Supplement to

Glaucoma TODAY

Early Summer 2011

CME ACTIVITY

Evidence-based Best Practices for Glaucoma Care

- Why Do Patients With Glaucoma Go Blind?
- Practical Aspects of Glaucoma Care
- Identifying and Managing Early Glaucoma
- Challenging Glaucoma Cases

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A CME activity jointly sponsored by the Dulaney Foundation and Glaucoma Today. *Supported by an unrestricted educational grant from Allergan, Inc.*

Evidence-based Best Practices for Glaucoma Care

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Release date: June 2011. Expiration date: June 2012.

This continuing medical education activity is supported by an unrestricted educational grant from Allergan, Inc.

STATEMENT OF NEED

The goal of this continuing medical education (CME) supplement is to provide current, evidence-based information to help guide glaucoma specialists and general eye care professionals in deciding on appropriate therapy for their patients with glaucoma. Factors that may influence this decision include disease type and stage, risk factors, patients' adherence to therapy, and evidence of efficacy, safety, tolerability, and convenience of the various treatments, such as topical agents, individually or in combination, and surgical interventions.

A recent analysis of studies relevant to emerging glaucoma treatments identified 42 citations focusing on

- monotherapy
- prostaglandin analogues
- combination therapy
- combination versus monotherapy and fixed-combination therapy
- side effects, safety and stability, and efficacy
- long-term effects of treatment
- cost-effectiveness and implications to the health care system.[1]

Focusing on these issues, clinicians can use today's therapies to benefit every type of patient, including older and younger patients, those with high- and normal-tension glaucoma, and those with low and greater visual field loss.[2]

Challenges remain, however. Lack of compliance with medications and effective use of therapy are central issues, often because of the complexity of regimens, adverse effects, the cost of medications, and patients who are forgetful or lack understanding of the disease.[3,4] Another major challenge is an increasing volume of new treatments, used in varying combinations. The result has been the development of complicated guidelines and algorithms needed to make sound clinical decisions.[3,4]

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TARGET AUDIENCE

This certified CME activity is designed for glaucoma specialists and general eye care professionals.

LEARNING OBJECTIVES

Upon completion of this activity, participants should be able to

- evaluate and treat the various types and stages of glaucoma
- recognize and address disease progression
- evaluate topical therapies, including agents to be used as monotherapy or in combination, as well as fixed-combination agents

METHOD OF INSTRUCTION

Participants should read the CME activity in its entirety. After reviewing the material, please complete the self-assessment test, which consists of a series of multiple-choice questions. To answer these questions online and receive real-time results, please visit http://www.dulaney-foundation.org and click "Online Courses."

Upon completing the activity and achieving a passing score of over 70% on the self-assessment test, you may print out a CME credit letter awarding 1 *AMA PRA Category 1 Credit.*™ The estimated time to complete this activity is 1 hour.

ACCREDITATION AND DESIGNATION

This activity has been planned and implemented in accordance with the Essential Areas and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of the Dulaney Foundation and *Glaucoma Today*. The Dulaney Foundation is accredited by the ACCME to provide continuing education for physicians. The Dulaney Foundation designates this print activity for a maximum of 1 *AMA PRA Category 1 Credit.*™ Physicians should claim only the credit commensurate with the extent of their participation in the activity.

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FACULTY/STAFF DISCLOSURE DECLARATIONS

Dr. Gross has received grant/research support from Alcon Laboratories, Inc., and Allergan, Inc.; he is a consultant to Alcon Laboratories, Inc., Allergan, Inc., Merck & Co., Inc., and Ono Pharmaceutical Co., Ltd.; and he is on the speakers' bureaus of Alcon Laboratories, Inc., Allergan, Inc., and Ono Pharmaceutical Co., Ltd.

Dr. Katz has received grant/research support from Airie Pharmaceuticals, Inc., Allergan, Inc., Lumenis, Ltd., Pfizer, Inc., and Glaukos Corporation; he is a consultant to Alcon Laboratories, Inc., Allergan, Inc., and Glaukos Corporation; and he is on the speakers' bureaus of Alcon Laboratories, Inc., Allergan, Inc., and Merck & Co., Inc. He is a stock/shareholder of Glaukos Corporation.

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All others involved in the planning, editing, and peer review of this educational activity have indicated they have no financial relationships to disclose.

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Why Do Patients With Glaucoma Go Blind?

Large, well-accepted studies suggest there must be something more we can do for our patients.

BY L. JAY KATZ, MD

According to best estimates, more than 200,000 people in the United States are blind from glaucoma, out of about 4 million with the disease. Worldwide, 6 million people out of 67 million with the disease are blind. Glaucoma is the second leading cause of irreversible blindness in the United States, number one worldwide. Among African Americans and Latinos in the United States, it is the leading cause of blindness.[1]

Why do people become blind from glaucoma? We can look to society, patients themselves, and physicians for some of the reasons, namely

1. Lack of access to health care
2. Nonadherence to medical therapy
3. Inadequate treatment

To date, the only factor we have been able to modify to regulate this disease is IOP. We are aware, however, that there may be IOP-insensitive factors, such as blood flow or neurodegeneration, that may be amenable to treatment in the future.

In this enduring material, we discuss evidence-based best practices for glaucoma care, using representative cases that demonstrate how new data from recent studies may influence our clinical decisions.

CASE 1: SIMPLIFYING A COMPLEX REGIMEN

A 76-year-old woman with glaucoma is evaluated for poorly controlled IOP. She is using latanoprost once a day, timolol twice a day, brimonidine three times a day, and pilocarpine four times a day, but she has not reached her target IOP. She has rheumatoid arthritis, and her hands are deformed because of that. When we review her schedule and ask her to show us how she instills her medications, we see that she has a great deal of difficulty getting the drops—any of the drops—into her eyes. She mentions that her husband is available to help with her drops in the morning and the evening.

To help this patient gain better IOP control, our most reasonable options include trabeculectomy, reviewing and simplifying the regimen, adding brinzolamide three times a day, or continuing the same medications, while encouraging adherence.

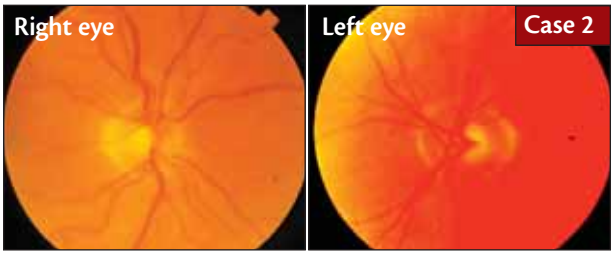

Figure 1. Note that this patient's right optic nerve has a smaller cup than the left, and there is a small disc hemorrhage inferiorly in the left eye.

