2018

MELTON, THOMAS, AND VOLLMER'S

21st CENTURY PERSPECTIVE ON GLAUCOMA PATIENT CARE


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Activity Contents

From the Authors

Dear Colleagues:

Welcome to this special activity on glaucoma patient care. There are two notable disease processes, among many, in which optometrists should hold impeccable competence: These two processes are glaucoma and dry eye disease.

In this activity, we will comprehensively cover all the salient features of glaucoma patient care, including diagnosis, medical therapy and numerous clinical pearls.

We will introduce newly approved glaucoma medications and discuss how they can be integrated into the contemporary care of patients with glaucoma.

As the population ages, the demand for ever-expanding eye care services grows, especially in the care of patients with glaucoma. With these newer ophthalmic medicines, the ability to lower intraocular pressure has never been more advanced.

We hope you find the information shared herein will enable you to provide state-of-the-art glaucoma care in your respective practices.

Sincerely,

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Disclosure: Drs. Melton and Thomas are consultants to, but have no financial interests in, Bausch + Lomb and Icare. Dr. Vollmer has no financial interests in any company.

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Diagnostic Considerations

Introduction

The title of this activity is clear: Optometrists treat patients with glaucoma — not just glaucomatous optic neuropathy. Treating fellow human beings makes the disease entity that much more important, and more challenging. Most people think that as long as they see well, their eyes are fine. Few truly understand the importance of regular eye care and screenings for asymptomatic diseases, such as glaucoma.

Human beings are not utopic patients, and many seem oblivious to the need for consistent adherence to and compliant use of their medications. To further complicate matters, pharmacies and insurance companies make their own bureaucratic intrusions into our best efforts to prescribe attentively for our patients. These companies may have legitimate concerns, but they pale in comparison to the higher calling of preserving sight and enhancing quality of life. One final sobering perspective is that lawsuits regarding “missed glaucoma” are commonly successful. Indeed, the most common reason (by far), “failure to diagnose,” represents the pinnacle of litigation. Before delving into therapeutic intervention, particularly regarding topical medications, let’s take a brief look at diagnostic considerations. After all, proper therapy is predicated upon a solid diagnosis.

Lest one think either diagnosis or medical management is always crystal clear, we want to assure the reader that many cases are diagnostically nebulous; fortunately, therapy is relatively less challenging.

Diagnostic considerations

Optometrists should first consider patient history to screen for a positive family history of glaucoma, particularly among siblings. A positive parental history is less important than a positive contemporary sibling history. Most patients are in their 50s or 60s when they receive a diagnosis of glaucoma; this means that your glaucoma suspect patient could have parents who were most likely diagnosed in the latter part of the 20th century. At that time, intraocular pressure (IOP) of more than 21 mm Hg was generally treated as glaucoma, irrespective of optic nerve head health, and pachymetry was not yet known to be of importance. Therefore, we place more diagnostic consideration on the ocular health status of the siblings, who are more likely to have been diagnosed using more recent diagnostic guidelines.

Beyond a solid family history of disease, we next carefully evaluate the character of optic nerve head anatomy. This is the most critical diagnostic maneuver, especially noting the neuroretinal rim tissue

integrity, particularly the inferotemporal and superotemporal tissues of the optic nerve, as these tissues are most susceptible to IOP microtrauma **(Figure 1)**.

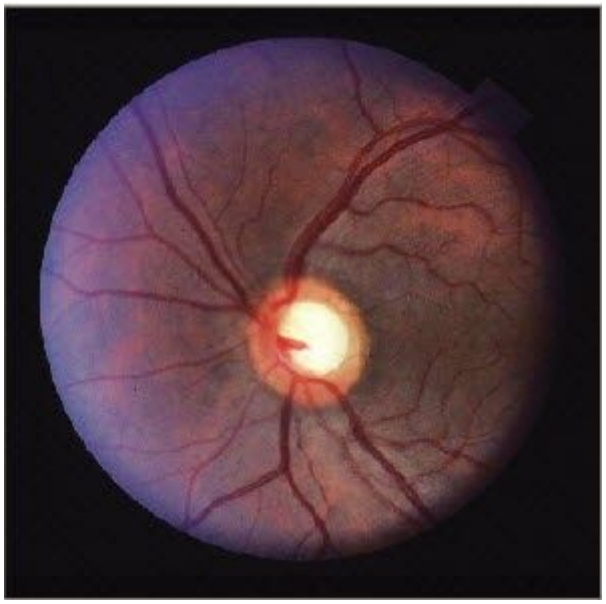


Figure 1. This image shows a suspicious-appearing optic nerve head, but note the healthy-appearing neuroretinal rim tissues, which honors the ISNT — or inferior, superior, nasal, temporal — rule.

Next, measure IOP with either a Goldmann (Haag-Streit) or Icare tonometer **(Figure 2)**. Note, however, that IOP without pachymetry is relatively worthless. It is critical to know if the cornea is thin (<500 µm), either physiologically or from alteration via refractive surgery, normal (500 µm to 580 µm) or thick (>580 µm). A physiologically thin cornea is an independent risk factor for glaucoma, while a cornea thinned through refractive surgery must be accounted for in roughly estimating its impact on IOP measurements. It is stressed that no accurate nomograms exist for calculating exact IOP based on corneal thickness. All that is needed is a characterization of thin, normal or thick — nothing more.

Figure 2. The Icare Tonometer (left) is a handheld unit that requires no topical anesthesia, which is a superb upgrade from air-puff tonometry, and may ultimately replace the Goldmann tonometer (right) as the gold standard.

Patient case: Acute onset of floaters

In our practices, we commonly see normotensive patients with cup-to-disc (C/D) ratios of 0.7 (or higher) who have been diagnostically "missed," because the normal IOPs lured the previous eye doctor into diagnostic complacency. The following example is a case study of a patient seen by one of us (RM):

A 62-year-old woman experiences an acute onset of floaters, and rather than see her habitual optometrist, she seeks medical attention elsewhere, because she now has a symptom that she thinks requires the care of an ophthalmologist; she decides to visit a large ophthalmology clinic where she saw one of us (RM). This is a common patient behavior, primarily because optometrists fail to educate their patients that they can provide comprehensive eye care. It is imperative that optometrists inform their patients that they are skilled to care for a wide array of eye conditions and do not just perform routine eye exams for glasses and contacts.

In this example case of the female patient with the sudden onset of floaters, the obvious diagnosis is an acute posterior vitreous detachment (PVD), but the new doctor (RM) she ended up seeing at the clinic observes a C/D ratio of 0.7 and feels obligated to conduct a comprehensive glaucoma workup at the follow-up visit in 1 month (Note: The large disc hemorrhage **[Figure 3]**, which occurred at the time of the PVD, had resolved by the 1-month follow-up visit). The patient's IOP measurements were 18 mm Hg in the right eye and 19 mm Hg in the left eye at the initial visit (coincidentally, the patient's

mother is also being actively treated for glaucoma). At the 1-month follow-up visit, the patient's floaters had greatly subsided, and repeat retinal examination revealed no tears or breaks.

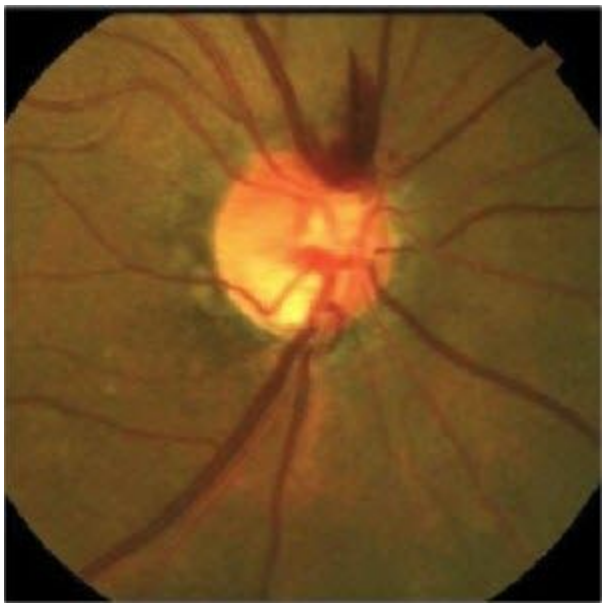


Figure 3. This large disc hemorrhage resulted from the microtrauma of an acute, symptomatic PVD and was fully resorbed by the patient's 1-month follow-up visit. More important to note is the thin neuroretinal rim tissue inferiorly.

The patient's visual fields **(Figure 4)** perfectly correspond to the appearance of her optic nerve heads showing thinned inferior retinal nerve fiber layer. Because her impressive visual field loss occurred over many years, the patient was asymptomatic to her visual field loss (remember, the goal of glaucoma care is to keep the patient asymptomatic for as long as they live). So, in this respect, all is well.

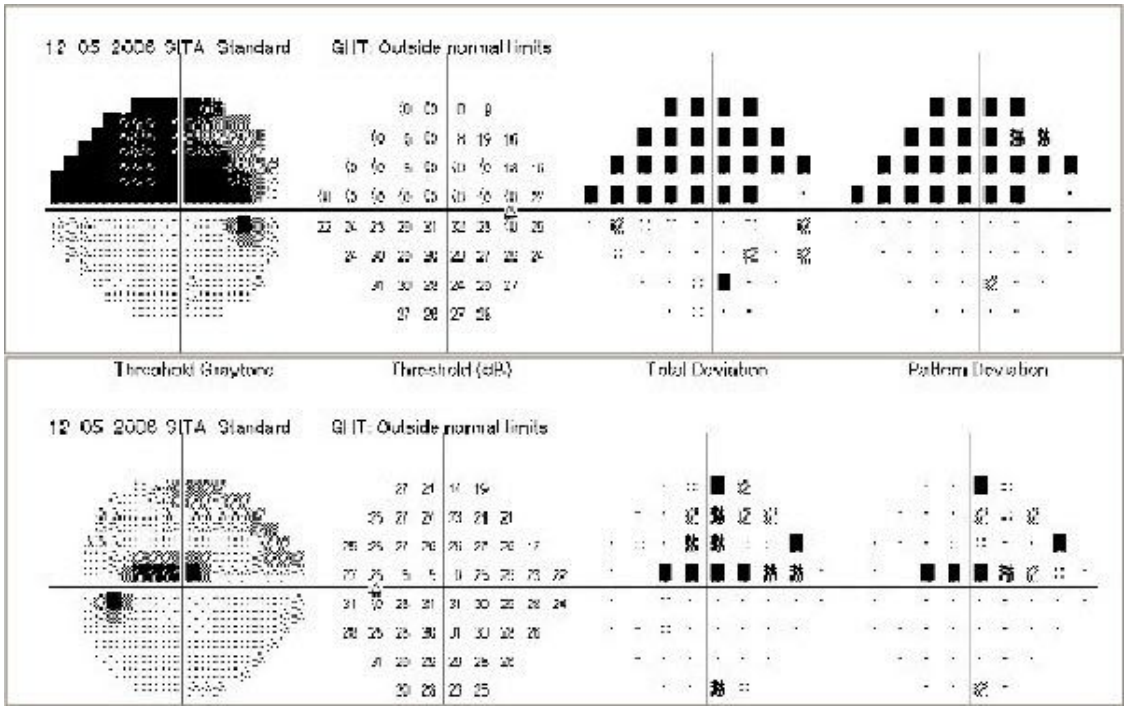


Figure 4. Looking at the pattern deviation probability plots, one can readily note near-total superior loss OD and early superior loss OS. Because the patient's scotomas evolved over several years, she was asymptomatic to this loss of field.

The patient's IOP measurements at follow-up were even lower than at her initial presentation (16 mm Hg in the right eye and 15 mm Hg in the left eye). This clearly demonstrates the relative unimportance of IOP compared with attentive ophthalmoscopy via slit lamp-with-condensing-lens observation. Despite efforts to have the patient return to her optometrist of many years, she chose to stay with her new doctor. This case illustrates the importance of not only providing good comprehensive care to patients but also ensuring your patients know you are skilled to treat a variety of eye conditions.

