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Glaucoma 2019

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IOP, intraocular pressure.

INDICATIONS AND USAGE

Rhopressa® (netarsudil ophthalmic solution) 0.02% is indicated for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

DOSAGE AND ADMINISTRATION

The recommended dosage is one drop in the affected eye(s) once daily in the evening.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

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.

Contact Lenses: Contact lenses should be removed prior to instillation of Rhopressa® and may be inserted 15 minutes following its administration.

ADVERSE REACTIONS

The most common ocular adverse reaction observed in controlled clinical studies with Rhopressa® dosed once daily was conjunctival hyperemia, reported in 53% of patients. Other common (approximately 20%) adverse reactions were: corneal verticillata, instillation site pain, and conjunctival hemorrhage. Instillation site erythema, corneal staining, blurred vision, increased lacrimation, erythema of eyelid, and reduced visual acuity were reported in 5-10% of patients.

The corneal verticillata seen in Rhopressa®-treated patients were first noted at 4 weeks of daily dosing. This reaction did not result in any apparent visual functional changes. Most corneal verticillata resolved upon discontinuation of treatment.

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

References: 1. Rhopressa Prescribing Information. Irvine, CA: Aerie Pharmaceuticals, Inc; 2017. **2.** MMIT:12/2018.

aerie® Pharmaceuticals, Inc.

RHOPRESSA® (netarsudil ophthalmic solution) 0.02%
Rx Only

BRIEF SUMMARY
Consult the Full Prescribing Information for complete product information.

INDICATIONS AND USAGE
RHOPRESSA® (netarsudil ophthalmic solution) 0.02% is indicated for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.

DOSAGE AND ADMINISTRATION
The recommended dosage is one drop in the affected eye(s) once daily in the evening.

If one dose is missed, treatment should continue with the next dose in the evening. Twice a day dosing is not well tolerated and is not recommended. If RHOPRESSA is to be used concomitantly with other topical ophthalmic drug products to lower IOP, administer each drug product at least 5 minutes apart.

WARNINGS AND PRECAUTIONS
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 previously contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial surface.

Use with Contact Lenses
RHOPRESSA contains benzalkonium chloride, which may be absorbed by soft contact lenses. Contact lenses should be removed prior to instillation of RHOPRESSA and may be reinserted 15 minutes following its administration.

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

The most common ocular adverse reaction observed in controlled clinical studies with RHOPRESSA dosed once daily was conjunctival hyperemia which was reported in 53% of patients. Other common (approximately 20%) ocular adverse reactions reported were: corneal verticillata, instillation site pain, and conjunctival hemorrhage. Instillation site erythema, corneal staining, blurred vision, increased lacrimation, erythema of eyelid, and reduced visual acuity were reported in 5-10% of patients.

Corneal Verticillata
Corneal verticillata occurred in approximately 20% of the patients in controlled clinical studies. The corneal verticillata seen in RHOPRESSA-treated patients were first noted at 4 weeks of daily dosing. This reaction did not result in any apparent visual functional changes in patients. Most corneal verticillata resolved upon discontinuation of treatment.

USE IN SPECIFIC POPULATIONS
Pregnancy
There are no available data on RHOPRESSA use in pregnant women to inform any drug associated risk; however, systemic exposure to netarsudil from ocular administration is low. Intravenous administration of netarsudil to pregnant rats and rabbits during organogenesis did not produce adverse embryofetal effects at clinically relevant systemic exposures.

Animal Data
Netarsudil administered daily by intravenous injection to rats during organogenesis caused abortions and embryofetal lethality at doses ≥0.3 mg/kg/day (126-fold the plasma exposure at the recommended human ophthalmic dose [RHOD], based on C_{max}). The no-observed-adverse-effect-level (NOAEL) for embryofetal development toxicity was 0.1 mg/kg/day (40-fold the plasma exposure at the RHOD, based on C_{max}).

Netarsudil administered daily by intravenous injection to rabbits during organogenesis caused embryofetal lethality and decreased fetal weight at 5 mg/kg/day (1480-fold the plasma exposure at the RHOD, based on C_{max}). Malformations were observed at ≥3 mg/kg/day (1330-fold the plasma exposure at the RHOD, based on C_{max}), including thoracogastroschisis, umbilical hernia and absent intermediate lung lobe. The NOAEL for embryofetal development toxicity was 0.5 mg/kg/day (214-fold the plasma exposure at the RHOD, based on C_{max}).

Lactation
There are no data on the presence of RHOPRESSA in human milk, the effects on the breastfed infant, or the effects on milk production. However, systemic exposure to netarsudil following topical ocular administration is low, and it is not known whether measurable levels of netarsudil would be present in maternal milk following topical ocular administration. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for RHOPRESSA and any potential adverse effects on the breastfed child from RHOPRESSA.

Pediatric Use
Safety and effectiveness in pediatric patients below the age of 18 years have not been established.

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

NONCLINICAL TOXICOLOGY
Carcinogenesis, Mutagenesis, Impairment of Fertility
Long-term studies in animals have not been performed to evaluate the carcinogenic potential of netarsudil. Netarsudil was not mutagenic in the Ames test, in the mouse lymphoma test, or in the *in vivo* rat micronucleus test. Studies to evaluate the effects of netarsudil on male or female fertility in animals have not been performed.

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Program
12:30-1:30 p.m.

Programs

Saturday, Oct. 12

Update on a Treatment Option for Wet Age-Related Macular Degeneration, Diabetic Macular Edema, and Diabetic Retinopathy
Speakers: Jordana G. Fein, MD, MS, and Ehsan Rahimy, MD
Presented by Regeneron Pharmaceuticals and designed for U.S. retina specialists.

Sunday, Oct. 13

CONNECTiiNG THE DOTS: Evidence Based Perspectives on Dry Eye Disease
Speakers: Terry Kim, MD, W. Barry Lee, MD, FACS, Marguerite B. McDonald, MD, FACS, and Elizabeth Yeu, MD
Presented by Novartis Pharmaceuticals and designed for U.S. eye care specialists.

Monday, Oct. 14

Life is Beautiful When the Pupil Behaves
Speakers: Eric D. Donnenfeld, MD, John A. Hovanesian, MD, Steven M. Silverstein, MD, Denise M. Visco, MD, and Keith A. Walter, MD
Presented by Omeros Corporation and designed for U.S. cataract surgeons.

Check aao.org/eyenet/corporate-events for updated program information.

** These programs are non-CME and are developed independently by industry. They are not affiliated with the official program of AAO 2019 or Subspecialty Day. By attending a lunch, you may be subject to reporting under the Open Payments Program (Sunshine Act).*

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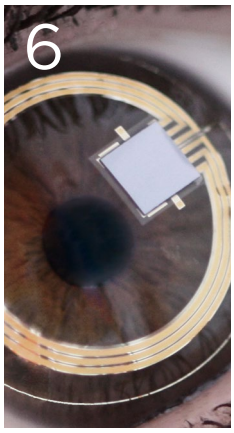

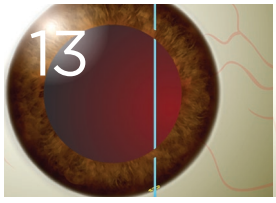

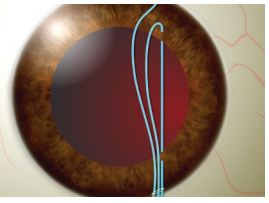

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Setting Meaningful Pressure Goals for Patients With Glaucoma

Elevated intraocular pressure (IOP) is a well-recognized risk factor for glaucoma, and efforts to lower IOP—often to a prespecified target—are a mainstay of glaucoma management. Yet whether and how to set a pressure goal and apply it as a therapeutic guide remains a source of contention among ophthalmologists.

TRACKING PRESSURE. *New pressure monitoring devices, the Triggerfish Sensor (left) and HOME tonometer (right), allow for around-the-clock monitoring to help track peak pressures.*

Target IOP: Defined and Debated

In the Academy's 2015 *Preferred Practice Pattern* (*PPP*) for primary open-angle glaucoma (POAG), an expert panel defined target pressure as the upper limit of a range of IOPs in which "visual field loss is unlikely to significantly reduce a patient's health-related quality of life over his or her lifetime."[1]

Opinions. Target setting gives the practitioner a clear therapeutic goal, said L. Jay Katz, MD, of Wills Eye Hospital in Philadelphia. "It would be a mistake not to have a target pressure because lowering pressure is what we're doing with every therapy for glaucoma."

