics and location of axonal transport blockade by acute intraocular pressure elevation in primate optic nerve. Invest Ophthalmol Vis Sci. 1976;15(8):606-16.
3. Howell GR, Libby RT, Jakobs TC, et al. Axons of retinal ganglion cells are insulted in the optic nerve early in DBA/2J
glaucoma. J Cell Biol. 2007;179(7):1523-37.
4. Downs JC, Roberts MD, Burgoyne CF, et al. The mechanical environment of the optic nerve head in glaucoma. Optom Vis Sci. 2008; 85(6): 425-35.
5. Morgan WH, Chauhan BC, Yu DY, et al., Optic disc movement with variations in intraocular and cerebrospinal fluid pressure. Invest Ophthalmol Vis Sci. 2002 Oct;43(10):3236-42.
6. Killer HE, Jaggi GP, Flammer J, et al. Cerebrospinal fluid dynamics between the intracranial and the subarachnoid space of the optic nerve. Is it always bidirectional? Brain. 2007 Feb;130(Pt 2):514-20. Epub 2006 Nov 17.
7. Berdahl JP, Fautsch MP, Stinnett SS, et al. Intracranial pressure in primary open angle glaucoma, normal tension glaucoma, and ocular hypertension: a case–control study. Invest Ophthalmol Vis Sci. 2008;49:5412-8.
8. Zhang Z, Liu D, Jonas JB, et al. Axonal transport in the rat optic nerve following short-term reduction in cerebrospinal fluid pressure or elevation in intraocular pressure. Invest Ophthalmol Vis Sci. 2015 Jul;56(8):4257-66.
9. Fleischman D, Fautsch MP, Stinnett SS, et al. (2011, May) Cerebrospinal fluid pressure drops significantly with age: A new risk factor for POAG? Poster session presented at the Association for Research in Vision and Ophthalmology Annual Meeting, Fort Lauderdale, Fla.
10. Guedes G, Tsai JC, Loewen NA. Glaucoma and aging. Curr Aging Sci. 2011 Jul;4(2):110-7.
11. Grant WM, Burke JF Jr. Why do some people go blind from glaucoma? Ophthalmology. 1982 Sep;89(9):991-8.
12. Malihi M, Moura Filho ER, Hodge DO, et al. Long-Term Trends in Glaucoma-Related Blindness in Olmstead County,
Minnesota. Ophthalmology 2014;121:134-41.
13. Quigley HA, Broman AT. The number of people with glaucoma worldwide in 2010 and 2020. Br J Ophthalmol. 2006 Mar;90(3):262-7.
14. NASA. International Space Station: Vision Impairment and Intracranial Pressure (VIIP) - 05.04.17. Available at: https://www.nasa.gov/mission_pages/station/research/experiments/1038.html (last accessed Nov. 28, 2017).

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.

Distributed by:

Bausch + Lomb, a division of

Valeant Pharmaceuticals North America LLC

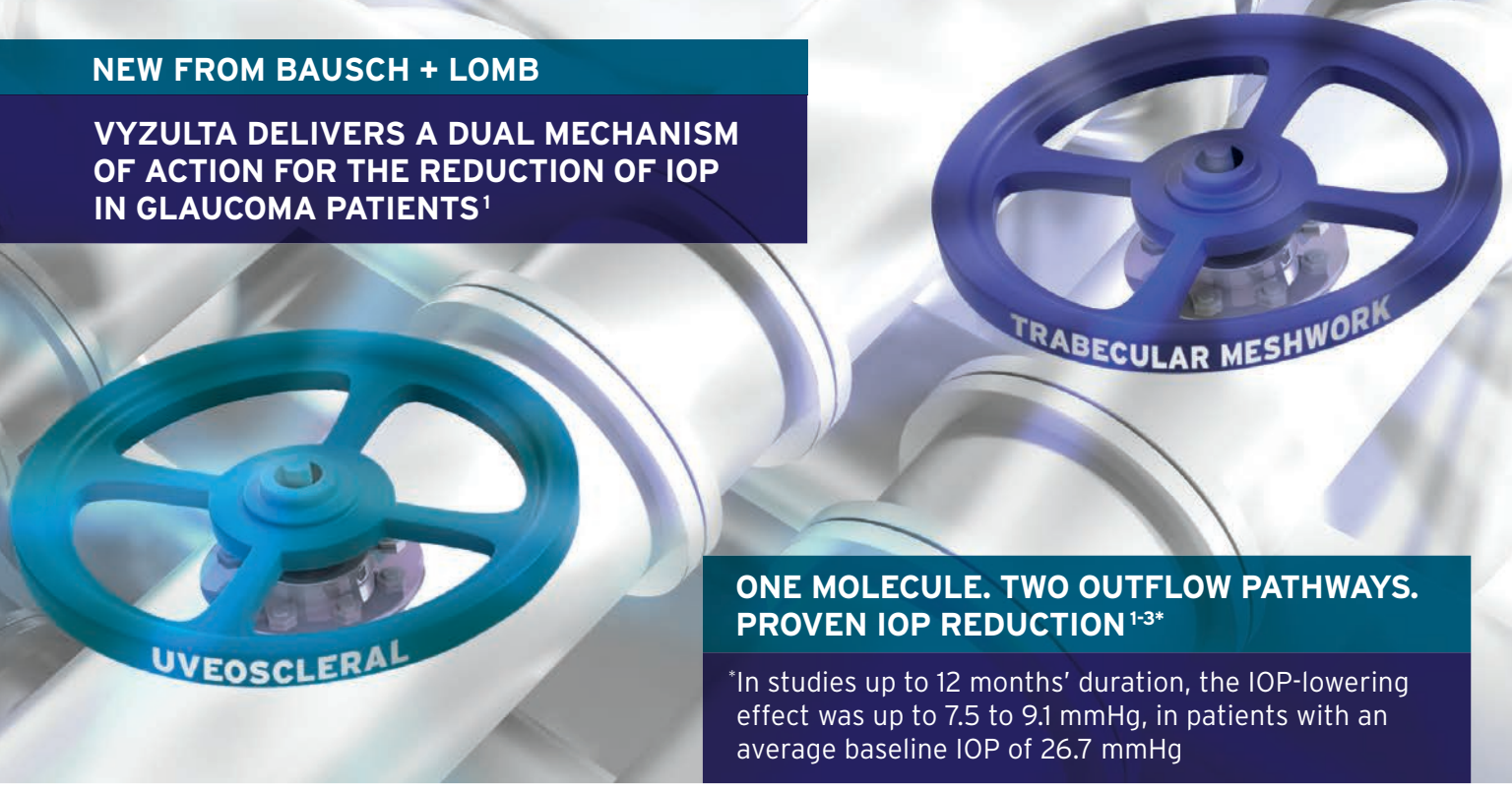
Bridgewater, NJ 08807 USA

U.S. Patent Numbers: 6,211,233; 7,273,946; 7,629,345; 7,910,767; 8,058,467.

Based on 9464800 11/2017 VYZ.0055.USA.16 Issued: 11/2017

NEW FROM BAUSCH + LOMB

VYZULTA DELIVERS A DUAL MECHANISM OF ACTION FOR THE REDUCTION OF IOP IN GLAUCOMA PATIENTS[1]



ONE MOLECULE. TWO OUTFLOW PATHWAYS. PROVEN IOP REDUCTION[1-3*]

*In studies up to 12 months' duration, the IOP-lowering effect was up to 7.5 to 9.1 mmHg, in patients with an average baseline IOP of 26.7 mmHg

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 (CONTINUED)

- 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 next page.

References:

1. VYZULTA Prescribing Information. Bausch & Lomb Incorporated. 2017.
2. Weinreb RN, Sforzolini BS, Vittitow J, Liebmann J. Latanoprostene bunod 0.024% versus timolol maleate 0.5% in subjects with open-angle glaucoma or ocular hypertension: the APOLLO study. *Ophthalmology*. 2016;123(5):965-973.
3. Medeiros FA, Martin KR, Peace J, Sforzolini BS, Vittitow JL, Weinreb RN. Comparison of latanoprostene bunod 0.024% and timolol maleate 0.5% in open-angle glaucoma or ocular hypertension: the LUNAR study. *Am J Ophthalmol*. 2016;168:250-259.