Any of these options is potentially correct, but reviewing and simplifying the regimen would be my preference. Knowing the patient's husband can help her in the morning and the evening, we should be able to simplify her regimen to twice-a-day dosing, possibly using fewer bottles, which may solve the problem. In this case, it did.

If we could be certain of a perfect outcome, trabeculectomy would be a good choice. There are always risks with surgery, however, and we prefer to try to control pressures medically.

Adding another medication might be beneficial if the patient were able to get the drops in her eyes. The concern is that adding a drop makes the regimen more complex and even more difficult for her.

Keeping the same medications and encouraging adherence may help in some cases. With constant prodding and re-education, patients sometimes improve their adherence but only if you provide this kind of feedback constantly. In this instance, however, the patient's regimen is so complex and it is so difficult for her to instill the medications herself that encouraging adherence probably will not be successful.

Adherence and Persistence

In a 2008 study, more than half of the patients surveyed did not adhere to their glaucoma therapy regimen, or they instilled their drops improperly.[2] Other studies have report-

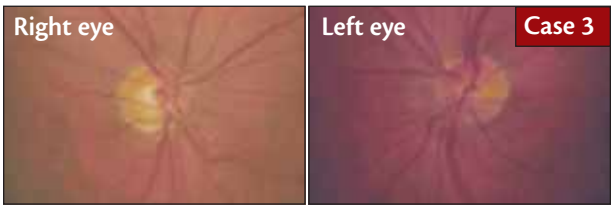

Figure 2. Note vertical cupping and loss of the rim inferiorly in the right eye and a healthier-looking optic nerve head in the left eye.

ed similar findings.[3,4] We can also look at persistence by reviewing prescription renewal rates through pharmacies and formularies. If patients are renewing their prescriptions regularly, they are more likely to be using their medications than if the renewals are sporadic and infrequent. This appears to be a more reliable measure of adherence and persistence than asking patients directly.[5] Studies using electronic monitors often found that patients said they used their medications much more regularly than they actually did.[6]

Studies have also shown that persistence and adherence are best with the prostaglandin analogues, which are once-a-day drugs.[7] When a second medication is added, not only does adherence decrease for the second medication compared to the first, but when a patient is using two medications, he or she is less likely to use the first one than when it was prescribed as monotherapy.[8]

Adding more medications really does affect patients' adherence to their medical regimens. Therefore, we need to aim for the simplest regimen possible. Patients admit that if they take one medication a day, as opposed to two or more, they are more likely to use it on a regular basis.[9]

The cost of a medicine can affect adherence to medical therapy, and that is important. In a 2009 study, however, nearly 45% of patients using an electronic monitoring device who knew they were being monitored and were provided free medication used their drops less than 75% of the time.[10]

Educating patients is another important factor in improving adherence. This should involve emphasizing the importance of glaucoma care, ensuring that patients understand the purpose of their medications, and being sensitive to side effects.

CASE 2: ADDING A FIXED-COMBINATION AGENT

An 82-year-old man is evaluated for treatment of primary open-angle glaucoma. His visual acuities are 20/25 OD and 20/30 OS. Central corneal thickness measurements are 545 and 540 µm, with some asymmetry. The right optic nerve has a smaller cup than the left, and there is a small disc hemorrhage inferiorly in the left eye (Figure 1).

Baseline pressures were 29 mm Hg in the right eye and 34 mm Hg in the left eye. Although a prostaglandin analogue and a ß-blocker reduced the pressures, they were still above the target of 20 mm Hg. We continued the prostaglandin, stopped the ß-blocker, and added the fixed combination of brimonidine and timolol. With that additional medication (but the same number of bottles), pressures were reduced to 17 mm Hg and 19 mm Hg. The patient tolerates this regimen well and appears to be using his drops as prescribed. His discs and visual fields have been stable for 2 years.

CASE 3: EXTREME NONADHERENCE

A 58-year-old man, a physician, has ocular and systemic hypertension. Baseline IOPs were 43 mm Hg and 30 mm Hg, and visual acuities were 20/30 OD and 20/35 OS. The patient had undergone cataract extraction in both eyes, somewhat complicated in the right. Figure 2 shows vertical cupping and loss of the rim inferiorly in the right eye and a healthier-looking optic nerve head in the left eye. Visual fields showed a defect on the right and possible early visual field loss on the left.

The patient was started on timolol monotherapy, but he did not return for follow-up. Five years later, the patient returned for evaluation. He was still using timolol, which he self-prescribed. His pressures were 32 mm Hg and 26 mm Hg, and he was legally blind with markedly excavated cups. Which of the following is the best treatment for this patient?

a. Start with monotherapy and add more medications as needed

b. Prescribe multiple medications, including a fixed combination (timolol-dorzolamide or timolol-brimonidine) and a prostaglandin analogue

c. Perform laser trabeculoplasty

d. Perform filtering surgery

Starting with monotherapy and adding more medications as needed is a reasonable option, and that was done in this case, although we would have to ask ourselves: How likely is it that this patient will achieve target pressures with one medication?

In retrospect, prescribing multiple medications, including a fixed-combination and a prostaglandin analogue, would have been a better choice for this patient. With this regimen (along with regular follow-up visits), he would have been more likely to reach target pressures. Another important consideration is that this regimen is close to maximum medical therapy, so if target pressures were not reached, the treating physician could move quickly beyond medical therapy.

Laser trabeculoplasty helps with adherence. Unfortunately, its effect is modest, similar to using a single medication, and it is not likely this patient will reach target pressures with laser trabeculoplasty alone.

Filtering surgery alone can quickly reduce pressures, but when IOPs are extremely high, there are risks, such as choroidal detachment and suprachoroidal hemorrhage.

Going straight to filtering surgery is an option for this patient, especially if the treating physician is convinced he will not use anything medically. In most cases, however, patients and doctors prefer to start with medication before moving to surgery.

CASE 4: PROSTAGLANDIN INTOLERANCE

A 58-year-old woman has ocular hypertension, a family history of glaucoma, and low diastolic blood pressure. Her visual acuity is 20/20 OU, IOPs are 34 mm Hg and 32 mm Hg, with central corneal thicknesses of 520 and 515 µm. She has small cups with some asymmetry.