Diagnostic summary

Although glaucoma diagnosis is usually straightforward, sometimes it can be challenging. If the comprehensive evaluation is inconclusive, do not worry. Clearly, the case is not obvious glaucoma, so simply see the patient every few months for follow-up, repeating the indicated testing as often as is medically necessary. If diagnostic testing remains stable over the years, then it is not glaucoma, because by definition, glaucoma is a progressive optic neuropathy. If, over time, the evaluation yields enough data to make a firm diagnosis, then, depending on numerous factors and considerations, continue to attentively follow the patient, or initiate treatment. There are two pivotal

challenges in caring for patients: making a timely and accurate diagnosis; and determining whether and when to initiate therapy.

Both aspects of patient care require good training, clinical seasoning and deep thought. Remember, if there is a struggle with such decision-making, do not hesitate to get a second opinion from an optometric colleague, and understand that any other doctor will be challenged as well.

In summary, optometrists should perform at least the following diagnostic steps:

- Screen for family history of glaucoma, especially among siblings.
- Study the optic nerve head, especially the inferotemporal and superotemporal rim tissues.
- Obtain IOP and pachymetry measurements.
- Obtain a nerve fiber layer analysis if there is any doubt. If the nerve fiber layer analysis is questionable or pathological, then obtain a 24-2
- ·visual field.
- Perform gonioscopy **(Figures 5, 6)** if there is questionable angle patency.

By performing these diagnostic maneuvers, it would be virtually impossible to miss glaucoma.

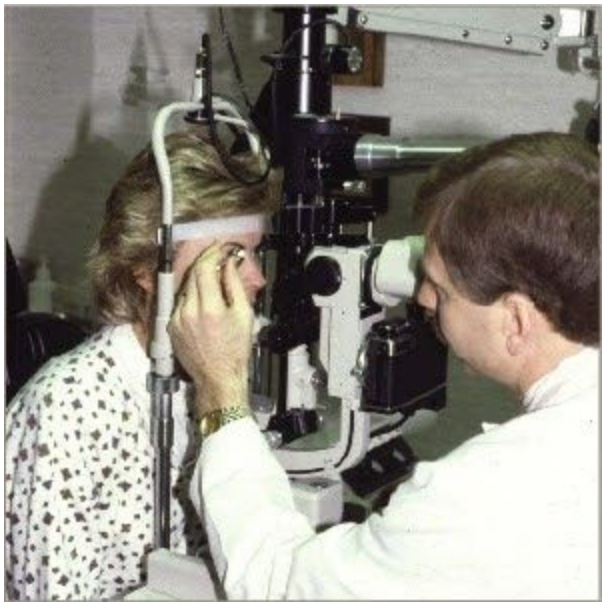


Figure 5. Performing four-mirror gonioscopy.

Figure 6. The four-mirror gonioscope (top), our favorite, and the Goldmann three-mirror lens (bottom).

Oral Topiramate

Topiramate (Topamax, Janssen) is a commonly used medication specifically indicated for seizure disorders as well as for the prevention of migraine headaches **(Figure 7)**. However, it is even more commonly used off-label to help treat a variety of other conditions, including obesity, eating disorders, bipolar disorder, obsessive-compulsive disorder, idiopathic intracranial hypertension, neuropathic pain and other esoteric conditions. Topiramate is well known to be able to cause ciliary body effusion, which is uncommon but results in anterior rotation of the iridolenticular diaphragm. Such rotation induces myopia by moving the lens anteriorly, and increases IOP by (usually incomplete) angle-closure. This iatrogenic event is bilateral because it is an idiosyncratic expression of an orally administered drug.

Figure 7. Oral topiramate (Topamax).

Topiramate-induced myopia and ocular hypertension results from swelling (effusion) of the ciliary body. Therefore, medical management is unique and distinctly different from that of typical anatomic angle-closure. The first step is to stop the topiramate. If the patient is using the drug for seizure control, then the prescribing neurologist (or if after office hours, then the on-call neurologist) needs to be consulted. However, for other less critical uses such as for the prevention of migraine headache

or weight loss, the patient should just unilaterally discontinue using the drug and notify the prescriber as soon as it is practical to do so. We also need to relax the ciliary body; thus, a cycloplegic agent, such as cyclopentolate is used. Never use pilocarpine because as an anticholinergic, it can induce slight swelling of the ciliary body, which is the exact process we are trying to counter. Next, depending on how high the IOP has risen, timolol and/or brimonidine can be administered. Prostaglandins are much slower onset agents and rarely have a role in any acute IOP rise.

Last, there is no role for laser photoiridotomy in the treatment of topiramate-induced angle-closure. Therefore, this is a clinical condition that a competent optometrist can fully manage and would not require management from an ophthalmic surgeon. Furthermore, such events do not cause glaucoma but cause only a transient rise in IOP. Interestingly, and distinct from anatomic angle-closure, there is usually little or no pain associated with this condition, and the cause for patient presentation is the induced myopia, and thus blurred vision is typically the chief complaint.

Assessing After-Hours IOP

It is well established that many, if not most, patients sustain their highest intraocular pressure readings outside of office hours. Until April 2017, there was no instrument with which a patient could check his or her own IOP in the comfort of home. Thankfully, the rebound Icare tonometer that has gained widespread use in eye doctors' offices has been reconfigured to allow patients to measure their own eye pressures via the Icare HOME tonometer **(Figure 8)**. Neither the in-office instrument nor the Icare HOME tonometer requires anesthesia, as the testing/measurement procedure is painless.

Figure 8. Icare HOME tonometer.

Many patients who develop glaucomatous optic neuropathy never show an IOP above 21 mm Hg during office hours (this is often categorized as low-tension or normal-tension glaucoma), but how many of these patients actually have IOPs above 21 mm Hg after office hours? We now have the technology to determine more of the true nature of patients' IOP behavior.

In some patients, glaucomatous atrophy progresses despite apparently controlled IOP, based on in-office readings; however, it may well be that these patients experience higher (and as yet undetected) IOPs outside of regular office hours. Now, with rebound tonometry for in-home use, we

can establish a more comprehensive IOP profile of these patients and provide them a higher level of care. Consult www.icare-usa.com for more details.

Many glaucoma patients take oral antihypertensive drugs. It is important that such medications be taken in the morning hours (or certainly by lunch), as it is well known that diastolic blood pressure can become quite low during the sleep cycle; thus, taking an antihypertensive medicine at bedtime may further suppress an already physiologically lowered nocturnal blood pressure. Having such pathologically low diastolic pressure can diminish blood flow to the optic nerve, thereby potentiating damage to the optic nerve and worsening the glaucoma. It would be beneficial to have a parallel technology that allowed patients to monitor blood pressure at home during sleep cycles. It is important to note that pathologically low diastolic blood pressure also sets the stage for stroke and nonarteritic anterior ischemic neuropathy.

Glaucoma, in many ways, is an enigmatic disease. Whatever optometrists can do to bring further insight and characterization of IOP behavior can enhance our ability to optimize patient care.

The Risks of Undetected Narrow-Angle Glaucoma

Most cases of glaucoma are straightforward, but a large subset of patients develop narrow-angle glaucoma **(Figure 9)**. These patients tend to be older, hyperopic women with Asian ancestry, particularly that of Chinese. Screening for this less common expression of glaucomatous optic neuropathy by expert slit lamp examination is critical. If the angles appear to be Van Herick grade 1 or lower, then gonioscopy should be performed. If the angles are judged to be potentially occludable, then either laser photoiridotomy must be performed, or clear lens extraction must be considered. For patients older than 50 years of age with significant hyperopia, the latter would be the preferred option, as this would provide enhanced visual function and eliminate the risk for angle-closure. For doctors who have anterior segment OCT technology available, this could either replace gonioscopy or be adjunctive. Gonioscopy is real-time viewing of in vivo tissues and further allows for quantifying the degree of angle pigmentation. An image of angles judged to be occludable is seen in **Figure 10**. There is a hint of plateau configuration as well.

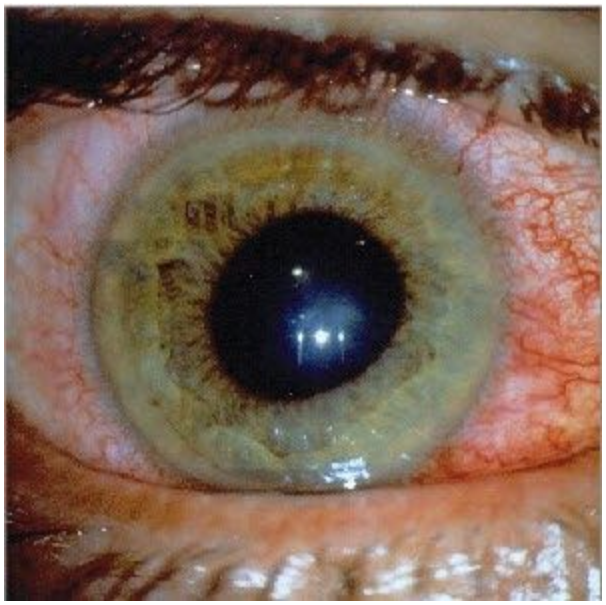


Figure 9. An eye in acute angle-closure; note the mid-dilated, out-of-round pupil.

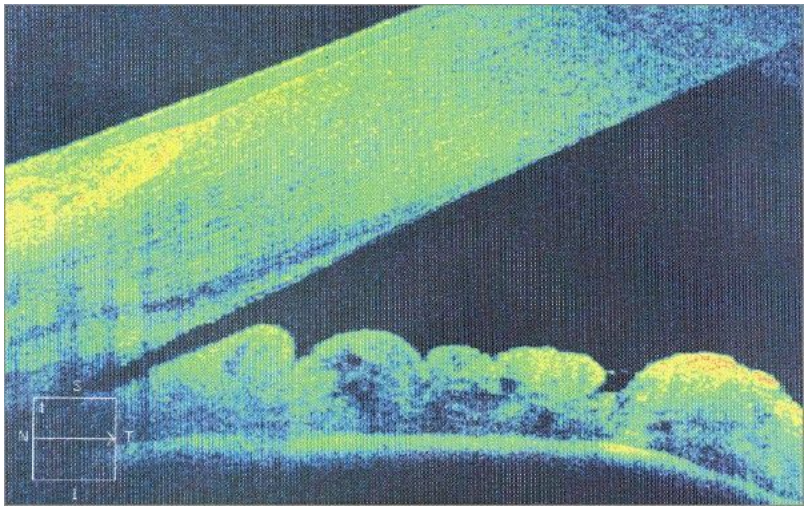


Figure 10. An anterior segment OCT image of an occludably narrow iridocorneal angle.

Ocular Perfusion Pressure

Ocular Perfusion Pressure

Stated simply, a good blood supply to the optic nerve is essential for its health. A sort of tug-of-war occurs here, in which the intraocular pressure presses against the optic nerve head, and systemic blood pressure tries to perfuse these same tissues. Again, simply stated, the ocular perfusion pressure is the arithmetic difference between the diastolic blood pressure and IOP. When this number is 50 or lower, there is an increasing risk for glaucomatous progression. For example, if the patient has a blood pressure of 110/65, and IOP is 20 mm Hg, then the ocular perfusion pressure is 45 mm Hg, thus placing this patient at increased risk for glaucoma development and/or progression.

The concern here is twofold: First, a subset of patients has quite suppressed nocturnal hypotension and are known colloquially as — “dippers” — that is, their diastolic blood pressure dips low enough to suboptimally perfuse the blood supply to the optic nerve. Of note, these same individuals are also at risk for anterior ischemic neuropathic events. Second, because of an epidemic of systemic hypertension in the United States, numerous patients take medication to reduce their hypertension with the general intent of reducing their risk for stroke; however, these medicines, especially calcium channel blockers, can greatly decrease blood pressure. Thus, this subset of patients — “dippers” — who have glaucoma and who take one or more of these oral hypotensive medications, could be experiencing suboptimally low nocturnal blood pressure.