Even so, Kuldev Singh, MD, MPH, of Stanford University in California, cautioned that having a target IOP does not necessarily lead to better medical care. The natural history of glaucoma cannot be predicted prospectively and depends, in part, on factors that we don't fully understand.[2] He explained, "When we're setting a target IOP, we're trying to predict the pressure that will allow patients to see well for the rest of their lives, without knowing the patient's life span or the relationship between IOP and disease progression for that individual."

Ahmad A. Aref, MD, MBA, from the University of Illinois College of Medicine in Chicago, said that the concept of target setting can be valuable in practice, but only if the physician recognizes that "the target is not written in stone."

Measuring IOP

When and how should IOP be measured? Dr. Katz noted that eye pressures vary during the day, and the highest pressures usually occur outside of office hours. During the night, pressures often peak.[3] "Ideally, you would ask the patient to be checked at different times of day and obtain a diurnal curve of the pressure," he said.

The reality, however, is that measurements are limited by practicality and logistics, said Dr. Aref. Even conscientious patients whose disease status is urgent may not come in for multiple IOP checks, especially if they have to go through all kinds of barriers to make it into the office for an eye pressure check, he said.

New technology. Dr. Katz noted that emerging technologies may soon make it easier to determine peak pressures at baseline and after treatment. The HOME tonometer (iCare) and the Triggerfish Sensor smart contact lens (Sensimed AG) have recently been approved for use in the United States and can gener-

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BY JENNIFER S. GRIFFIN, MS, CONTRIBUTING WRITER, INTERVIEWING **AHMAD A. AREF, MD, MBA, L. JAY KATZ, MD,** AND **KULDEV SINGH, MD, MPH.**

ate many IOP-related measurements in a day, he said. In a recent study, ocular volume and elasticity–derived parameters obtained by a contact lens sensor for a 24-hour period offered a better explanation of glaucoma progression rates than did a series of traditional, in-office IOP measurements.[4]

Setting the Initial Target

Although there is no universally accepted formula for calculating a target pressure, much of the decision-making is based on the peak IOP at baseline, said Dr. Katz.

Methods of target setting. Dr. Aref summarized three methods for setting a target IOP for a new glaucoma patient: 1) a percentage reduction from the baseline pressure, 2) a fixed number or range based on the disease stage, or 3) a formula that includes individual factors such as age, visual field loss, and baseline pressure. His preferred method is the percentage reduction from baseline. The 2015 *PPP* concurs that "a reasonable initial treatment in a POAG patient is to reduce IOP 20%-30% below baseline."[1] Well-known randomized controlled trials support this recommendation.[5-7]

Dr. Aref also considers factors like risk tolerance and life expectancy to help establish a safe target IOP. Dr. Katz added that family history can give important clues about how the glaucoma may progress.

Determining baseline IOP. Dr. Aref noted that he often sees referred patients who already have a diagnosis of glaucoma and are on treatment. In these cases, "I make every effort to determine the patient's unmedicated baseline IOP, either by contacting the physician who started the patient's treatment, or, if I think the patient's optic nerve can handle it, with a drug washout."

Assessing structure and function. To gauge glaucoma severity, Dr. Aref and his team use structural measures, such as stereoscopic optic disc examination and optical coherence tomography, as well as functional methods, such as automated visual field tests. "Based on these assessments, we can stage a patient's glaucoma as ocular hypertension or mild, moderate, or severe glaucoma." He added that some physicians then select a fixed target IOP based on disease stage, for example, 18 mm Hg for mild glaucoma, 15 mm Hg for moderate glaucoma, and 12 mm Hg for severe glaucoma. It is important to clarify that staging based on structural and functional measures for the purpose of target pressure determination does not always correspond with current ICD-10 glaucoma staging definitions, which only take into account functional data, he said.

The Safety Factor

The concept of target IOP does not address the safety of the therapies required to reach a predetermined pressure level, Dr. Singh said. "You have to ask yourself, 'What are the risks of getting to that IOP goal, and are they worth taking?'" This is especially true when the patient has mild glaucoma or when disease progression has not been observed, he said.

Incremental risk. You should never treat a patient to the point beyond which the expected harm of the next therapeutic step would be greater than the expected benefit, given what you know about that patient's disease at that time, Dr. Singh said. This thinking lies at the foundation of starting with relatively safe treatments, like eyedrops, before advancing to riskier surgical options. He added that this dynamic approach, based on risks and benefits of therapy, is more abstract than setting an IOP target and treating until you reach it. Yet he emphasized that the dynamic approach is "unquestionably the one used by most experienced practitioners."

Advanced disease. Dr. Singh considers the concept of target IOP to be "hypothetically useful in very severe glaucoma," in which risks of glaucomatous visual loss considerably outweigh risks of treatment. Dr. Katz summed it up as "Generally, the more severe the disease, the more aggressive we are with trying to reach a low target pressure."

Changing the Goal

"The target IOP is fluid, and we may decide that the target set initially was overly conservative or aggressive," said Dr. Katz. He added, "Each of the patient's eyes may have a different pressure goal, and the target can change over the course of the disease."

Dr. Singh said that with a target pressure approach, ophthalmologists need to be prepared to change the IOP goal at every visit, based on available clinical findings and the safety profile of the remaining therapeutic options.

The 2015 *PPP* states that physicians should adjust the initial target pressure as indicated by disease course and severity,[1] but Dr. Singh noted that this recommendation omits mention of the side effects and risks of treatment. He stressed that these factors "should be at the forefront of your mind, especially because glaucoma does not always lead to visual impairment."

Realistic Expectations

Although Dr. Singh does not dispute that lowering IOP can slow glaucoma progression, he said, "the notion that achieving a target IOP will completely arrest the disease is problematic." Instead, he advocates thinking in terms of rates of change. "Glaucoma is always progressing because of the aging component of ganglion cell loss layered onto the disease component." Accordingly, he said that practitioners should take time to inform patients that glaucoma management is complex, the disease course can be unpredictable, and treatment adherence is strongly recommended, but it will not guarantee a good outcome.

Dr. Singh and his colleagues have identified several obstacles to meaningful IOP targeting: suboptimal measuring tools, the uncertainty of a patient's life span, unforeseeable complications of therapy, and the likelihood that the patient's priorities or risk tolerance may shift during the course of the disease.[8]

The Bigger Picture

"The main goal is preserving the patient's vision," said Dr. Aref. "The status of the patient's optic nerve and visual field are the metrics that I'm actually following, but they don't change rapidly. The IOP is a surrogate for those more important measures."

Dr. Singh added, "We must make

decisions within the limits of resolution of our diagnostic tools."[8] He explained that specifying and achieving a target IOP are not necessarily indicative of treatment success, disease stabilization, or an eliminated risk of blindness. "Ultimately, glaucoma care is not about the IOP or even about saving every ganglion cell and optic nerve fiber. Rather, it is about optimizing the patient's health."

Dr. Aref reiterated that the target pressure is a starting point. "Even in two hypothetical patients with the same baseline pressures, same targets, and same visual fields, you may end up treating each very differently."

Dr. Katz added, "There is considerable science behind what we do in managing glaucoma, but there is art to it as well. You must weigh a lot of factors specific to the patient."

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Glaucoma and Exercise: What to Tell Your Patients

Can I or can't I? Should I or shouldn't I? Ophthalmologists are often asked about the effects of exercise—particularly yoga—on glaucoma. As the science is continuing to unfold, considerable uncertainty remains. But a combination of evidence-based recommendations and common sense can go a long way when talking with glaucoma patients about exercise.

Aerobic Exercise: Definitely

There's no question that aerobic exercise is crucial to overall good health. As for glaucoma, Robert Ritch, MD, at New York Eye & Ear Infirmary of Mount Sinai in New York City, tells his patients, "It's simple. If it's good for your heart, it's good for glaucoma. If it's good for your brain, it's good for glaucoma."

Dr. Ritch advises 45 minutes of aerobic exercise three to four times a week. The research supports this guidance:

- In one study, aerobic exercise (such as walking, swimming, biking, or working out on stationary machines) at a brisk level for 30 to 45 minutes three to four times a week lowered intraocular pressure (IOP) and improved blood flow to the brain and the eye.[1]
- In a recent study, all measures of physical activity—average steps per day, minutes of basic (nonsedentary) movement, and greater time spent doing moderate-to-vigorous physical activity—were associated with slower rates of visual field (VF) loss in a treated group of glaucoma patients.

