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IMPORTANT PRODUCT INFORMATION

CAUTION: FEDERAL (USA) LAW restricts this device to sale by or on the order of a physician.

INDICATION: The CyPass® Micro-Stent is indicated for use in conjunction with cataract surgery for the reduction of intraocular pressure (IOP) in adult patients with mild to moderate primary open-angle glaucoma (POAG).

CONTRAINDICATIONS: Use of the CyPass Micro-Stent is contraindicated in the following circumstances or conditions: (1) in eyes with angle-closure glaucoma; and (2) in eyes with traumatic, malignant, uveitic, or neovascular glaucoma or discernible congenital anomalies of the anterior chamber angle.

MRI INFORMATION: The CyPass Micro-Stent is magnetic resonance (MR) Safe: the implant is constructed of polyimide material, a non-conducting, non-metallic, non-magnetic polymer that poses no known hazards in all magnetic resonance imaging environments.

WARNINGS: Gonioscopy should be performed prior to surgery to exclude peripheral anterior synechiae (PAS), rubeosis, and other angle abnormalities or conditions that would prohibit adequate visualization of the angle that could lead to improper placement of the stent and pose a hazard.

PRECAUTIONS: The surgeon should monitor the patient postoperatively for proper maintenance of intraocular pressure. The safety and effectiveness of the CyPass Micro-Stent has not been established as an alternative to the primary treatment of glaucoma with medications, in patients 21 years or younger, in eyes with significant prior trauma, chronic inflammation, eyes with an abnormal anterior segment, eyes with chronic inflammation, eyes with glaucoma associated with vascular disorders, pseudophakic eyes with glaucoma, eyes with uveitic glaucoma, eyes with pseudoxfoliative or pigmentary glaucoma, eyes with other secondary open-angle glaucomas, eyes that have undergone prior incisional glaucoma surgery or cilioablative procedures, eyes with laser trabeculoplasty performed ≤ 3 months prior to the surgical screening visit, eyes with unmedicated IOP less than 21 mmHg or greater than 33 mmHg, eyes with medicated IOP greater than 25 mmHg, in the setting of complicated cataract surgery with iatrogenic injury to the anterior or posterior segment, and when implantation is without concomitant cataract surgery with IOL implantation for visually significant cataract. The safety and effectiveness of use of more than a single CyPass Micro-Stent has not been established.

ADVERSE EVENTS: In a randomized, multicenter clinical trial comparing cataract surgery with the CyPass Micro-Stent to cataract surgery alone, the most common postoperative adverse events included: BCVA loss of 10 or more letters at 3 months after surgery (8.8% vs. 3.8%); worsening of visual field mean deviation by 2.5 or more decibels (6.7% vs. 9.9%); IOP increase of 10 or more mmHg 30 or more days after surgery (4.3% vs. 2.3%); and corneal edema 30 or more days after surgery, or severe in nature (3.5% vs. 1.5%).

ATTENTION: PLEASE REFER TO THE INSTRUCTIONS FOR A COMPLETE LIST OF CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, AND ADVERSE EVENTS.
LASER-ASSISTED CATARACT SURGERY IN THE GLAUCOMA PATIENT

LASER CATARACT SURGERY: OPPORTUNITIES & CHALLENGES · Robert Noecker, MD
TIPS TO IMPROVE COMPLIANCE AND PATIENT SATISFACTION · Inder Paul Singh, MD
MONITORING GLAUCOMA PROGRESSION WITH OCT · Christopher Leung, MD
CHALLENGES & UNMET NEEDS IN GLAUCOMA THERAPY · Eydie Miller-Ellis, MD
CLEAR LENS EXTRACTION IN ANGLE CLOSURE DISEASE · Sunee Chansangpetch, MD & Shan C. Lin, MD
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New Trends in Cataract Surgery

MIGS and other procedures are changing the landscape of glaucoma management & treatment

In this issue of *Glaucoma Physician*, we expand into new areas, looking to build upon the information presented in the inaugural issue in March. We are entering a unique time in the world of glaucoma. Never before have there been so many new advances happening simultaneously in the medical, surgical, and diagnostic areas.

At the American Society of Cataract and Refractive Surgery meeting in Los Angeles last month, it was striking to see how much interest there was in glaucoma. Glaucoma subspecialty day seemed to offer more new information than ever before. Advances in office-based testing allow us to see and evaluate structures of the eye as they relate to glaucoma better than ever. Efforts are under way to validate technologies, such as electrophysiology and imaging of the angle. Laser treatments continue to evolve into gentler, less side effect-prone procedures. Surgical therapies are tapping into new pathways for increasing outflow safely.

Glaucoma surgery, especially performed in conjunction with cataract surgery, is no longer considered a last-ditch option after the patient has failed every other therapeutic pathway. New MIGS devices have changed both the risk profile of glaucoma surgery and surgeons’ perceptions of whether it is wise to do in conjunction with cataract surgery.

It is widely accepted that performing cataract surgery alone in a patient with early glaucoma tends to have a favorable effect on IOP control, at least for a while. Performing a MIGS procedure with iStent (Glaukos) or CyPass (Alcon), for example, or using goniotomy with the Trab360 device (Sight Sciences), Kahook Dual Blade (New World Medical), or endoscopic cyclophotocoagulation increases the probability of success in achieving a certain lower target IOP. Xen (Allergan) offers a way to achieve filtration-level IOPs without the trauma of traditional techniques. With these less traumatic procedures, there is less visual downtime and recovery required compared with traditional glaucoma surgery.

Just as we have done with glaucoma medical and office-based laser therapy, we now can customize the treatment plan to fit each patient’s profile. Those who have some trabecular function may benefit from a canal-based procedure that continues to use the enhanced dominant natural pathway. On the other hand, if that pathway is too compromised, we can go a whole new direction and shunt aqueous into the suprachoroidal space with a CyPass or into the subconjunctival space with Xen.

The other trend we are seeing in cataract surgery is the movement toward premium options for patients. More patients, especially those with glaucoma, are interested in having their astigmatism corrected or their near vision enhanced through toric, accommodating, or multifocal IOLs. In the past, we would be much more hesitant to combine surgery in patients pursuing one of these options. However, with the introduction of MIGS, combined surgery with premium options can have excellent outcomes.

In this issue, we explore the role of laser cataract surgery in the glaucoma patient. This technology presents both opportunities and challenges in this population.

It is, indeed, an exciting time in glaucoma.

Dr. Noecker specializes in the medical, laser, and surgical management of glaucoma and cataracts at Ophthalmic Consultants of Connecticut.
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Cataract surgery in the glaucoma population tends to be more difficult than conventional cataract surgery in many cases. There is a higher incidence of patients with small pupils. There are more patients with shallow anterior chambers. There is a higher rate of patients with small hyperopic eyes. Mature lenses are also frequently encountered. Pseudoexfoliation is present in glaucoma patients at a higher rate than in the non-glaucoma population. Problems with zonular integrity occur more frequently in this group, along with poor pupil dilation.

Many glaucoma patients have had prior surgery — either glaucoma or otherwise. Patients with prior intraocular surgery tend to have lower corneal endothelial cell counts, and patients who have undergone prior filtering surgery often have relatively high levels of astigmatism.

Traditional cataract surgery alone has a number of limitations in efficacy and safety, which can impact surgeon confidence. Complications in cataract surgery are currently 10 times that of LASIK, and predictability of visual outcomes is only half that of LASIK. Endothelial cell loss, vitreous loss, cystoid macular edema, endophthalmitis, and retinal detachment are risks associated with surgery. Also, improvements are needed in astigmatic correction, predictability of effective lens position, and presbyopic correction.\(^1,2\)

**Benefits and Considerations**

In laser-assisted cataract surgery, the phaco machine is still used to remove the lens, but studies\(^3\) show the laser can facilitate the procedure when used to make the capsulorhexis, corneal incisions, arcuate incisions, and can soften the nucleus.

The technology that makes femtosecond laser-assisted cataract surgery possible is the real-time OCT imaging of the anterior segment of the eye. The laser systems provide an image of the cornea, iris, and lens. This imaging allows for accurate placement of the laser incisions and provides information about anatomical placement not previously available in cataract surgery.\(^4\)

Laser cataract surgery provides some significant advantages over traditional phacoemulsification techniques. Studies\(^5\) have shown that the anterior capsulotomy can be up to 10 times more precise than one created manually. The laser fragments the lens and softens the nucleus, which can significantly reduce the amount of ultrasound energy needed to remove the nucleus. Arcuate incisions for astigmatism correction can be very accurate and provide for very precise control of the depth, location, and length of the incisions. It is also possible to create intrastromal incisions.\(^6\)

The corneal incisions used for the phacoemulsification portion of the case can be created with the laser in a very efficient manner. Because these incisions can be configured in real time in terms of location, length, and multiple dimensions, the end result can be better architecture and reproducibility compared with manually created incisions. Because the tissue planes are cleaner, the incisions may seal better as well.

In terms of economics, patients usually pay for a cataract procedure in which a femtosecond laser is used. Cost safe harbors are those situations in which a refractive IOL is used, as the more precise capsulorhexis can aid in IOL placement.
positioning. The other scenario that justifies the use of the laser is the presence of astigmatism, which supports a need for astigmatic incisions.