For more information about VYZULTA and how it works, visit vyzultanow.com

VYZULTA™
(latanoprostene bunod ophthalmic solution), 0.024%

BAUSCH + LOMB

OGS Honoree Lecture

Ocular Surface Disease and Topical Glaucoma Therapy

Robert D. Fechtner, MD

The intersection of glaucoma and ocular surface disease (OSD) is becoming increasingly clear as research into OSD grows. The latest insights come from a groundbreaking report published in July 2017 by the Tear Film and Ocular Surface Society (TFOS) involving 150 experts from around the world. The information greatly expands our understanding of the pathophysiology of dry eye disease (DED) and the pivotal roles tear film hyperosmolarity and ocular surface inflammation play in dry eye and ocular surface diseases.[1]

The report, in addition to outlining the physical toll on patients, underlines the psychological cost to sufferers of uncontrolled dry eye complications such as chronic pain and blurred vision, which may restrict core activities as well as pleasurable pursuits.[1]

For those of us in glaucoma care, this foundational research should highlight the importance of a glaucoma management strategy that accounts for the patient's ocular surface health at every step along the way—from diagnosis to treatment and management. Ignoring the signs and symptoms of DED or OSD, and neglecting to treat these chronic and progressive conditions likely will lead to an increasingly destabilized tear film and intensified patient discomfort. This will negatively impact quality of life further for the individual already burdened with two ocular diseases.

The takeaway from reports such as the second International Dry Eye Workshop (DEWS II) is that if you are caring for patients with glaucoma, you must simultaneously have an OSD practice.

Seeing OSD With New Eyes

At a 30,000-foot view, we learn from DEWS II that dry eye's central mechanism of evaporative water loss leads to hyperosmolar tissue damage.[1] So DED, either directly or by inducing a cascade of inflammatory events, contributes to a loss of epithelial and goblet cells that in turn decreases surface wettability, promotes early tear film break-up and further amplifies hyperosmolarity in an unforgiving spiral known as the "vicious circle."[1]

On a granular level, we find that the process of blinking is a two-phase tear film model in which meibomian lipid films (consisting of exterior polar and non-polar lipids) spread over a mucoaqueous interior (consisting of an aqueous component mixed with proteins or mucins). Using capillary action, the upper lid pulls a layer of tears across the cornea and sends the lipid layer upward, possibly dragging aqueous tears along with it.[1] Between blinks, the tear film thins, primarily due to evaporation.[1] However, mucin's high-hydration, water-holding properties might suppress further tear evaporation or enhance spreading of the tear film lipid layer.[1] As such, mucin appears to be critical to ocular surface health, so deregulation of its synthesis should be viewed as a contributor to OSD.

Figure 1. DEWS II & The Tear Film's Central Role

DEWS II, a follow-up to its 2007 predecessor, changed the definition of DED, based on peer-reviewed evidence, to the following:

Dry eye is a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles."[1]

The report authors note that this latest definition clarifies that tear film hyperosmolarity and ocular surface inflammation, along with neurosensory abnormalities, have causal etiologic roles and contribute to the common mismatch between signs and symptoms.[1]

The mucoaqueous is sort of a "soup" that can change and destabilize the tear film; but we don't know how. Diagnostically, we must determine which tests will help define healthy limits for the tear film; therapeutically, we must find strategies to restore overall ocular surface health when those limits have been crossed.

Scope of OSD in the General Population

As well as understanding the pathophysiology of OSD, the clinician treating glaucoma must appreciate the size and demographic of the burden. Several large health studies assessing the OSD prevalence of OSD in the general population reveal nearly 10% of women over 75, and almost 8% of men over 80 report symptoms of DED—a significant demographic.[2,3]

One study looking at DED rates in U.S. women participating in the Women's Health Study showed rising prevalence with age—from 5.7% in women older than 50, to 9.8% in those ≥75.[2] Compared with white women, Hispanic (OR=1.81, CI=1.18 to 2.80) and Asian (OR=1.77, CI=1.17 to 2.69) women reported more severe symptoms, and dry eye symptoms increased with age.

In a companion study looking at DED rates in U.S. men, disease probability increased with age here as well—from 3.90% in men 50 to 54, to 7.67% in those 80 and older ($p<.001$).[3] High blood pressure (OR, 1.28; CI, 1.12 to 1.45) and benign prostatic hyperplasia (OR, 1.26; CI, 1.09 to 1.44) were associated with higher risk.[3] The likely reason: DED was a side effect of several medical therapies for these conditions.

A third study examined DED prevalence in an elderly population in Salisbury, Md.[4] After completing a standardized questionnaire on dry eye symptoms, subjects underwent Schirmer's and rose Bengal tests, and anatomic assessment of the meibomian glands. A total of 14.6% (363 of 2,482) were categorized as symptomatic, reporting one or more dry eye symptom often or all of the time.

However, obstacles persist in pinpointing DED and OSD populations. The DEWS II and Schaumberg et al. studies tell us that a reasonable expectation would be to detect OSD in about 10% to 15% of the general populace, with a greater fre-

quency in women than men. Yet, many papers reflect a wide variation in DED rates (between 5% and 50%). Contributing to this discrepancy is the lack of a standardized worldwide definition, although the hope is that DEWS II will move us in that direction. Lastly, few studies look at younger subjects despite increasing reports of digital eye strain among individuals ages 18 to 39.[5]

Diagnosing DED Amid Mismatched Signs & Symptoms

The notorious discrepancy between DED symptoms and signs has made dry eye disease historically difficult to detect and treat. Patients can present with significant symptoms and very few physical signs, and they also can have dramatic physical manifestations with no symptoms. Given the complexity of aligning signs with symptoms, eye care professionals have turned to surveys as one tool to uncover disease.

The Ocular Surface Disease Index (OSDI), a 12-item questionnaire to rank severity of OSD and assess functional impacts, was developed during clinical trial testing of cyclosporine A treatment for DED.[6] The OSDI was later co-opted

Test results	OSDI	Schirmer test	Lissamine Green	TBUT
Normal	41 (41%)	39 (39%)	79 (78%)	22 (22%)
Mild to Moderate	33 (33%)	27 (27%)	22 (22%)	13 (13%)
Severe	27 (27%)	35 (35%)	0 (0%)	66 (65%)

Leung EW et al. Prevalence of Ocular Surface Disease in Glaucoma Patients. J Glaucoma. 2008; 17:350–355.

FIGURE 2. OSD PREVALENCE IN GLAUCOMA PATIENTS
Using the OSDI, Leung et al. evaluated the prevalence of OSD in glaucoma patients and determined that 33% of individuals reported mild-to-moderate symptoms and 27% reported severe symptoms in at least one eye—reflecting that 60% of glaucoma subjects had OSD.
Images: Robert D. Fechtner, MD

for broader research applications; but, having been validated in a specific population and applied in another, it was not appropriately validated for these other segments.

One research team used the OSDI to evaluate OSD prevalence in glaucoma subjects.[7] They determined that 33% of individuals reported mild-to-moderate symptoms and 27% reported severe symptoms in at least one eye—reflecting that as many as 60% of glaucoma subjects had OSD.[7] The Schaumberg et al. studies tell us a reasonable expectation would have been to detect OSD in about 10% to 15% of patients, so this much higher OSD rate in glaucoma subjects was an indicator that something unique was happening in these patients.

In a multi-center study, our group and others surveyed 630 glaucoma patients treated with eye drops who completed the OSDI over the span of a year.[8] This prospective, observational study enrolled, at 10 different sites, patients with primary open-angle glaucoma (POAG) or ocular hypertension on a topical intraocular pressure (IOP)-lowering medication regimen. A total of 305 patients—or 48.4%—had an OSDI score pointing to mild (n=134, 21.3%), moderate (n=84, 13.3%) or severe (n=87, 13.8%) OSD symptoms. So again, these results led us to wonder why glaucoma patients had a higher prevalence of OSD than the Schaumberg et al. population.