EXERCISE CAUTION. *Patients with glaucoma may need to modify or skip certain poses, such as downward-facing dog.*

At baseline, participants walked an average of 5,313 steps and averaged 148 minutes of nonsedentary activity and 11 minutes of moderate-to-vigorous activity per day. Each incremental increase in activity was associated with less decline in VF, although the observed effects were small. But significantly boosting those levels each day—walking an additional 5,000 steps, engaging in an additional 2.6 hours of nonsedentary activity, or exercising for 120 minutes at a moderate-to-vigorous level—decreased the average rate of VF loss by approximately 10%.[2]

- Results of a meta-analysis showed that exercise in sedentary people had a greater IOP lowering effect than it did in people who were already active.[3] "It's important for clinicians to tell their patients who are not motivated to exercise that it's actually the patients who have not been active who do the best in terms of lowering eye pressure with exercise," said Yvonne Ou, MD, at the University of California, San Francisco.

Clues from animal research. According to Dr. Ou, recent animal studies add to the evidence that physical activity protects against glaucoma damage.

In a murine study that examined the role of exercise in a transient ocular hypertension model, exercise was able to reverse signs of age-related vulnerability to optic nerve injury, such that the signs of injury in older mice that had completed the exercise regimen were similar to young mice that were not exercised.[4] The investigators then went on to show that exercise may prevent the injury-induced loss of brain-derived neurotrophic factor (BDNF) in the retina. (The group also has recently demonstrated that a high-fat high-sucrose diet made the mouse optic nerve more vulnerable to injury, but that exercise did not offset the negative effects of this diet.[5])

Strength Training: Maybe

Lack of clarity. Relatively few studies have been conducted on weight train-

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BY GABRIELLE WEINER, MS, INTERVIEWING **ROGER COLE, PHD, YVONNE OU, MD,** AND **ROBERT RITCH, MD.**

ing's effect on IOP. Moreover, the results have been contradictory:

- Several years ago, Dr. Ritch's group evaluated the effect of bench pressing on IOP in 29 normal subjects, and a number of them experienced rises in IOP during the exercise.[6] "The study hasn't been done in people with glaucoma, but I presume that glaucoma patients would have a more exaggerated response," Dr. Ritch said.
- In another study of 30 healthy individuals, the opposite occurred: Dynamic resistance exercises (chest and leg presses) induced moderate postexercise decreases in IOP.[7]

Advice for patients? Given the lack of clarity, Dr. Ritch's guidance for glaucoma patients comes down to the amount of weight being lifted. Is a patient working with 10-, 20-, or 30-pound weights—or much more than that? "I caution patients with glaucoma about bench pressing 200 pounds, but a definitive study has not been done. If a patient has mild glaucoma, I tell them to go ahead with their routine unless they [experience] severe damage. I had one patient who lost his 3-degree island of vision in the middle of doing a crunch, and IOP can also rise in patients doing push-ups. I basically tell them to use common sense."

Avoid the Valsalva maneuver. It's crucial that the person continues to exhale during periods of maximum exertion. This helps the patient avoid the Valsalva maneuver, in which a person exhales forcefully with a closed mouth and nose and the windpipe is blocked by the closed epiglottis—which can increase IOP dramatically.

Yoga: It Depends

There's no clear evidence to suggest that certain yoga poses—especially if they are held for short periods—are detrimental to people's glaucoma, but there is reason for caution.

Just say no to headstands. Back in 1980, Dr. Ritch saw a 45-year-old woman with normal-tension glaucoma who had 5-degree fields. She had continued to progress despite consultation with clinicians at 12 institutions.

As it turned out, she had been standing on her head for 20 minutes a day for 20 years. When her IOP was measured while she was performing a headstand, it was 60 mm Hg. In contrast, it was 15 mm Hg while she was sitting. Dr. Ritch proceeded to take all of his lab colleagues and stand them on their heads. Everyone's IOP roughly doubled.

Analyzing Asana

Modifications of yoga poses allow practitioners to experience many of the benefits of the full poses without pushing, overstretching, and incurring injuries. The following modifications may be appropriate for some glaucoma patients, as they help the person achieve gradation from minimal to large increases in IOP by attending to the relative heights of the eyes, heart, and the rest of the body.

Inversions

Legs-up-the-wall pose (Viparita Karani). If a patient goes from sitting on the floor to lying on her back with her legs up a wall, IOP rises only a little, Dr. Cole said, and even that can be partially reversed by elevating the head on a folded yoga blanket.

For a slightly steeper version of this inversion, which can be more calming, at the possible expense of slightly higher pressure in the eyes, he recommended adding a folded blanket or two under the pelvis and rolling the shoulders back to lift the chest (lifting the chest elevates the heart a little).

Plow pose (Halasana) and shoulderstand (Sarvangasana). For a strong inversion that is expected to produce only a moderate increase in IOP, consider plow pose or full shoulderstand.

"Although these poses raise the heart, abdomen, and pelvis [and in the case of shoulderstand, the legs] quite high—and you can't mitigate these factors by raising the head because that would flex the neck too strongly—they are unlikely to raise IOP to an extreme," Dr. Cole said. This is because the flexed position of the neck raises the eyes somewhat relative to the heart.

By contrast, headstand (Sirsasana) is likely to increase IOP maximally because it places the eyes as far as possible below the heart while lifting the abdomen, pelvis, and legs as far as possible above the heart.

Forward Bends

Forward seated bend pose (Paschimottanasana). In the full version of this pose, the person sits on the floor, bends forward, and rests the head on the knees. But modifying the pose—by having the person rest the forehead on a padded chair seat—keeps the eyes above the heart and most of the rest of the body below it, presumably keeping IOP low.

Forward standing bend pose (Uttanasana). As with the seated version, the person bends forward from the waist and the head is brought toward the knees. Standing in front of a chair that has a high stack of blankets on the seat, bending forward, and resting the forehead on the stack will likely raise IOP much less than bending forward without support and hanging the head.

Downward-facing dog pose (Adho Mukha Svanasana). Two modifications to consider in practicing downward-facing dog pose: 1) Rest the hands on a chair (on the seat or on the top of the chairback), or 2) place the hands on the floor while elevating the forehead on a yoga block or on one or more folded blankets. Either modification will probably prevent IOP from rising as much as it would if the head were allowed to dangle downward or rest on the floor.

Another option: Practice the pose at the wall. In this variation (commonly known as half dog), the hands are placed on the wall, and the person steps back from the wall, bending forward at the hips. The head is kept in line with the arms and not allowed to drop down toward the floor.

Subsequent studies and case reports tested headstand pose, demonstrating a twofold rise in IOP.[8] "Doing headstands and shoulderstands is a real no-no for glaucoma patients, especially if you're going to do them for 20 minutes a day," Dr. Ritch said.

What about downward-facing dog? But what about other head-down positions? Yoga students routinely practice a number of poses in which the head is positioned below the heart.

In a recent study, Dr. Ritch and his colleagues had glaucoma patients and a cohort of healthy participants perform a series of four inverted yoga positions—downward-facing dog, standing forward bend, plow, and legs-up-the-wall poses.[9] The researchers captured the IOP in each group at five time points: 1) at baseline, while seated, 2) immediately after assuming the pose, 3) two minutes later, while still holding the pose, 4) immediately after performing the pose, in a seated position, and 5) 10 minutes later, after resting in the seated position.

Both groups of participants showed a rise in IOP in all four yoga positions, with the greatest increase of pressure—almost 10 mm Hg—occurring during downward-facing dog. After a few minutes of rest, all eye pressures returned to normal.

Can modifications help? For glaucoma patients, the safest way to practice yoga is to avoid inversions altogether, said Roger Cole, PhD, a research scientist and Iyengar yoga instructor based in Del Mar, California. However, he said, when a patient who has mild glaucoma also has a passion for yoga, their ophthalmologist and yoga teacher may be able to help them design a modified practice that diminishes the potential effects on IOP.

"The most important factor determining an inverted posture's effect on IOP appears to be the vertical distance of the eyes below the heart," said Dr. Cole. "Elevating the legs, pelvis, and abdomen above the heart may also raise IOP but seems to have a smaller effect."

For example, he noted, "in Dr. Ritch's yoga study, the two postures that placed the eyes furthest below the heart [downward-facing dog and standing forward bend poses] raised IOP by about 10 mm Hg even though the feet remained on the floor." In contrast, he said, "the two postures that kept the eyes at or only slightly below heart level while lifting the legs, pelvis, or abdomen the most [plow and legs-up-the-wall poses] raised IOP by 4 mm Hg, on average." Knowing this makes it easier to select and modify inversions based on their likelihood of raising IOP (see "Analyzing Asana").