Another general concern is that of the incomplete capsulorhexis, though newer software decreases this risk compared with earlier versions. At the beginning of the phacoemulsification portion of the case, the surgeon should evaluate the continuous capsulorhexis edge and use a cystotome or forceps to confirm completion. The surgeon should not hydrodissect until confirmed complete or a radial tear may develop. If incomplete, the capsulorhexis can be completed with forceps or cystotome.

Another risk in laser-assisted cases is capsular block syndrome. This is more likely due to perfectly round capsulotomy, which results in no specific point for fluid to escape. “Fluffed-up” cortex at the capsulotomy edge may block fluid egress. Bubbles in the capsular bag already create intralenticular pressure and, as a result, excessive hydrodissection should be avoided.

In eyes with small pupils due to pseudoexfoliation or other pathology, several considerations should be taken into account. Maximal preoperative dilation should be achieved. For example, 10% phenylephrine should be used for poorly dilating pupils. Preoperative NSAIDs may help to maintain dilation during the laser and phacoemulsification portions of the procedure.

During the laser portion of the case, the capsule diameter should be adjusted down to avoid coming within 0.5 mm of the iris, because laser application near the iris can cause further papillary constriction. The time lapse between the laser and phacoemulsification portions of the case should be minimized. Intraoperative Omidria (Omeros) should be considered to maintain and possibly dilate the pupil further.

Glaucomatous eyes that have undergone prior surgery present a challenge to using the femtosecond laser. There are concerns that preexisting filtering blebs can be traumatized by the suction and contact with the laser system. Remarkably, this does not seem to occur and blebs are left intact after the femtosecond laser phase of the procedure. The more common problem is in the context of large, overhanging filtering blebs that can interfere with achieving suction of the laser onto the cornea. The laser system can compress the bleb enough to achieve suction and fixation, but it is not uncommon to need extra manipulations to proceed.

Another issue that pertains to filtering surgery is the incidence of subconjunctival hemorrhage after the laser portion of the case. There are theoretical concerns that the conjunctival hemorrhage may result in trauma to the conjunctiva and buttonholes if filtering surgery is performed at the same time; however, this seems to be a low occurrence event. The hemorrhage may affect the amount of blood at the time of filtering surgery, but does not seem to impact the performance of the case or outcomes after surgery.

Subconjunctival hemorrhage does not appear to be an issue when performing a glaucoma drainage device tube procedure at the same time as the laser-assisted portion of the case. There may be more inflammation of the conjunctiva at the time of surgery, but there is no alteration in the integrity of the conjunctiva.

Another concern is whether a prior tube changes the effect of the laser. The femtosecond laser appears capable of working through a tube that is slightly long. If the tube is directly on top of the lens capsule, the capsulorhexis
Laser-assisted cataract surgery requires additional planning if the procedure is to be performed in combination with angle-based surgery.

refractive outcome must be considered. MIGS devices, such as the iStent (Glaukos) or CyPass (Alcon), appear to cause minimal changes on the astigmatism correction calculations. This holds true for related procedures, such as angle procedures (e.g., goniotomy), ab interno canalo-plasty, or endoscopic cyclophotocoagulation. The latter group of procedures can cause some bleeding, inflammation, or corneal edema that may slightly delay optimal visual recovery.

More aggressive IOP-lowering procedures, such as filtering procedures using the Ex-Press (Alcon) shunt or a trabeculectomy, are more likely to induce refractive changes and cylinder than the MIGs procedures. Any glaucoma procedures that require suturing near the limbus induce the change of cylinder being introduced. Therefore, minimal suturing techniques are preferred in astigmatism-reduction cases.

The same holds true for cases with early IOP lowering. Certain procedures, such as trabeculectomy, are more likely to result in low IOP early in the post-op course. As a result, there may be a hyperopic shift that occurs in the refractive error. If there is anterior segment shallowing with a shift in IOL position, there may be a myopic shift in refraction.

Careful Planning

If the IOP is expected to be much lower after surgery, the effect of significant IOP lowering should be taken into account in the preoperative calculations. For this reason, MIGS procedures or MIGS-like procedures that create dramatic IOP changes are preferred, if possible. An advantage of the laser-created capsulorhexis in this situation is that the IOL is less likely to shift out of its position in the capsular bag, due to the preciseness of the opening created.

Laser-assisted cataract surgery also requires additional planning if the procedure is to be performed in combination with angle-based surgery. The presence of arcuate incisions can alter the view of the angle when gonioscopy is performed. Arcuate placement planning should be done to move the incision away from the temporal aspect of the cornea so the view is compromised the least. This may mean that a larger nasal arcuate incision is placed versus two separate temporal and nasal arcuate incisions.

Care must be taken in planning the placement of temporal clear corneal incisions if angle surgery is to be done, as well. The laser-assisted incisions tend to seal a bit tighter than manual incisions and may result in a bit more local edema around the incision. These incisions can, at times, be more anterior in location than a manual incision. Therefore, careful pre-op planning should be done to ensure that the temporal incision does not significantly alter the view of the angle with the gonioscopy lens.

If it does appear that the incision created with the laser may be anterior or tight, consider performing the angle-based glaucoma procedure before the phacoemulsification portion of the case. This way, the view may be better and the MIGS procedure may be performed more easily. There does not seem to be any adverse effect on either portion of the procedures if the angle based surgery is performed first. The only drawback may be that the view of the angle isn’t as open as it would be after the cataract is removed.

The other factor than can affect visualization is the presence of air bubbles created from the laser portion of the case. Use of viscoelastic to push the bubbles aside is important but in some instances, additional bubbles rise into the anterior chamber from the lens. If the gonioscopic procedure is performed

continued on page 27
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Like many of my colleagues, I find compliance to be a huge hurdle in the management of glaucoma patients. It is difficult, if not impossible, to keep them on track. Consider all that they face:

• Needing medication for the rest of their lives
• Waiting at the pharmacy to receive prescribed medications
• Paying an office copay every 3 to 4 months
• Undergoing one of many in-office tests.

What’s more, studies have shown that noncompliant patients tend to be dissatisfied with the wait time or cost of the examination, and that noncompliance with medicine use is linked to increased disease severity.1,2

In the end, each time, they’re waiting for the doctor to say, “Everything looks good, keep taking your drops, and we will see you in 4 months.” Imagine how this must feel to them, especially when their vision isn’t getting any better.

Like other subspecialties and disease states in ophthalmology, we glaucoma specialists are striving to achieve that “20/happy” patient. In our practice, we have learned that there are five key ways to improve compliance and achieve greater patient satisfaction.

1 Educate Patients
Everything begins and ends with patient education; it is the foundation for following the other tips listed below. We view the first appointment as the initial “investment” in the patient.

My staff and I spend a few more minutes to ensure patients understand that glaucoma is progressive, not reversible, and often has no symptoms. We stress that not every patient needs the same treatment or target pressure. We also manage expectations by explaining that they’ll need to see us every 4 to 6 months, whether they’re treated or not, and that we’ll need to conduct multiple tests every year to ensure the glaucoma isn’t progressing.

Our patients also know that the target pressure range is evolving and may change if the nerve is not stable. And, I educate patients on the impact of not consistently taking the prescribed medication.

“As consumers, we place value in everything we purchase, whether a car, computer, phone, or even coffee; we justify the cost based on our understanding of the value, so it is imperative that patients understand the value of the medication we prescribe.”

2 Manage Cost Concerns
Cost has become an even bigger issue as more and more branded drops are being substituted for generics. Many patients don’t understand the differences between their medications, let alone differences between branded versus generic medications.

Patients often return to our office on a medication we did not prescribe. This can happen when the patient goes to the pharmacy and is told the cheaper substituted medication is the “same as the one prescribed.”

As consumers, we place value in everything...
we purchase, whether a car, computer, phone, or even coffee; we justify the cost based on our understanding of the value, so it is imperative that patients understand the value of the medication we prescribe.

To this end, we developed a form that we give to all patients whenever we prescribe a brand-name medication (See Table 1 on page 16). This form helps distinguish the subtleties between the proprietary medication and its generic counterpart.

Patients are also told to ask the pharmacy to tell them the difference in cost after running it through insurance. In a study we conducted in our office, using this educational technique, we found that 65% of our patients changed to a brand-name medication after they understood the difference.

3 Simplify the Dosing Regimen
The dosing regimen is another important barrier. Multiple studies have demonstrated that adding a second or third bottle decreases compliance.\textsuperscript{3,4} We offer SLT as a first-line therapy and are more aggressive offering SLT before adding a second or third medication. Now with the various MIGS options, we can surgically reduce the drop burden much earlier in the disease, even in mild to moderate patients. Regardless of how well controlled their IOP and ONH are, if they're complaining of cost, we offer SLT or MIGS options.

However, when additional medications are necessary, we try to maximize one class of medication, if at all possible, by either switching within class or encouraging compliance with current medications before we add a second one. If we do add a medication, we try to find complementary mechanisms of action, and often rely on combination medications to achieve the target IOP.