After discussing the risks of glaucoma progression with her doctor, the patient opted for treatment, even though her discs are relatively healthy and her visual fields are good. She started using a prostaglandin analogue, but she did not tolerate it because of hyperemia. A ß-blocker alone reduced her pressures, but she did not achieve her target pressure of 22 mm Hg. The ß-blocker was stopped, and the patient started using a fixed combination of brimonidine and timolol twice a day. Her pressures were reduced to 20 mm Hg and 19 mm Hg, with excellent tolerability, and she has remained stable on that regimen.

Is there something more?

Are there factors other than pressure that cause progression in glaucoma? We have discussed this possibility for more than 100 years, and we have evidence from some large, well-accepted studies suggesting there must be something more we can do for our patients with glaucoma.[11] The landmark Normal Tension Glaucoma Study showed that patients who were treated and achieved a marked pressure reduction, at least 30% below baseline, did much better than the untreated control group.[12] What is important to note, however, is that 12% of the patients who were treated aggressively still progressed during this study. The question is: Did the glaucoma progress because pressures were not low enough, or was there something more than pressure causing progression in this population?

This famous graph from the Advanced Glaucoma Intervention Study (Figure 3) shows high-tension glaucoma patients whose target pressures were below 18 mm Hg.[13] In subgroup analysis, subjects in the group with a mean IOP of 12.3 mm Hg seem to have an incredibly stable course when we look at their perimetry results, compared to the other subgroups, where there was definite progression over the course of the trial. Keep in mind, however, that the flat graph with the mean IOP of 12.3 mm Hg is showing an average of the entire group. When we look more closely, we see that, within that group, about one-fourth had sustained progressive change in their visual field, which means that one-fourth got worse. We can also imagine then that one-fourth seemed to get better on serial perimetry, and they averaged out. This would suggest, however, that perhaps

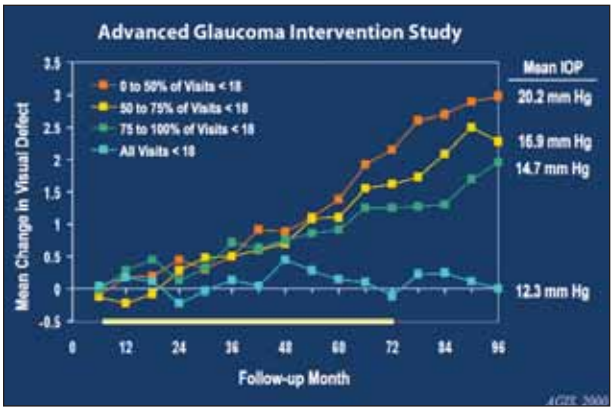

Figure 3. It is important to note that the graph with the mean IOP of 12.3 mm Hg is showing an average of the entire group.[13]

certain individuals with very low IOPs progress. So, whether a patient has normal-tension or high-tension glaucoma, something more than pressure regulation may be necessary.

In an editorial more than a decade ago, Caprioli noted that, during the course of the disease, various factors seem to have different degrees of importance in different patients.[14] In one patient, for example, a pressure of 60 mm Hg is an important predictor of progression, more so than anything else. Someone else, however, may have a pressure of 11 mm Hg and be continually getting worse. This seems to suggest we should be looking at—and potentially treating— something other than pressure in those individuals. Whether that treatment is neuroprotective or something to improve blood flow, we are all looking for that next step beyond pressure regulation.[15,16] ●

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Practical Aspects of Glaucoma Care

Glaucoma specialists discuss the impact of recent studies on clinical practice.

L. Jay Katz, MD: When caring for patients with ocular hypertension, how important is it to examine structure with imaging or disc photography as opposed to testing visual fields?

Ronald L. Gross, MD: Both are important. The Ocular Hypertension Treatment Study (OHTS) found that the first sign of glaucomatous damage in the majority of subjects was structural, but in a substantial number of subjects, about a third, an abnormal visual field was the first sign.[1] In general, we believe the nerve changes before the field, but in some cases, that is not true. For that reason, we must follow both structure and function.

Dr. Katz: How often do you see patients who have glaucoma?

Dr. Gross: It is important to set a good baseline, particularly for visual field testing, which should be done fairly quickly. That usually takes at least two reliable visual field tests. As for analyzing structure, it is important to have an objective record, such as optic nerve photographs or image analysis. Once we have obtained good baseline data, we usually repeat the testing for the average patient once a year.

Dr. Katz: Do you use standard white-on-white perimetry, or do you sometimes use other types of visual field analysis?

Dr. Gross: Typically, we use the Swedish interactive threshold algorithm (SITA) standard 24-2 field. We have found that short-wavelength automated perimetry (SWAP), which is blue-on-yellow, is not as useful as we once thought it was, since similar numbers of patients show abnormalities earlier in SWAP and standardized automated perimetry. For that reason, we depend on white-on-white. Some of the newer technologies, such as frequency doubling, may be useful, and some data suggest it detects defects earlier. We do not have a large amount of data, however, to tell us exactly where it fits into our evaluation.

Dr. Katz: Based on the OHTS, we could use an algorithm to help predict the risk of glaucoma development over 5 years. Do you use the algorithm and discuss it with your patients?

Dr. Gross: In general, I do not calculate a specific number for a patient, but the idea of a risk analysis is important. Understanding that older patients, patients with higher pressures, and those with thinner corneas have the highest risk of developing glaucoma and then determining low, medium, or high risk for an individual patient are helpful. Often, patients will decide if treatment is appropriate, but their decision may well be influenced by their risk.

Dr. Katz: I do not use the algorithm, either; I use the same risk factors in determining the relative risk of disease progression. I agree that it is critically important for patients to have a role in the decision-making process, but they rely a great deal on us for advice. How do you come to common ground in terms of pushing in one direction or the other—treatment versus observation—to reach a decision with a patient who is a glaucoma suspect?

Dr. Gross: We would all like to say we do not have a bias, but I admit I do. In general, the lower the risk is, the more I am biased toward watching the patient. The higher the risk is, the more I favor treatment. Regardless of their decision, it is most important that patients continue to be observed.

Dr. Katz: Suppose a patient appears to have a very low risk, say 5% over 5 years, but chooses treatment to feel more comfortable about lowering his or her pressure. What is your opinion of that choice?