What does all this mean? Patients with normal-tension glaucoma who also take an oral hypotensive medication could be unintentionally hindering the health of the optic nerve. In these situations, which are common, we revisit the medical history. If a patient is taking one of these oral hypotensive drugs in the evening, then we write the prescribing doctor and ask him or her to consider directing the patient to take the blood pressure medication(s) in the morning, rather than in the evening. This is a well recognized and scientifically sound consideration, and one that requires a team approach with general medical providers. Furthermore, this is yet another reason it is important to measure the patient’s blood pressure in the office, especially if he or she is a glaucoma patient who has normal IOP.

Finally, unless we are checking the IOP at different times of the day or are embracing Icare HOME tonometry, what we assume to be normal-tension glaucoma could well be missed (or undetected) increased IOP. Of course, pachymetry also must be considered in assessing IOP.

Missed Glaucoma

A male patient in his 50s visited our office once he moved to the area. He previously was being followed for 3 years as a glaucoma suspect by an ophthalmologist (it could have just as easily been an optometrist) in his former city of residence. The patient's intraocular pressures had always been in the low 20s mm Hg with normal pachymetry readings, and his optic nerve head had had C/D ratios of about 0.7 in both eyes.

When this patient was seen by one of us, his intraocular pressures were indeed in the low 20s mm Hg, but his visual fields showed several nasal scotomas. Something did not seem quite right with this picture, so the patient was asked to return the next morning for a repeat IOP measurement.

The patient was a school teacher and had always been seen by his previous doctor in the late afternoons; his initial visit with us also was in the late afternoon. Thankfully, it was summertime, and the patient was able to visit the next morning, as we requested. His intraocular pressures at 8:30 a.m. were in the low 30s mm Hg, and now the clinical picture made complete sense. When we obtained this patient's medical records from the previous office, it became evident that the patient's second visual field test performed there showed evidence of progression, yet the chart stated "no change" (probably because the doctor was looking at the gray scale plots **[Figure 11]** and not at the pattern deviation probability plots, which clearly showed probable progression). We know the second field was indeed true progression because the third visual field, obtained in our office, showed even further progression **(Figure 12)**.

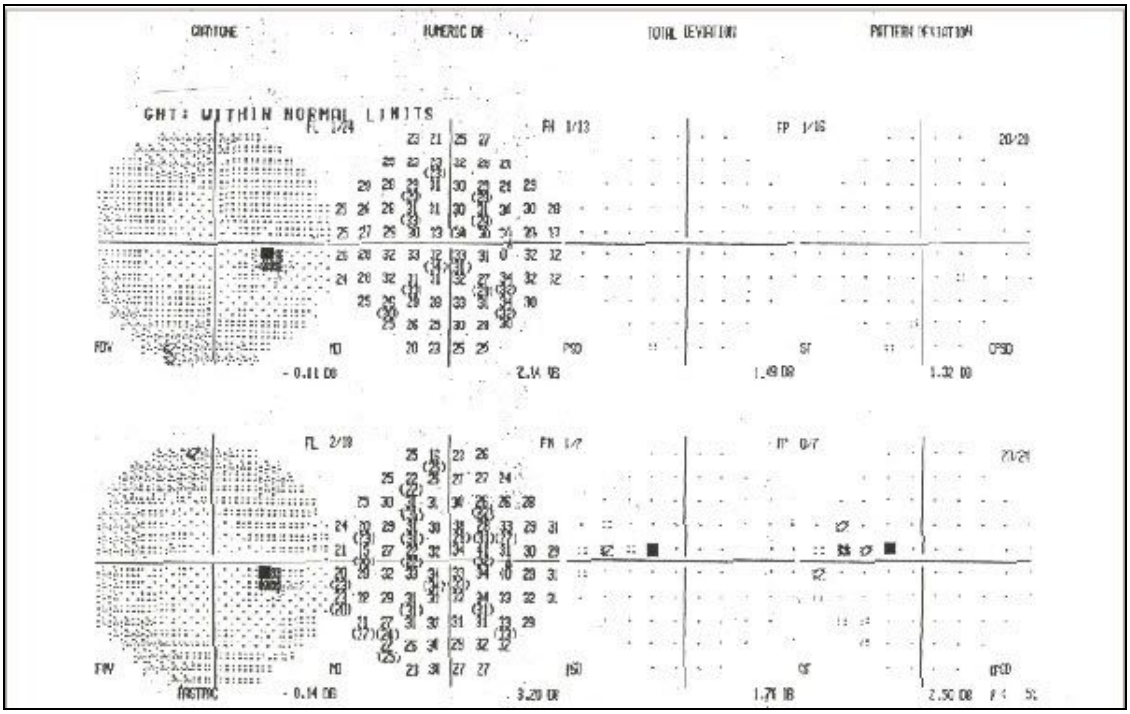


Figure 11. This eye doctor's chart noted "no change" because he was looking at the gray scale, not the pattern deviation probability plots in which a cluster of nasally located scotomas were readily observed.

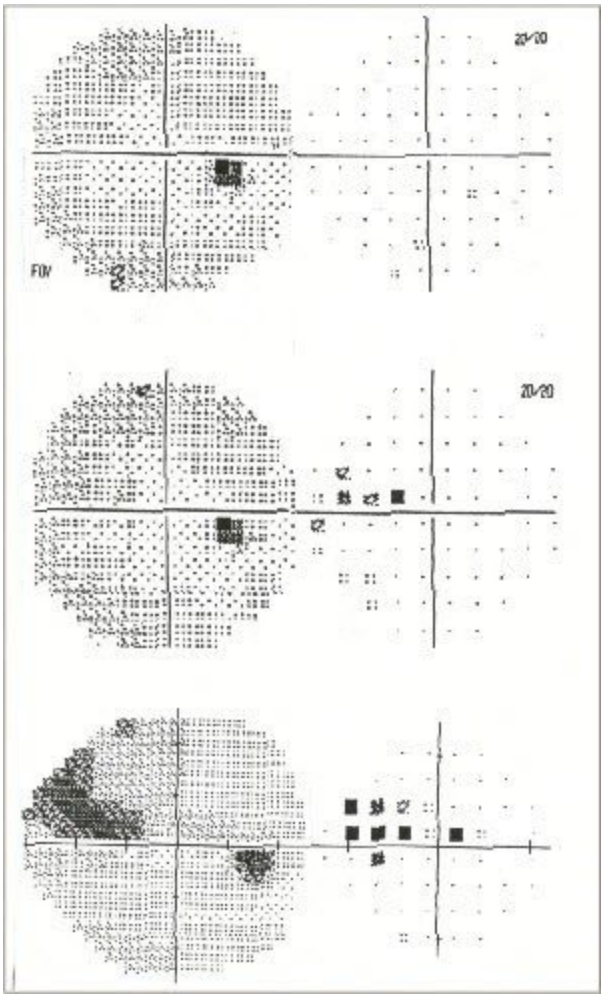


Figure 12. After obtaining a third visual field, it can be readily observed that the cluster of nasal scotomas seen previously has grown, indicating progressive glaucomatous optic neuropathy.

Now, we have a solid diagnosis mandating therapeutic intervention. At that time, latanoprost was prescribed, and a few years later, a second drop was added to the patient's regimen to achieve a target range of IOP. Had we first seen the patient in 2018, we would have initiated therapy with Vyzulta (latanoprostene bunod 0.024%, Bausch + Lomb) in the hope that it would outperform latanoprost and delay the need for adding a second drop by a few years.

Two lessons can be learned from this case. First, it is important check IOP at different times of the day to avoid missing swings in the diurnal pattern (Icare HOME tonometry would further enhance this search for peak IOP by including IOP readings outside of regular office hours). Second, the eye doctor must know how to competently read and interpret visual field data.

For neurologic fields, observing the gray scale of a 30-2 is sufficient, because most neurologic field cuts are relatively absolute, whereas in glaucomatous optic neuropathy the compromised tissues tend to cause softer visual field defects.

The key to glaucoma care is to be ever vigilant. Miss nothing and provide careful, attentive follow-up care.

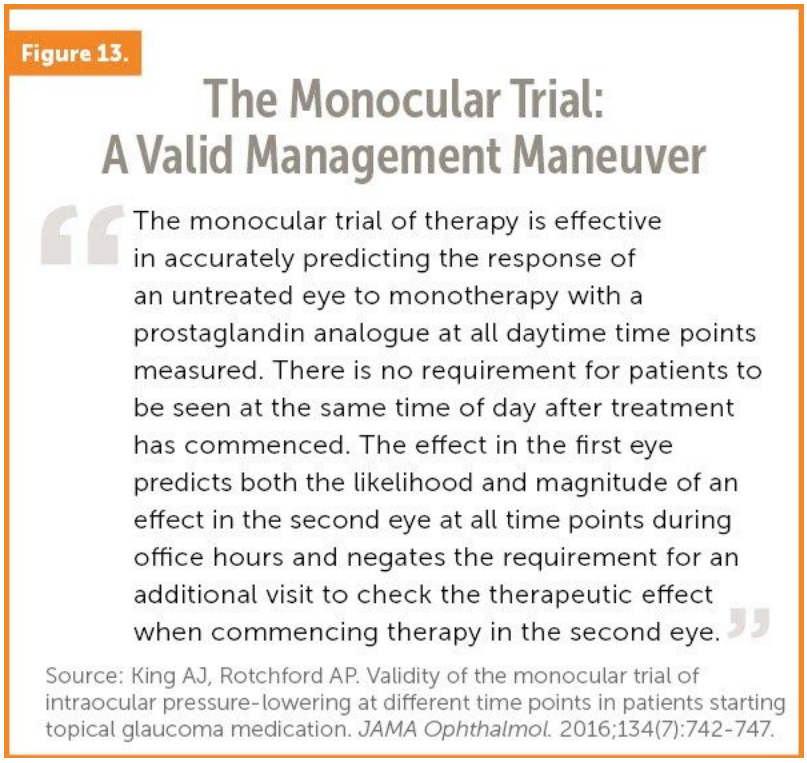
The Monocular Therapeutic Trial

The monocular trial has been both endorsed and maligned over the years, yet the consensus of expert study and opinion solidly supports this management maneuver; we have found it to be highly complementary to our care of patients with glaucoma over the decades.

Note that timolol exerts a slight crossover effect, such that the untreated eye will demonstrate about 20% of the effect seen in the treated eye. This behavior needs to be taken into consideration when assessing efficacy. The other commonly used glaucoma medications do not demonstrate such a crossover effect.

Our standard approach with monocular trials is to provide a sample of the intended drug to be used in the eye with the highest baseline IOP or in some cases, in the eye with more advanced optic nerve head damage.

Optometrists should thoroughly discuss with the patient that the sole purpose of the medication is to reduce the pressure inside the eye, and that he or she will not feel any differently or see any better while using any topical glaucoma drop. Explain to the patient that the only way to tell if the drug is of benefit is to remeasure the eye pressure at an appropriate interval. If a meaningful reduction is achieved, then ask the patient to continue using the drop indefinitely and almost always in both eyes. By performing this monocular trial, optometrists can avoid being led astray by physiological diurnal fluctuations **(Figure 13)**.



Then, there is the reverse monocular discontinuation trial. Americans are on the move — mostly from colder to warmer climates. As such, we see an increase of patients who have been previously treated for glaucoma by other eye doctors whose level of expertise is unknown to us. Depending on the patients' abilities to describe their medical history, evaluation and care, and most importantly, the anatomic status of the optic nerves, presenting IOP and current eye drops, we normally ask them to discontinue their eye drops and allow us to recheck their IOP in 3 to 4 weeks. We also ask patients to sign a records release form so that we can obtain their previous medical records and thereby more comprehensively ascertain what has and has not been done in the past. We often find a need to restart the drops, but now we have a better idea of the patient's untreated baseline IOP. However, in about 25% of these patients, we find no need to continue the drop(s), as either the drop(s) were not working, or the patient was simply being treated for disease they did not have.

Glaucoma is a disease for which optimum management is predicated upon great attention to detail; critical, dynamic thought is always in play.

Spend Time With Your Glaucoma Patients

It is well known that patient education and thus, patients' understanding of their condition(s), enhances adherence and compliance with their medications and follow-up visits **(Figures 14, 15)**.

Figure 14.