I also provide written instructions for all medications prescribed — even if it's just one medication — and suggest reminder strategies for taking medications. For example, setting a daily alarm or marking off each day on a calendar when the drops are used.

Patients can integrate their medication regimen into their daily routine by storing the medications next to their toothbrush or pillbox to serve as a visual reminder. In addition, we always ask family and caregivers to be present at the appointment, because this second person can also help patients remember the treatment plan.

4 Address Side Effects
Managing side effects of medications is a fundamental part of glaucoma patient management. Setting proper expectations ahead of time can decrease the “shock” of an adverse event. For instance, telling a patient a drop might burn or turn the eye a bit red prepares the patient, so he or she doesn't overreact if an adverse event does occur.
Changing the time of dosing can also help. In a nonpublished study we conducted in 2007, we asked patients taking a PGA who complained of morning hyperemia to self report hyperemia when the dosing time was changed to earlier in the day and tears were used 5 minutes after. By changing the time of dosing from bedtime to earlier in the evening, patients reported 50% less hyperemia.

**Treat Concomitant Conditions**

A major part of my practice involves identifying and treating coexisting conditions, namely ocular surface disease. There are very few other conditions in the eye that have as many associated symptoms, including, pain, redness, photophobia, and most important, fluctuating vision.

These symptoms can affect quality of life, and often impact our patients’ ability to stay compliant with our recommendations. Although we, as providers, are focused on the IOP, patients are focused on the symptoms of dry eye. If we don’t address those symptoms, it’s hard for patients to trust us, and they may stop taking their medications.

Doctors are often overwhelmed and don’t have time to focus on dry eye during their busy day. After conducting a retrospective analysis on patient’s symptomology, we found “fluctuating vision” provided the highest sensitivity to dry eye diagnosis. Now, I just ask patients, “Does your vision fluctuate throughout the day or with each blink?” If they say “yes,” I work on the premise that they have ocular surface disease until proven otherwise.

Sometimes, the dry eye disease can be confused with adverse events from glaucoma drops. Although adding more medications affects compliance, when adding a dry eye drop, we are treating unpleasant symptoms that can help their vision, which is why they’re often more compliant when adding dry eye medications to their daily medication regimen.

At the end of the day, we’re trying to protect our patients from losing vision while maintaining a high quality of life. It’s not always easy, but keeping these 5 key tips in mind can help.

### References


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Vision loss from glaucoma is directly related to the progressive degeneration of the optic nerve. Slit-lamp biomicroscopy and optic disc photography are conventional techniques used to examine glaucomatous changes of the optic nerve head. However, these techniques are subjective with high inter-observer variability, even among glaucoma specialists. OCT provides an objective platform to quantify the configuration of the optic nerve head and thickness of the retinal nerve fiber layer (RNFL). The RNFL is composed of the axons of retinal ganglion cells. Documenting RNFL thickness is therefore important both for diagnosing and monitoring glaucoma. With a low test-retest variability, OCT RNFL thickness measurements are useful for determining progressive RNFL thinning in glaucoma patients.

The RNFL is composed of the axons of retinal ganglion cells. Documenting RNFL thickness is therefore important both for diagnosing and monitoring glaucoma. With a low test-retest variability, OCT RNFL thickness measurements are useful for determining progressive RNFL thinning in glaucoma patients. Here, I will examine recent research findings supporting progressive RNFL thinning measured by OCT as a useful tool for prediction of future visual field loss in patients with glaucoma.

Is progressive RNFL thinning predictive of visual field loss in glaucoma patients?

In a 5-year prospective study, my colleagues and I investigated whether progressive RNFL thinning is predictive of progressive visual field (VF) loss in glaucoma. We analyzed 139 primary open-angle glaucoma patients (240 eyes) by performing RNFL imaging and VF testing at 4-month intervals over 5 years. RNFL measurements were obtained from the Cirrus HD-OCT (Zeiss) using the “optic disc cube” scan, generating an RNFL thickness map in an optic disc region of approximately 6x6 mm². Progressive RNFL thinning was then determined by Guided Progression Analysis (GPA) (an event-based change analysis) and Trend-based Progression Analysis (TPA) of serial registered RNFL thickness maps (Figure 1).

We found that 27.1% and 48.8% of eyes had progressive RNFL thinning based on GPA and TPA, respectively, and 12.5% of eyes had VF progression by the Early Manifest Glaucoma Trial (EMGT) criteria (likely progression) during follow-up. The specificities of GPA and TPA were between 81.7% and 100% (determined by the proportion of eyes with significant RNFL thinning in 25 normal subjects followed weekly for 8 consecutive weeks and the proportion of eyes with significant RNFL thickening in the glaucoma group). Notably, eyes with progressive RNFL thinning detected by GPA and TPA had approximately 4-fold and 8-fold increases in risk of development of VF progression, respectively.

Eyes with progressive RNFL thinning also had a faster rate of decline of visual field index than eyes without. Our findings that progressive RNFL thinning determined by GPA and TPA is predictive of detectable functional decline verifies the significance of detecting progressive RNFL thinning and its relevance to the consideration of initiation or augmentation of IOP-lowering treatment for glaucoma patients.

The study provides long-term prospective data indicating that progressive RNFL thinning...
thinning is a useful biomarker to inform disease deterioration behavior. This study also highlights two elements in the interpretation of OCT findings.

1. Although the two-dimensional circumpapillary RNFL thickness measurements are widely adopted in many OCT instruments for analysis of RNFL abnormalities, the RNFL thickness map brings a wealth of data to reveal the three-dimensional topology of the distribution of RNFL. Analysis of longitudinal RNFL thickness map data with GPA/TPA is useful to detect progressive RNFL thinning that is relevant to the risk assessment of VF loss in glaucoma.

2. GPA and TPA respectively perform event-based and trend-based analyses of RNFL thicknesses at individual superpixels (50x50) of the RNFL thickness map (6x6mm). The map format is a powerful means for change analysis because it allows a fenced-in approach in a topographical fashion to show reduction of RNFL thickness over time. GPA tells us whether change has occurred. TPA not only shows us whether change has occurred but also shows the rate of change.

**Is the rate of change of RNFL thickness predictive of visual field loss in glaucoma patients?**

In a follow-up study, we demonstrated that glaucoma patients who had a faster rate of RNFL thinning carried a higher risk of visual field loss. We examined the rates of RNFL thinning in 89 patients with primary open-angle glaucoma who showed progressive RNFL thinning by TPA in the original study. We found that the mean and the peak rates of change of RNFL thickness are predictive of visual field loss in glaucoma patients.
Detection of progressive RNFL thinning with GPA/TPA represents an important change in the management of glaucoma patients. Progressive RNFL thinning is a powerful indicator for us to know whether a patient would have a high risk of developing visual field loss.

Progressive RNFL thinning measured from the rates of change of RNFL thickness map (Figure 2) were indicative of VF worsening. For each micrometer-per-year increase in the peak and the mean rates of RNFL thinning, the hazard ratios of development of VF progression were 1.12 and 1.39, respectively. While progressive RNFL thinning is not necessarily associated with VF worsening, our findings underscore the relevance of using TPA to measure the rates of RNFL thinning to inform the risk of VF loss in glaucoma.

How does detection of progressive RNFL thinning impact the management of glaucoma patients?

Clinicians manage glaucoma patients by lowering the IOP. The rationale of lowering the IOP is predicated on all landmark glaucoma treatment trials, which have consistently demonstrated reduction of IOP to be associated with a reduced risk of VF progression. For example, in the Early Manifest Glaucoma Trial, each mmHg increase in IOP during follow-up was associated with 12% increase in risk of development of VF progression.6

Initiation or addition of IOP lowering therapy should therefore be seriously considered in eyes detected with progressive RNFL thinning as eyes with progressive RNFL thinning are also at a higher risk of development of VF progression compared with those without (4-fold increase in risk for progressive RNFL thinning detected by GPA and 8-fold increase in risk for progressive RNFL thinning detected by TPA). Treatment decision of glaucoma patients should not be based on IOP levels alone. Glaucoma patients may progress in relatively normal IOP levels and a significant proportion of glaucoma patients in Asia do not have high IOP at presentation. Following the changes of the RNFL with OCT is a powerful means to inform clinicians when to treat and when to increase treatment in patients with glaucoma.

Conclusions

Detection of progressive RNFL thinning with GPA/TPA represents an important change in the management of glaucoma patients. Progressive RNFL thinning is a powerful indicator for us to know whether a patient would have a high risk of developing visual field loss. It is exciting to make use of this important information in our clinical practice because it carries meaning to our management of glaucoma patients.

References

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The aim of glaucoma medical therapy is to slow the progression of optic neuropathy and visual field loss. Primary open-angle glaucoma (POAG) inevitably progresses in the absence of treatment, and lowering IOP is currently the only treatment approach that can slow progression. All current interventions for POAG, whether pharmaceutical or surgical, are aimed at reducing IOP. As demonstrated in several large clinical trials, IOP reduction can prevent progression of optic nerve damage and visual field loss in both early and late stages of the disease.1-5 According to the American Academy of Ophthalmology’s (AAO) 2016 Preferred Practice Pattern for management of POAG, the goal of therapy is to lower IOP enough to slow or stop disease progression in order to maintain good functional vision.6

Available medications can lower IOP effectively for many patients, but not all, and little has changed in the ophthalmologist’s medical armamentarium in the past 20 years.