Advice to Yoga Practitioners

Dr. Cole offers the following advice to yoga students with glaucoma:

- Have your glaucoma medically treated before practicing.
- Get your doctor's OK before practicing inverted postures or any pose that places your head below your heart.
- Modify or substitute inverted poses to reduce their effects on eye pressure.
- Enter inverted postures slowly.
- Avoid strenuous inversions. Yoga is not about "no pain, no gain."
- Exhale gently and slowly. Avoid holding the breath or restricting the exhalation. If you practice pranayama (yoga breathing techniques), avoid the classical exhalation phase of the Ujjayi breath, as it involves making a "haaaah" sound through a restricted throat. Instead, exhale normally.
- Practice a form of yoga that has you move slowly, provides props, and adapts postures to your needs. Iyengar yoga is the best-known example of this approach.
- Find a teacher who is compatible with you, willing to work with special needs, and knowledgeable about adapting postures.
- Practice mindfully. "Relax your mind and body everywhere you can, then do whatever it takes to get into the pose as far as is reasonable for you at that moment, without disturbing your mind," Dr. Cole said.

Take-Home Message

The last thing a clinician wants to do is discourage patients from exercising. Rather, it's critical to ask patients about their activities and discuss limits and modifications when necessary.

Finally, what about Dr. Ritch's patient, who had been standing on her head for 20 minutes a day for 20 years? She stopped doing headstand pose—and her glaucoma stopped progressing.

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Single-Pass Four-Throw Pupilloplasty: A Treatment for Angle-Closure Glaucoma?

Angle closure compounded by peripheral anterior synechiae (PAS) is one of the biggest challenges we face as glaucoma surgeons, said Sanjay Asrani, MD. PAS can irreversibly impair flow through the trabecular meshwork,[1] resulting in angle-closure glaucoma that persists despite first-line treatment. If PAS have been present for longer than six months, the chances of reestablishing function of the trabecular meshwork are very low, even if you remove the adhesions and anatomically restore the angle, said Dr. Asrani, who is at Duke University in Durham, North Carolina.

After treatment, recurrence of adhesions is a constant concern, said Alan Crandall, MD. In chronic angle-closure glaucoma, the iris often is atrophic, and conventional measures to resolve PAS deteriorate during long-term follow-up, he said. Dr. Crandall is at the Moran Eye Center in Salt Lake City.

A New Approach

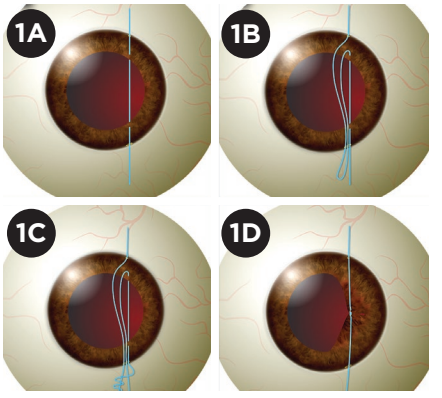
In 2017, Amar Agarwal, MD, tried something different to treat angle-closure glaucoma in phakic patients. He performed a new technique—single-pass four-throw pupilloplasty (SFT)—in combination with lens extraction.[2] He found that the procedure opened the angle, released associated PAS, and secured the iris centrally to help prevent recurrence of the PAS. Dr. Agarwal is with Dr. Agarwal's Eye Hospital and Eye Research Centre in India.

Other techniques, such as a Siepser slipknot, can also be used for pupilloplasty. However, "In the evolution of anything we do surgically, we're trying to make procedures as elegant, as safe, and as cost-effective as we can," said Dr. Crandall. "And this is the case with SFT because you're placing one suture multiple times. It's much less time-consuming than a Siepser knot and just as effective."

No matter what treatment is used, angle closure inevitably causes damage to the trabecular meshwork, said Dr. Asrani. But SFT and medical therapy, if implemented in the early stage of the disease, might be enough to restore aqueous flow and stabilize IOP, obviating the need for more invasive interventions such as trabeculectomy or tube surgery, he said. "When I look at this technique, I think of the patients I could have helped with it."

Traditional Treatments

First-line therapies for angle-closure glaucoma include pilocarpine eyedrops, laser surgery, goniosynechiolysis, and cataract extraction, depending on the severity and underlying cause. If initial treatment fails, surgeons usually turn to trabeculectomy or implantation of a drainage device, said Dr. Asrani.



SFT PUPILLOPLASTY. *(1A) A needle is passed through the proximal and distal portions of the iris tissue. (1B) The proximal and distal portions of the iris are approximated, and a loop of suture is withdrawn. (1C) The suture end is passed through the loop four times. (1D) When the suture ends are pulled, the loop slides inside the iris tissue, yielding a stable knot.*

Laser surgery. Laser peripheral iridotomy is the mainstay for pupillary-block angle closure. However, in angle closure caused by plateau iris, iridotomy will not resolve the narrow angle or prevent PAS. In these cases, argon laser peripheral iridoplasty and pilocarpine eyedrops are initial options, but over time, the iris usually migrates back to the periphery, and PAS recur, said Dr. Asrani.

Synechiolysis and lens removal. Dr. Asrani noted that even goniosynechiolysis coupled with lens removal is a temporary fix because the inflamed iris remains close to the trabecular meshwork and tends to readhere. "In contrast," Dr. Asrani said, "SFT pu-

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BY JENNIFER S. GRIFFIN, MS, CONTRIBUTING WRITER, INTERVIEWING **AMAR AGARWAL, MD, SANJAY ASRANI, MD,** AND **ALAN CRANDALL, MD.**

Amar Agarwal, MD

pilloplasty along with synechiolysis prevents recurrence of PAS by keeping the pupil taut. For patients who have angle closure with a chronically dilated pupil, SFT also will improve the optics by reducing glare."

Techniques and Outcomes

Dr. Agarwal performs SFT pupilloplasty under peribulbar anesthesia, with supplemental anesthesia given as needed.[2] He prefers maintaining the anterior chamber with fluid, rather than viscoelastic, because "fluid will wash away hyphema, which may occur when PAS are broken." He also recommends using an endoilluminator for good visualization, especially if the cornea is hazy.

Technique. An end-opening forceps is used to grasp the iris and pull it toward the center of the pupil at 60-degree intervals around the pupillary margin. Dr. Crandall pointed out, "This 'pull and release' technique partially detaches the PAS and informs the surgeon about the extent of the adhesions and the amount of iris tissue available for reconstruction."

With the proximal iris held with forceps, a straight needle with a 10-0 or 9-0 nonabsorbable polypropylene suture is inserted. From the other end, a 26- or 30-gauge needle is passed through a clear-corneal incision into the distal iris. The straight needle is docked into the lumen of the 26- or 30-gauge needle, and the two are withdrawn together through the distal incision. A loop is created at the suture exit side with a Sinskey hook, and four throws of the distal end of the suture are made through this loop. The ends of the suture are pulled apart to yield a self-locking, helical knot that lies flat against the iris. The suture ends are trimmed with a microscissors, leaving 1-mm ends. (See video posted with this article at aao.org/eyenet.)

Dr. Agarwal explained his rule of thumb for SFT knot placement. "If PAS are observed around more than 270 degrees of the pupillary margin, carry out six-point traction (i.e., three SFT knots); if the PAS constitute less than 270 degrees, you only need four-point traction to sufficiently constrict the pupil."

Recent findings. In a 2018 study coauthored by Dr. Agarwal, SFT pupilloplasty was performed following cataract surgery in five patients with angle-closure glaucoma and PAS.[2] By six to eight months postoperatively, all patients had fewer PAS, an open angle, lower IOP, and better visual acuity. "As an adjunct to PAS lysis and to prevent further synechiae development, SFT makes sense theoretically, but it is early in its development," said Dr. Crandall.

Benefits of SFT

Anatomy. "In SFT pupilloplasty, you are not introducing an artificial drainage pathway, as in trabeculectomy or valve placement," said Dr. Agarwal. "Instead, you are enabling function of the existing trabecular meshwork. You are restoring, rather than changing, the anatomy." Dr. Crandall agreed, "It makes physiologic sense as treatment for chronic angle-closure glaucoma."