Dr. Gross: I think that is perfectly reasonable. Conversely, I may have a patient with pressures in the 30s who chooses to be observed. I may be worried, but if I have talked to him or her and he or she understands the risks and chooses to be observed, I think it is his or her personal choice.

Dr. Katz: When you start therapy, what treatment path do you choose, and how effective is that for this population?

Dr. Gross: I tell patients that lowering IOP is the only treatment that has been proven effective in studies and that we usually can do that with drops.[2-4] I mention that we have surgeries that can accomplish the same thing, but for most patients, medications are the first choice.

Dr. Katz: Let's discuss the normal-tension glaucoma patients, the other side of the coin. These are people who have pressures in the so-called normal or average range, and they have progressive visual field loss and changes in their optic nerve heads. Has your approach to managing these patients changed based on recent information?

Dr. Gross: When taking care of these patients, we must answer some difficult questions: Is this glaucoma? Does this patient need to be treated? Are there other factors in play?

We have good data from the Collaborative Normal-Tension Glaucoma Study that we should lower the IOP.[5] In doing so, however, we often must consider other factors, such as perfusion pressure, diastolic blood pressure, and cardiac arrhythmias, to name a few. We need to determine if those are present and if they are, if we can do something about them to improve the patient's status. On the other hand, we need to consider if there is something we can do to affect the health of the optic nerve and the neurons of the retinal ganglion layer. We have some new data from the Low-Tension Glaucoma Treatment Study (LoGTS), which has looked at this question in a scientific way for the first time.[6]

The LoGTS was a randomized, prospective, multicenter trial that examined timolol versus brimonidine as monotherapy for patients with low-tension glaucoma. These patients' pressures were in the teens and rarely, if ever, elevated. Much to the surprise of many of us, visual field analyses by several methodologies showed substantially better preservation of the visual field in the brimonidine group than in the timolol group, even though these agents are equivalent in their ability to lower IOP.

Lowering pressure is important, and prostaglandin analogues are still more efficacious in general than other classes, but given the results of this study, we may need to consider the role of brimonidine in our normal-tension patients.

Dr. Katz: What would you do if you learned your patient had extremely low diastolic blood pressure and was taking blood pressure medication?

Dr. Gross: This is an easier case, because we can ask the internist if the patient's regimen can be modified to avoid very low blood pressures, which may be affecting his glaucoma. Often more frustrating is the patient who has low blood pressure and is not being treated for hypertension. That can be much more difficult to address.

Dr. Katz: Do you ever advocate for 24-hour blood pressure monitors for these types of patients?

Dr. Gross: It is not a routine test that I do, but in isolated instances with progression without an explanation or evidence of systemic hypotension, it may be helpful.

Dr. Katz: Every patient is different. In a typical patient, what is maximum medical therapy, and how can we enhance adherence in the day-to-day management of glaucoma?

Dr. Gross: Unfortunately, we do not have a good way to assess adherence. In general, I assume it is probably a lot worse than patients tell us or than we think it is. Something we can do to improve adherence is simplify medication regimens as much as possible—limit the number of bottles patients use and limit the number of instillations per day—to make them more manageable.

Maximum medical therapy is different for every patient, but in general, if a patient is using a prostaglandin analogue and a fixed-combination drop, then he is using three classes of medication and two bottles. We know that adding a fourth class (and a third bottle) will not add much in the way of efficacy. For the average patient, that may well represent maximum medical therapy. What do you think?

Dr. Katz: Because of the cost issue, the side effect profile, and the limited additivity of using multiple medications, I think two bottles, maybe three, is the maximum from which most patients will benefit. So, I agree with you. I think there are some general principles that we can follow in caring for our patients, and you summarized them very nicely.

In closing, I would add we do need some general guidelines for caring for our patients with glaucoma, but we still must individualize care. That is where our abilities as clinicians come through, in deciding on the best approach after discussion with the patient. ●

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Identifying and Managing Early Glaucoma

Representative cases show the numerous manifestations of early glaucoma.

BY RONALD L. GROSS, MD

CASE 1: OCULAR HYPERTENSION

A patient has elevated IOP, normal visual fields, and a normal optic nerve—a classic presentation of ocular hypertension (OHT). The superior neuroretinal rim may be somewhat thin but not enough to be diagnostic. Over a 13-year period, visual fields have remained essentially unchanged, but the superior rim has become thinner, which is evidence of damage and continued loss (Figure 1).

At this point, the patient would be better defined as having mild glaucoma, that is, normal, standard white-on-white Humphrey visual fields (Carl Zeiss Meditec, Inc., Dublin, CA), but with evidence of change in the optic nerve attributable to glaucoma.

CASE 2: GLAUCOMA SUSPECT

A 59-year-old man has a family history of glaucoma and elevated IOP, which was never treated. His medical history was not contributory. Visual acuities were 20/20 OU, angles were open, and on initial examination, his pressure was 26 mm Hg OU. We measured his IOPs on a modified diurnal curve, early morning, late afternoon, and in between. His pressures fluctuated between 22 mm Hg and 28 mm Hg during that time. His initial visual field was normal in the right eye. We observed a large amount of cupping of the optic nerves (Figure 2), but the neuroretinal rim was intact. It followed the "ISNT" rule, with the inferior rim the thickest, followed by the superior, nasal, and temporal rims. This patient was a glaucoma suspect, with a normal field and what may be an optic nerve that is normal for him.

We observed this patient for 8 years. His medical history, visual fields, and optic nerves were unchanged; his vision remained good, and his pressures ranged from 22 mm Hg to 29 mm Hg. During this time, we learned of the importance of central corneal thickness (CCT) and noted this patient's CCT was somewhat thick, which could explain why his pressure was elevated.

The patient moved to another state and returned 5 years later. On examination, his pressure was 28 mm Hg. His visual field (Figure 3) shows what appears to be a definite defect on the inferior arcuate distribution; it is relatively mild but certainly present. As we know, by the time a field defect is present, the optic nerve has likely changed. Comparing the optic nerve to where it was 5 years previously, we see evidence of neuroretinal rim loss, probably more profound superiorly than inferiorly, but a definite change from where it was before.

Treating OHT

What is the best treatment for OHT? Is it medication, laser trabeculoplasty, possibly no treatment, depending on the individual patient's risk, or should we begin to consider one of the newer surgeries, such as canaloplasty (iScience Interventional, Menlo Park, CA) or Trabectome (NeoMedix Corp., Tustin, CA)?