Common IOP-Lowering Therapies
Currently, five classes of IOP-lowering agents, which work by mechanisms affecting aqueous production and outflow, are available. These include: prostaglandin analogs (PGAs), β-blockers, carbonic anhydrase inhibitors (CAIs), α-2 adrenergic agonists, and miotics (also known as parasympathomimetics).6 Combination medications are also available. Eye drops may combine an α-2 adrenergic agonist and a β-blocker; a CAI and a β-blocker; or an α-2 adrenergic agonist and a CAI.

As my first-line treatment for glaucoma therapy, I offer PGAs or laser trabeculoplasty (ALT or SLT) if the glaucoma progression is not rapid. Some patients know they can’t tolerate putting drops in their eyes and opt for laser surgery immediately. For those who elect medication, I choose a PGA as my first-line therapy.

If a patient doesn’t respond well to or cannot tolerate PGAs, I typically move them to a β-blocker or add a β-blocker to their course of treatment. PGAs are used once daily, and I’ve found that patients are more compliant with a once-a-day medication schedule. If needed, I would next move patients to an α-agonist or CAI. The typical treatment goal with these medications is an IOP of less than 21 mmHg, and to lower the pressure by at least 20% for patients with mild glaucoma and by as much as 40% or 50% for those with moderate to severe glaucoma.7

But even with these therapies, many patients still don’t have their IOP lowered enough to stop disease progression. Why?

Medication Noncompliance
Many patients don’t adhere to their glaucoma treatment regimen, which results in failure to lower IOP to their target pressure. Studies across a range of populations show that medication nonadherence and dosing errors are widespread among patients being treated for glaucoma. In 2009, a prospective study assessing adherence with PGA monotherapy observed patients (N=196) for 3 months using an electronic dose-monitoring dispenser.8

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Dr. Miller-Ellis is professor of clinical ophthalmology at the Perelman School of Medicine at the University of Pennsylvania, and director of the Glaucoma Service at the Scheie Eye Institute. She specializes in the diagnosis and medical/surgical management of complex glaucoma. She also treats patients with glaucoma secondary to other diseases of the eye or systemic disease, as well as patients with both cataracts and glaucoma.

Dr. Miller-Ellis is on the advisory board for Alcon, is a consultant for Inotek Pharmaceuticals, and has received research funding from Allergan and Aerie Pharmaceuticals.
Nearly 45% of patients took less than 75% of their doses, and almost 20% of patients took less than 50% of their doses, even when they knew they were being electronically monitored.\(^8\)

A 2017 study of glaucoma medication prescription refill rates from two pharmacy dispensing databases in a total of 3,615 patients indicated unsatisfactory adherence for glaucoma patients. Satisfactory adherence (defined as medications available at least 80% of the time) over a 12-month period ranged from 30% to 37% in this analysis.\(^9\) In addition, a 2015 retrospective study evaluating patterns of glaucoma medication adherence over 4 years of follow-up found that of 1,234 newly diagnosed open-angle glaucoma patients, 7.5% of enrollees were never adherent, 14.9% had persistently very poor adherence, and 9.5% had declining adherence in the first year. What’s more, for most patients newly started on glaucoma medications, adherence patterns observed in the first year of treatment reflected adherence patterns over the subsequent 3 years.\(^10\)

Patients may not understand that glaucoma requires lifelong therapy, unlike, for example, systemic hypertension, in which patients may be able to decrease the use of medication through dietary and lifestyle modifications. Other patients may understand the need to maintain a schedule of prescribed medication but are unable to keep to that schedule for various reasons. They may have arthritis, poor hand-eye coordination, muscle weakness, or another medical condition that keeps them from being able to squeeze a dropper or steady their hand to instill the drops in their eyes. In addition, patients may fail to reach the target dose of their medication if they develop side effects that prevent them from using their medication regularly as prescribed.

A 2017 review identified risk factors for poor adherence to medical glaucoma therapy, including, as discussed, lack of understanding among patients about their disease, as well as the cost, complexity, or side-effect profile of the medication regimen.\(^11\) Researchers have been challenged to definitively link nonadherence to outcomes such as IOP or visual field loss, which may have to do with problems in study design or simply the difficulty of directly demonstrating how poor adherence affects this slowly progressing disease.\(^11\)

**Need for Adjunctive Therapy**

Despite the advantages of PGAs and the availability of multiple drug options, data shows that a significant proportion of glaucoma patients may not reach target IOP with a single-agent course of treatment: in one large cohort study of a claims database (n=5,933), 42% of patients prescribed a PGA required adjunctive therapy within 30 days.\(^12\) Adjunctive therapy for additional pressure reduction is relatively common and often necessary for patients to achieve their individual target IOP levels.

Of course, additional medications increase the complexity of treatment and dosing schedules and can become another factor that can lead to noncompliance.\(^13\) The use of multiple drops also can increase the risk of side effects, which, again, become an issue for patient noncompliance.\(^12\)

**Targeting Aqueous Outflow**

Anatomically, two pathways are generally understood to be responsible for aqueous humor outflow: the trabecular meshwork (TM), or so-called conventional pathway, and the uveoscleral, or non-conventional, pathway.\(^14\) Today, we lower IOP primarily by decreasing aqueous humor production or enhancing uveoscleral outflow.

Of the several classes of glaucoma medications now in common clinical use, three — CAIs (systemic or topical), \(\alpha\)-2 adrenergic agonists, and \(\beta\)-blockers — are secretory suppressants that decrease aqueous humor production, and one — PGAs — lower IOP primarily by enhancing uveoscleral aqueous outflow.\(^15\) Alpha-2
Adrenergic agonists are also associated with decreased episcleral venous pressure or increased uveoscleral outflow.6

With the exception of miotics, none of the currently available drugs work by primarily enhancing aqueous outflow through the trabecular meshwork (TM). In adults, the majority of aqueous outflow moves through the TM, which is compromised in glaucoma patients.14 This may account for why so many glaucoma patients require more than one class of IOP-lowering medication, and why some require surgical intervention. SLT, for example, treats the TM directly to enhance its outflow capability, which results in lowered IOP. However, the efficacy of SLT is roughly equivalent to monotherapy with a PGA, thus adjunctive medication or incisional surgery may still be necessary to achieve the IOP goal.6,15

A 2017 review identified risk factors for poor adherence to medical glaucoma therapy, including lack of understanding among patients about their disease, as well as the cost, complexity, or side-effect profile of the medication regimen.11

Sustained Delivery

Because patients don’t always adhere to their medical therapy regimen, sustained-release platforms for IOP-lowering drugs, which would take the responsibility of adhering to a dosing regimen out of a patient’s hands, are being investigated.

Some of the sustained-release platforms for IOP-lowering currently in development include intraocular delivery, such as injectable depotsof the intravitreal, intracameral, or subconjunctival space; and extraocular delivery, such as conjunctival inserts placed into the fornices, and punctal plugs. Under the sustained-release model, patients would potentially see their physician every 3 to 6 months, depending on the method used, to have the device removed and replaced.

Looking Ahead

Challenges to the medical management of glaucoma center around inadequate long-term IOP-lowering for some patients and difficulty with medication adherence, arising from a host of factors, in others. Taken together, studies on strategies to improve adherence (e.g., robust patient education, simplified drug regimens, or electronic reminder systems) suggest that an individualized approach, tailored to each patient’s needs, is most likely to be effective.11

In the future, such strategies, combined with innovations in pharmacology, drug delivery, and even surgery, could improve the situation for glaucoma therapy considerably.11

Editor’s note: Medical writing support was provided by Jean Thilmany of Ethis Communications and funded by Bausch + Lomb.

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1. The AGIS Investigators. The Advanced Glaucoma Intervention Study (AGIS).
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Clear Lens Extraction in Angle Closure Disease

Results from the EAGLE trial provide key insights into the treatment of glaucoma

By Sunee Chansangpetch, MD, and Shan C. Lin, MD

Phacoemulsification cataract surgery (phaco) is a potential approach for reducing IOP in glaucoma patients. The effect is typically mild in those without glaucoma, and appears to be greater in eyes with glaucoma, particularly with angle closure disease.

Angle closure disease is a clinical spectrum that encompasses patients in three categories: primary angle closure suspect (PACS), primary angle closure (PAC), and primary angle closure glaucoma (PACG). PACS is defined in an eye that has 180 degrees or more of occludable angle. An occludable angle is present when the gonioscopy examination shows grade 1 or less (Shaffer classification system). PAC is defined in those eyes that meet PACS criteria and also have presence of peripheral anterior synechiae and/or IOP greater than 21 mmHg. PACG is PAC with optic nerve and/or visual field abnormalities that define glaucoma. The term ‘acute angle closure glaucoma’ (acute ACG) is used to represent angle closure eyes with rapid IOP elevation.