A simpler knot. Dr. Agarwal said that surgeons who prefer the Siepser slipknot or cerclage can adapt those pupilloplasty maneuvers to treat angle-closure glaucoma. However, Dr. Crandall noted, "SFT is technically easier, less time-consuming, and as effective as other pupilloplasty techniques."

Safety. Dr. Agarwal considers SFT to be safer than multiple-pass pupilloplasty techniques. "When you go for a second or third pass, you are manipulating the anterior chamber, and you can damage the iris and cornea," he said. Additionally, in SFT pupilloplasty, the knot is self-retaining and is not tied, thereby reducing bulk in the anterior chamber.[3]

Considerations

Despite its advantages, SFT pupilloplasty combined with lens removal is not a one-size-fits-all solution for angle-closure disease.

Phakic status. Narang et al. noted that SFT cannot be performed in phakic eyes and that lensectomy should be done in the same surgical session,[3] regardless of whether a visually significant cataract is present. However, this apparent drawback may be counterbalanced by the reported benefits of lens removal in angle-closure glaucoma. Results of a randomized controlled trial demonstrated that clear lens extraction is more efficacious and more cost-effective than laser peripheral iridotomy plus topical medical treatment in patients with primary angle closure and high IOP with or without glaucoma.[4] Nevertheless, some surgeons have questioned the validity of clear lens extraction for angle closure, given the surgical risks and loss of accommodation with lens removal.[5,6]

Inflammation. Because SFT pupilloplasty is an intraocular procedure, inflammation is a concern. "If the patient has fixed pupillary dilation with chronic angle closure in uveitis, SFT may chronically inflame the iris. Additionally, the inflamed eye structures could remain in apposition, so PAS might not be prevented," Dr. Asrani cautioned. "However, benefits of preventing PAS and reducing glare using SFT may have to be balanced with the risk of persisting iritis in such cases."

Tissue tears. "In general, the surgeon should be careful to avoid overtightening the helical knot, which could tear the iris tissue,"[3] said Dr. Agarwal. He added that extreme care should be exercised when performing SFT in eyes with secondary angle-closure glaucoma involving atrophic patches of the iris, such as in Urrets-Zavalia syndrome (UZS).[2] Nevertheless, Dr. Agarwal said that SFT pupilloplasty—performed carefully—does open the angles well in cases of UZS.

Fundus visualization. Dr. Agarwal and his colleagues reported that patients treated with SFT pupilloplasty still can undergo mydriasis, although the extent of pupillary dilation in SFT-treated eyes is less than that in untreated eyes.[7] Dr. Asrani pointed out that decreasing the pupillary opening, by means of SFT pupilloplasty, can limit the examination and treatment of retinal conditions. However, he said, "If the patient needs retinal treatment, the retinal surgeon can snip the SFT suture and reopen the pupil." Dr. Agarwal added that an Nd:YAG laser also could be used to undo the pupilloplasty.

Cosmesis. "In terms of aesthetic results," Dr. Crandall said, "pupillary cerclage is probably better than

SFT. However, cerclage is technically challenging and time-consuming. And although cerclage may appear cosmetically better, it is not functionally better, he said. Moreover, Dr. Agarwal pointed out, "Cerclage is especially difficult to perform in the setting of PAS."

Too late? "If angle-closure glaucoma goes untreated," said Dr. Agarwal, "fibrosis can occur," and SFT pupilloplasty would not be sufficient to normalize aqueous outflow. He noted, "Such patients would need additional medical treatment or even a shunt procedure or trabeculectomy."

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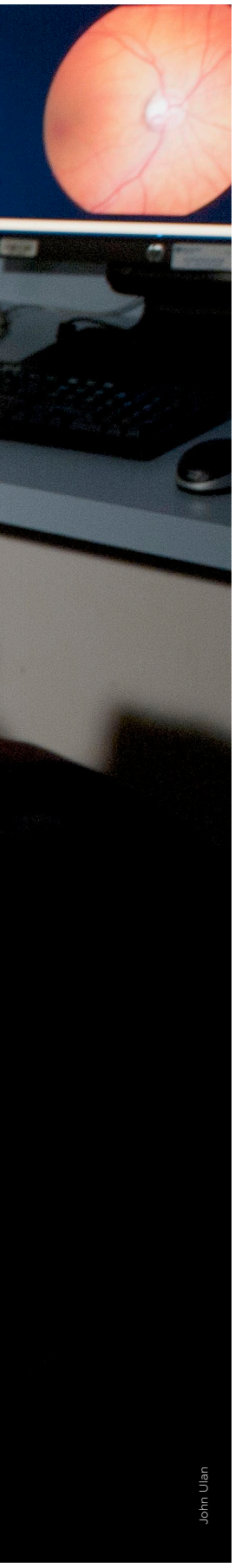
Dr. Crandall is professor and senior vice-chair of ophthalmology and visual sciences and director of glaucoma and cataract at the Moran Eye Center, University of Utah, Salt Lake City. *Financial disclosures: Alcon: C,L; AqueSys: C; ASICO: C; Excel-Lens: C; Glaucoma Research Foundation: C; Glaukos: C; Iantech: C; iSportGames: C; Ivantis: C; iVeena: C; Johnson & Johnson: C; Mastel: C; New World Medical: C; Omeros: C.*

See the disclosure key, page 5.

EXTRA **MORE ONLINE.** Use the QR code below to view a video of the single-pass four-throw pupilloplasty technique, or find a video of the procedure posted with this article at aao.org/eyenet/archive.



John Ulan

The Promise of Teleglaucoma:

Increasing Outreach, Expanding Access to Care

Can teleglaucoma reach patients whom traditional eye care has missed?

By Annie Stuart, Contributing Writer

First you heard of telemedicine, then teleophthalmology. Thanks to an abundance of technology, the evolution continues. Today it takes many forms. Remote screenings can be done at drugstore kiosks and on personal computers and smartphones. And distance management can happen with home-monitoring devices and apps or in optometry offices via real-time or asynchronous consultation with an ophthalmologist. And the options are only proliferating.

Now a band of glaucoma experts is making the concept their own with teleglaucoma. Chronic, progressive, and largely silent, glaucoma poses challenges for patients and eye care providers alike. Teleglaucoma—the use of electronic technologies to remotely find and enhance management of patients with or at risk of glaucoma—has the potential to help ensure continuity of care and preserve vision in an aging population, said Albert S. Khouri, MD, in Newark, New Jersey.

"The patient-physician relationship in glaucoma is really critical," said Karim F. Damji, MD, in Edmonton, Alberta. "But not every patient needs to be seen for everything, and there are smart ways to leverage technology to improve holistic care."

Benefits

Access to care. Teleglaucoma could increase access to eye care for people in medically underserved areas, said Paula Anne Newman-Casey, MD, in Ann Arbor, Michigan. "This includes impoverished populations and people living in rural or remote areas or countries where they wouldn't otherwise have access to medical expertise."

It also offers the potential to shift the paradigm from first-come, first-served to needs based, said Dr. Khouri. "We can develop teleglaucoma standards where patients with more advanced or progressive disease cut the line and are seen first, literally saving the vision of those patients."

Of course, said Dr. Damji, "not all patients are good candidates for teleglaucoma. For example, patients experiencing acute angle-closure glaucoma or those with concomitant mental health issues are better seen in person."

Efficiency and convenience. Patients may appreciate that telemedicine allows them to be seen quickly, rather than waiting months for an appointment in a big eye center, said Dr. Damji. In one northern Alberta program, optometrists work in teleconsultation with a glaucoma specialist to handle ongoing patient management.[1,2]

We can't underestimate the patient's need for convenience, for which some patients may even be willing to pay extra, said Lama A. Al-Aswad, MD, MPH, in New York City. Today, many glaucoma patients must take time off work and spend a couple of hours for testing. "In the future," she said, "home monitoring and ophthalmology kiosks may allow patients greater control over their time."

Cost. As an added benefit, this approach is

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TEACHING. *Dr. Damji leverages remote fundus images when he teaches residents and fellows.*

expected to save money. A cost-effectiveness analysis of teleglaucoma screening in Canada demonstrated that implementing teleglaucoma in rural Alberta and targeting an at-risk population was cost-effective when compared with an in-person exam.[3]

Resident education. Teleglaucoma may also have a superb application in resident education, said Dr. Khouri, who is program director of the ophthalmology residency at Rutgers New Jersey Medical School. "For example, it can make it possible for the attending physician to give direct feedback based on objective data—images and readings—through telemedicine, not just a description over the phone."