Role of Medication

We know some systemic medications can lead to dry eye symptoms in other disease segments, so we began to question if the glaucoma patient's topical treatment regimen might be prompting dry eye symptoms.[3]

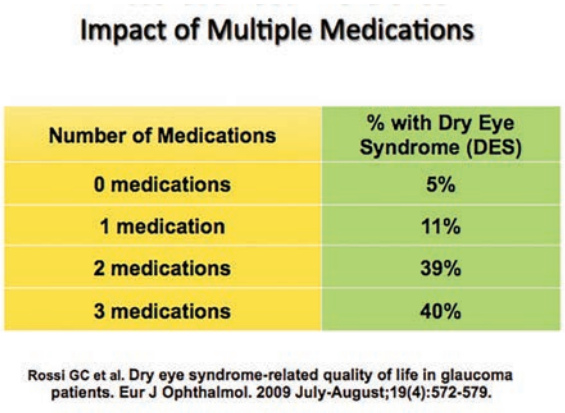
A rigorous study assessing DED-related quality of life in glaucoma subjects divided individuals into three groups by number of eye drops instilled per day compared with 20 controls.[9] Participants completed ocular exams and the 25-item National Eye Institute Visual Function Questionnaire (NEI-VFQ), Glaucoma Symptom Scale (GSS) questionnaire and OSDI. DED was defined as presence of punctate keratitis and decreased break-up time.[9] Researchers found that topically treated glaucoma patients presented with DED more often than controls (p=0.01). Zero or one medication had a fairly low reported incidence of severe DED, two medications yielded 39% of reported severe symptoms and three medications produced 40% of severe symptoms reporting.[9]

Returning to the Leung et al. study, investigators used a multivariate logistic regression model to evaluate the association between the number of benzalkonium chloride (BAK)-containing eye drops and OSD clinical test results.[7] Though not sufficiently powered to be conclusive, the study found that more glaucoma drops led to additional OSD symptoms.

For many clinicians, eye drops are their preferred IOP-lowering strategy for glaucoma patients, so they often prescribe multiple solutions at one time. Yet the medications are also an iatrogenic weapon against a healthy ocular surface. Given that a number of studies implicate the ophthalmic preservative BAK, it behooves us to consider whether components of these topical medications are negatively impacting our patients, and whether that second and third drop are absolutely necessary.[7,10,11] Once the tear film is destabilized, you can't simply remove the implicated drops; you often must start at the beginning of treatment to stabilize eye health.

Diagnostic & Treatment Considerations

Identifying the glaucoma patient with OSD will require diagnostic approaches the clinician may not routinely use. One important tool to screen for evaporative DED is tear break-up time testing (TBUT). TBUT is recorded as the number of seconds that elapse between the last blink and the appearance of the first dry spot in the tear film. Another key measurement, tear film osmolarity, will offer evidence of an unstable tear film and possible disease. Addition-



Impact of Multiple Medications

Number of Medications	% with Dry Eye Syndrome (DES)
0 medications	5%
1 medication	11%
2 medications	39%
3 medications	40%

Rossi GC et al. Dry eye syndrome-related quality of life in glaucoma patients. Eur J Ophthalmol. 2009 July-August;19(4):572-579.

FIGURE 3. IMPACT OF MULTIPLE GLAUCOMA MEDICATIONS
Researchers assessing DED-related quality of life in glaucoma patients found that two glaucoma medications yielded 39% of patients reporting severe DED symptoms and three medications produced 40% of severe reported symptoms.

ally, meibography, an in vivo technique to visualize the morphology of the meibomian glands, can reveal functional problems.

Short questionnaires are effective in uncovering OSD symptoms. Surveys revealing blepharitis, meibomitis and use of artificial tears are obvious red flags. The electronic health record is also helpful in noting the patient's use of artificial tears, or the patient might disclose this upon direct questioning.

Therapeutically, it's essential to treat underlying OSD instigators to restore tear film homeostasis. But sometimes just supplementing the eye with a topical solution or removing a toxin is enough to break the vicious circle.

OSD's inflammatory component should come under control with prescription medications; however, those drugs shouldn't be a lifelong strategy if we can address foundational causes, restore the cornea health and shut down inflammatory mediators. It's also worth considering complementary techniques such as neuro stimulation to address aqueous deficiency.

Minor adjustments to the patient's work and life environment, such as humidifiers for work spaces and bedrooms, can positively impact the patient's quality of life. Also, examining possible irritants and the patient's medication list can turn up possible offenders. If an individual is on a systemic medication known to produce OSD symptoms, the primary care doctor might be willing to select an alternate drug.

Responsibility to the Patient

When a glaucoma patient comes in for a visit and is on two glaucoma eye drops and artificial tears, investigate the drops and try to get the patient more comfortable, even if it means changing or discontinuing one of the medications. The field is fortunate to have good glaucoma medications, but they're tools with cutting edges. So we really need to be thoughtful as we manage our patients' therapies.

As a glaucoma surgeon, I will cheer the day I never again have to disturb the conjunctiva to put in an external tube with a reservoir or do a trabeculectomy. These procedures are truly disruptive to the ocular environment and often lead to significant complications. However, they remain some of the most effective surgical techniques to achieve very low IOP. For now, it's our duty as eye care providers to detect DED prior to surgery and not let glaucoma patients get to the OR with an unstable tear film and cornea.

We also owe it to concomitant disease patients to address their potentially diminished quality of life. OSD can have a profound impact on life quality factors. One study identified 450 participants in the Women's Health Study and 240 in the Physicians' Health Study who reported measurable negative impacts of DED on daily-living tasks, including reading, driving, using the computer, handling job responsibilities and watching television.[12]

Glaucoma patients with OSD are an important part of our patient base. If we pay no heed to their signs and symptoms, we're missing a clinical opportunity. The challenge is to get the ocular surface healthier while controlling pressure to a sufficient level.

Importantly, we must investigate underlying causes of OSD and environmental factors, and rapidly address those. We need to choose interventions wisely and attempt to restore tear homeostasis. The glaucoma patient's ocular surface status should be evaluated regularly to ensure timely detection and treatment of pathologic signs to minimize damage and ease the patient's additional ocular burden.

Robert D. Fechtner, MD, is professor and chair of ophthalmology, SUNY Upstate Medical University in Syracuse, NY.

1.Nelson JD, Craig, JP, Esen A, et al. TFOS DEWS II Report. Ocul Surf 2017; 2017 July;15(3):269-650
2. Schaumberg DA, Sullivan DA, Buring JE, et al. MR Prevalence of dry eye syndrome among US women. Am J Ophthalmol 2003;136 (2) 318-26.
3. Schaumberg DA, Dana R, Buring JE, et al. Prevalence of dry eye disease among US men: estimates from the Physicians' Health Studies. Arch Ophthalmol. 2009;127(6):763-8.
4. Schein OD, Muñoz B, Tielsch JM, et al. Prevalence of dry eye among the elderly. Am J Ophthalmol. 1997 Dec;124(6):723-8.
5. The Vision Council: 2016 Digital Eye Strain Report. Eyes Overexposed: The Digital Device Dilemma. Available at: http://www. thevisioncouncil.org/sites/default/files/2416_ VC_2016EyeStrain_Report_WEB.pdf (last accessed December 19, 2017).
6. Schiffman RM, Christianson MD, Jacobsen G, et al. Reliability and validity of the Ocular Surface Disease Index. Arch Ophthalmol. 2000 May;118(5):615-21.
7. Leung EW, Medeiros FA, Weinreb RN, et al. Prevalence of ocular surface disease in glaucoma patients. J Glaucoma. 2008 Aug;17(5):350-5.
8. Fechtner RD, Godfrey DG, Budenz D, et al. Prevalence of ocular surface complaints in patients with glaucoma using topical intraocular pressure-lowering medications. Cornea. 2010 Jun;29(6):618-21.
9. Rossi GC, Tinelli C, Pasinetti GM, et al. Dry eye syndrome-related quality of life in glaucoma patients. Eur J Ophthalmol. 2009 Jul-Aug;19(4):572-9.
10. Keller N, Moore D, Carper D, et al. Increased corneal permeability induced by the dual effects of transient tear film acidification and exposure to benzalkonium chloride. Exp Eye Res. 1980 Feb;30(2):203-10.
11. Chang et al. United States Patent 7,851,504 B2. Dec. 14, 2010. Available at https://www.ip-navi.or.kr/biblio_attach/PATENT/US/US1510036_7851504.pdf (last accessed December 5, 2017.
12. Miljanovi B, Dana R, Sullivan DA, et al. Impact of dry eye syndrome on vision-related quality of life. Am J Ophthalmol. 2007 Mar;143(3):409-15.