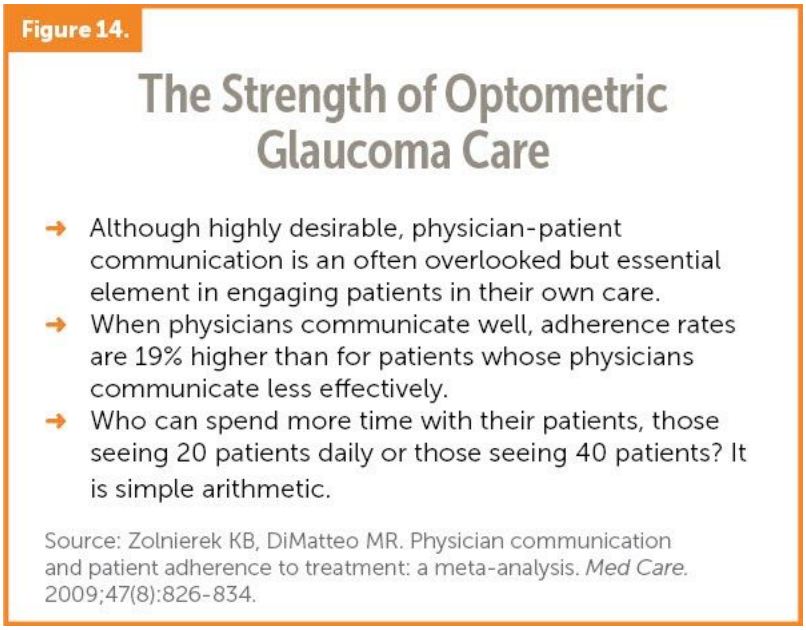


Figure 15.

Help for Nonadherent Patients

Inability to competently instill eyedrops is a key reason for nonadherence.

- Demonstrate to patients exactly how to instill an eyedrop.

Forgetfulness is a second major reason for nonadherence.

- Brainstorm with patients.
- Set a timer if necessary.

Skepticism about glaucoma causing vision loss, or skepticism about glaucoma medicines mitigating that risk may be yet another reason for nonadherence.

- Engage in effective doctor-patient communication.

Source: Newman-Casey PA, Robin AL, Blachley T, et al. Most common barriers to glaucoma medication adherence: a cross-sectional survey. *Ophthalmology*. 2015;122(7):1308-1316.

Many conditions should be “owned” by optometrists (because these are almost always nonsurgical conditions). Three common ones include glaucoma, dry eye disease and hydroxychloroquine (such as Plaquenil from Sanofi-Aventis) retinal toxicity. Spending quality face-to-face time with patients is vitally important to ensure excellence of care. Doctors who see around 25 patients a day should be much better positioned to provide excellent care than a doctor who sees twice that many patients per day; it just makes sense.

Preventing Vision Loss: Importance of Optometry

Optometry is a profession dedicated to preserving and enhancing vision. Therefore, there may be no higher calling for optometrists than to prevent vision compromise or loss in people who are at risk for, or who have glaucoma.

As reported in the November 2017 issue of Primary Care Optometry News, American Optometric Association President Christopher J. Quinn, OD, addressed the Optometric Glaucoma Society during its meeting held just before the 2017 American Academy of Optometry meeting in Chicago, and made quite clear that "*Glaucoma is a serious public health problem in this country. Optometry is the solution … Glaucoma is a disease that this profession should own.*"

Robert D. Fechtner, MD, concurred, stating "*There's no way to take care of this epidemic, except through partnership. The optometric portion of care is the largest portion.*"

Although modulating IOP (no medications are available yet to "treat" glaucoma), is reasonably straightforward, the greatest challenge is in making the diagnosis. This challenge includes not missing glaucomatous optic neuropathy in patients presenting with IOPs in the normal range.

Historically, IOP has been the rudder steering further workup. This is a grossly inadequate algorithmic approach, because a large subset of glaucoma or glaucoma suspect patients do not present with elevated IOP. Medicolegal surveillance clearly shows that, by far, the most common reason doctors of optometry are successfully sued is for failure to diagnose. Virtually 100% of such cases could be avoided if greater attention is paid to the nuanced study of the optic nerve head.

Complicating this situation is the realization that many people experience their highest IOP outside of traditional office hours. Therefore technology, such as the Icare HOME tonometer may facilitate our ability to uncover missed ocular hypertension patients.

Rather than the IOP being the finding that causes us to pursue a comprehensive glaucoma evaluation, our diagnostic approach needs to quickly shift to an attentive study of the optic nerve head. This is best accomplished with a magnified stereoscopic evaluation of this tissue.

Therapeutic management of IOP

Considering that the only known approach to halting or slowing optic nerve atrophy is reducing IOP, we want to focus on the issue of critical medical management. As is reasonably well understood, the physiologic internal ocular plumbing is quite simple: aqueous humor is produced by the

nonpigmented epithelium of the ciliary body and drained through the trabecular meshwork and, to a lesser extent, the uveoscleral tissue. It is also understood that the weak links in aqueous flow are the outflow pathways. Thus, the primary focus of pharmacologic intervention is enhancing aqueous outflow.

However, two commonly used and effective drug classes — nonselective beta-adrenergic receptor blockers and carbonic anhydrase inhibitors — reduce aqueous production as their mode of action. Alpha-adrenergic receptor agonists have somewhat dual mechanisms of action by both inhibiting aqueous production and enhancing unconventional (uveoscleral) outflow.

Pilocarpine, a parasympathomimetic agent, now minimally used because of the largely aggravating ocular adverse effects, nicely enhances conventional (trabecular) outflow by stimulating the contraction of the longitudinal muscles of the ciliary body, thus enlarging the trabecular pores.

The most efficacious class of IOP-lowering medicines, the prostaglandins, stimulates extracellular matrix metalloproteinases in the uveoscleral tissues to make them more porous, thus enhancing aqueous outflow through these unconventional (uveoscleral) tissues.

For historical perspective, the modern era of glaucoma medicines began in 1978, with the advent of timolol **(Figure 16)**. Initially, timolol was administered twice daily, but further research found that once-daily administration shortly after awakening worked as well or nearly as well as twice-daily administration.

Figure 16. Timolol ophthalmic solution.

It was nearly 2 more decades until the prostaglandins (beginning with Xalatan [latanoprost, Pfizer]) entered the market, which relegated timolol (and numerous other beta-blockers) largely to second-tier status. Latanoprost had exclusive status until other prostaglandin competitors entered the market a few years later.

It has since been another 2 decades, and now a new generation of a nitric oxide-donating prostaglandin is available for the care of our patients. The options for medical reduction in human IOP are now more numerous than ever and require us to gain a keener understanding of how all these drugs best play a role in the enduring care of our patients.

Prostaglandins

Let us take a more detailed look at each of these drug classes and develop a more fine-tuned appreciation for their strengths and weaknesses. We will start with the most commonly prescribed class, the prostaglandins. As we shared above, when prostaglandins entered the market in the mid-1990s, this drug class was the single most beneficial contribution to our modest glaucoma armamentarium that had been made in decades. Xalatan then, and generic latanoprost now, is the most commonly prescribed prostaglandin. Despite containing 0.02% benzalkonium chloride (BAK), latanoprost is the most tolerable medication of this class. Its new mechanism of action of enhancing

uveoscleral outflow by potentiating resident extracellular matrix metalloproteinases within the uveosclera, thus making the tissue more porous, was revolutionary.

Generally, traditional prostaglandins reduce IOP by about 30% and have mild conjunctival hyperemia as the most common adverse effect. In phase 3 studies on prostaglandins, two things were learned:

- The drugs perform best when taken in the evening.
- Once-daily dosing is more effective than twice-daily dosing.

Although prostaglandins are best used in the evenings, compliance is enhanced when patients can most consistently remember to instill them. Therefore, if a patient reports that he or she takes all medications with breakfast, then the prostaglandin can also be administered at this habituated time. These medicines work almost as efficiently when taken in the morning, so if this is the time of greatest likelihood for compliance, then morning dosing is fine.

Although uncommon, patients with hazel-colored irides can sustain generalized darkening of these tissues, which is usually only a concern when treating patients with unilateral glaucoma. Even more uncommon is periorbitopathy **(Figure 17)**, which represents a decrease in the population of adipose tissues in the orbit, thus causing a deepening of the superior sulcus, and occasionally an enophthalmic appearance. When reflected against their sight-saving benefits, these adverse effects are relatively inconsequential.

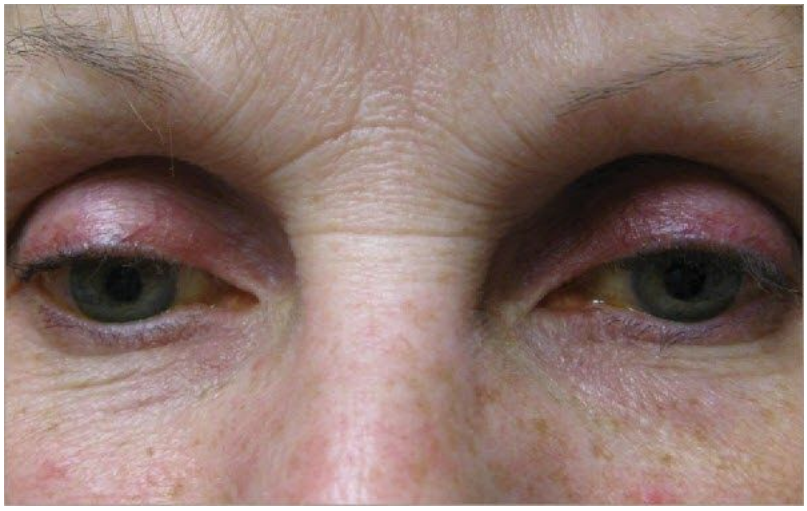


Figure 17. This patient developed periorbitopathy after a few years on a prostaglandin.

Some years later, Travatan Z (travoprost, Alcon), which is BAK-free, and Lumigan (bimatoprost, Allergan) entered the market, followed by tafluprost (Zioptan, Akorn), which is the only preservative-free prostaglandin, a few years later **(Figure 18)**. Like latanoprost, tafluprost is stored under refrigeration until dispensed to the patient.

Figure 18. Latanprost, travoprost (Travatan Z), bimatoprost (Lumigan) and tafluprost (Zioptan) ophthalmic solutions.

The prostaglandin market had a quiescent period for several years until November 2017, when Vyzulta (latanoprostene bunod 0.024%, Bausch + Lomb) broke the silence **(Figure 19)**.

Figure 19. Latanoprostene bunod (Vyzulta).

This totally new, single-entity, dual-action upgrade to the first-generation prostaglandins raises the efficacy to a higher level. The latanoprostene bunod molecule is cleaved into two distinct entities by resident esterases in the anterior eye tissues. Two compounds result from this cleaving: latanoprost acid (the metabolically active form of latanoprost) and butanediol mononitrate, which is subsequently metabolized into nitric oxide, which is thought to relax the smooth muscles of the trabecular meshwork, thereby enhancing conventional (trabecular) outflow. In phase 2 studies, latanoprostene bunod reduced IOP an additional 1.23 mm Hg beyond that of first-generation latanoprost.

Supplementing Glaucoma Treatment

We know about half of all patients with glaucoma will require a second medication along the care continuum. This is yet another reason to reduce the IOP as low as is practical to delay this additional burden as long as possible. It is well known that, as additional drops are added to the regimen, compliance and adherence decline. When prescribing transitions from a single, once-daily drop to the addition of a completely new medication, similar compromise often occurs.

The FDA-approved package insert states that Vyzulta is indicated for “the reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension.” Note that it does not say for “elevated” intraocular pressure but simply for “reduction of intraocular pressure,” thus acknowledging (planned or unplanned) that many patients have normal-pressure glaucoma or are glaucoma suspects. The package insert further shares that, “the IOP-lowering effect of Vyzulta is up to 7 to 9 mm Hg.”

Like latanoprost, Vyzulta is stored under refrigeration long-term at the pharmacy; however, once dispensed to the patient, it can be kept at room temperature for several weeks. Vyzulta is approved for once-daily use (preferably instilled in the evening). This medication is approved for persons ages 16 and older. Mild conjunctival hyperemia was observed in about 6% of study patients. Vyzulta is preserved with 0.02% BAK (just like latanoprost).