A growing body of evidence demonstrates that IOP is significantly reduced after phaco. Data from a recent review paper showed that the IOP lowering is modest in primary open-angle glaucoma with a 13% IOP reduction, and the reduction in number of medications is modest as well. Results are significantly better in eyes with angle closure disease. PACG provides a nearly 30% reduction in IOP and 53% decrease in number of medications. For acute ACG, the pressure goes down substantially (71%), and there is almost no need for post-phaco medications. Among open- and closed-angle glaucomas, subsequent trabeculectomy was found to be uncommon after phaco in this review.

Is cataract extraction safe and effective for patients with angle closure disease?

With aging, the crystalline lens thickens and loses its clarity, becoming a cataract. The thick cataractous lens could worsen the preexisting narrow anterior chamber angle in an angle closure patient. Hence, it seems reasonable that cataract extraction would be an option for the management of PACG. Numerous studies over the past decade also support this idea.

Anatomical studies using ophthalmic imaging have demonstrated that the angle deepens substantially after lens extraction in eyes with angle closure, even with an existing laser peripheral iridotomy (LPI). A Japanese group evaluated more than 100 patients who had residual angle closure. After undergoing cataract surgery, all eyes experienced improvement of the angle as assessed by ultrasound biomicroscopy (UBM). Likewise, a study from India showed an increase in angle parameters measured by anterior segment optical coherence tomography (AS-OCT). Thus, mechanically, the angle improves significantly after phaco.

For the IOP-lowering aspect, a research group in Hong Kong conducted a trial in people who had cataract when presenting with acute ACG. They compared outcomes between early phaco versus standard care including LPI, and phaco showed far greater success (defined as pressure less than 21 mmHg after treat-
ment). At 18 months, phaco was more effective than LPI, particularly in acute attacks with IOP > 55 mmHg. From the same study, the phaco group also outperformed in three categories: medication, IOP, and gonioscopy grading.

Another study focused on eyes having PACG with controlled IOP and a coexisting cataract and aimed to compare the effect of phaco alone versus combined phaco-trabeculectomy. Although the combined group was shown to be more effective in IOP control, the study also demonstrated that IOP and number of medications decreased substantially after phaco alone. Furthermore, the phaco group had significantly less complications. Interestingly, no significant differences in visual acuity and visual field (VF) progression were observed during the 2-year study period.

What about clear lens extraction?

There are many studies that support cataract extraction as a method to improve IOP control in situations of concomitant cataract and angle closure. However, what about performing phaco in an eye without a visually significant cataract? Is this approach the optimal first-line therapy for angle closure instead of standard LPI?

Data from a case series in 2013 suggested a benefit of performing clear lens extraction. They reported five cases of acute ACG or PACG. All patients were using maximally tolerated medications with IOP ≥ 21 mmHg. All cases were on the verge of trabeculectomy or tube surgery. None of them had a visually significant cataract, and best-corrected vision was close to or equal to 20/20. Clear lens extraction was performed. Four of the cases were considered successes, with fewer medications, well-controlled IOP, and no need for additional surgery. Three out of the four were essentially "complete successes" and did not need any glaucoma medications afterward. Only one of the five cases was unsuccessful, with unchanged IOP, medications, and visual acuity after surgery, and required a trabeculectomy.

Learnings from the EAGLE Study

The best evidence so far that supports the role of initial clear lens extraction is the recently published EAGLE (Effectiveness in Angle Closure Glaucoma of Lens Extraction) study. The authors reported the effectiveness of performing phacoemulsification in patients with a clear lens and concomitant PAC/PACG. This was a multicenter, randomized, controlled trial in 30 hospitals in five countries: Australia, mainland China, Hong Kong, Malaysia, Singapore, and the United Kingdom. Randomization was to clear lens extraction versus standard care, including LPI and topical medication, as first-line therapy. The study included people who were 50 years or older without symptomatic cataract and they had to be newly diagnosed PAC with IOP > 30 mmHg or PACG. Main outcomes were evaluated for three co-primary endpoints: patient-reported health status, IOP, and cost-effectiveness ratio. Of 419 total subjects, most were PACG (263), and enrollees were randomized into clear lens extraction (208) and standard care (211). The final outcomes were assessed at 3 years.

Along with the safety of performing primary phaco, the EAGLE study reported the relatively consistent superiority of clear lens extraction in terms of clinical benefits and quality of life.

Health status was evaluated using the European Quality of Life 5 Dimensions (EQ-5D) survey, which includes mobility, self care, usual activity, pain/discomfort, and anxiety/depression. The group that had clear lens extraction had overall better results. However, although the clear lens extraction group had better outcomes, it may be interpreted that the actual differences in terms of absolute values seem mild, e.g., with a EQ-5D difference in post-treatment change between the two groups of 0.052 (95% CI 0.015 to 0.088) (Table 1).

IOPs at the 3-year follow-up were improved in both groups. IOP decreased from 29.5 mmHg to 16.6 mmHg in the clear lens extraction group and from 30.3 mmHg to 17.9 mmHg in the standard care group. Though IOP reductions were better in the clear lens extraction group, the actual difference was not
that substantial (1.18 mmHg with 95% CI 0.38 to 1.99). There was also a difference between the two groups in terms of fewer medications in the clear lens extraction group.

For the cost-effectiveness analysis, the cost was higher in the surgical group. Also, the quality adjusted life year (QALY) value was greater in the surgery group. The incremental cost effectiveness ratio (ICER), which is the difference of the cost divided by the difference of treatment effect, was GBP 14,284 per QALY. This result met the criteria for level of acceptable incremental cost. It should be noted that although the clear lens extraction group started off with high initial procedure costs, the incremental costs in this group are partly offset over the follow-up period. It can be assumed that there would be a trend of improvement in cost effectiveness of clear lens extraction over longer-term follow-up. However, the ICER reported here was calculated only for the subsets in the UK, thus, it may not be applicable to other geographical settings, such as third world countries.

Besides these three primary endpoints, the EAGLE study also reported other outcomes including additional measures of quality of life, vision, and safety of each treatment. For the vision-related quality of life assessment, the National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ-25) as well as Glaucoma Utility Index outcomes were assessed and found to be better in the clear lens extraction cohort. Best-corrected visual acuity was tested with ETDRS charts, and also showed better results in the clear lens extraction group. However, the visual field data demonstrated no significant difference, which is not surprising due to the relatively short follow-up. Longer-term follow up, such as 5 years, may be necessary to realize the benefit of performing clear lens extraction compared with standard care.

In terms of adverse effects, there were no serious adverse events in either group. Notably, there was only 1 out of 208 cases in the surgery arm that required additional glaucoma surgery, while the control group had about 10% of participants needing additional surgery, most of which were lens extraction and trabeculectomy.

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Time</th>
<th>Clear lens extraction</th>
<th>Standard care</th>
<th>Difference in change between two groups* (95% CI)</th>
<th>p-value</th>
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<tr>
<td>EQ-5D</td>
<td>Baseline</td>
<td>0.867</td>
<td>0.876</td>
<td>0.052 (0.015 to 0.088)</td>
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<td></td>
<td>36 months</td>
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<td>IOP (mmHg)</td>
<td>Baseline</td>
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<td></td>
<td>36 months</td>
<td>16.6</td>
<td>17.9</td>
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<td>Medications (eye drops)</td>
<td>Baseline</td>
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<td>36 months</td>
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<td>NEI-VFQ-25</td>
<td>Baseline</td>
<td>86.8</td>
<td>87.4</td>
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<td>36 months</td>
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<td>0.843</td>
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<td>Visual acuity (ETDRS letters)</td>
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<td>77.0</td>
<td>2.99 (0.99 to 5.00)</td>
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<td></td>
<td>36 months</td>
<td>79.9</td>
<td>76.6</td>
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<tr>
<td>Visual field MD (dB)</td>
<td>Baseline</td>
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<td>-5.4</td>
<td>0.08 (-0.59 to 0.75)</td>
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<td>36 months</td>
<td>-4.7</td>
<td>-5.0</td>
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</table>

*Difference in change between clear lens extraction vs. standard care; EQ-5D = European Quality of Life 5 Dimensions; NEI-VFQ-25 = National Eye Institute Visual Function Questionnaire-25.
The EAGLE study provides answers to long-awaited questions regarding the benefit of using phaco as a first-line treatment for primary angle closure disease. The study has the advantages of being multicenter, with a pragmatic design and large sample size. Along with the safety of performing primary phaco, the study reported the relatively consistent superiority of clear lens extraction in terms of clinical benefits and quality of life. Nevertheless, the generalizability of the compelling results is something we need to bear in mind. First, the study population was limited to individuals aged 50 years and older. To perform phaco in younger subjects who may still have their accommodation preserved could result in negative effects on their quality of life. Second, the study excluded advanced glaucoma cases and most of subjects in the trial were in the mild stage of glaucoma with an average MD -3 to -4 dB. Additional benefits and safety of clear lens extraction in moderate and advanced cases have not yet been proven. Third, it should be emphasized that only the PAC subjects who had IOP > 30 mmHg were recruited for the study. This subset is likely not very common in routine practice. Ultimately, the investigators in the EAGLE study should be congratulated for providing important data regarding the treatment of angle closure glaucoma that can have practical and far-reaching applications in the real world.