When we decide to treat a patient who has OHT, medication is typically our first line, given the patient's acceptance and risk profile. Laser trabeculoplasty is rarely an option, as it is restricted to the patient with OHT who has a very high risk profile, specifically, thin corneas, high pressures, and older age.

The idea of not treating these patients is important. The decision should result from a discussion centering

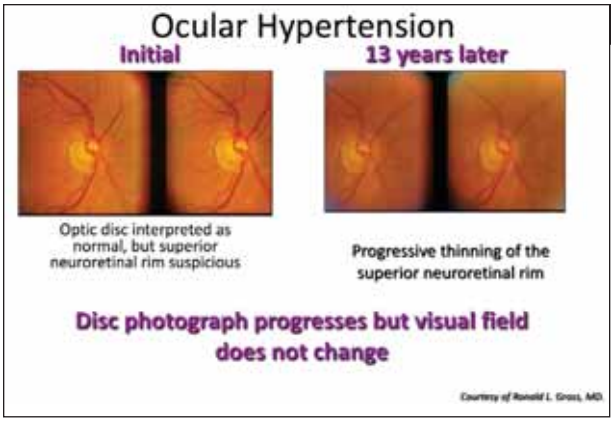

Figure 1. Over a 13-year period, visual fields have not changed, but the superior rim has become thinner.

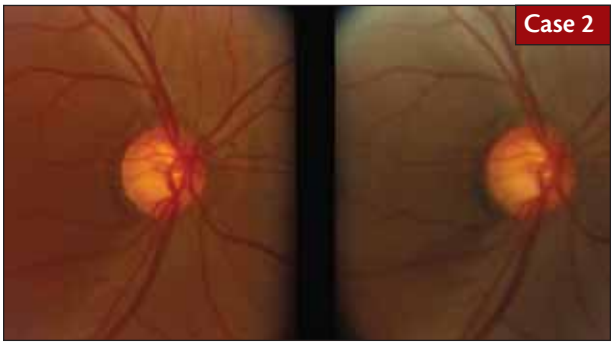

Figure 2. Initial examination showed a large amount of cupping and an intact neuroretinal rim.

on risk between the clinician and the patient. Typically, these patients are in one of two categories. First is the patient who says, "If there's anything you can do to decrease my risk of developing glaucomatous damage, I want it." For these patients, treatment is appropriate. Conversely, a patient may say, "If I absolutely have to have a medication, I will take it, but I would rather you monitor my status, and when the risk outweighs the potential benefits of not treating me, I am willing to take the medication." I have had patients with a high risk for OHT opt for no treatment. This is acceptable as long as the patient understands the risks and is willing to return for appropriate follow-up. We must remember that a person with OHT does not have definitive damage, and we are trying to prevent that from occurring.

The newer surgeries that avoid formation of a bleb may have a much better side effect profile than trabeculectomy,[1] but they may not be advisable to use in a patient without manifest damage.

Determining structural or functional damage

If we are going to observe and not treat patients who are at risk for development of glaucomatous damage, we must be able to identify progression if it occurs. How do we determine if the patient has true structural or functional damage? Should we look for atrophy of the remaining neuroretinal rim, focal thinning of the neuroretinal rim, asymmetry between the superior and inferior hemifields on visual field testing, or a retinal nerve fiber layer distribution of the visual field defect?

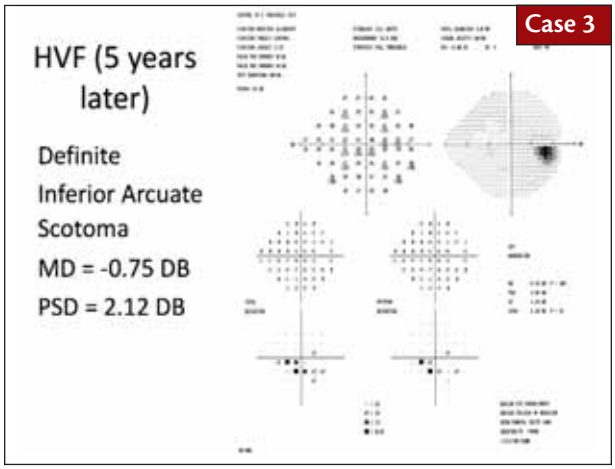

Figure 3. Visual field shows a mild but definite defect on the inferior arcuate distribution.

Atrophy of the intact neuroretinal rim does not occur in glaucoma. When cupping occurs, you can expect atrophy or paleness of the optic nerve within that cup, but the remaining neuroretinal rim is not pale. If it is, then some other etiology of nonglaucomatous optic nerve damage should be investigated.

Focal thinning of the neuroretinal rim is expected and common. Typically, there are two types of progression: focal thinning of the neuroretinal rim or a generalized increase in cupping associated with generalized thinning of the rim tissue.

In my second case, an inferior arcuate defect was distinct from what was found in the superior hemifield. Asymmetry between the superior and inferior hemifields is assessed in the glaucoma hemifield test on the Humphrey Visual Field Analyzer (Carl Zeiss Meditec, Inc., Dublin, CA) and can be useful in determining if a subtle defect is true damage or just scatter.

Finally, we must remember that perimetry measures only the visual field, not the glaucomatous visual field. When a visual field defect is present, we must be sure it is consistent with an intrinsic defect in the retinal nerve fiber layer and in the optic nerve and not indicative of some other disease, such as central etiology from a tumor. ●

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Challenging Glaucoma Cases

Far from being unusual, challenging cases such as these present regularly in clinical practice.

BY JONATHAN S. MYERS, MD

CASE 1: LOW-TENSION GLAUCOMA

A 40-year-old woman received a diagnosis of glaucoma and was referred for further evaluation. She has a history of low blood pressure and migraine headaches. She has multiple disc hemorrhages. Her highest IOP was 19 mm Hg, and central corneal thickness is average. Figure 1 shows scans of both eyes taken with optical coherence tomography (OCT). The thickness profile of the right eye shows a definite reduction inferiorly. The quality of the scan of the left eye is not quite as good, but it clearly shows thinning of the nerve fiber layer. The cup is large compared to the surrounding rim, and little rim tissue remains. In the right eye, the border of the retinal pigment epithelium (RPE) does not reach the edge of the optic nerve's scleral canal. The OCT uses the RPE edge as the limit of the optic nerve. In the right eye, the OCT sets the optic nerve border more peripherally than as seen on clinical examination, and the cupping that was seen clinically is less evident.