We have been using Vyzulta in these four scenarios:

- As first-line therapy to reduce IOP as low as possible. Short of hypotony, you really cannot have too low of an IOP.
- As treatment for patients in whom target IOP is nearly achieved with any of the older generation prostaglandins. We could easily add a once-daily beta-blocker to the treatment regimen of these patients, but this would require the acquisition of another topical preserved eye drop that might not be necessary. (Of course, there is also preservative-free timolol that could be used if necessary.)
- As therapy for patients who have asthma, or for patients who are nonresponders to beta-blockers. In these patients, Vyzulta alone might achieve target IOP.
- As a therapy option when a traditional prostaglandin and a beta-blocker come close to but do not achieve target IOP. Replacing the prostaglandin with Vyzulta might meet treatment goals.

Every Millimeter Counts

“The risk reduction could be about 19% per mm Hg, confirming results from the [Early Manifest Glaucoma Trial] and Canadian Glaucoma Study, and showing that intraocular pressure reduction is highly effective, and that every mm Hg of pressure counts. These results should … serve as a stimulus to the pharmaceutical industry to continue development of new and even more potent drugs.”

Source: Heijl A. Glaucoma treatment: by the highest level of evidence. *Lancet*. 2015;385(9975):1264-1266.

“Elevated IOP is a strong [risk] factor for glaucoma progression, with the [hazard ratio] increasing by 11% for every 1 mm Hg of higher IOP.”

Source: Bengtsson B, Leske MC, Hyman L, Heijl A; Early Manifest Glaucoma Trial Group. Fluctuation of intraocular pressure and glaucoma progression in the Early Manifest Glaucoma Trial. *Ophthalmology*. 2007;114(2):205-209.

“Progression is related to the magnitude of initial IOP change from baseline to the first follow-up visit. This initial change in IOP was strongly and inversely associated with progression. Thus, an IOP reduction of 1 mm Hg from baseline decreased the risk of progression by about 10% in these analyses.”

Source: Leske MC, Heijl A, Hussein M, et al. Factors for glaucoma progression and the effect of treatment: the Early Manifest Glaucoma Trial. *Arch Ophthalmol*. 2003;121(1):48-56.

“Our current understanding of the relationship between IOP lowering in glaucoma onset and progression translates to the effect of each mm Hg IOP reduction on the development of progression of visual field loss.”

Source: de Moraes CG, Liebmann JM, Medeiros FA, Weinreb RN. Management of advanced glaucoma: characterization and monitoring. *Surv Ophthalmol*. 2016;61(5):597-615.

Glaucoma In a Nutshell

Definition: An enigmatic optic neuropathy characterized by progressive optic nerve head cupping that is either caused by or moderated by intraocular pressure and various other factors such as age, genetic predisposition, race, central corneal thickness, trauma and concurrent intraocular disease.

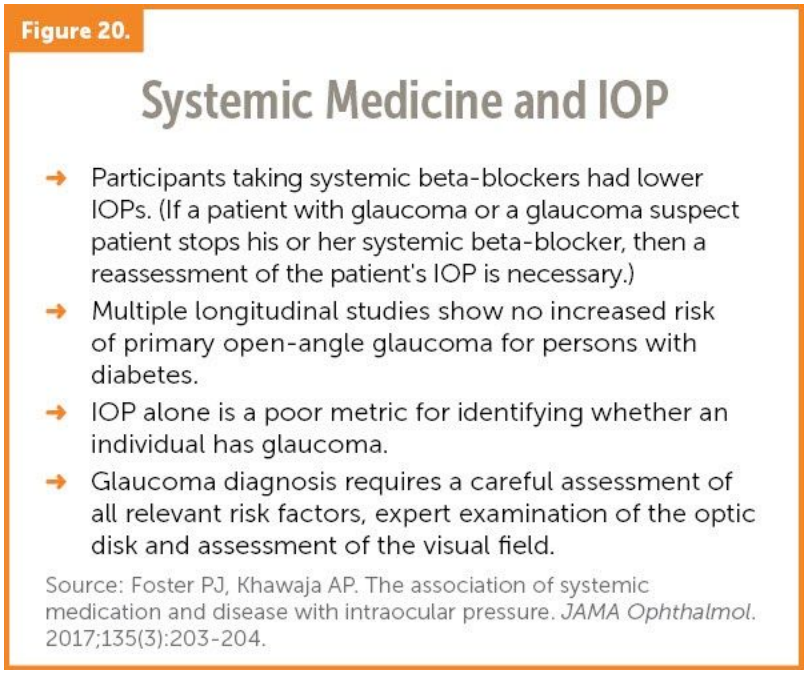
- Glaucoma is a common finding that is usually diagnosed during the course of routine eye examinations.
- When detected early and treated properly, almost all patients remain asymptomatic for life.
- With the newer medicines, such as prostaglandins, alpha-adrenergic agonists, carbonic anhydrase inhibitors and beta-blockers, IOP can usually be lowered to a pressure at which further loss of optic nerve axons is halted or slowed sufficiently to keep the patient asymptomatic.

Treatment: Reduce IOP to a safe level.

- Reduce aqueous humor production.
    - beta-adrenergic receptor antagonists (beta-blockers)
    - alpha-adrenergic receptor agonists (alpha agonists)
    - carbonic anhydrase inhibitors
- Enhance aqueous humor outflow.
    - prostaglandins (uveoscleral outflow)
    - pilocarpines (trabecular outflow)
        - Vyzulta works on both outflow pathways.
    - Netarsudil

Adjunctive Therapies: Beta-Blockers

If the newest generation of prostaglandins fails to achieve target IOP range, then we generally add a nonselective beta-blocker such as timolol to be administered shortly upon awakening **(see Figure 20)**. This dosing schedule is successful for patients who work first, second or third shifts, because the adrenergic system is largely active while we are awake and is physiologically down-regulated when we sleep, even if we habitually sleep during the day. This largely explains why beta-adrenergic receptor antagonists do little or nothing while we sleep.



Numerous studies have found that once-daily instillation sufficiently reduces IOP and is much easier for patients to use than medications requiring twice-daily instillation. Such once-daily administration obviously reduces the cost by 50%, as compared with the early-on, traditional twice-daily use of these medications.

Because melanin pigments bind a portion of the beta-blocker medicine, we use the 0.5% formulation for African-American patients (a higher percentage of the formulation is needed because of the binding difference of the melanin pigments), and 0.25% for Caucasian and Asian patients.

Beta-blockers for the patient with asthma

Systemically, beta-blockers are consistently in the top 10 of most prescribed medications. This clearly demonstrates their benefit to human medicine. The only relative contraindication for the use of beta-blockers is in patients with asthma. Note that we use the word “relative” as opposed to “absolute” contraindication. It is now well established that a sizable minority of patients with asthma can safely use a topical beta-blocker. On those rare occasions when we need to prescribe a beta-blocker in the treatment of a patient with asthma, we have a written confirmation in our medical record from the patient’s asthma physician stating it is permissible for us to do so **(Figure 21)**. This has enabled us to safely and efficiently achieve target IOP in this small subset of patients.

I have had the privilege to begin caring for this forty-eight year old gentleman dating back in April 2015 for his ongoing glaucoma. He is reasonably well-controlled on a prostaglandin eye drop but I feel the need to further decrease his intraocular pressure. I almost always add a topical ophthalmic beta-blocker in these circumstances. Mr. Curry tells me that he had asthma when he was a younger boy but has not been bothered by asthma now in over thirty years. As his internist, I would greatly value your perspective on the safety of my using a topical beta-blocker in his care. If you would drop me a quick a note, and give me your perspective on this therapeutic intervention, I would be most grateful.

Thank you for your help in our mutual care of this gentleman.

Sincerely,

Randall Thomas

Randall K. Thomas, OD, MPH

Figure 21. This is an example of a succinct letter to the patients' primary care physician. Once written approval is obtained, then it is reasonable to try a topical beta-blocker in some patients with asthma.

One could argue the point for simply bypassing the beta-blocker class altogether in patients with asthma and just prescribe a topical carbonic anhydrase inhibitor or topical alpha-2 adrenergic receptor agonist **(Figure 22)**. This is a reasonable alternative approach, but the patient then would incur higher cost and require twice-daily dosing — both of which are known to negatively affect adherence and compliance.

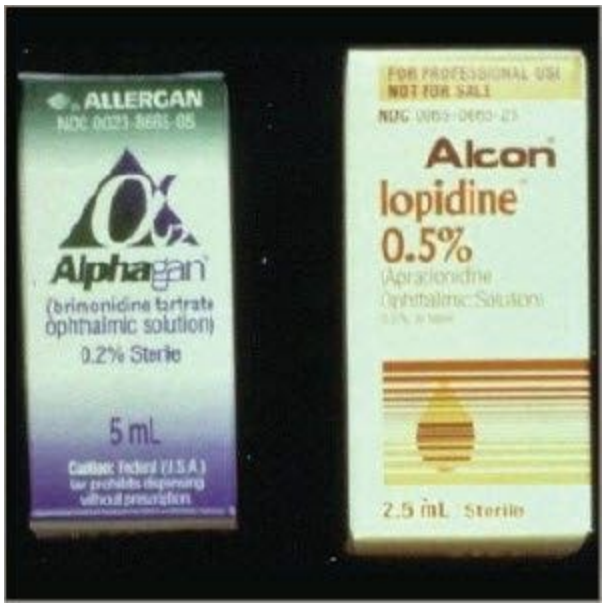


Figure 22. Brimonidine tartate (Alphagan, Allergan) and apraclonidine hydrochloride (Iopidine, Alcon) ophthalmic solutions.

Most patients achieve target IOP with a prostaglandin alone. When our hand is forced to add a second drop to the treatment regimen, we almost always prescribe a beta-blocker. We instruct the patient to administer the prostaglandin in the evening and administer the beta-blocker shortly after awakening. We never use a combination drop as additive therapy, unless therapeutic trials of the two individual generic drugs have demonstrated efficacy, and the drugs are truly necessary to achieve target IOP.

While the wisdom of conducting such trials has had its detractors over the years, the preponderance of the literature supports their general use, and we conduct such trials as a matter of conscientious habit. Yes, there is a crossover effect with the beta-blockers in that whatever effect is seen in the actively treated eye, an approximately 20% effect will be seen in the fellow eye; we consider that in

assessing overall efficacy. Although we strive to schedule the follow-up IOP recheck visit near the same time of day as the initial check, there is some thought that it really does not make a meaningful difference, and this could well be true. Specifically regarding the beta-blocker trial, we ask the patient to instill the drop every morning, except for the morning of the follow-up visit; this enables us to be certain of good 24-hour efficacy.

The key to successful glaucoma treatment is keeping dosing schedules as simple as possible; however, there are many times when it becomes necessary to resort to the three other categories of IOP-lowering medicines, which are alpha-2 adrenergic receptor agonists, carbonic anhydrase inhibitors and, more recently, a Rho-kinase inhibitor.

Adjunctive Therapies: Alpha-2 Adrenergic Receptor Agonists, Carbonic Anhydrase Inhibitors, Rho-Kinase Inhibitors

Alpha-2 adrenergic receptor agonists

Brimonidine is the only alpha-2 selective adrenergic receptor agonist available. It is FDA-approved for three-times-daily administration. Brimonidine is rarely used three times daily because of expense and clinical need. It is well established that brimonidine works for about 8 hours, and that its effect is minimal during the sleep cycle. This is why we instruct our patients to instill the drop first thing in the morning (within 10 to 15 minutes of waking), and then to instill the second drop about 8 hours later (generally 4:00 p.m. to 5:00 p.m.), to harness the medicine's greatest therapeutic action. We further instruct our patients to use a timer or recurring reminder on their cell phone to enhance compliance with the afternoon drop.