**Promising Results**

Cataract surgery is a safe and effective surgical option for PACG patients with coexisting cataract. The EAGLE study provides excellent evidence to support clear lens extraction in PAC and PACG patients in terms of efficacy, safety, quality of life, and cost effectiveness. Future studies and analyses will provide additional answers regarding clear lens extraction in younger subjects and earlier and later forms of angle closure disease.

**Evolving Technology**

Femtosecond laser-assisted cataract surgery is an established but evolving technology that provides image-guided laser cataract surgery. It is computer-controlled and provides laser accurate incisions for the treatment of astigmatism. This technology can create improved capsulotomies in difficult eyes. Using the laser results in reduced phacoemulsification time and energy. It can be advantageous in many glaucoma patients who need cataract surgery.

At the same time, there are special considerations when performing laser-assisted cataract surgery on glaucoma patients undergoing combined operations. The impact of the laser portion of the case on angle viewing is most important. The impact of IOP lowering on refractive outcome must be considered, and the role of suturing in the glaucoma portion of the case must be taken into account in the calculation of astigmatism reduction.

As the glaucoma surgery landscape changes, more patients will be candidates for premium cataract surgery. This presents opportunities and challenges. Laser-assisted cataract surgery can provide excellent refractive results, but these may be more variable than those seen in patients who have not undergone previous glaucoma interventions.

**References**

These days, “innovation,” “excitement,” and “new hope” are common keywords in articles about glaucoma therapy. As industry veterans know, that was not always the case. Glaucoma Physician sat down with Rick Lewis, MD, cofounder of Sacramento Eye Consultants and chief medical officer of Aerie Pharmaceuticals, to talk about the progress of glaucoma therapies through his nearly 40-year career and where his company’s pipeline drug, netarsudil, fits into that evolution.

Q. Your career has covered a great deal of ground in the clinical setting and in industry. Can you talk about that path?

A. I went to medical school at Northwestern, did my residency at UC Davis, fellowship at the University of Iowa, and worked in academics, private practice, and industry, performing clinical research for glaucoma products that are available now. When I left UC Davis and went into practice, eventually serving as president of the American Glaucoma Society, I continued relationships with industry and contributed to the development of topical drugs, sustained-release drug delivery, and minimally invasive glaucoma surgery (MIGS). When I took on the part-time position at Aerie a few years ago, that change was really part of the same continuum, of battling glaucoma clinically by pushing forward.

Q. Advances in glaucoma treatment have been headline news in recent years. What do these developments mean to you after nearly four decades in the specialty?

A. It’s remarkable. When I began treating glaucoma, we only had topical beta blockers, which affect the heart and lungs. When prostaglandins were launched with latanoprost in the 1990s, they transformed treatment. Suddenly, we could control pressure with a once-a-day drop that had none of the beta blocker systemic side effects. That option previously didn’t exist. Its safety and efficacy quickly made latanoprost the market-leading glaucoma treatment.

Fast forward another decade, and I was very involved in the development of MIGS devices. Trabeculectomy had long been (and still is) the gold standard for glaucoma surgery, but its short- and long-term complications created a desire for effective surgeries that were safer and less invasive. It’s the same concept physicians are applying to many different specialties, including neurology and cardiology. The results were the development of a subconjunctival option with Xen Gel Stent (Allergan), a canal space stent in iStent (Glaukos), and the suprachoroidal CyPass (Alcon). Surgeons can achieve the same or similar efficacy to trabeculectomy with a safe ab interno approach, and it opens the door for more candidates. We can’t overstate how MIGS is changing the treatment of glaucoma. However, the need for better, more specific medications to treat glaucoma is as great now as it ever was. Medical therapy for glaucoma isn’t going away.

Q. Aerie has two once-daily drops in the pipeline now, netarsudil 0.02% (Rhopressa) and a combination product of netarsudil 0.02% and latanoprost 0.005% (Roclatan). Will netarsudil represent another milestone in the treatment of glaucoma?

A. Before discussing netarsudil, it’s important to review its development history. The late Dr. David Epstein at Duke University envisioned a treatment for glaucoma that was directed at the source of the disease: the trabecular meshwork. He worked with Casey Kopczynski, today the chief scientific officer at Aerie, to screen molecules and found a few that worked in the laboratory. Together, they founded Aerie, and they spent more than a decade developing a compound for commercialization. Netarsudil is the fruit of those labors.
Netarsudil is the first of a novel class of drugs called rho kinase (ROCK) inhibitors to be developed for glaucoma. It would be the first agent since prostaglandins debuted more than 20 years ago to use a new mechanism of action for the treatment of glaucoma. Netarsudil appears to reduce IOP primarily by increasing outflow through the trabecular meshwork, the main drain for normal eyes. This has been demonstrated in both preclinical studies with the molecule and in clinical studies with topical ocular administration of netarsudil ophthalmic solution.1

The NDA for Rhopressa was filed in February. We will likely file the NDA for Roclatan within the next year. Roclatan grew out of the question of whether a combination product could maximize IOP reduction. Earlier efforts to develop a combination product with a prostaglandin in the U.S. were unable to show sufficient efficacy over a prostaglandin alone to warrant approval. In a multicenter prospective study, the combination of netarsudil and latanoprost lowered IOP >1 mmHg more than either drug used alone. And neither netarsudil nor the combination product has demonstrated any serious or drug–related systemic side effects.

Q. Much has been written about MIGS revolutionizing glaucoma treatment, the idea being that safe, minimally invasive procedures can eliminate or reduce the need for drugs. Now Aerie may have a new drug. Where does that development fit into 21st Century glaucoma treatment?

A. As a surgeon who helped develop MIGS devices, I share my colleagues’ enthusiasm for the procedures. However, there is no surgery that makes IOP-lowering drugs obso-

“"We’re on the cusp of not only novel new IOP-lowering medications, but also of long-term drug delivery systems and MIGS-drug combination approaches. I think, in the next 5 to 10 years, we will see more exciting breakthroughs."

— Rick Lewis, MD, cofounder of Sacramento Eye Consultants and chief medical officer of Aerie Pharmaceuticals

le. Drops are the first-line treatment for glaucoma. Although MIGS procedures have less risk than trabeculectomy or tube shunt, the lowest risk is still drug treatment. Furthermore, some patients aren’t candidates for MIGS, and even patients who have MIGS or other procedures often continue to need IOP-lowering drops.

Beyond filling the existing role of IOP-lowering medications, Rhopressa has been developed with the goal of offering better performance and compliance — the two goals that govern all glaucoma patients to achieve better pressure reduction with one drop per day.

Q. Any turning point is a good place to look back and to look forward. What do you think about your long journey as a glaucoma specialist, and how do you envision the decade ahead?

A. Thirty years ago, I had patients using beta blockers twice a day and pilocarpine four times a day. Surgeries were crude, with high complication and failure rates, and we couldn’t control scarring. As a result, glaucoma was a very frustrating field. It was not innovative, and many ophthalmologists didn’t want to specialize in this disease.

Now, glaucoma is a very desirable field. We see multiple new approaches to diagnosis and therapy — an explosion of knowledge and of our power to treat the disease. It’s such a dynamic landscape today. We’re on the cusp of not only novel new IOP-lowering medications, but also of long-term drug delivery systems and MIGS-drug combination approaches. I think in the next 5 to 10 years, we will see more exciting breakthroughs.

I feel very lucky to have seen so much in private practice, academic practice and industry development, and now seeing the field develop and mature for the future. I think we’re just seeing the beginning today. I hope new ophthalmologists will be active and involved and keep moving the treatment of glaucoma forward. GP

References


Medical Science Liaisons Link Physicians With R&D

Alcon is the first company to deploy an MSL team in the field of ophthalmic surgery

By Arthur Chan, PhD, MBA

ntroduced by The Upjohn Company in the 1960s, medical science liaisons (MSLs) are a familiar entity in the pharmaceutical industry. MSLs are medical professionals who serve as a company’s customer-facing research and development (R&D) field force, developing relationships and working with physician-customers in a variety of ways. However, it wasn’t until recently that medical device companies began using MSLs, and Alcon became the first company to develop an experienced team in the field of ophthalmic surgery.

Scientific Exchange Goes Both Ways

The impetus for the formation of Alcon’s MSL team was to reinvigorate both the product pipeline and its commitment to customer experience. In addition, the FDA has increased its pace of product approvals, and the products are increasingly complex and advanced, creating a greater need for companies to support customers’ peer-to-peer discussions with physicians about the science and the data behind the technologies.

Our North American MSL team consists of nine members whose work supports 23 products across six product families. Two are ophthalmologists, four are optometrists, and three hold PhDs. Their backgrounds are as diverse as engineering and private practice. As a scientific resource, they are uniquely equipped to have in-depth discussions with physicians. By conveying information — such as risk-benefit ratios, the clinical and statistical significance associated with clinical studies, and which products are best suited for which patients — our experts increase physician confidence as they use our products and help ensure the best possible patient outcome. But the MSL-physician relationship is definitely a two-way street. As the bridge between our external customers and our internal R&D department, we listen to the ideas leading physicians have for advancing existing products and developing new ones, and bring these ideas back to the company. We guide physicians through Alcon’s investigator-initiated study process and encourage their involvement as we design our clinical trials and launch new products.