MIGS

Minimally Invasive Glaucoma Surgery

John Berdahl, MD

When looking at today's strategies for lowering intraocular pressure (IOP) in glaucoma patients, the answer to the question of whether we need better solutions should be a resounding and emphatic yes. We continue to be constrained by issues of patient medication compliance and the limits of traditional glaucoma surgery.

Consider a senior female patient of mine who underwent two trabeculectomies on her left eye in recent years with the hopes of relieving dangerously high pressure. After these two highly invasive surgeries, her IOP returned to 34 mmHg. Even when trabeculectomies are successful in lowering IOP, they have associated risks. One study found that patients who underwent trabeculectomies had a nearly 25% chance of needing cataract surgery at five years.[1]

When comparing another IOP-lowering procedure, tube shunt surgery, with trabeculectomy in eyes with previous cataracts or failed glaucoma surgeries, failure rates were higher in the trabeculectomy group.[2,3] That is not to give tubes a gold star, as the devices still have a five-year failure rate of about 30% compared with 47% in trabeculectomies.[3] And tubes have troubling potential side effects such as double vision and corneal edema.

Turn to medication IOP-lowering strategies, and the picture isn't much brighter. You find that more than 90% of patients are non-compliant with their dosing regimens, with nearly 50% discontinuing medications before six months.[4] In one seminal study, only 20% of patients showed "persistently good adherence" at one year and 15% did at five years.[5]

That is not to chide all patients, as some have good intentions for medication compliance but aren't able to administer their eye drops correctly. Periodically I ask my patients to show me how they instill their drops. A portion of them, not only don't get all or any solution into their eyes, but some scrape their eyes with the bottle, potentially introducing bacteria or viruses into the eye. The scene is, frankly, disturbing for me to watch as their doctor.

So if we can do something to bide time until a patient needs a first, second or third invasive surgery that brings with its potential complications and reoperations, it's a win. Minimally Invasive Glaucoma Surgery (MIGS) can fill this surgical gap, and a surge of players has arrived in this space, making it hard for the average clinician to keep up.

MIGS Primer

Iqbal "Ike" Ahmed, MD, coined the term MIGS in 2009 to distinguish a new generation of glaucoma procedures from traditional surgeries. He defined these up-and-coming interventions as ab interno procedures that induce minimal disruption of normal anatomy/physiology, have a high safety profile, are able to lower IOP and offer rapid recovery.

The goal of MIGS is to slow glaucoma progression, reduce eye pressure and eliminate or minimize eye drop use. Types of MIGS include trabecular meshwork bypass surgery (devices that incise the trabecular meshwork to move aqueous through the collector channels), suprachoroidal/supraciliary shunts (tubes that act as a gateway to connect the anterior eye to the suprachoroidal space by creating a controlled cyclodialysis cleft) and subconjunctival stents (stents that direct flow from the anterior chamber into the subconjunctival space).

In the trabecular meshwork bypass surgery space, the iStent (Glaukos) is one example. It forges a bypass through the trabecular meshwork, Schlemm's canal and collector channels to improve natural fluid outflow. The surgeon uses a goniolens and gonioscopic landmarks to correctly position the device for alignment. Conversely, the Kahook Dual Blade (New World Medical), another MIGS in this category, acts as a wedge to lift and excise the trabecular meshwork, allowing greater access to the collector channels.

Moving to suprachoroidal shunts, one type of device, the Cypass (Alcon) is inserted below the scleral spur and advanced into the supraciliary space, bypassing the traditional outflow pathway.

MIGS

Device	Company	Site	Availablility	Approval
iStent	Glaukos	Trabecular Meshwork	Yes	PMA
KDB	New World Medical	Trabecular Meshwork	Yes	Class 1
Trabectome	NeoMedix	Trabecular Meshwork	Yes	510K
ABiC	Ellex	Trabecular Meshwork	Yes	510K
Visco 360	SightScience	Trabecular Meshwork	Yes	510K
Cypass	Alcon	SupraChoroidal	Yes	PMA
Xen	Allergan	Sub-Conjuntival	Yes	510K
ECP	EndoOptiks	Ciliary Body	Yes	510K
Hydrus	Ivantis	Trabecular Meshwork	Trials	PMA
iStent inject	Glaukos	Trabecular Meshwork	Trials	PMA
iStent supra	Glaukos	SupraChoroidal	Trials	PMA

FIGURE 1. TODAY'S MIGS LANDSCAPE
Minimally Invasive Glaucoma Surgery (MIGS) has exploded in recent years. Here is a lineup of some devices in the space.
Images: John Berdahl, MD

In the subconjunctival category, the Xen gel stent (Allergan), is advanced by the surgeon using a preloaded needle; the needle sleeve is retracted, leaving in place the gel implant—similar to a hard macaroni noodle that becomes gelatinous once implanted.

Now in clinical trials, a supraciliary microstent known as the iStent Supra (Glaukos) is inserted through a clear corneal incision in the aqueous humor to access the suprachoroidal space. The device is placed below the scleral spur and above the iris.

Considerations for MIGS

As a general rule, potential MIGS candidates should be individuals with cataracts and glaucoma or ocular hypertension; pseudophakic patients with uncontrolled glaucoma; or occasional phakic patients with uncontrolled glaucoma.

Six factors that should go into an assessment for MIGS include: eye pressure, visual fields (VFs), OCT imaging scans, family history, central corneal thickness (CCT) and appearance of the optic nerve. Add that information into a clinical puzzle with a goal of reducing eye pressure to between 15 mmHg and 18 mmHg, and brainstorm the best and safest way to get there. If a patient has a borderline need for MIGS, corneal hysteresis (CH)—a biomechanical property related to the eye's ability to absorb shock—can sway the decision. Low CH is independently associated with glaucomatous damage and disease progression and can be more revealing than other risk factors, including IOP and CCT.[6]

A patient presenting with high eye pressure on the first visit typically has more MIGS options available than one starting with lower pressure since some trabecular bypass devices won't reduce pressure enough in the latter individual. If someone comes in at an acute stage, with severely damaged retinal ganglion cell axons and very poor VFs, we likely don't have time to assess whether a safer procedure might be acceptable, so we would probably move to a trabeculectomy or a tube shunt immediately.

Efficacy of MIGS

MIGS fill a huge void in the surgical space, but it is essential to learn what the scientific literature tells us about their safety and effectiveness for patients. Most studies confirm the IOP-lowering benefits of these procedures and also show a reasonably good safety profile and low complication rate.

My team conducted a study on 464 enrolled subjects (108 at three years)—the largest eye stent study published until now—and evaluated the safety and efficacy of the iStent trabecular microbypass stent combined with cataract surgery in individuals with pseudoexfoliation glaucoma (PXG).[7] The preoperative mean IOP dropped from 20 mmHg ± 6.95 mmHg (SD) to 15.54 mmHg ± 3.83 mmHg ($p<.01$) at one year and 14.51 mmHg ± 2.79 mmHg ($p<.01$) at two years. The preoperative mean number of glaucoma medications of 1.41 ± 1.04 fell to 0.71 ± 0.94 at two years postoperatively ($p<.01$).