For the treatment of patients with glaucoma, brimonidine is available in four ways:

- The original 0.2% concentration (to which a sizable minority of patients ultimately develop an allergic response **[Figure 23]**);
- A 0.15% concentration, which has less potential for allergy but is more expensive compared with the 0.2%, even though both are available generically;
- A 0.1% concentration, which remains brand name-protected as Alphagan-P (Allergan); it performs equally as well as the 0.2% and 0.15% counterparts but is more expensive. Because the odds for successful therapy are with us from both an efficacy and tolerability perspective, we always prescribe the 0.2% concentration because of cost, and we typically only default to a topical carbonic anhydrase inhibitor if allergy develops. As always, marketing and pharmacy expense force all of us to try to balance cost, tolerance and efficacy — it's an ever-dynamic game.
- A combination of 0.2% brimonidine and 0.5% timolol (Combigan, Allergan).

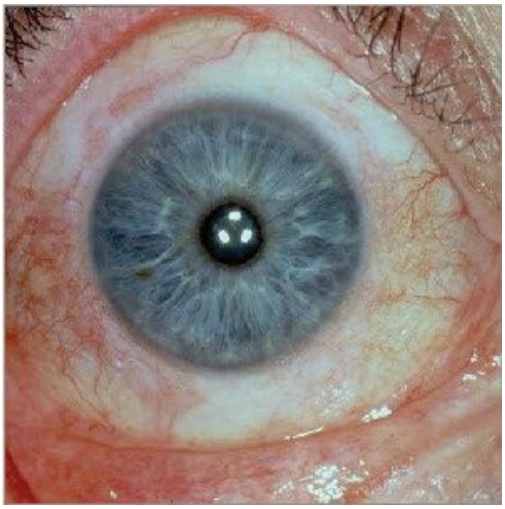


Figure 23. An allergic reaction to the original 0.2% concentration of brimonidine. This can occur with the 0.15% and 0.1% concentrations as well, but is less common.

Carbonic anhydrase inhibitors

The next to last category of commonly used glaucoma medicines is represented by two clinically equal topical carbonic anhydrase inhibitors: dorzolamide 2% ophthalmic solution (original brand name, Trusopt [Merck]), and brinzolamide 1% ophthalmic suspension (original brand name Azopt [Alcon]) **(Figure 24)**. Note that brinzolamide is the only suspension glaucoma medicine (except for Simbrinza [Alcon], which contains brinzolamide, which also makes it a suspension formulation).

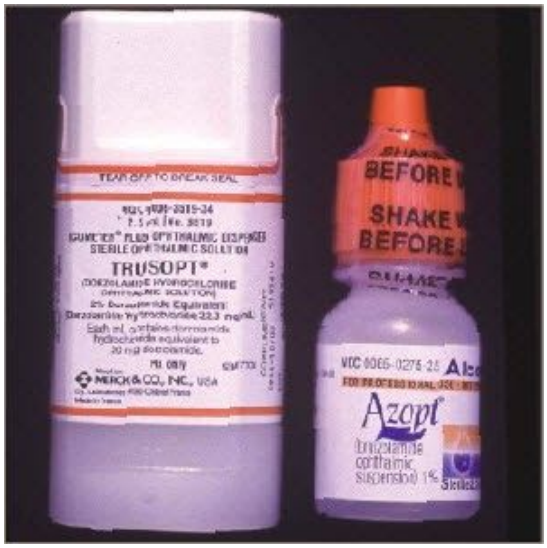


Figure 24. Trusopt and Azopt carbonic anhydrase inhibitors.

Carbonic anhydrase inhibitors, like beta-blockers, and to some degree, alpha-2 adrenergic receptor agonists, all suppress aqueous production at the ciliary body. Carbonic anhydrase inhibitors ultimately reduce IOP about 15%, which is the reason they are used as third- or fourth-tier therapy options. Like the alpha-2 adrenergic agents, carbonic anhydrase inhibitors are also FDA-approved for three-times-daily administration, but they are commonly prescribed twice daily, since the third drop would be instilled near bedtime. There is some evidence of a weak reduction in IOP during the sleep cycle, but without solid evidence as to optimum dosing, we question the wisdom of an encumbering third dose and attending expense balanced against efficacy.

Rho-kinase inhibitor

The final category contains a single-entity drug, Rhopressa (netarsudil ophthalmic solution 0.02%, Aerie Pharmaceuticals). Rhopressa **(Figure 25)** is a Rho-kinase inhibitor, which is thought to enhance the trabecular meshwork egress of aqueous humor. This drug was approved in late 2017 and is now available.

Figure 25. Rhopressa Rho-kinase inhibitor.

Rhopressa, which is preserved with 0.015% BAK, comes in a 4-mL opaque bottle filled to 2.5 mL. It is to be dosed once daily in the evening. In phase 3 studies, Rhopressa performed similarly to timolol, reducing IOP by about 5 mm Hg. Where Rhopressa will fit into the flow chart of therapeutic intervention is yet to be determined. Its 53% rate of conjunctival hyperemia may be a limiting factor in its use. Obviously, we will all need a year or so to assess its role in glaucoma patient care.

Combination Drugs

The two salient virtues in using combination drugs are simplicity of dosing schedule and reduced ocular surface exposure to preservatives.

A quick note regarding potential ocular surface toxicity from preservatives (most notably BAK): If a patient has concurrent dry eye disease and glaucoma, thoughtful consideration should be given to reducing such exposure. Preservative-free glaucoma medicines and preservative-free artificial tears are available. The problem with all these preservative-free eye drops is that they are more expensive than their preserved counterparts; thus, we again are faced with the challenge of balancing cost, efficacy and safety.

Only three preservative-free glaucoma medicines are available:

- timolol;
- tafluprost; and
- a combination of generic dorzolamide and timolol (Cosopt, Akorn). Cosopt is also available in a standard preserved bottle.

Quite a few preservative-free artificial tears are available. Our favorite is Ocusoft's Retaine MGD, which is a lipid-based formulation. When both a glaucoma drop and an artificial tear are needed, perhaps the most practical approach is to use the glaucoma drop of your choice with a preservative-free artificial tear. Before we get into the details regarding the three combination glaucoma drugs, let us give a thoughtful overview: First, these combination drugs contain two inexpensive generic drugs that, when combined, become an expensive, brand name-protected medicine. (Note that brinzolamide and dorzolamide share common efficacy, so one could easily be substituted for the other.) Most importantly, it is critical that each component drug is known to be effective for the patient before logical thought would allow them to be used together. This is basic common sense, and the efficacy of each ingredient medication can easily be determined via a monocular therapeutic trial.

Furthermore, these less expensive generic ingredient drugs alone may achieve target pressure; thus, prescribing an individual drug would represent a substantial cost-saving to the patient. Simply

prescribing a combination drug to a patient is senseless unless both drugs are known to be needed and efficacious.

Three combination drugs are available **(Figure 26)**:

- 0.5% timolol with 0.2% brimonidine (Combigan);
- 0.5% timolol with 2% dorzolamide (Cosopt); and
- 0.2% brimonidine with 1% brinzolamide ophthalmic suspension (Simbrinza).

Figure 26. Combigan and Cosopt ophthalmic solutions and Simbrinza ophthalmic suspension.

Combigan

Let's look at Combigan, a combination of 0.5% timolol and 0.2% brimonidine: First, it would be more ideal to have a high-technology combination drop dispenser in which the dual dose (the combination) is administered first thing in the morning, and then the next dose (the late afternoon dose) would only dispense the brimonidine drop, considering that a beta-blocker only needs to be used once daily. Second, we wish we had the option to prescribe such a combination drop with 0.25% timolol.

To be sensitive to cost, we sometimes have the patient instill Combigan (expensive) in the morning, and then use generic 0.2% brimonidine (relatively inexpensive) for the afternoon dose, because twice-daily timolol is not medically needed.

Cosopt

Cosopt, a combination of 0.5% timolol and 2% dorzolamide, comes in a preserved multidose bottle and in a preservative-free unit dose delivery system. Our experience has been that the unit dose rendition is priced close to the bottled version. When the cost is close, we always go with the preservative-free option.

Both combination drugs combine either a once-daily drop or twice-daily drop with a drop that is FDA-approved for three-times-daily dosing.

It has been our observation that brimonidine slightly outperforms a topical carbonic anhydrase inhibitor; therefore, when we are forced to use a combination drug, we tend to prescribe Combigan. However, if the ocular surface is significantly compromised, we typically prescribe preservative-free Cosopt (timolol/dorzolamide).

Prescribing glaucoma medication can be like playing a chess game — one must consider the impact of every therapeutic move.

Simbrinza

Last, we will look at Simbrinza, a medication that does not contain a beta-blocker but includes the ingredient drugs of brimonidine 0.2% and brinzolamide 1% ophthalmic suspension. Both ingredient drugs are approved for three-times-daily use, but in practical usage, they are widely prescribed twice daily — early in the morning and mid- to late afternoon. As a suspension, Simbrinza must be shaken well before each instillation.

The perfect scenario for use of Simbrinza would be in a patient who did not respond to timolol, or in a patient with significant asthma and a clinical need to use both ingredient medications as evidenced by successful therapeutic trials of each individual ingredient drug.

It is clear, then, that prescribing for glaucoma can be quite simple or it can be incredibly complex, but it is our duty and obligation to patients to be knowledgeable, thoughtful and always patient-centric in our prescribing behavior.

Summary

In summary, we initiate IOP-lowering therapy with one of these three medications: Vyzulta, a regular prostaglandin (almost always latanoprost) or timolol, all depending on multiple patient characteristics.

If Vyzulta or another prostaglandin performs well but does not achieve target IOP range, then we prescribe a therapeutic trial of timolol. If asthma precludes the use of a beta-blocker, then we consider 0.2% brimonidine or dorzolamide twice daily.

If a combination of any of these two options fails to achieve target IOP range, then the thought process becomes more challenging. It is important for optometrists to be knowledgeable about the different medications available and thoughtfully work through the decision-making process.

Therapeutic Intervention

The most critical decision regarding therapeutic intervention is based on a two-pronged question: Does the patient merit initiation of therapy, and second, what is the overall best medication(s) to achieve target IOP range? Equally competent glaucoma doctors will vary substantially in both aspects, exemplifying how medical care is often more art than science.

Depending on numerous factors, we consider the following approach: Begin with Vyzulta, a traditional prostaglandin or a beta-blocker. Based on the current literature, if Vyzulta does not achieve target IOP range, then it is doubtful that another prostaglandin drug option would be helpful. Thus, if Vyzulta alone does not achieve target range, then we would add a nonselective beta-blocker, such as generic timolol, administered once daily shortly after awakening.

If this same patient were to have clinically significant asthma, then we could consider adding Rhopressa, primarily because of its once-daily administration. More common adjunctive drug options would be generic 0.2% brimonidine, but because its IOP reduction falls to trough after about 8 hours and does little or nothing during the sleep cycle, we would prescribe this drop to be used shortly after awaking, and then the patient would use a second drop about 8 hours later. Although this approach may be more effective than using Rhopressa (and this has not yet been borne out in rigorous scientific studies), we are concerned about patient compliance with twice-daily therapy, as opposed to once-daily therapy; this is certainly a prime consideration in managing patient dosing schedules.

Although topical carbonic anhydrase inhibitors do exert some reduction in IOP during the sleep cycle, these medicines only reduce IOP by about 15% during the diurnal cycle, so we generally turn to these as a last resort.

We rarely, if ever, recommend adding or switching to any combination drug, unless we have performed a monocular therapeutic trial of each individual component to ensure that each drug is providing a meaningful reduction in IOP and is truly needed. Then, and only then, can a combination drug be intelligently and responsibly prescribed. Furthermore, and perhaps most importantly, it may well be that one of the ingredient drugs in a combination drug could achieve target IOP range alone. This must be determined before encumbering the patient with a more expensive combination drug.

Although we have traditionally used brimonidine or a topical carbonic anhydrase inhibitor, such as dorzolamide solution or brinzolamide suspension, as second-line adjunctive drugs, we may begin using Rhopressa in this capacity because of its once-daily administration. Until we have had ample

opportunity to determine the efficacy of these newer medicines, we cannot know with any certainty where they might best serve our patients. Keeping dosing regimens simple is a key element in enhancing patient adherence.