Many ophthalmologists have developed technologies or started companies that they want to share with us. The MSL team was heavily involved in the company’s entry into the microinvasive glaucoma surgery (MIGS) space with the CyPass Micro-Stent. After recognizing the early work indicating how MIGS could change the way glaucoma surgery is performed, we immersed ourselves in the subject matter and began developing relationships with glaucoma surgeons. The team spent more than 90 hours in training for the CyPass launch, including didactic learning and surgical observation. We are currently involved in identifying clinical research sites, training physicians who are interested in research collaborations, and supporting the CyPass sales and marketing team.

Keeping the Pipeline Primed

Ophthalmic surgeons have been very receptive of our MSL team, which isn’t surprising. Ophthalmologists tend to be innovative, entrepreneurial, and cognizant of the benefits of working closely with industry. As we work in the MIGS space and explore frontiers in many others, we’re connecting with our thought-leading customers in a host of ways. As a field-based unit, we’re interacting with our physicians when there is a need for our expertise at conferences, in physician offices and ORs, and also via phone, email, and social media. We’re getting young surgeons involved with R&D and clinical research, educating them on how to work with us while being compliant, and we are increasingly impressed with the progressive ideas they bring to the table.

At the end of the day, we’re all here because we want patients to see their best throughout their lifetime. Making an MSL team part of achieving that goal enhances Alcon’s ability to create a partnership with our customers as we develop the latest and greatest surgical technologies, and provide scientific evidence and data to help our customers be better doctors for their patients.

Dr. Chan is head of Medical Science and the Surgical Medical Science Liaison team at Alcon.
Coding, Coverage, and Payment for New MIGS Technology

How and when to code for these procedures

By Kevin J. Corcoran, COE, CPC, CPMA, FNAO

In medicine, progress is often viewed in the context of something new: a new technique, a new device, a new drug, or a new understanding of disease processes. Our enthusiasm for novelty is balanced against the need for proof, which is the foundation of evidence-based medicine. In the face of morbidity and mortality, patients grasp for medical therapies in their hope for relief or a cure — some with little or no supportive scientific evidence. Sometimes, purported evidence is nothing but chicanery to enrich the seller by duping the gullible and the desperate. If the damage done by this deceit masquerading as progress was limited to just a few patients, we might see it as the cost of experimentation — trial and error. However, if the damage strikes at the heart of our healthcare system through inflated healthcare expenditures with negligible benefits, then society pays a heavy price, and confidence in medicine erodes. It’s as if we still lived in the nineteenth century with medical practice involving potions, concoctions, and caveat emptor. This unfortunate outcome is prevented in large part by Medicare, Medicaid, and other third-party payers who decide — on behalf of beneficiaries and with input from medical experts — what is worthwhile and how much it is worth. A lay patient with a horrid disease isn’t a good judge of the merit of a proposed treatment, and this is particularly true if the patient has no financial responsibility for his choice. Additionally, the seller of the new treatment is not an unbiased judge of its value. The process of vetting something new in medicine by payers and other interested parties is a long one, and is entirely independent of demonstrating safety and efficacy to the US Food and Drug Administration (FDA).

Coding Is The First Step

Arguably, the crown jewel of the American Medical Association is its copyright of the Current Procedural Terminology (CPT) manual, which is a prime reference source for governments and payers to administer health care. The main body of the manual tabulates well-accepted medical procedures as permanent Category I codes. One of the manual’s appendices tabulates new, emerging technology, services, and procedures as temporary Category III codes — those ending with the letter “T.” These are CPT codes on probation for 5 years, and sometimes longer. To a great degree, a Category III code provides a mechanism for identifying a procedure on a claim for reimbursement that would otherwise fall into a miscellaneous CPT code for lack of specificity within Category I. This is useful for tracking purposes by payers, although a Category III

FIGURE 1. THE EVIDENCE-BASED MEDICINE TRIAD

code is no guarantee of coverage or payment. For example, under the Centers for Medicare & Medicaid Services (CMS) Clinical Trial Policy, implemented in 2000 as a result of an executive memorandum by then President Clinton, Medicare pays for routine patient costs in certain clinical trials that are pre-qualified prior to payment. A Category III code is useful to report the procedure to Medicare that is under investigation within the clinical trial. At present, there are a number of Category III codes for minimally invasive glaucoma surgery (MIGS) (Table 1).

Once a Category III code is assigned, billers and coders have a unique, specific procedure code to report on a claim for the new procedure. The CPT manual doesn’t provide an option to choose a not so accurate, but reasonably close, Category I CPT code rather than the accurate Category III code. Looking for a better-paying CPT code is known as “code shopping” and represents a questionable billing practice and potential healthcare fraud. A possible motivation for code shopping is noncoverage of almost all Category III codes as the default position of Medicare, Medicaid, and third party payers. Substituting a Category I code, with established coverage and payment, would garner quick reimbursement, yet it is prohibited. Surgeons and staff are obliged to use the most recent CPT instructions and to understand the descriptors for the applicable Category III codes.

Confusion can occur when terminology in the CPT code description is obscure or esoteric. Additionally, surgical techniques might not be appreciated by billing staff trying to abstract an operative report. For assistance with parsing these MIGS Category III codes, review Table 2, which was prepared by the certified procedural coders at Corcoran Consulting Group. Additional information is available in CPT Assistant and from ophthalmic professional

### TABLE 1. CATEGORY III CPT CODES FOR MIGS

<table>
<thead>
<tr>
<th>CPT CODE</th>
<th>DESCRIPTION</th>
<th>NEW TECHNOLOGY</th>
</tr>
</thead>
<tbody>
<tr>
<td>0191T</td>
<td>Insertion of anterior segment aqueous drainage device, without extraocular reservoir, internal approach, into the trabecular meshwork; initial insertion</td>
<td>iStent</td>
</tr>
<tr>
<td>0253T</td>
<td>Insertion of anterior segment aqueous drainage device, without extraocular reservoir, internal approach, into the suprachoroidal space</td>
<td>iStent Supra</td>
</tr>
<tr>
<td>+0376T</td>
<td>… each additional device (in addition to 0191T)</td>
<td>iStent Inject</td>
</tr>
<tr>
<td>0449T</td>
<td>Insertion of anterior segment aqueous drainage device, without extraocular reservoir, internal approach, into the subconjunctival space; initial insertion</td>
<td>Xen Gel Stent</td>
</tr>
<tr>
<td>+0450T</td>
<td>… each additional device (in addition to 0449T)</td>
<td>Xen Gel Stent</td>
</tr>
<tr>
<td>0474T</td>
<td>Insertion of anterior segment aqueous drainage device, with creation of intraocular reservoir, internal approach, into the suprachoroidal space</td>
<td>CyPass</td>
</tr>
</tbody>
</table>

All CPT codes © 2017, American Medical Association

### TABLE 2. KEY TERMINOLOGY

| Extraocular reservoir | “Reservoir” refers to the plate in Ahmed, Baerveldt, and Molteno aqueous shunts; “Extraocular” refers to the placement of these devices on the outside of the globe |
| External approach     | Term refers to a surgical approach from outside of the eye as occurs with Ex-Press, InnFocus, and SOLX glaucoma drainage devices (In Latin, “ab externo”) |
| Internal approach     | Term refers to a surgical approach from inside the eye as occurs with iStent, Xen, and CyPass glaucoma drainage devices (In Latin, “ab interno”) |
| Additional device     | Term refers to a second (or third) glaucoma drainage device implanted at the same time as the initial device of the same type |
| Suprachoroidal space  | Term refers to a space lying between the sclera and choroid; applies to the CyPass glaucoma drainage device |
| Subconjunctival space | Term applies to the space between the conjunctiva and sclera; applies to the Xen glaucoma drainage device |
societies, such as the American Academy of Ophthalmology, the American Society of Cataract and Refractive Surgery, and the American Glaucoma Society.

**Coverage Takes Time**

Before paying for a new MIGS procedure assigned to a Category III code, Medicare Administrative Contractors (MACs) and other third party payers are generally skeptical and need persuading.

- Where is the scientific literature?
- Who are the physician champions of the procedure? Are there many or just a few?

Information about the new procedure trickles in slowly. Each MAC or payer makes its own coverage and payment decision. Although there is a tendency to “follow the leader,” there is no obligation to create a homogeneous policy across different jurisdictions. Unless the central office of CMS creates a national coverage determination, which is rarely done, the process is de-centralized and slow. Local coverage determination (LCD) policies are the norm, because CMS devolves decision-making to the MACs.

When this system was set up, the Medicare carriers had the staffing and direct experience with paying claims that did not exist in Baltimore — the home of the Health Care Financing Administration (HCFA) now known as the Centers for Medicare & Medicaid Services.