Implementation Challenges

Telemedicine has come a long way since it was introduced in the 1960s and '70s, yet in today's Internet-enabled world, teleglaucoma still faces challenges.

A complex disease. Diabetic retinopathy (DR) is ideal for a telemedicine-based approach because it requires only a single modality of imaging for diagnosis, said Dr. Newman-Casey. In contrast, "glaucoma requires multiple imaging modalities and ancillary testing to make a good diagnosis." This includes structural assessment of the optic nerve through photographs or optical coherence tomography (OCT), as well as functional assessment through visual field testing. When evaluating a patient's risk of disease progression and deciding on the ideal treatment regimen, ophthalmologists take into account other parameters as well, such as central corneal thickness, intraocular pressure (IOP), and family history, she said.

"Because the diagnosis and management of glaucoma are more complex, it's more difficult to do remotely," said Dr. Newman-Casey. "That being said, it's not impossible."

Validation and standardization. "If you ask doctors to begin using a new technology," said Michael F. Chiang, MD, in Portland, Oregon, "they will often ask, 'Can you prove to me that I'm going to get the right answer?'" The same holds true for teleglaucoma. "You need to demonstrate that you can get the right diagnosis at a distance."

Notably, teleglaucoma needs "models or standards that are validated for image acquisition, transfer, and interpretation as well as tonometry and structure and function testing," said Dr. Khouri. In addition, agreement is needed on questions such as when to refer patients for follow-up, said Dr. Al-Aswad.

Another challenge? "Sometimes the technology evolves so fast that by the time you construct and complete a clinical trial, the technology has evolved, making the data obsolete," said Dr. Khouri, who is currently conducting a clinical trial at Rutgers to compare findings from teleglaucoma evaluations (visual acuity, tonometry, optic nerve, and OCT readings) to a standard clinical exam.[4]

Medical liability. Another need is clear-cut regulation. "There is a range of liability issues in telemedicine, including HIPAA and confidentiality concerns," said Dr. Khouri, "and all of these need to be sorted out for the field to progress." An umbrella license for telemedicine is also urgent, added Dr. Al-Aswad, who cited her inability to read images of New Jersey patients when her mobile eye van crosses into that state from New York, where she has her practice.

Reimbursement. Widespread adoption of teleglaucoma also won't happen without legislation concerning reimbursement, said Dr. Al-Aswad.

"An ongoing challenge of telemedicine in the United States is reimbursement, which has been limited, particularly for the store-and-forward models that are most common in ophthalmology," said Dr. Chiang. Dr. Newman-Casey noted that the reimbursement code used for picture-based store-and-forward screening or diagnosis is not enough to cover the equipment or services provided. "However," she said, "this is now undergoing scrutiny as the patient's burden for monitoring chronic disease becomes more apparent."

To improve reimbursement models for telemedicine, said Dr. Chiang, "we'll need evidence of diagnostic accuracy to demonstrate for providers that these technologies work, evidence of cost-effectiveness to demonstrate for payers that they should be covered, and discussion with policymakers, which the Academy has been involved with. In some diseases like DR and retinopathy

John Ulan

of prematurity, there is fairly extensive literature demonstrating diagnostic accuracy and cost-effectiveness. For other diseases, there has been far less work."

Reimbursement needs to be carefully thought out, Dr. Newman-Casey pointed out. "We don't want to incentivize patients to not come in to see their provider when it's important that they do so. We want to have some contact with people to make sure they're not having trouble taking their medications—that cost and side effects aren't a barrier and that they know how to put eyedrops in."

Continuity of care. In fact, lack of follow-up and face-to-face contact can be one of the biggest challenges with teleglaucoma, said Dr. Khouri. "Once you identify patients through screening, many may not present back to doctors for continuity of care." However, he said, continued improvements in technology may help remove some of these obstacles. For example, telepresence now allows a remote physician to have access to data in real time. "With synchronous audiovisual communication, you can more comfortably evaluate the patient and make recommendations," he said.

An Array of Teleglaucoma Models

Teleglaucoma has multiple arms, said Dr. Al-Aswad. In addition to synchronous and asynchronous relay of data, a variety of models can be used for screening and management.

Screening. Given that more than 50% of Americans with glaucoma don't know they have the disease,[5] screening may be the lower-hanging fruit for teleglaucoma. "With effective tools, teleglaucoma has the potential to detect the disease early, which is critically important given that severe damage can occur despite a lack of symptoms," said Felipe A. Medeiros, MD, PhD, in Durham, North Carolina.

One model is consultation-based telehealth. For example, a rural ophthalmologist might remotely collect data to transmit to the nearest glaucoma subspecialist, said Dr. Chiang.

Another model is community-based screening. Dr. Al-Aswad and her team have developed a real-time (synchronous) teleophthalmology program in New York City, where they use a mobile van to screen individuals for the four leading causes of blindness, including glaucoma. This includes video consultation with an eye care provider. (See sidebar, "An Urban Model for Teleophthalmology.") Densely populated areas like this can help facilitate community-based screening, said Dr. Newman-Casey.

Dr. Khouri and his team have also developed and reported on a protocol to detect eye disease in high-risk populations in Newark and other parts of New Jersey.[6,7] "Our teleophthalmology protocols rely on high-resolution imaging and software filters that enhance the detection of vision-threatening diseases," said Dr. Khouri. "Imaging the ganglion cell and nerve fiber layers is important in the early detection of glaucoma. We do screening events at soup kitchens, community centers, churches, temples, and mosques. When we identify patients with pathology, we make recommendations and refer patients to the university hospital for management."

Monitoring. Another strength for telemedicine is monitoring. "As long as we have effective teleglaucoma methods to monitor these patients, they don't need to be coming to the hospital all the time for follow-up," said Dr. Medeiros. An alternative is to have a trained technician conduct tests on glaucoma suspects or patients who are stable, a method that has been piloted in the United Kingdom.[8] "The physician then reviews the data online, reports and signs off, and alternates a virtual visit with an in-person visit," said Dr. Damji.

Home monitoring. "I think the future of teleglaucoma is patients becoming active participants in monitoring their disease," said Dr. Al-Aswad. "I envision that the patient will do home testing—measuring IOP and visual fields, for example—and transmit that data to me. If the patient is stable, I will only see him or her once a year."

Dr. Al-Aswad refers to a study she was involved in using home tonometry to understand disease progression and fluctuation of IOP. Home testing allowed her to spot and treat high IOP in a patient whose test results in the office had all appeared normal.

There are still lots of logistics to work out with home monitoring, said Dr. Chiang. Should patients self refer or be responsible for calling their doctor if their pressure is above a certain cutoff? Or should the data automatically trans-

John Ulan

GRADING. *Dr. Damji in the process of teleglaucoma grading.*

mit to some central service and flag the system if there is a concern?

Information overload is another risk with home monitoring. "You can get an overwhelming amount of data with a lot of noise built in," said Dr. Khouri. "But as the technology improves, you will be able to filter out the noise. Or with a product such as iCare HOME, for example, you could ask patients to monitor once a day or customize testing, as needed."

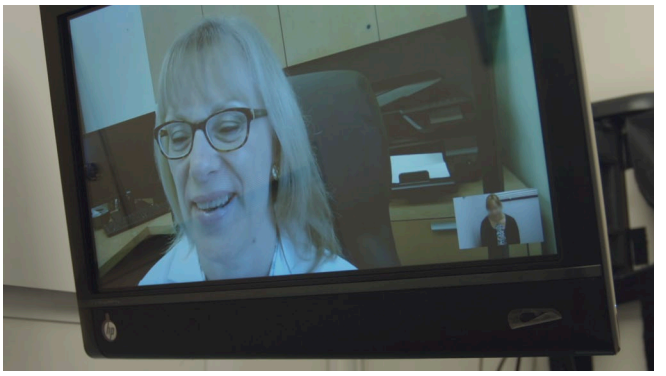
Collaborative care. Shared management, another model, can take several forms.

ODs. In Northern Alberta, we've developed shared-care guidelines,[9] said Dr. Damji. "We collaborate with a large network of optometrists, who manage the patient on the front line. They provide us with structured information, using an asynchronous, store-forward system. We then provide feedback on the particular patient based on the history, exam, and testing, and we advise how soon a patient needs to be seen."