Micromanaging the Various Diagnostic Tests In Glaucoma

There are two notable aspects of glaucoma patient care: First, many factors must be considered in the glaucomatous evaluation, and therefore optometrists are not required to micromanage every minor nuance of these various tests. Second, with rare exception, glaucomatous optic neuropathy is a slowly progressive disorder, which gives ample time to methodologically ponder the course of patient management.

Intraocular pressure is a dynamic measurement that varies throughout the day. A patient whose IOP was 18 mm Hg at the previous office visit but now measures 20 mm Hg at the current office would not necessarily require initiation of therapy or addition to current therapy. Depending on the stage of glaucoma, one would always recheck the IOP in 2 to 4 more months. Again, there is no rush.

Visual fields are notoriously variable. Altering patient management based on the results of a single visual field test is only valid in exceedingly rare circumstances. Numerous studies have confirmed that, at the very least, two (and preferably three) corroborating fields are required to determine true change.

Corneal pachymetry is, for most all, a stable parameter. There is no precise, valid nomogram to help us determine if we must alter IOP by a certain amount based on corneal pachymetry results. However, we know that a patient who has a cornea that is considerably thicker than normal may have a slightly artificially inflated IOP measurement. And, we know that patients with corneas that are physiologically thinner than normal have — to some imprecise degree — an increased risk for developing glaucoma (or sustaining progression). If the cornea is thin secondary to refractive surgery, then one can generally estimate that the IOP measurement may read a bit lower than if the cornea were of normal thickness.

Even “objective” tests are only relatively objective, as seen in **Figure 27**, which shows apparent loss in high-quality nerve fiber layer measurements. The nerve fiber layer does indeed appear to be steadily thinning, until the fourth annual measurement shows it has normalized. This shows how important it is to not focus on one diagnostic parameter, but rather to be attentive to the comprehensive diagnostic assessment.

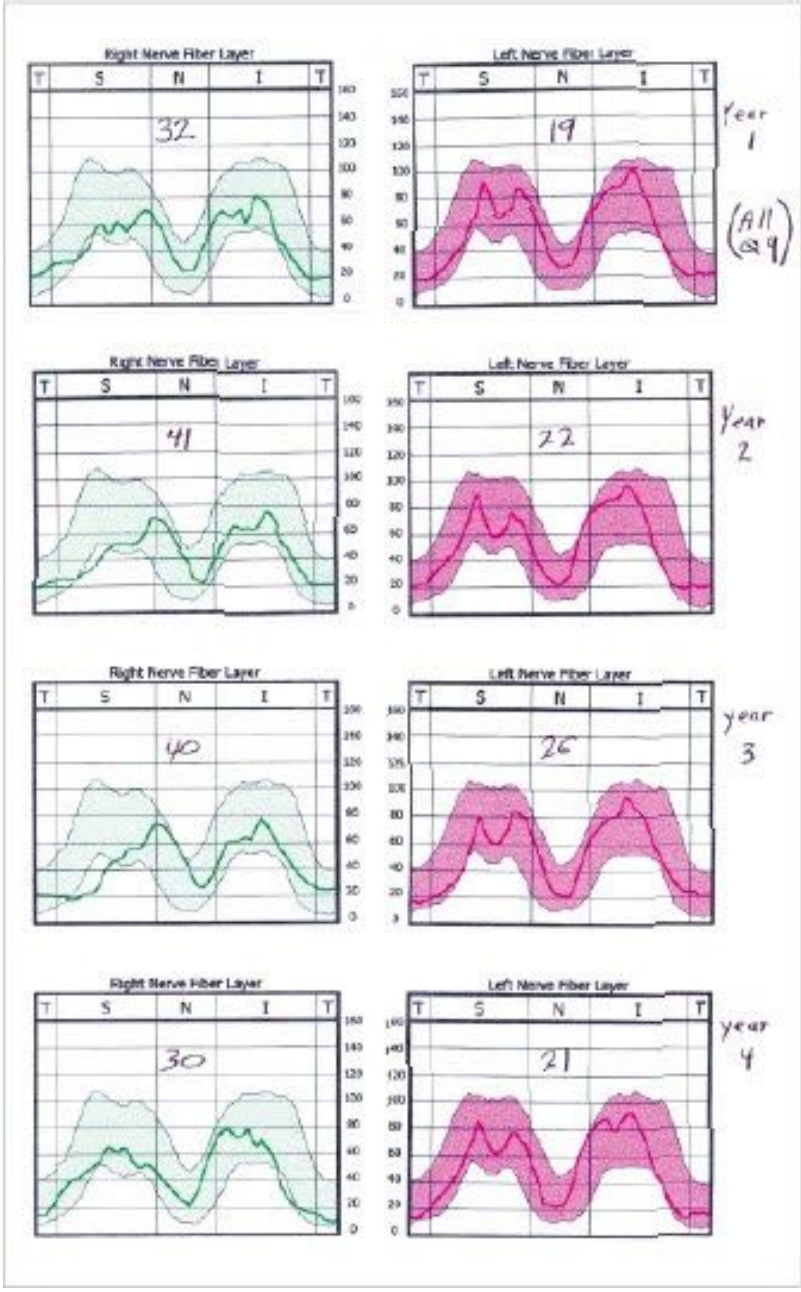


Figure 27. Here is an assessment of the retinal nerve fiber layer (RNFL), which, in theory, is completely "objective," but as seen here, there can be variability. Look attentively at the superior nerve fiber layer thickness of the right eye.

These are some common examples of instances in which an eye doctor can be led astray if he or she attempts to micromanage diagnostic tests.

Remember to look at all the following to form a comprehensive assessment of the patient. Then and only then can logical, accurate conclusions be made in assessing the stage of risk or the presence of frank disease.

- Family history, especially siblings;
- Age and health status;
- Medicines taken for systemic ailments;
- Intraocular pressure and corneal pachymetry;
- Nerve fiber layer assessment;
- Visual field assessment; and
- Attentive study of the optic nerve head — here you are invited to micromanage every detail, such as color, cup depth, concentricity of the optic cup to the disc rim (ie, is there
- neuroretinal rim erosion or thinning at certain locations such as inferotemporally or superotemporally), pallor and vessel abnormality such as collateral vessels (from prior branch retinal vein occlusion).

Finally, all these tests and clinical observations must be critically analyzed by the astute optometric physician.

How Inattentiveness Led to Litigation

One of us (RT) just completed defending a medical malpractice case against one of our colleagues. The following describes how the lack of clinical attentiveness set the stage for this lawsuit:

A 44-year-old man presented for his first-ever eye examination with incipient presbyopia complaints. During the encounter, the technician was attempting tonometry, and the patient was slightly uncooperative. Nonetheless, the technician was able to obtain pressure readings of 23 mm Hg for the right eye and 18 mm Hg for the left eye. The patient's examination was fully unremarkable, and he was easily correctable to 20/20 in each eye at both distance and near with +1.25 readers. The comprehensive dilated examination was charted to be entirely normal with a C/D ratio of 0.2 in both eyes. The doctor considered rechecking IOP, but because the technician reported the patient was somewhat apprehensive and uncooperative, the doctor chose not to repeat tonometry, especially considering the patient was relatively young with healthy-appearing optic nerves. With such IOP asymmetry, it would have been wise to at least note in the chart, "no evidence of pigment dispersion syndrome or pseudoexfoliation syndrome; the patient gives no history of ocular trauma," as these are common causes for asymmetric IOPs. However, none of these negative findings were charted.

At the time of this patient's initial examination, he was unaware that his mother had glaucoma; this was discovered a couple of years later. In cases in which there is any suspicion for glaucoma at all, always encourage the glaucoma suspect patient to discuss his or her status with family members and ask about any relative ocular histories.

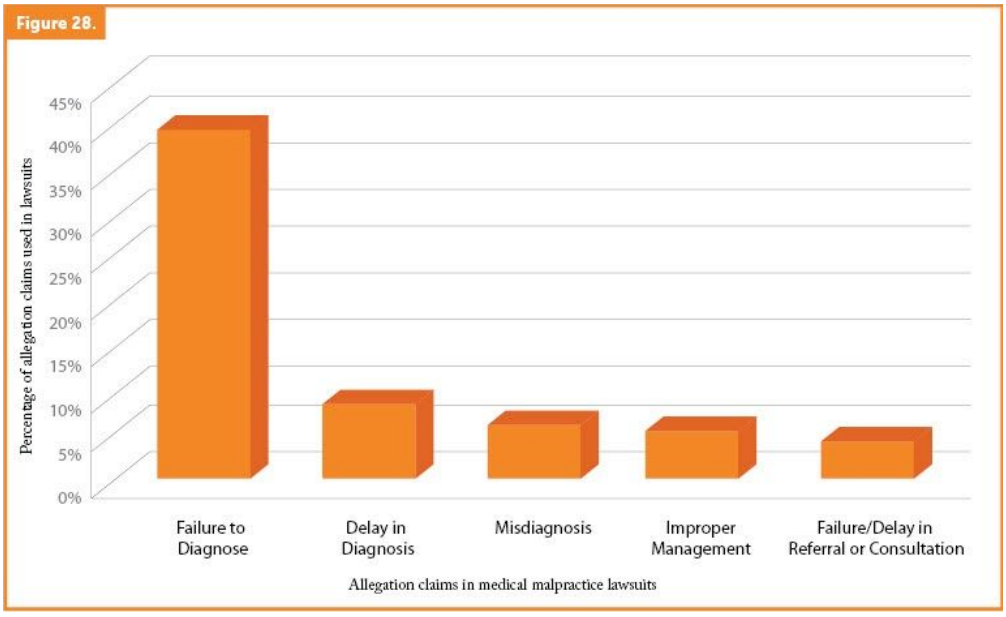
Two terrible oversights occurred in the above case:

1. In the electronic health record, the only problems charted were "refractive error/presbyopia," and "return in 1 year for an annual examination"; there was no mention whatsoever of the patient being a glaucoma suspect.
2. The patient was not rescheduled to return in 2 or 3 months for a recheck of the IOPs and to perform pachymetry, or any other diagnostic testing that might have been deemed appropriate.

Unfortunately for all, the patient was a "no-show" for his annual exam, despite timely telephone outreach by the office staff. In retrospect, the patient's failure to return for his annual visit was the only positive event that dampened the impact of the ultimate settlement.

Here is how the case played out: Two and a half years later, the patient noticed a loss of vision in his left eye, and presented to another eye care provider's office, where he was found to have increased IOP into the low 30s mm Hg. He was also found to have a C/D ratio of 0.8 in the left eye (yet he still had a C/D ratio of 0.2 in the right eye). He had lost the inferior half of his visual field in his left eye. Obviously, the patient's glaucoma had progressed far more rapidly than was typical. He was thought to have plateau iris syndrome, which may have accounted for the rapid progression of the disease state.

This patient will suffer permanent vision loss by his own negligence — that is, his failure to follow up in a timely manner — and the optometrist's negligence to explain to the patient the vital importance of the attentive follow-up care. Such scenarios **(Figure 28)** are fully preventable and require only basic, prudent follow-up of any findings out of the norm such as asymmetric IOP.



Types of Glaucoma

Pigment dispersion syndrome

Pigment dispersion syndrome represents an asymptomatic slit lamp discovery. When the iris is sufficiently posteriorly positioned, the posterior pigmented iris epithelium rubs against the lenticular zonules, which can result in liberation of the pigmented cells. If this process continues for several years, enough pigmented cells can clog the trabecular meshwork, resulting in a secondary glaucoma referred to as *pigmentary glaucoma*.

Both pigment dispersion syndrome **(Figure 29)** and pigmentary glaucoma are characterized by:

- iris radial transillumination defects;
- heavy pigmentation of the trabecular meshwork; and
- pigmented debris on the face of the iris and/or on the corneal endothelium (known as a *Krukenberg's spindle*).