To summarize, individuals with moderately high preoperative IOPs can get up to 4.5 mmHg of IOP lowering when combining an iStent and cataract surgery, and up to a 50% reduction in medications. However, we found the strategy didn't work well in people with lower eye pressures. For example, those with 14 mmHg to 17 mmHg had only about a 1-mmHg reduction. Another paper similarly found that stent implantation plus cataract surgery yielded lower pressures and the need for fewer medications than cataract surgery alone a year after the procedures.[8] The question then becomes whether the cataract surgery is the real workhorse and the stent is essentially an ornament.

My team also studied the iStent in pseudophakic eyes with open-angle glaucoma.[8] The preoperative mean IOP of 20.26 mmHg ± 6 mmHg was reduced to 16.34 mmHg ± 3.78 mmHg ($p<0.01$) at one year and 13.62 mmHg ± 4.55 mmHg ($p<0.01$) at two years.[9] The preoperative mean number of glaucoma medications—1.95 ± 1.01—fell to 1.69 ± 1.28 ($p>0.05$) at one year postoperatively.[9] The safety profile appeared favorable with a low rate of IOP spikes; only one patient required additional surgery.[9] In other words, pressures came down to 13 mmHg on average and medication use dropped by about 30% at two years. It's clear that the iStent lowered IOP in pseudophakes. One side note to mention was that preoperative IOPs were somewhat higher than the average cataract patient. The reason is because I wouldn't perform surgery on an eye that didn't already require it unless the patient wasn't tolerating medications or disease was rapidly progressing. Again, the advanced glaucoma patient was a good fit for this procedure.

Our research also revealed positive findings for the Kahook Dual Blade.[10] Preoperative eye pressures were 17.5 mmHg vs.13 mmHg postoperatively, so this approach successfully lowered eye pressure as well. Medication use dropped by 0.8 for all eyes and by 0.7 for those that received Kahook Dual Blade combined with cataract extraction.

Looking at the suprachoroidal space and supraciliary microstenting, the CyPass Micro-Stent (Transcend Medical) with cataract surgery yielded about a 7.4 mmHg drop in pressure compared with 5.4 mmHg from cataract surgery alone; 85% of microstent subjects did not require IOP medications at two years.[10] No vision-threatening microstent-related adverse events (AEs) occurred, and visual acuity was high in both groups through two years.[11]

Moving into the subconjunctival space with the Xen gel stent, positive findings were seen here as well.[12] The stent was placed ab interno in individuals whose prior filtering/cilioablative procedures had failed or whose IOPs on maximum-tolerated medical therapy were uncontrolled, with medicated IOPs ≥20 and ≤35 mmHg, and visual field mean deviation ≤-3 dB. At two years, 75.4% reported ≥20% IOP lowering from baseline on the same or fewer medications.[12] No intraoperative complications or unexpected postoperative AEs were reported.[12] Note that this cohort was a refractory glaucoma set that had previously undergone glaucoma surgery.

The MIGS Surgeon

Three categories of surgeons tend to be interested in MIGS surgeries: comprehensive ophthalmologists, high-volume cataract surgeons and glaucoma surgeons. They each have a unique perspective on the addition of MIGS to their clinical practices.

The comprehensive ophthalmologist and the high-volume cataract surgeon generally want to know if enough cases would present to be able to get good at the procedures and how these procedures might change the daily practice flow. The glaucoma surgeon likely would consider whether MIGS could lower eye pressure enough in more severe glaucoma patients.

In the case of the high-volume cataract surgeon, it's been borne out in studies that roughly 20% of people undergoing cataract surgery have a concurrent diagnosis of glaucoma.[13,14]

If the average U.S. cataract surgeon handles 400 cataract cases a year, they would see roughly 40 to 80 patients who also had glaucoma—enough cases to become decent at performing MIGS.

PREPARING FOR SURGERY
When getting in position for trabecular meshwork bypass surgery, the surgeon uses a goniolens and gonioscopic landmarks for proper orientation of the device, and proceeds through a series of steps to correctly align the device for implantation.

At the very least, patients must be informed about the possibility of MIGS. I think it's incumbent upon us to make sure patients know all of their options for glaucoma surgery.

The Financials

Medicare patients with supplemental insurance generally will have no or very low out-of-pocket expenditure for indicated MIGS procedures. However, some of these surgeries are performed "off-label," diminishing the likelihood of reimbursement. We did a cost analysis comparing MIGS to other procedures, specifically drops and selective laser trabeculoplasty, and found that the cost-benefit ratio was favorable for MIGS in a long-term Markov model.[15]

In every case, we first educate patients about what we think is best for their eye. Then we tell them historically what percentage of time the procedure has been covered by their insurance. If individuals want to proceed and choose to potentially pay for the entire cost, we have them sign Advance Beneficiary Notice of Noncoverage forms.

If a patient can't afford the procedure, we seek an alternative solution. Maybe we do a Kahook Dual Blade, which will usually be covered, or a trabeculectomy or tube shunt. Creative thinking helps customize a plan for each patient.

End Game

Going back to my patient who unsuccessfully underwent two trabeculectomies but was still dealing with IOPs of 34 mmHg after the surgeries, we decided to move her to a MIGS procedure. We implanted two iStents in her left eye. One week later, she spoke to us on video to report how she was doing. Her pressure had dropped by nearly 20 mmHg to 15 mmHg.

"Can you believe it?" she exclaimed into the camera. "I am so happy."

Based on the body of research on MIGS and anecdotal experience, it's obvious that MIGS are not only expanding our surgical toolbox, but they are offering an alternative IOP-lowering strategy to serious and refractory glaucoma patients who want to avoid, or have not been successful with, traditional approaches. Beyond that, these evolving devices have restored quality of life for many patients who have reached the limits of established technologies, and offered them a brighter vision of the future.

John Berdahl, MD, is an ophthalmologist at Vance Thompson Vision in Sioux Falls, SD.

1. Musch DC, Gillespie BW, Lichter PR, et al. Visual field progression in the Collaborative Initial Glaucoma Treatment Study the impact of treatment and other baseline factors. Ophthalmology. 2009;116(2):200-7.
2. Gedde SJ. The Tube Versus Trabeculectomy Study Group. Results from the tube versus trabeculectomy study. Middle East Afr J Ophthalmol 2009; 16(3):107-11.
3. Gedde SJ, Schiffman JC, Feuer WJ, et al. Treatment outcomes in the tube versus trabeculectomy (TVT) study after five years of follow-up. Am J Ophthalmol. 2012 May;153(5):789-803.
4. Nordstrom BL, Friedman DS, Mozaffari E, et al. Persistence and adherence with topical glaucoma therapy. Am J Ophthalmol. 2005 Oct;140(4):598-606.
5. Newman-Casey PA, Blachley T, Lee PP, et al. Patterns of glaucoma medication adherence over four years of follow-up. Ophthalmology. 2015 Oct;122(10):2010-21.
6. Medeiros FA, Meira-Freitas D, Lisboa R, et al. Corneal hysteresis as a risk factor for glaucoma progression: a prospective longitudinal study. Ophthalmology. 2013 Aug;120(8):1533-40.
7. Ferguson TJ, Swan R, Ibach M, et al. Trabecular microbypass stent implantation with cataract extraction in pseudoexfoliation glaucoma. J Cataract Refract Surg. 2017 May;43(5):622-6.
8. Samuelson TW, Katz LJ, Wells JM, et al. Randomized evaluation of the trabecular micro-bypass stent with phacoemulsification in patients with glaucoma and cataract. Ophthalmology. 2011 Mar;118(3):459-67.
9. Ferguson TJ, Berdahl JP, Schweitzer JA, et al. Evaluation of a Trabecular Micro-Bypass Stent in Pseudophakic Patients With Open-Angle Glaucoma. J Glaucoma. 2016 Nov;25(11):896-900.
10. Radcliffe N, Abdullah S, Jasek M, et al. (2017, March) A Novel Dual Blade Device for Goniotomy:Six-Month Follow-up. Poster session presented at the American Glaucoma Society 27th Annual Meeting, Coronado CA.
11. Vold S, Ahmed II2, Craven ER, et al. Two-Year COMPASS Trial Results: Supraciliary microstenting with phacoemulsification in patients with open-angle glaucoma and cataracts. Ophthalmology. 2016 Oct;123(10):2103-12.
12. Grover DS, Flynn WJ, Bashford KP, et al. Performance and safety of a new ab interno gelatin stent in refractory glaucoma at 12 months. Am J Ophthalmol. 2017 Nov;183:25-36.
13. Shrivastava A, Friedman D, Singh K, et al. (2016, April) Prevalence of glaucoma in a cataract surgery population. Poster presented at the American Society of Cataract and Refractive Surgery.
14. Kung JS, Choi DY, Cheema AS, et al. Cataract surgery in the glaucoma patient. Middle East Afr J Ophthalmol. 2015 Jan-Mar; 22(1):10-17.
15. Berdahl JP, Khatana AK, Katz LJ, et al. Cost-comparison of two trabecular micro-bypass stents versus selective laser trabeculoplasty or medications only for intraocular pressure control for patients with open-angle glaucoma. J Med Econ. 2017 Jul;20(7):760-6.6