Techs. In Atlanta, April Maa, MD, has created and implemented a collaborative screening program called Technology-Based Eye Care Services, which allows the Veterans Affairs to reach underserved veterans. A trained ophthalmology technician is stationed in a primary care clinic. This person follows a detailed protocol to collect information about the patient's eyes, which is then interpreted remotely. Patients with likely abnormal findings are scheduled for a face-to-face exam in the eye clinic.[10]

Dr. Newman-Casey said she thinks this model works well because screening doesn't take up much space in the family practice office and nonophthalmic staff members aren't expected to capture the ocular data. "If this model were expanded to provide glaucoma monitoring in low-risk patients, the ophthalmic technicians' role could be expanded to provide glaucoma education as well," she said.

SCREENING. *A patient is examined in Dr. Al-Aswad's mobile unit.*



CONSULTING. *In Dr. Al-Aswad's mobile unit, a physician at an academic center speaks with a patient.*

Portable Technologies

A variety of types of portable technologies are being developed for remote screening and monitoring of glaucoma. "It's incumbent upon us to test these devices more thoroughly before rolling them out for patient care," said Dr. Newman-Casey. "I would love to see industry take a greater role in validating new instruments in the population in which they'll be used."

Portable cameras. In fact, Dr. Newman-Casey recently conducted an instrument validation study in Nepal to compare the reliability of information that clinicians could obtain from either a traditional tabletop fundus camera or a portable, lightweight, less expensive fundus camera that requires no dilation. The researchers found no clinically significant difference in reliability between the two cameras.[11] "This lays the groundwork for using the portable camera as part of population-based screening for glaucoma," said Dr. Newman-Casey.

Smartphones. Smartphones are another way to visualize the optic nerve. When equipped with special lenses, they can get very good pictures of the back of the eye, said Dr. Medeiros.[12]

"I can foresee the day where patients can obtain a selfie of their own eyes," added Dr. Damji, "and obtain more than just structural information. The device could take photographs of the front and back of the eyes, assist in visual acuity/visual field and eventually other aspects of testing, and provide a template for structured history taking. The patient could then send all this data through a patient electronic portal into an artificial intelligence (AI) filter and then very quickly receive feedback from an eye care professional."

Tablets. "There's also the potential to use the portable camera on a tablet in conjunction with perimetry software, such as the iPad-based Visual Fields Easy App, which is being used in Nepal," said Dr. Newman-Casey. (On the computer, Peristat is a free, web-based visual field test that can be used on monitors 17 inches or larger.)

Lama A. Al-Aswad, MD, MPH

The iCare HOME tonometer can be connected to a tablet, thus making it possible for that data to be transmitted to your office, something that Dr. Al-Aswad is doing with her patients.

Virtual reality goggles. Taking the next step in technology, Dr. Medeiros' lab has done an initial validation of a portable approach using virtual reality goggles to assess visual field defects. Called the nGoggle, it consists of a brain-computer interface that uses a wireless, dry electroencephalogram, electrooculogram systems, and a head-mounted display.[13] (See "The New World of Virtual Reality," *EyeNet*, October 2018.)

"We have optimized the nGoggle's algorithm for testing and incorporated eye tracking to better detect loss of fixation and ensure testing reliability," said Dr. Medeiros. He hopes to soon begin studies to validate the home-based application.

Artificial Intelligence

Dr. Medeiros is also working with AI. He predicts that AI will be implemented in primary care practices for opportunistic screening of eye diseases within the next five years. "The future is AI and doctors working together to provide better care for our patients," said Dr. Al-Aswad. "It will help us practice at the top of our license, manage disease, and prevent blindness—not replace us."

Optic disc photos. "A model that excites me is the Pegasus system," said Dr. Damji. The retinal analysis decision support system can provide quick grading of the nerve and additional aspects for DR, he said. "Using deep learning, it has the potential to develop a comparable ability in assessing optic disc photographs for glaucoma."

Using OCT to train AI. One challenge in using AI to evaluate fundus photographs for glaucoma, said Dr. Medeiros, is that an AI algorithm—when taught by using human-based grading as reference—will simply replicate the doctors' errors, which are especially common in the early stages of the disease. "We know that ophthalmologists, even glaucoma specialists, tend to perform poorly when trying to detect glaucoma based on a photograph of the optic disc. Therefore, an AI algorithm trained on that is not going to be different," he said.

"An alternative is to use an objective instrument such as OCT, which can give us a much more accurate, precise, and quantifiable assessment of structure," said Dr. Medeiros. "An AI algorithm trained to predict OCT measures from optic disc photographs can give you a quantitative and precise measurement of the amount of nerve damage." Dr. Medeiros and his team have used

An Urban Model for Teleophthalmology

Between 2007 and 2014, Dr. Al-Aswad conducted a screening program in high-risk communities of New York City—and did so without the help of teleglaucoma. "Whether or not they had insurance, 57% had never previously been seen by an eye doctor, which was astonishing to me," she said.

MOBILE UNIT. *Dr. Al-Aswad's mobile center brings screening for glaucoma and other blinding conditions to at-risk communities in the New York area.*

This became the seed for what she and her team ultimately built—telemedicine to screen for leading causes of blindness in high-risk, poor communities in the city. "In 12 months, we've screened close to 1,300 individuals for the four leading causes of blindness," said Dr. Al-Aswad.

It took two to three years to build the program, which included creating the team, acquiring a mobile unit with state-of-the-art equipment for ophthalmology, building a data-capturing system, and ensuring connectivity and security. The free screening includes visual fields, anterior and posterior segment OCT images of the optic nerve, and retina and fundus photographs of the retina.

Recently, Dr. Al-Aswad collaborated with GlobeChek to add the first GlobeChek kiosk to her screening program. "In addition, we screen for comorbidities of eye disease, checking hemoglobin A_{1C}, blood pressure, and body mass index," said Dr. Al-Aswad. "After the technicians complete the screening, the individuals go to a private area in the mobile unit, where they have a videoconference with an ophthalmologist or optometrist to discuss the results."

The eye care physician then gives a recommendation for follow-up. "If it's an emergency, like angle-closure glaucoma, we send them directly to an ER at a safety net hospital," she said. "If it's not an emergency, we send them to the community ophthalmologist or optometrist in their area. This has not only been helpful to the patients, but we're also learning a lot about these eye diseases."

Lama A. Al-Aswad, MD, MPH

more than 30,000 pairs of optic disc photos and spectral-domain OCT (SD-OCT) retinal nerve fiber layer retinal (RNFL) scans to train AI to assess the photos and predict the actual estimate of nerve damage.[14] "In a validation study, we found a very strong correlation between the predicted and observed RNFL thickness values—between what the AI algorithm could see in the photo and the SD-OCT result," said Dr. Medeiros.

Although the researchers have not yet implemented this AI approach in a teleglaucoma setting, Dr. Medeiros is optimistic about its potential. An AI algorithm trained this way to assess optic nerve damage from photographs would be much less expensive than an OCT system and, therefore, potentially suitable for large-scale deployment, he added. "Because it provides a quantitative estimate of nerve damage—not just a 'yes' or 'no' diagnosis—it may also be used for monitoring over time," he said, adding that the algorithm has not yet been tested for this kind of follow-up.

More is better? Currently, most AI models rely on either optic nerve head photos or OCTs to determine pathology, said Dr. Khouri. "But, in time, I predict they will integrate both structure and function, and the accuracy of detection will be even better."

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EXTRA **MORE ONLINE.** See this article at aao.org/eyenet/archive for a sidebar on prerequisites for a successful teleglaucoma program.

MEET THE EXPERTS

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Felipe A. Medeiros, MD, PhD Professor of ophthalmology at Duke University, vice chair for technology and director of clinical research at the Duke Eye Center, and director of the Duke Visual Performance Laboratory, all in Durham, N.C. *Relevant financial disclosures: Carl-Zeiss Meditec: S; Heidelberg Engineering: S; Ngoggle Diagnostics: P; Reichert: S.*

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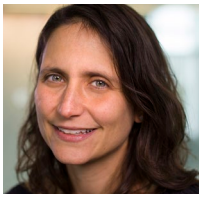

See the disclosure key, page 5. **For full disclosures,** see this article at aao.org/eyenet/archive.

Rocklatan® (netarsudil and latanoprost ophthalmic solution) 0.02%/0.005%
Rx Only

BRIEF SUMMARY
Consult the Full Prescribing Information for complete product information.

INDICATIONS AND USAGE
Rocklatan® (netarsudil and latanoprost ophthalmic solution) 0.02%/0.005% is indicated for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.