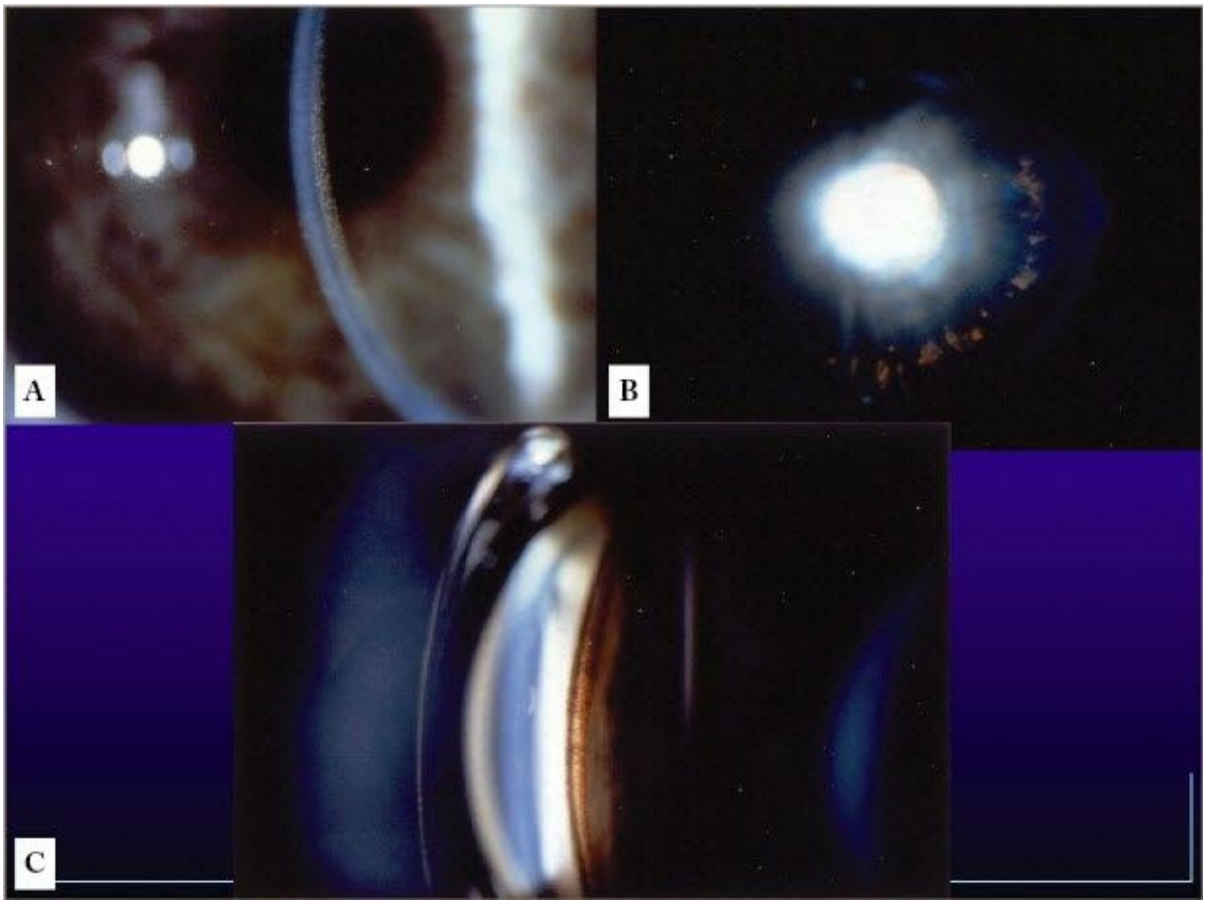


Figure 29. A, Iris pigmented debris on the corneal endothelium. B, Iris retroillumination defects. C, Heavily pigmented trabecular tissues from all the iris pigmented epithelial debris accumulating there.

Pigmentary glaucoma occurs when there is consistently elevated IOP with resultant glaucomatous optic atrophy.

Pigmentary glaucoma

The conversion to pigmentary glaucoma occurs in 30% to 50% of patients with pigment dispersion syndrome. The typical patient with pigmentary glaucoma is young, myopic and male. Pigmentary glaucoma usually occurs after several years of pigment dispersion, and it is a bilateral asymmetric disorder. These patients will have radially shaped iris transillumination defects, best seen when the room is darkened, the slit lamp is on low power setting and a small beam of light is shown through the nondilated pupil. This floods the eye with light, thus retroilluminating the iris, thereby revealing

these defects. Of note, patients with ocular albinism also have iris retroillumination defects, but here the entire iris homogeneously transilluminates, giving a uniformly pink color to the entire iris.

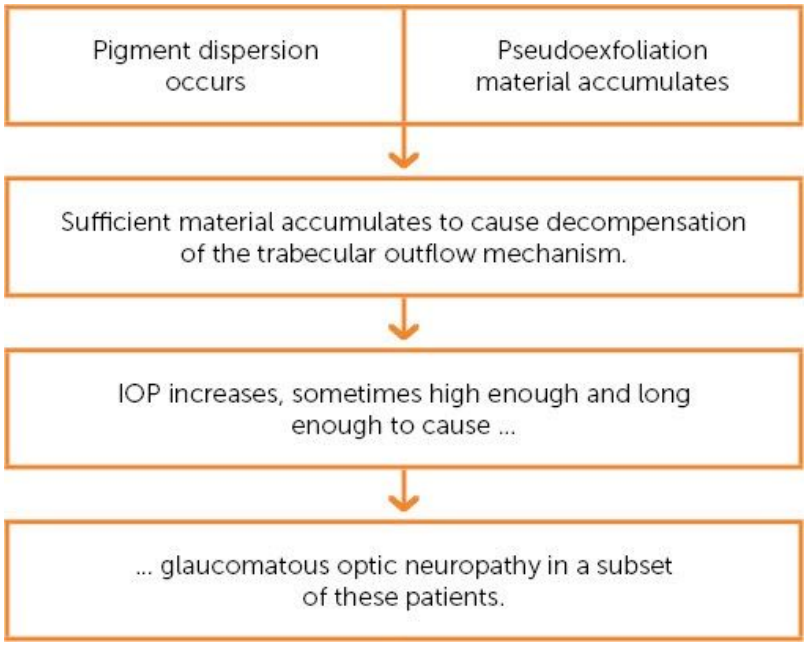
The obvious separation between pigment dispersion syndrome and pigmentary glaucoma is the presence of increased IOP and optic neuropathy in pigmentary glaucoma.

Because of the unique iris anatomy in pigment dispersion disease, the “sagging” iris tends to be deep and concave in its posterior bowing configuration, and this accentuates the iris pigment chaffing from the posterior iris epithelium. Because of a relative pupillary block, the pressure in the anterior chamber can be slightly higher than the pressure in the posterior chamber. This results in more iris concavity, potentiating posterior iris epithelial chaffing and liberation of pigmented cells. This mechanism explains why laser photoiridotomy is commonly helpful in decreasing or halting further zonular chaffing of the iris epithelium; the laser opening in the peripheral iris permits the pressure in the posterior and anterior chamber to become equal, which then permits the effect of the relative pupillary block to be neutralized, thus allowing the iris diaphragm to move anteriorly enough to diminish or halt the pigment dispersion process. It is important to note that such laser therapy can be effective in mitigating the dynamics of the dispersion process but has limited or no therapeutic benefit once pigmentary glaucoma has developed.

Therapy for pigmentary glaucoma is similar to that of primary open-angle glaucoma.

Pseudoexfoliation syndrome and pseudoexfoliation glaucoma

Just as pigment dispersion syndrome can progress to pigmentary glaucoma, pseudoexfoliation syndrome can progress to pseudoexfoliation glaucoma. Similarly, both syndromes are commonly present for years before causing increased IOP, and ultimately, glaucomatous optic neuropathy. Both disease pathways involve a four-step process:



This unique secondary glaucoma is called *pseudoexfoliation* because true lens capsular exfoliation is seen mostly in two occupations — glassblowers and iron industry workers. Since this entity looks similar to that of true exfoliation, it is called *pseudoexfoliation*.

Pseudoexfoliation glaucoma **(Figure 30)** is a bilateral (although it can be rather asymmetric), lenticular capsular abnormality seen most commonly in people older than age 70. Unilateral exfoliation is almost always a precursor of bilateral disease.

- The subset of glaucoma patients with pseudoexfoliation is approximately 5% to 10%.
- It is not associated with any known systemic disease. There is no known genetic influence.
- Small, whitish flakes in the pupillary region of the lens face are commonly seen even before dilation; however, the dilated view of the anterior lens capsule is classic.
- As in pigment dispersion, there is pigmentation of the trabecular meshwork; however, exfoliative
- debris is less distinct than the melanin pigmentation seen in pigment dispersion. This exfoliative pigmentation band is referred to as Sampaolesi's line.
- Increased IOP is seen in most patients with pseudoexfoliation. As with all the glaucomas, if the IOP is high enough long enough, then glaucoma can result.

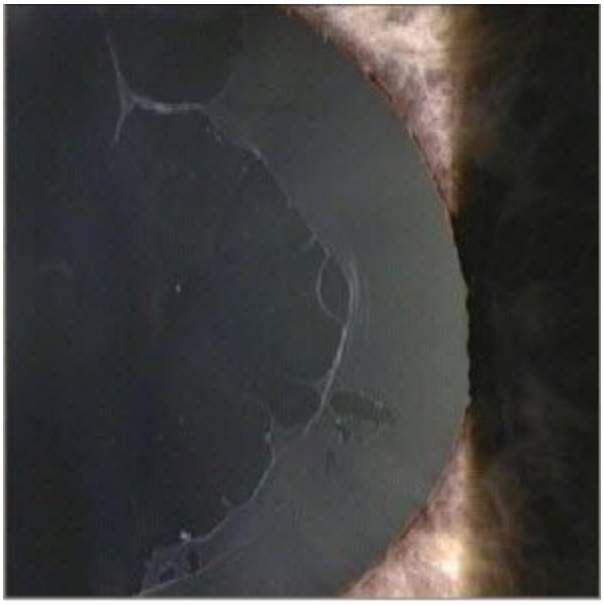


Figure 30. Best seen with pharmacologic dilation, this image shows the classic appearance of exfoliative material on the lenticular face.

Where and how is this exfoliative material generated? It is thought to represent abnormal basement membrane synthesis of the lens epithelium, ciliary body epithelium, iris pigment epithelium, trabecular endothelial cells and possibly other sites.

Patients with pseudoexfoliative glaucoma tend to have higher IOPs than patients with primary open-angle glaucoma, and as a result, their medical management tends to be more challenging. Nonetheless, therapy of this subtype of glaucoma is quite similar to the management of primary open-angle glaucoma.

In both pigment dispersion and exfoliative glaucoma, laser trabeculoplasty can be effective.

With an increasingly aging population, the need for eye care services related to glaucoma continues to grow, and optometrists should be the primary caregiver for this predominately medically managed eye disease.

Clinical Pearls

Any optic nerve head that looks abnormal, yet not glaucomatous, likely merits a 30-2 visual field test, especially if there is generalized or sectoral pallor of the optic nerve. Most patients with glaucoma have pink, well-perfused neuroretinal rim tissues and no pallor. Optic nerve tissue pallor more commonly results from nonglaucomatous processes such as compressive lesions. We like the 30-2 test pattern because it tests more targets along the vertical midline, which would be a more sensitive screen for neurological defects, as they almost invariably respect the vertical midline.

Optometrists should meticulously analyze and obsessively study the details of the optic nerve head tissues. Do not let subtle parapapillary atrophy wrongfully skew the assessment of the cup-to-disc anatomic relationship. Furthermore, in mostly older patients with presumed normal-tension glaucoma, the glaucomatous cupping can be incredibly subtle. One must really study the peripheral neuroretinal rim anatomy to search for a 0.8 or 0.9 cup that, at casual glance, may appear to be 0.3 to 0.5 cup.

Remember that patients with highly advanced cupping usually maintain normal vision, so if vision is inexplicably reduced, then consider one or more of the following:

- visual field testing;
- subtle epithelial basement membrane dystrophy in the visual axis;
- macular OCT to rule out subtle maculopathy;
- potential acuity visometry to rule out the elusive “clear cataract”; and/or
- corneal topography to rule out subtle anatomical variations on the corneal surface.

Of course, you must have requisite diagnostic instrumentation available to provide these evaluations. If you do not have the necessary diagnostic workup instrumentation, then please refer the patient to an optometric colleague who does. Do consider the great virtue of intraprofessional consultation and cooperation.