Visual fields (Figure 2) correlate closely to the OCT findings. There is a dense superior arcuate defect with nasal step in the right eye, whereas in the left eye, there is a dense superior and inferior arcuate defect similar to a central island. How would you manage this patient with apparent open-angle glaucoma?

In young patients with myopic discs and less pronounced visual field losses, suspicious optic nerves, even with visual field loss, could be physiologic in nature, and clinicians might opt to observe. In this case, however, with the more advanced visual field changes, this patient should be treated.

Because this patient may have advanced disease and her highest pressure was 19 mm Hg, fairly aggressive treatment is appropriate. In the Collaborative Normal Tension Glaucoma Study (CNTGS), the goal of treatment was a 30% reduction in IOP.[1] For this patient, a pressure of 13 mm Hg would be a reasonable goal. In the CNTGS, reducing pressures by 30% reduced the progression rate from 35% to 12%. Even with that aggressive pressure reduction, however, 12% of the treated patients in that study progressed. Furthermore, only about half of the patients were able to achieve those pressure goals with

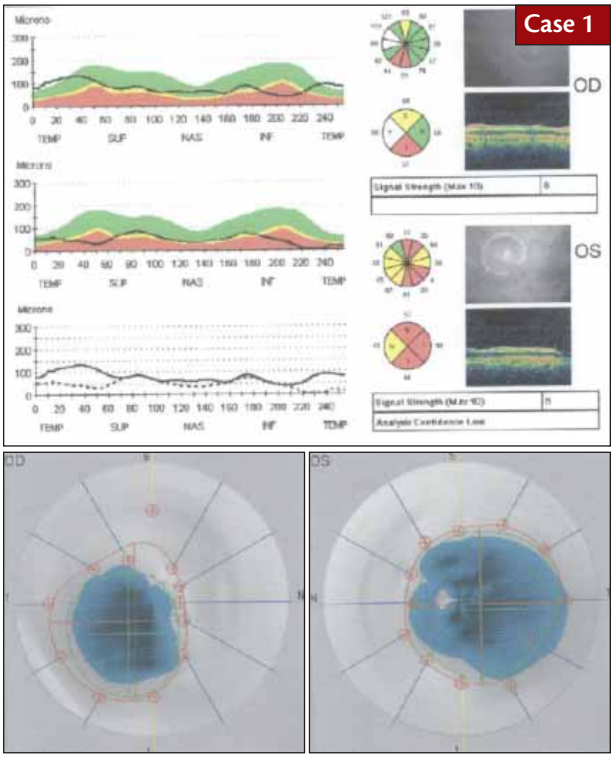

Figure 1. OCT scans of a 40-year-old patient newly diagnosed with glaucoma.

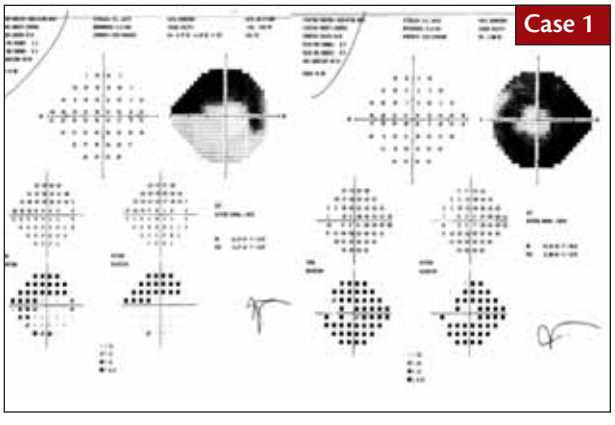

Figure 2. Visual fields correlate closely to OCT findings.

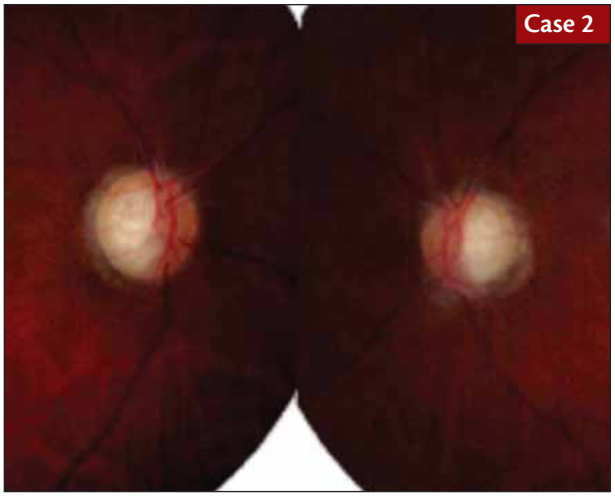

Figure 3. Note the advanced cupping of both optic nerves.

only medications or laser treatment. By committing to an aggressive pressure goal, you may be committing to a more aggressive form of treatment.

Various first-line treatment options are available. Topical ß-blockers have been shown to be effective pressure-reducing agents for most patients, and once-a-day dosing is usually sufficient. Some clinicians may avoid a topical ß-blocker as a first choice in patients with low-tension glaucoma because of hemodynamic considerations.[2] Specifically, there are concerns that a reduced heart rate or, possibly, reduced blood pressure may lead to reduced perfusion of the optic nerve in patients with abnormal autoregulation of blood flow, which may be associated with low-tension glaucoma and migraines. The literature is complex and varied, but there may be reductions in some of the hemodynamic parameters in the retrobulbar and intrabulbar circulation.

Another option for this patient is a topical prostaglandin analogue. Prostaglandin analogues offer once-daily dosing, have a safe systemic profile, and often achieve good reductions in IOP.

A twice-daily α-agonist, such as brimonidine, is also an option for this patient. In the Low-Pressure Glaucoma Treatment Study (LoGTS), patients with low-tension glaucoma were randomized to either timolol or brimonidine and observed for 4 years.[3] Both groups had similar reductions in IOP. Interestingly, after 4 years, visual field progression was statistically less frequent in the brimonidine-treated patients (9%) than in the timolol-treated patients (31%). These findings were seen with three different field grading algorithms. The research does not directly answer the question of why brimonidine proved more effective than timolol in preserving visual field. Possible explanations include a neuroprotective effect of brimonidine or a deleterious effect of timolol on the optic nerve directly or via hemodynamic effects.