DOSAGE AND ADMINISTRATION
The recommended dosage is one drop in the affected eye(s) once daily in the evening.

If one dose is missed, treatment should continue with the next dose in the evening. The dosage of Rocklatan® should not exceed once daily. Rocklatan® may be used concomitantly with other topical ophthalmic drug products to lower IOP. If more than one topical ophthalmic drug is being used, the drugs should be administered at least five (5) minutes apart.

CONTRAINDICATIONS
None.

WARNINGS AND PRECAUTIONS
Pigmentation
Rocklatan® contains latanoprost which has been reported to cause changes to pigmented tissues. The most frequently reported changes have been increased pigmentation of the iris, periorbital tissue (eyelid), and eyelashes. Pigmentation is expected to increase as long as latanoprost 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, pigmentation of the iris is likely to be permanent, while pigmentation of the periorbital tissue and eyelash changes have been reported to be reversible in some patients. Beyond 5 years the 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 Rocklatan® can be continued in patients who develop noticeably increased iris pigmentation, these patients should be examined regularly.

Eyelash Changes
Rocklatan® contains latanoprost which may gradually change eyelashes and vellus hair in the treated eye; these changes include increased length, thickness, pigmentation, the number of lashes or hairs, and misdirected growth of eyelashes. Eyelash changes are usually reversible upon discontinuation of treatment.

Intraocular Inflammation
Rocklatan® contains latanoprost which 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 because it may exacerbate inflammation...

Macular Edema
Macular edema, including cystoid macular edema, has been reported during treatment with latanoprost. Rocklatan® 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.

Herpetic Keratitis
Reactivation of Herpes Simplex keratitis has been reported during treatment with latanoprost. Rocklatan® should be used with caution in patients with a history of herpetic keratitis. Rocklatan® should be avoided in cases of active herpes simplex keratitis because it may exacerbate inflammation.

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

Use with Contact Lenses
Contact lenses should be removed prior to the administration of Rocklatan® and may be reinserted 15 minutes after administration.

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

Rocklatan®
The most common ocular adverse reaction observed in controlled clinical studies with Rocklatan® was conjunctival hyperemia which was reported in 59% of patients. Five percent of patients discontinued therapy due to conjunctival hyperemia. Other common ocular adverse reactions reported were: instillation site pain (20%), corneal verticillata (15%), and conjunctival hemorrhage (11%). Eye pruritus, visual acuity reduced, increased lacrimation, instillation site discomfort, and blurred vision were reported in 5-8% of patients.

Other adverse reactions that have been reported with the individual components and not listed above include:

Netarsudil 0.02%
Instillation site erythema, corneal staining, increased lacrimation and erythema of eyelid.

Latanoprost 0.005%
Foreign body sensation, punctate keratitis, burning and stinging, itching, increased pigmentation of the iris, excessive tearing, eyelid discomfort, dry eye, eye pain, eyelid margin crusting, erythema of the eyelid, upper respiratory tract infection/nasopharyngitis/influenza, photophobia, eyelid edema, myalgia/arthralgia/back pain, and rash/allergic reactions.

DRUG INTERACTIONS
Although specific drug interaction studies have not been conducted with Rocklatan®, in vitro studies have shown that precipitation occurs when eye drops containing thimerosal are mixed with latanoprost ophthalmic solution 0.005%. If such drugs are used, they should be administered at least five (5) minutes apart.

The combined use of two or more prostaglandins or prostaglandin analogs including latanoprost ophthalmic solution 0.005% is not recommended. It has been shown that administration of these prostaglandin drug products more than once daily may decrease the IOP lowering effect or cause paradoxical elevations in IOP.

USE IN SPECIFIC POPULATIONS
Pregnancy
There are no available data on netarsudil ophthalmic solution use in pregnant women to inform any drug associated risk; however, systemic exposure to netarsudil from ocular administration is low. Intravenous administration of netarsudil to pregnant rats and rabbits during organogenesis did not produce adverse embryofetal effects at clinically relevant systemic exposures.

Animal Data
Netarsudil administered daily by intravenous injection to rats during organogenesis caused abortions and embryofetal lethality at doses ≥0.3 mg/kg/day (126-fold the plasma exposure at the RHOD, based on C_{max}). The no-observed-adverse-effect-level (NOAEL) for embryofetal development toxicity was 0.1 mg/kg/day (40-fold the plasma exposure at the RHOD, based on C_{max}).

Netarsudil administered daily by intravenous injection to rabbits during organogenesis caused embryofetal lethality and decreased fetal weight at 5 mg/kg/day (1480-fold the plasma exposure at the RHOD, based on C_{max}). Malformations were observed at ≥3 mg/kg/day (1330-fold the plasma exposure at the RHOD, based on C_{max}), including thoracogastroschisis, umbilical hernia and absent intermediate lung lobe. The NOAEL for embryofetal development toxicity was 0.5 mg/kg/day (214-fold the plasma exposure at the RHOD, based on C_{max}).

For latanoprost, in 4 of 16 pregnant rabbits, no viable fetuses were present at a dose that was approximately 80 times higher than the RHOD. Latanoprost did not produce embryofetal lethality in rabbits at a dose approximately 15 times higher than the RHOD.

Lactation
There are no data on the presence of netarsudil or latanoprost in human milk, the effects on the breastfed infant, or the effects on milk production. However, systemic exposure to netarsudil following topical ocular administration is low, and it is not known whether measurable levels of netarsudil would be present in maternal milk following topical ocular administration. It is also not known whether latanoprost or its metabolites are excreted in milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Rocklatan® and any potential adverse effects on the breastfed child from netarsudil and latanoprost.

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

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

NONCLINICAL TOXICOLOGY
Carcinogenesis, Mutagenesis, Impairment of Fertility
Long-term studies in animals have not been performed to evaluate the carcinogenic potential of netarsudil. Netarsudil was not mutagenic in the Ames test, in the mouse lymphoma test, or in the *in vivo* rat micronucleus test. Studies to evaluate the effects of netarsudil on male or female fertility in animals have not been performed.

Latanoprost was not carcinogenic in either mice or rats when administered by oral gavage at doses of up to 170 mcg/kg/day (approximately 2800 times the recommended maximum human dose) for up to 20 and 24 months, respectively. Latanoprost was not mutagenic in bacteria, in mouse lymphoma, or in mouse micronucleus tests. Chromosome aberrations were observed in vitro with human lymphocytes. Additional *in vitro* and *in vivo* studies on unscheduled DNA synthesis in rats were negative. Latanoprost has not been found to have any effect on male or female fertility in animal studies.

For additional information, refer to the full prescribing information at www.Rocklatan.com.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit MedWatch or call 1-800-FDA-1088.

aerie®
Pharmaceuticals, Inc.

Manufactured for: Aerie Pharmaceuticals, Inc., Irvine, CA 92614, U.S.A.

ONCE-DAILY
rocklatan®
(netarsudil and latanoprost ophthalmic solution) 0.02%/0.005%

Superior efficacy. Optimal simplicity.[1,2]

Once-daily Rocklatan® significantly lowers IOP in patients with open-angle glaucoma or ocular hypertension—superior to latanoprost and netarsudil at every measured timepoint in phase 3 clinical trials.[1,2]

The first and only once-daily fixed-dose combination of prostaglandin + ROCK inhibitor

IOP — Nearly 60% of Rocklatan® patients achieved a target pressure of 16 mmHg or less[2]

The majority of ocular adverse events were mild and tolerable, with minimal systemic adverse events[1,3]

QD — Once-daily dosing relieves treatment burden and may improve adherence and treatment outcomes[1,4]

IOP: intraocular pressure; ROCK: rho kinase

Visit Rocklatan.com to learn more about this innovative drop for elevated IOP

IMPORTANT SAFETY INFORMATION

Contraindications
None.

Warnings and Precautions
- Pigmentation changes
- Eyelash changes
- Intraocular inflammation
- Macular edema
- Herpetic keratitis
- Bacterial keratitis
- Contact lens wear

Adverse reactions
Rocklatan®: The most common ocular adverse reaction is conjunctival hyperemia (59%). Five percent of patients discontinued therapy due to conjunctival hyperemia. Other common ocular adverse reactions were: instillation site pain (20%), corneal verticillata (15%), and conjunctival hemorrhage (11%). Eye pruritus, visual acuity reduced, increased lacrimation, instillation site discomfort, and blurred vision were reported in 5-8% of patients.

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Please see brief summary on the adjacent page.

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aerie Pharmaceuticals, Inc.