Outreach

Glaucoma in Developing Countries

Robert D. Fechtner, MD

Serving as the executive vice president of the World Glaucoma Association for several years has brought me into contact with a much wider glaucoma community than I could have ever known as a practitioner in the United States. My eyes have been opened to the varied experiences of glaucoma patients and doctors trying to fight glaucoma in many lower-income and developing countries around the world.

I also have been humbled to learn that the skills I acquired in school and in the field to diagnose, treat and manage glaucoma as an American physician don't necessarily translate to many parts of the world. I have come to understand that if we, as a global community, are going to make a dent in the staggering rates of glaucoma blindness occurring across all of the globe's socioeconomic groups, we have to understand what strategies are realistic and sustainable to aid glaucoma patients in areas where resources are limited, scarce or nonexistent.

Characteristics of Developing Countries

The World Bank defines low- to middle-income economies as those having less than $3,955 per gross per capita income.[1] When you look at the breadth of countries and regions that fall into this category, the reality is that the majority of the world's population lives in the developing world.

The biggest medical challenge facing such areas is a lack of access to routine and specialized medical care. When services are available, not everyone has equal access to the physicians or medical supplies, which can be strained and not geographically well-distributed. Other obstacles include aging populations, extreme terrain, poverty and illiteracy. Since more severe forms of glaucoma can be unforgiving, by the time symptoms are present in patients who have not received early or ongoing treatment or management, it's often too late to significantly change patient outcomes.

When you look at the enormous financial cost to treat glaucoma patients in a developed nation, the magnitude of the burden seems almost insurmountable for a lower-income country. A 2013 study on the cost of vision loss and eye disorders in the United States found that glaucoma and disorders of the optic nerve had an astonishing $5.8 billion price tag at that time.[2] In New York alone, where I practice, eye disorder and vision expenditures can reach $10 billion.[2] These are just the direct costs spent largely on medication and office visits, which don't account for the indirect expenses absorbed by patients and their families as they seek treatment.

So when you think of the scope of financial resources necessary to treat the glaucoma patient today, it becomes apparent why many glaucoma patients in the world's lower-income communities might be going under- or untreated.

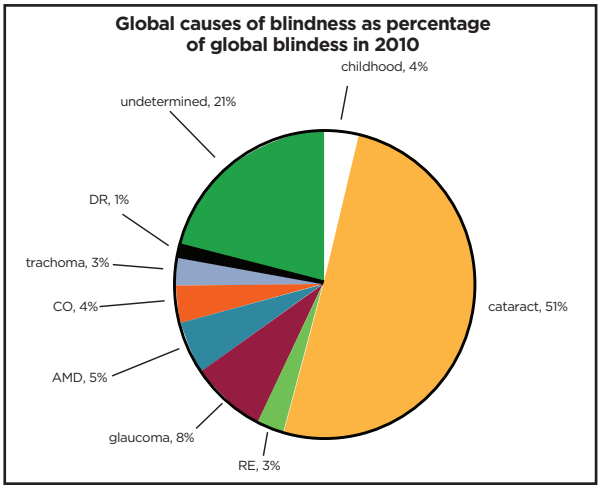
Glaucoma Impact

The first tough question I pondered as I learned more about glaucoma in less developed parts of the world was: Given the abundance of health challenges and problems facing developing nations, is blindness from glaucoma worth addressing? To answer, we must first know some basic information about glaucoma incidence and blindness.

Estimates put the number of worldwide suspected glaucoma cases at around 70 million, with that number expected to increase to 111.8 million in 2040.[3,4] The World Health Organization (WHO) ranks glaucoma as the leading cause of irreversible blindness and visual impairment, and the second (to cataracts) leading cause of global blindness.[5,6] Unlike cataracts, glaucoma generally cannot be reversed.

One publication estimated that the world community would see 79.6 million people with open-angle glaucoma (OAG) and angle-closure glaucoma (ACG) in 2020, of which bilateral blindness would be present in 5.9 million cases of OAG and 5.3 million cases of ACG.[7]

When looking at a breakdown of the causes of global vision impairment and blindness, 2010 WHO data found that cataracts accounted for 51% of total blindness.[8] This may explain why international efforts are often directed at



cataract blindness. In this same breakdown, glaucoma was responsible for 8% of blindness.[8] Other conditions included: undetermined, 21%; AMD, 5%; corneal opacities, 4%; childhood, 4%; trachoma, 3%; onchocerciasis, 3%; and diabetic retinopathy, 1%. Glaucoma is a fairly large component of the blindness-causing disease picture, so this chronic, progressive disease certainly rises to a level worthy of consideration for the world's resources.

Targeted Populations

With so many global communities in dire need of glaucoma care, the next difficult question is which parts of the world to target.

One study revealed that individuals in Asia and Africa would be disproportionally affected by primary OAG and primary ACG glaucoma cases.[4] And a 2004 WHO bulletin suggested that ACG was reaching "epidemic proportions" in China and other parts of Asia.[5]

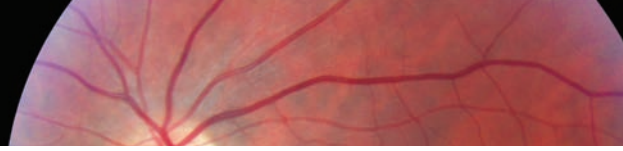
The WHO has cited a lack of trained ophthalmologists as a major factor limiting the diagnosis and care of people with glaucoma in developing countries.[9] In 2004, Europe reportedly had one ophthalmologist for every 10,000 people, India had one ophthalmologist for every 400,000 people and Africa had one ophthalmologist or less for every million.[9]

These doctor-patient ratios are somewhat shocking. What I view as my daily clinical load seems insubstantial when colleagues on another continent could have a million people seeking their services.

Work in the Himalayas

We know from the 2010 WHO data that cataracts account for about 51% of total blindness in the world, making cataract programs a high priority for global eye resources. Perhaps we can look to cataract strategies happening in developing areas of the world as a model for glaucoma.

In one cataract study, public health officials in the Tibet Autonomous Region of China conducted a survey of blindness, eye diseases and eye care service utilization to assist



the development of a 10-year blindness prevention and treatment plan, determine the prevalence of blindness and visual impairment, and assess cataract surgical coverage and outcomes in the region.[10]

Among the 15,900 people enumerated, 12,644 were examined for a response rate of 79.6%.[10] The crude prevalence of blindness (better visual acuity [VA] of less than 6/60) was 2.3%; age and gender-adjusted blindness prevalence was 1.4% (CI, 1.3 to 1.5). Researchers found visual impairment in 10.9% (CI, 10.5 to 11.2) of the population.[10] Cataracts were the primary cause of blindness (50.7%), followed by macular degeneration (12.7%) and corneal opacity (9.7%).[10]

Researchers concluded that blindness was a serious public health problem in Tibet.[10] They added that, as elsewhere in the world, women had an excess burden of blindness compared with men, and that about 75% of blindness in Tibet could be prevented or treated.