Many studies show that laser trabeculoplasty, even in low-tension glaucoma, can achieve pressure reduction. Its safety and efficacy have been shown to be equal to that of topical medications,[4,5] and it takes compliance out of the equation. Laser trabeculoplasty is effective initially in about 80% of patients, however, and the effect persists for only 2 to 4 years.[6] Selective laser trabeculoplasty reduces mean IOP and IOP variation in normal-tension glaucoma patients. Although it can be a helpful adjunct, it often does not replace topical therapy.

As we think about our goal pressure of 13 mm Hg, we must acknowledge it may take more than one of these treatments to achieve that goal for this patient.

CASE 2: ADVANCED GLAUCOMA

A 70-year-old man has open-angle glaucoma. His initial IOPs were 20 mm Hg in the right eye and 42 mm Hg in the left eye. He recalls having a severe impact to his left eye from a tennis ball at age 40. His pressures have been well controlled with various medications (9 mm Hg to 17 mm Hg). His central corneal thickness is markedly reduced in both eyes (< 500 µm). He has had trabeculectomies in both eyes and a tube shunt in the left eye. Figure 3 shows advanced cupping of both optic nerves, and Figure 4 shows advanced field loss, with a central island in the right eye and a small central island in the left eye. The patient feels his vision has been worsening in recent years despite the pressure control. What should be done for this patient?

In certain patients, it may be advisable to measure pressures in the office throughout the day, as this may reveal pressure spikes that put the patient at a greater risk of progression. Serologies would not be unreasonable in this case. Although the patient clearly has open-angle glaucoma, he could also have an autoimmune-related or infectious retinopathy or optic neuropathy.

With progressive glaucoma, in the absence of explanations for visual field progression, some practice guidelines suggest magnetic resonance imaging to look for tumors

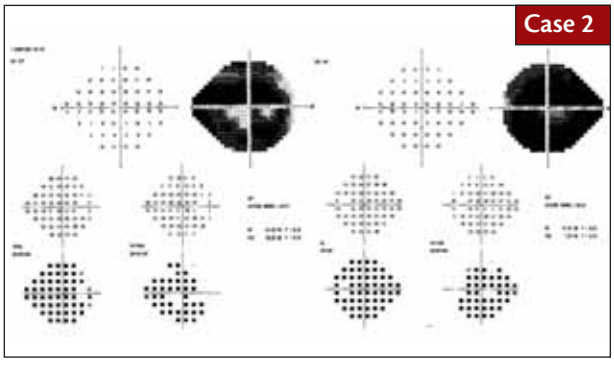

Figure 4. Note the advanced field loss, with a central island OD and a very small central island OS.

or other compressive lesions. This patient has had all of these tests, which were normal.

This patient has a history of hypertension, requiring multiple medications. We instructed him to monitor his blood pressure at home and found, with his current medication regimen, his blood pressure was fluctuating from very high in the morning to extremely low overnight. We consulted with the patient's cardiologist, who adjusted the medication regimen. The patient's overall blood pressure stabilized to a level that was safe for his heart and, at the same time, would maintain a more even perfusion to his optic nerve. We have evidence from the Los Angeles Latino Eye Study (LALES)[7] and others that uncontrolled or very low blood pressure may lead to greater risk of progressive optic neuropathy in glaucoma. Additionally, studies have shown that patients taking multiple blood pressure medications may be at greater risk for optic nerve cupping.[8]

CASE 3: COMPLEMENTARY THERAPIES FOR PRIMARY OPEN-ANGLE GLAUCOMA

A 71-year-old man with open-angle glaucoma has a history of myopia and combined cataract and glaucoma surgery. His central corneal thicknesses are 538 and 531 µm. His pressures had been 15 mm Hg or lower for years, but he had visual field progression in recent years and started taking dorzolamide and timolol. His pressures ranged from 8 mm Hg to 12 mm Hg with this regimen. On examination at this visit, his optic nerves are tilted with peripapillary atrophy, consistent with his history of myopia before cataract surgery. Glaucomatous optic neuropathy in the form of cupping is evident. As shown by the disc drawings (Figure 5), the clinician believed the glaucomatous cupping, not the tilt, was problematic. The patient said his vision was deteriorating almost on a weekly basis, making it more difficult to participate in activities he enjoys.

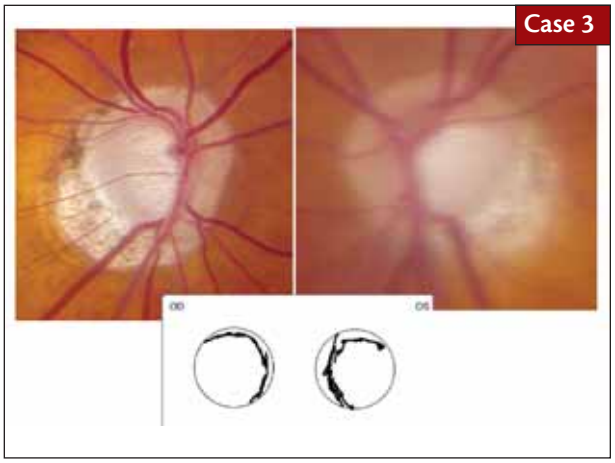

Figure 5. Glaucomatous optic neuropathy is evident.

At the top of the series of visual fields for the right eye (Figure 6), a central island is visible. Although there is a great deal of variation field to field, the last field in the series has almost the same mean deviation as the first field in the series. Visual fields for the left eye (Figure 7) show a dense paracentral scotoma with nasal extension consistent with glaucoma. In patients with myopia, we often see these paracentral scotomas earlier in the course of glaucoma. Although there may be an increased paracentral scotoma inferiorly early in this series of fields, significant progressive changes to match the patient's complaints are not obvious. On the 10-2 field from the left eye (Figure 8), we can see a dense defect approaching fixation that was also fairly stable on follow-up. When considering stability in such a scenario, we should remember that points registering "0" on the field are not necessarily blind to all stimuli but are beyond what the machine can test. Thus, real changes may not be evident. On the other hand, most clinicians are reluctant to consider aggressive interventions without objective evidence.

This patient has read just about everything there is to read about glaucoma, including information on alternative therapies that do not rely on pressure reduction. He asks what else can be done for him.

Many patients have heard that bilberry was used by pilots during World War II to improve night vision and ocular health. There is little evidence, however, that bilberry changes the course of glaucoma or improves visual function in patients who have glaucoma.