The speed with which MACs and other payers adopt a favorable coverage and payment policy is a direct result of the amount of supportive scientific information they receive from interested parties and the popularity of the procedure in the medical community. For example, the number of iStent procedures has grown rapidly within Part B Medicare, along with generally favorable LCDs (Table 3), largely through continuing discussions with MACs and other payers. This is not always the case for a new, emerging technology.

**Limitations of Coverage**

Before an LCD is issued, but after the Category III code becomes effective, there are claims for reimbursement by surgeons and facilities. The claims almost certainly face an uphill battle and scrutiny before payment is made, and subsequent claims face the same gauntlet even if the first claim was paid. Billers experience many hiccups during this process, and only the most determined surgeons with a strong belief in the new technology will persist. It is very tempting to let other surgeons go first and take a wait-and-see approach.

Once an LCD is issued, limitations of coverage remain.

- The list of covered ICD-10 diagnosis codes is short and restrictive
- Only certain stages of glaucoma are covered

---

**TABLE 3. VOLUME OF 0191T WITHIN PART B MEDICARE**

<table>
<thead>
<tr>
<th>YEAR</th>
<th>FREQUENCY</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>20</td>
</tr>
<tr>
<td>2011</td>
<td>11</td>
</tr>
<tr>
<td>2012</td>
<td>403</td>
</tr>
<tr>
<td>2013</td>
<td>8,808</td>
</tr>
<tr>
<td>2014</td>
<td>16,747</td>
</tr>
<tr>
<td>2015</td>
<td>20,768</td>
</tr>
<tr>
<td>2016</td>
<td>TBD</td>
</tr>
</tbody>
</table>

**TABLE 4. CY2017 MEDICARE FACILITY PAYMENT RATES**

<table>
<thead>
<tr>
<th>CPT Code</th>
<th>ASC</th>
<th>HOPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>0191T</td>
<td>$2,585</td>
<td>$3,939</td>
</tr>
<tr>
<td>0253T</td>
<td>$2,155</td>
<td>$3,417</td>
</tr>
<tr>
<td>+0376T</td>
<td>$0</td>
<td>$0</td>
</tr>
<tr>
<td>0449T</td>
<td>$2,360</td>
<td>$3,417</td>
</tr>
<tr>
<td>+0450T</td>
<td>$0</td>
<td>$0</td>
</tr>
<tr>
<td>0474T</td>
<td>TBD</td>
<td>TBD</td>
</tr>
<tr>
<td>65820</td>
<td>$1,750</td>
<td>$1,824</td>
</tr>
<tr>
<td>66174</td>
<td>$1,750</td>
<td>$3,417</td>
</tr>
<tr>
<td>66175</td>
<td>$1,750</td>
<td>$3,417</td>
</tr>
<tr>
<td>66183</td>
<td>$1,750</td>
<td>$3,417</td>
</tr>
</tbody>
</table>
Off-label use of the new technology is not covered
The place of service may be effectively constrained by the physician’s site-of-service differential or the reimbursement rate for the facility
Additional chart documentation with the claim may be required to demonstrate medical necessity.

Periodic revisions of LCDs can be expected. If all goes well, the provisions of the LCD become less restrictive over time, as experience accumulates and the new technology gains respect. After 5 years, with a strong track record of paid claims, AMA will consider promoting a temporary Category III code to permanent Category I status. This occurred in 2014 when 0192T was promoted to 66183, and in 2011 when 0176T was promoted to 66174 and 0177T to 66175. Alternately, a Category III code may sunset and be removed from the CPT manual if adoption of the technology is nonexistent or tepid.

Payment Limitations
The Medicare Physician Fee Schedule does not contain Relative Value Units for Category III codes — only Category I codes are assigned payment rates. The MACs adjudicate claims and set rates for surgeon claims for reimbursement, frequently with unexpected results. When the process works well, the Carrier Medical Directors seek input from Ophthalmology Carrier Advisory Committee members to identify a comparable surgical procedure that is very nearly equivalent to the new MIGS procedure. For example, National Government Services (NGS), the Medicare Administrative Contractor for Minnesota, Wisconsin, and Illinois, determined that the iStent procedure (0191T) is similar in work, surgical skill, instrumentation, and duration to trabeculotomy ab externo (65850). Furthermore, because the CMS software for claims processing contains no instructions for how to handle modifiers with Category III codes, this can lead to surprises. Because iStent is only inserted at the time of cataract surgery, there are two concurrent procedures. Some claims follow a traditional approach of reducing payment on the lesser procedure by 50%, while other claims are paid at 100% for both procedures. This leads to significantly different payment rates for surgeons around the country. For those ophthalmologists who comanage cataract surgery and use modifiers 54/55, there is no practical way to handle a concurrent claim for 0191T, or any other Category III code, for shared post-op care. The surgeon is obliged to perform the postop care, which just might be best for patients for a new MIGS procedure.

CMS does, in many cases, establish facility payment rates for Category III codes. The facility payment rates, for hospital outpatient departments and ambulatory surgery centers, fall with the Outpatient Prospective Payment System (OPPS) (Table 4).

Beneficiaries Financial Responsibility
As we’ve seen, reimbursement for new technology is bumpy and difficult to foresee. In cases where pre-authorization is denied or health insurance coverage is uncertain, the beneficiary may be financially responsible. Relatively few patients (~10%) can accept this uncertainty and have sufficient financial resources to pay out-of-pocket. Surgeons and facilities may face bad debt when the beneficiary refuses to pay after the fact. Additionally, the regulations of Part B and Part C Medicare generally favor the beneficiary, and do not hold them financially responsible unless the provider strictly follows the rules for financial waivers or the Advance Beneficiary Notice of Noncoverage (ABN).

In this regard, the presurgical informed consent process is conflated with economic counseling and financial arrangements. When the reimbursement uncertainty is too great, a surgeon must offer the patient an alternative glaucoma procedure or take a different tact for treatment.

A Slow Process
It is exciting to learn and perform a new surgical procedure. Optimism about something new is pervasive. Yet, payers are usually not enthralled, at least not initially. They need to be convinced. That takes time and persistence. Until the merits of the new procedure become manifest, reimbursement is hard to come by, and without reimbursement, it is very difficult for a surgeon or a facility to move forward.

So, it is a chicken and egg kind of problem. As we strive to practice evidence-based medicine, progress can be slow. Only the MIGS procedures with superior results and widespread surgeon acclaim can expect to garner reimbursement quickly. GP

References

Kevin J. Corcoran, COE, CPC, CPMA, FNAO, is president and co-owner of Corcoran Consulting Group.
Performing minimally invasive procedures shouldn’t be limited to cataract surgery. The Kahook Dual Blade’s intuitive design enables safe and precise excision of trabecular meshwork to access multiple collector channels and maintain natural outflow, anytime it is needed.

Learn how the Kahook Dual Blade lets you perform without limits. Visit KDBcert.com
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- Minimally invasive—a 6-mm gel stent designed to be implanted through a small corneal incision
- Established effectiveness and safety

INDICATIONS
The XEN® Glaucoma Treatment System (XEN® 45 Gel Stent preloaded into a XEN® Injector) is indicated for the management of refractory glaucomas, including cases where previous surgical treatment has failed, cases of primary open-angle glaucoma, and pseudoexfoliative or pigmentary glaucoma with open angles that are unresponsive to maximum tolerated medical therapy.

IMPORTANT SAFETY INFORMATION
CONTRAINDICATIONS
XEN® Gel Stent is contraindicated in angle-closure glaucoma where angle has not been surgically opened, previous glaucoma shunt/valve or conjunctival scarring/pathologies in the target quadrant, active inflammation, active iris neovascularization, anterior chamber IOL, intraocular silicone oil, and vitreous in the anterior chamber.

WARNINGS
XEN® Gel Stent complications may include choroidal effusion, hyphema, hypotony, implant migration, implant exposure, wound leak, need for secondary surgical intervention, and intraocular surgery complications. Safety and effectiveness in neovascular, congenital, and infantile glaucoma has not been established. Avoid digital pressure following implantation of the XEN® Gel Stent to avoid the potential for implant damage.

PRECAUTIONS
Examine the XEN® Gel Stent and XEN® Injector in the operating room prior to use. Monitor IOP postoperatively and if not adequately maintained, manage appropriately. Stop the procedure immediately if increased resistance is observed during implantation and use a new XEN® system. Safety and effectiveness of more than a single implanted XEN® Gel Stent has not been studied.

ADVERSE EVENTS
The most common postoperative adverse events included BCVA loss of ≥ 2 lines (≤ 30 days 15.4%; > 30 days 10.8%; 12 months 6.2%), hypotony IOP < 6 mm Hg at any time (24.6%; no clinically significant consequences were associated, no cases of persistent hypotony, and no surgical intervention was required), IOP increase ≥ 10 mm Hg from baseline (21.5%), and needling procedure (32.3%).

Caution: Federal law restricts this device to sale by or on the order of a licensed physician. For the full Directions for Use, please visit allergan.com or call 1-800-678-1605. Please call 1-800-433-8871 to report an adverse event.

1. XEN® Directions for Use. 2. CyPass® Directions for Use. 3. iStent® Directions for Use.

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