It makes tremendous sense that cataracts are the first priority to reduce worldwide sight loss, but we shouldn't overlook the opportunity for glaucoma interventions to have an impact on blindness as well.

Turning to a glaucoma study in Nepal, officials provided annual targeted glaucoma screenings, treatment and education between 2004 and 2007.[11] Data from three one-day screening clinics in 2006 showed that approximately 2% to 4% of patients 50 years of age or older were newly diagnosed with primary OAG (POAG). Primary-angle-closure (PAC) glaucoma patients were identified as well.

Slowing Glaucoma Rates

When it comes to glaucoma rates, one major concern is that the number of cases trends upward with age. Since the population is aging in many corners of the world, this is a growing problem. Given that PAC glaucoma can be acute and result in more visual morbidity than POAG, PAC patients might be one group in which scant resources could be turned into measurable, positive outcomes.

The first step to addressing the issue is to develop glaucoma screening and related public health strategies. However, putting in place programs in developing nations is not a straightforward process. For one thing, since resources are constrained, bringing practitioners to patients, or vice versa, and delivering some meaningful level of care are major obstacles. Second, you can detect or raise awareness of glaucoma, but if no reasonable treatment is available, public health initiatives will obviously be useless. As such, training human resources on accessible therapeutic tools also will be necessary. Finally, clinicians in developing countries tend to be less well-versed in conducting or reviewing research, so a number of respected researchers are now collaborating with colleagues in many parts of the world.

For an OAG population, treating individuals with functional loss who aren't blind could be a target for interventions. Beta-blockers might be the only affordable medication, but the drugs are often efficacious. Obstacles with incisional surgery are that it requires postoperative care. For example, trabeculectomy patients must be followed for a lifetime if the procedure happens to work beyond four or five years.[12]

With ACG, interestingly, cataract intervention programs might help prevent blindness in this more serious form of disease, given the findings of studies such as EAGLE.[13]

Innovative Research

We are fortunate that many researchers are actively seeking creative ways to lower IOP for glaucoma patients in financially strained parts of the globe.

One team characterized the 12-month IOP-lowering efficacy of selective laser trabeculoplasty (SLT) as the sole therapy for POAG in an Afro-Caribbean population.[14] Subjects in St. Lucia and Dominica were randomized to: rapid washouts of IOP-lowering medications followed by SLT, three-month delays followed by washouts and SLT, or six-month delays followed by washouts and SLT.[14]

The target IOP was a 20% or greater IOP decrease from post-washout baseline. Overall, 72 patients underwent SLT treatment. The mean IOP at enrollment was 15.4 mmHg ± 3.6 mmHg in right eyes and 15.4 mmHg ± 3.6 mmHg in left eyes, which rose to 21 mmHg ± 3.3 mmHg and 20.9 mmHg ± 3 mmHg, after washouts. The mean IOP at three, six, nine and 12 months ranged from 12.5 mmHg to 14.5 mmHg. The 12-month success rate was 78%, with transient photophobia and discomfort as common side effects.

Researchers concluded that SLT monotherapy safely provided significant IOP reduction in Afro-Caribbean eyes with POAG and that this treatment could play a role in preventing glaucoma vision loss and blindness in people of African descent living in low-resource regions. These findings have triggered efforts to roll out similar IOP-lowering initiatives in Africa.

Another somewhat-maverick team investigated the results of SLT performed directly on the sclera without a gonioscopy lens, at the Meir Medical Center in Kfar-Saba, Israel.[14] Adults with uncontrolled POAG or pseudoexfoliation glaucoma were randomized into two groups. Controls underwent conventional SLT using a gonioscopy lens for 360 degrees of the trabecular meshwork, while the other group had lasers using the same parameters with laser energy administered on the perilimbal sclera.

Thirty adults were randomized into two groups. The mean (±SD) pretreatment IOP was 20.21 mmHg ± 3.19 mmHg for subjects (n=14) and 21.14 mmHg ±2.98 mmHg for controls (n=14; p=0.43), dropping to 16 mmHg ±3.31 mmHg and 14 mmHg ± 2.45 mmHg (p=0.22) after one year. The average IOP reduction at one year was 20.83% for subjects and 33.77% for controls (p=0.528). Success—a decrease of ≥15% at six months with no additional medications, laser or glaucoma surgery—was achieved in 12 (85.7%) subjects and nine (69.2%) controls (p=0.385). Complications were mild and transient (n=30) but higher in controls (n=15; p<0.0001).

The conclusion: SLT applied directly to the perilimbal sclera might be as effective as the conventional procedure for one year.

These two sets of innovative researchers might be on to something. We need a few unorthodox ideas to have an impact on glaucoma care in the developing world.

EAGLE Trial

One transformative clinical trial that might help in our global glaucoma efforts, EAGLE, studied a new surgical method offering the IOP-lowering and vision benefits of cataract surgery.[13] Researchers randomly assigned subjects with PAC glaucoma, or angle-closure, and high IOP to receive clear-lens extraction, or standard care with laser peripheral iridotomy (LPI) and topical medical treatment.[13] The lens extraction group's IOP ended in the 16 mmHg to 18 mmHg range—lower than the LPI group. At 36 months, 60% of these individuals had an average pressure of 16.6 mmHg on no medication. Only one person in the group needed further surgery, while 24 people undergoing LPI went on to have other interventions, including 16 cataract surgeries and several glaucoma surgeries.

Researchers concluded that clear-lens extraction yielded greater efficacy and cost-effectiveness than LPI, and recommended it be considered for first-line treatment. This concept of clear-lens extraction is evolving. But from a global perspective, we hope to one day train local clinicians in developing nations to perform such a surgery to prevent blindness in one or both eyes in individuals at high risk of PAC glaucoma.

Digging In

Returning to my World Glaucoma Association responsibilities, our group is sponsoring a series of fellowships in partnership with the International Council of Ophthalmology. As part of the program, we're bringing African physicians to established teaching programs in developed countries and housing them from one to three months in a glaucoma unit so they can attend a World Glaucoma Congress meeting and gain additional training. The goal is to spark interest in practitioners in developing countries who want to bring the latest knowledge back home and spread the message about the urgent need for a global effort to fight glaucoma.

We can play a part in this battle by identifying where opportunities exist for us to be involved, sharing knowledge and resources, and possibly mentoring colleagues in other communities. Perhaps, we might all push ourselves to think and act a little more globally.

The 100 to 200 cases we might see in a week certainly makes an impact on patient lives, but imagine what we could accomplish with a forum to potentially touch millions of lives. My challenge to you would be: Reach out a little further, do something—just one thing—to learn about glaucoma in the developing world and see whether there's some area where you can make a difference.

Robert D. Fechtner, MD, is professor and chair of ophthalmology, Upstate Medical University in Syracuse, N.Y.