Eyebright is another popular supplement purported to aid vision. Perhaps it is helpful, but there are no controlled, randomized studies showing improvement in glaucoma.

Ginkgo biloba has been used to improve neuronal function in various diseases. In one study, 27 subjects with normal-tension glaucoma and established field loss

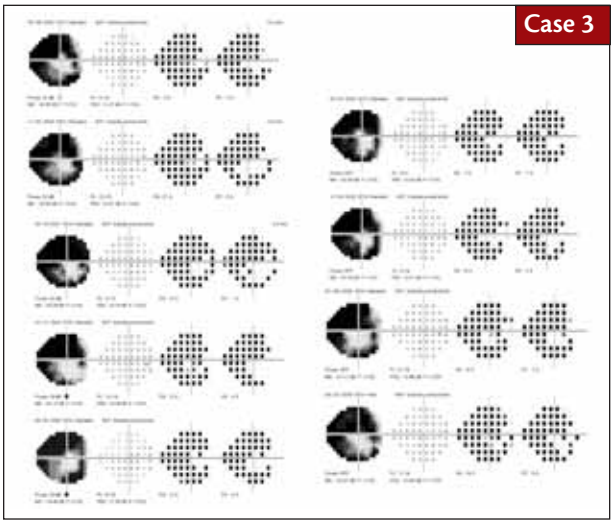

Figure 6. A central island is visible in the right eye.

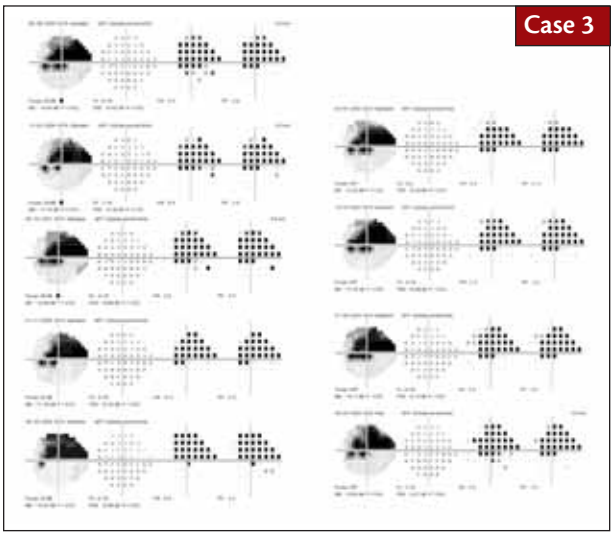

Figure 7. The left eye shows a dense paracentral scotoma with nasal extension.

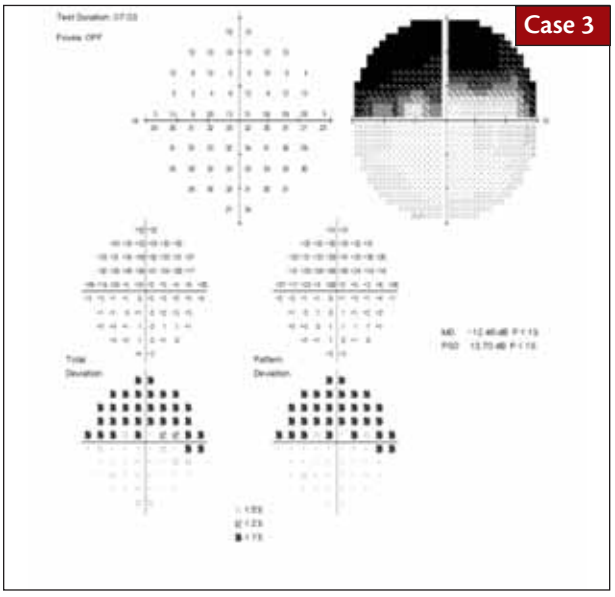

Figure 8. The 10-2 field shows a dense defect approaching fixation.

had baseline visual field testing on gingko biloba and placebo in a masked, randomized, crossover study.[9] Half the subjects took placebo and half ginkgo for 4 weeks and then underwent field testing. After washout, each group took the other treatment for 4 weeks and underwent field testing again. In this study, the patients' visual fields were better while they were taking ginkgo than placebo, with a more than 20% reduction in mean deviation. This was a limited study, and there have been no repeat or long-term studies. This study provides at least some reasonably scientific evidence, however, that ginkgo may be helpful for selected patients. At the same time, ginkgo can thin the blood, so it may not be a safe choice for patients with clotting disorders or patients taking blood thinners or high-dose vitamin E.

In a prospective, multicenter trial, patients with low-tension glaucoma were randomized to placebo or memantine. Although findings from this study have not been published, the company that funded the study reported the primary endpoint of better preservation of vision was not met with memantine. So, although it is used in other neurodegenerative diseases, we have no evidence to date that memantine is neuroprotective in glaucoma.

In the LoGTS, brimonidine was shown to be potentially neuroprotective in low-tension glaucoma. This patient is not currently taking brimonidine, so we could discuss those findings with him and consider adding that agent to his regimen or possibly substituting it for dorzolamide or timolol. ●

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CME QUESTIONS

1. In the discussion by Dr. Katz, which of the following is likely the most reliable method for confirming a patient's persistence with glaucoma therapy?

a. Asking family members or caregivers

b. Directly questioning the patient

c. In-office surveys

d. Reviewing prescription renewal rates

2. Which of the following glaucoma agents has been shown to have the best persistence and adherence?

a. α-agonists

b. ß-blockers

c. Carbonic anhydrase inhibitors

d. Prostaglandin analogues

3. Which of the following is the least preferred treatment for patients with ocular hypertension unless there is a high risk profile, ie, thin corneas, high pressures, and older age?

a. ß-blocker

b. Combination of ß-blocker and brimonidine

c. Laser trabeculoplasty

d. Prostaglandin analogue

4. Which of the following is most likely to be associated with progressive optic neuropathy in glaucoma?

a. High myopia

b. Thinning of central cornea

c. Uncontrolled or very low blood pressure

d. Use of multiple blood pressure medications

5. According to Dr. Gross, which of the following is the most appropriate visual field strategy for observing glaucoma patients?

a. Confrontational

b. SITA Fast

c. SITA Standard

d. SWAP (blue-on-yellow)

6. Which of the following may be potentially neuroprotective in low-tension glaucoma?

a. ß-blockers

b. Brimonidine

c. Brinzolamide

d. Memantine

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