1. World Bank Country and Lending Groups: Country Classification. Available at: https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups (last accessed January 24, 2018).
2. Cost of Vision Problems: The Economic Burden of Vision Loss and Eye Disorders in the United States. June 11, 2013. Presented To: Prevent Blindness America. Available at: https://www.preventblindness.org/sites/default/files/national/documents/Economic%20Burden%20of%20Vision%20Final%20Report_130611.pdf (last accessed January 25, 2018).
3. Quigley HA. Number of people with glaucoma worldwide. Number of people with glaucoma worldwide. Br J Ophthalmol. 1996 May;80(5):389-93.
4. Tham Y-C, Li X, Wong TY, et al. Global prevalence of glaucoma and projections of glaucoma burden through 2040. Ophthalmology. Nov 2014;121(11): 2081–90.
5. World Health Organization Bulletin. Glaucoma is second leading cause of blindness globally.
2004 Nov. 1. Available at: http://www.who.int/bulletin/volumes/82/11/feature1104/en/(last accessed January 31, 2018).
6. Kingman S. Glaucoma is second leading cause of blindness globally. Bull World Health Organ.
2004 Nov; 82(11): 887–888.
7. H Quigley HA, Broman AT. The number of people with glaucoma worldwide in 2010 and 2020. Br J Ophthalmol. 2006 Mar; 90(3): 262-7.
8. World Health Organization. Global Data on Visual Impairments 2010. Available at http://www.who.int/blindness/GLOBALDATAFINALforweb.pdf (last accessed January 25, 2018).
9. Bulletin of the World Health Organization. Glaucoma is second leading cause of blindness globally. November 2004. Available at: http://www.who.int/bulletin/volumes/82/11/feature1104/en/
(last accessed January 25, 2018).
10. Dunzhu S, Wang FS, Courtright P, et al. Blindness and eye diseases in Tibet: findings from a randomised, population based survey. Br J Ophthalmol. 2003 Dec;87(12):1443-8.
11. Thapa SS, Kelley KH, Rens GV, et al. A novel approach to glaucoma screening and education in Nepal. BMC Ophthalmology20088:21.
12. Gedde SJ, Schiffman JC, Feuer WJ, et al. Treatment outcomes in the tube versus trabeculectomy (TVT) study after five years of follow-up. Am J Ophthalmol. 2012 May;153(5):789-803.
13. Azuara-Blanco A, Burr J, Ramsay C, et al. Effectiveness of early lens extraction for the treatment of primary angle-closure glaucoma (EAGLE): a randomised controlled trial. Lancet 2016;1;388(10052):1389-97.
14. Geffen N, Ofir S, Belkin A, et al. Transscleral selective laser trabeculoplasty without a gonioscopy lens. J Glaucoma. 2017 Mar;26(3):201-7.

ABOUT THE OPTOMETRIC GLAUCOMA SOCIETY

The Optometric Glaucoma Society's (OGS) mission is to promote excellence in the care of glaucoma patients through professional education and scientific investigation. For more information: www.optometricglaucomasociety.org

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.

Distributed by:

Bausch + Lomb, a division of

Valeant Pharmaceuticals North America LLC

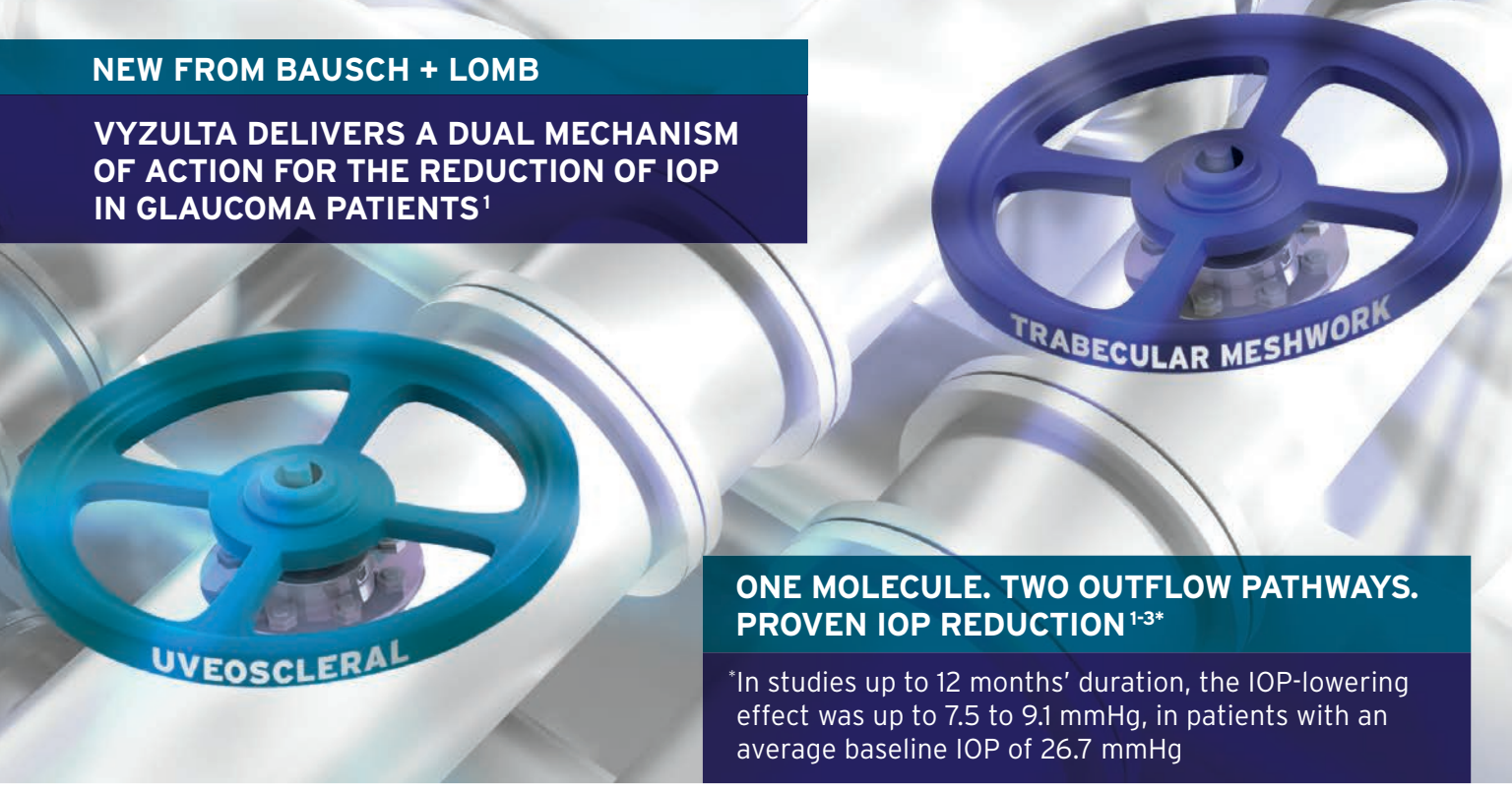
Bridgewater, NJ 08807 USA

U.S. Patent Numbers: 6,211,233; 7,273,946; 7,629,345; 7,910,767; 8,058,467.

Based on 9464800 11/2017 VYZ.0055.USA.16 Issued: 11/2017

NEW FROM BAUSCH + LOMB

VYZULTA DELIVERS A DUAL MECHANISM OF ACTION FOR THE REDUCTION OF IOP IN GLAUCOMA PATIENTS[1]



ONE MOLECULE. TWO OUTFLOW PATHWAYS. PROVEN IOP REDUCTION[1-3*]

*In studies up to 12 months' duration, the IOP-lowering effect was up to 7.5 to 9.1 mmHg, in patients with an average baseline IOP of 26.7 mmHg

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 (CONTINUED)

- 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 next page.

References:

1. VYZULTA Prescribing Information. Bausch & Lomb Incorporated. 2017.
2. Weinreb RN, Sforzolini BS, Vittitow J, Liebmann J. Latanoprostene bunod 0.024% versus timolol maleate 0.5% in subjects with open-angle glaucoma or ocular hypertension: the APOLLO study. *Ophthalmology*. 2016;123(5):965-973.
3. Medeiros FA, Martin KR, Peace J, Sforzolini BS, Vittitow JL, Weinreb RN. Comparison of latanoprostene bunod 0.024% and timolol maleate 0.5% in open-angle glaucoma or ocular hypertension: the LUNAR study. *Am J Ophthalmol*. 2016;168:250-259.

For more information about VYZULTA and how it works, visit vyzultanow.com

VYZULTA™
(latanoprostene bunod ophthalmic solution), 0.024%

BAUSCH + LOMB