Current Medical Treatment of Glaucoma

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With a wide range of medical therapies for glaucoma, it is imperative to assess both the efficacy and safety of an agent to make the best choice for the individual patient.

Medical therapy is the cornerstone of disease management for the majority of glaucoma patients. In the developed world, the standard initial intervention for glaucoma is a topical ocular medication, typically a prostaglandin analog (PGA). Non-pharmaceutical treatments, including laser therapies and surgery involving blebs, stents, and/or filtering devices, are typically withheld as options to fall back on when initial medical therapy fails.

Untreated glaucoma can cause progressive visual loss potentially leading to severe visual disability. Once the decision to begin medical treatment is made, the goal is clear: to reduce progression risk by preventing, or at least slowing, glaucomatous damage to the optic nerve. To this day, lowering intraocular pressure (IOP) has been the only means to accomplish this goal, regardless of the stage of the disease.

BENEFIT OF IOP REDUCTION

Elevated IOP has been established as the main risk factor for disease evolution in glaucoma, and there is strong evidence that strict IOP control can delay progression of the disease. In the Early Manifest Glaucoma Trial, each 1-mm-Hg decrease in IOP was associated with a roughly 10% reduction in the risk of visual field or optic disc progression. In the treated group (mean IOP reduction: 25%), progression risk decreased by half compared to untreated controls. In the Advanced Glaucoma Intervention Study, patients whose IOP was under 18 mm Hg at every visit over 6 years had almost no visual field progression, while patients whose IOP was over 18 mm Hg on half or more of their visits had worsening of about 0.63 units in visual field defect score.

Commonly used IOP-lowering drugs can be divided into four major classes: PGAs, beta-blockers, alpha-agonists, and carbonic anhydrase inhibitors (CAIs). Also available are fixed combinations of glaucoma drugs—usually from different classes and with additive mechanisms of action. With two or more agents combined into a single bottle, fixed-combination formulations aim to maximize efficacy and improve compliance.

PROSTAGLANDIN ANALOGS

Because they are relatively safe and can lower IOP by more than 30% with once-a-day dosing, PGAs are the most popular first-line agents for glaucoma in the US and much of the rest of the world. The introduction of PGAs almost 20 years ago revolutionized the management of glaucoma; at the time, only filtering surgery could reliably produce that degree of IOP-lowering. PGAs quickly became the drugs of choice for glaucoma, while the use of other medications, as well as surgery, dropped dramatically.

In addition to efficacy, the PGAs are notable for a paucity of systemic (cardiovascular or pulmonary) side effects because these compounds are rapidly cleared from the bloodstream. Mild ocular side effects, however, are not uncommon, including darkening of periocular skin, irreversible darkening of the iris, growth of lashes,
periorbital fat loss, stinging, and conjunctival hyperemia. Although most of these effects are cosmetic, some patients find them worrisome or unacceptable, making it important to counsel patients about the potential ocular effects of PGAs beforehand. Also, caution should be used when these medications are used in only one eye because of potential for asymmetric ocular side effects.

**BETA-BLOCKERS**

Beta-blockers were once the mainstay medical treatment for glaucoma. These agents lower IOP by decreasing aqueous production; the effect—at least a 25% pressure reduction—occurs primarily during the day.10 Although highly effective and generally well tolerated, in susceptible individuals beta-blockers can produce cardiovascular and respiratory side effects, including bradycardia, arrhythmia, heart block, and bronchiolar constriction. They can also cause sexual dysfunction. Adverse central nervous system effects are also common, ranging from weakness to depression to hallucinations. In people with diabetes, use of beta-blockers can mask hypoglycemic signs and symptoms, sometimes resulting in dangerously low blood sugar. Additionally, beta-blockers have the potential to raise serum triglycerides, and thereby increase the risk of cardiovascular disease. If used in patients who are highly allergic to substances like peanuts or insect venom, beta-blockers can reduce the efficacy of injected epinephrine.

Clinically, it is vital to identify patients who may be susceptible to these potential dangers. Contraindications to beta-blocker use include asthma, chronic obstructive pulmonary disease, bradycardia, and congestive heart failure. A careful clinical history is often helpful in recognizing patients at risk. When a topical beta-blocker is prescribed, patients should be told of its potential systemic side effects and instructed to measure blood pressure and pulse regularly.

**SELECTIVE ALPHA AGONISTS**

Alpha-2 agonists lower IOP by about 20-25%, but the dosing schedule for monotherapy—three times daily—is inconvenient. These agents can, however, be used in combination with other drugs, allowing for twice-a-day dosing. Alpha-2 agonists are generally well-tolerated but may stimulate alpha-2 receptors of the central nervous system and produce adverse systemic reactions such as low blood pressure and orthostatic hypotension. Alpha-2 agonists can also cause allergic responses, at rates ranging from 12% to 25%.11 They should be avoided or used with caution in children due to the potential for central nervous system depression.

The two selective alpha-agonists in clinical use today are apraclonidine and brimonidine. Apraclonidine, the first relatively selective alpha-2 agonist available, was initially used to treat open-angle glaucoma. Allergy and diminution of therapeutic effect with repeated use (tachyphylaxis) have limited its usefulness to short-term applications, such as preventing pressure spikes after anterior segment laser pro-
CARBONIC ANHYDRASE INHIBITORS

Reducing IOP by about 20%, CAIs have less IOP-lowering efficacy than PGAs. Because they reduce IOP by decreasing aqueous production, these sulfonamide agents are often used adjunctively with PGAs, which lower IOP by increasing non-trabecular aqueous outflow (uveoscleral outflow). Like PGAs, topical CAIs have no effect on blood pressure, heart rate, or pulmonary function.

But because they are sulfonamides, CAIs can cause allergic reactions in sensitive patients. Oral CAIs (eg, acetazolamide) are also associated with a number of systemic side effects, including dehydration, metabolic acidosis, renal calculus formation, paresthesias, taste disturbances, hematologic abnormalities, and sickle cell crisis in susceptible patients. Since topical CAIs (dorzolamide and brinzolamide) have become available, the use of oral CAIs today is generally limited to angle closure glaucoma and secondary forms of glaucoma such as uveitic glaucoma.

MEDICATION SELECTION

There are two key factors in selecting any medication: efficacy and safety. The PGAs are today’s preferred choice for initial therapy owing to their combination of greater IOP-lowering efficacy and systemic safety. Before initiating treatment, clinicians should obtain a thorough history and determine whether their drug of choice is safe for that particular patient. In the case of a PGA, the side effects are, as noted, mainly local and cosmetic. But when an alternative or a second agent is warranted, systemic risks such as cardiovascular or pulmonary disease or allergy become important considerations. Patients who take more than one topical eye medication at the same time of day must be reminded to wait at least 5 minutes between medications, so that each medication has sufficient time to penetrate into the eye.

A review of clinical evidence and expert opinions suggests that a PGA coupled with a topical CAI may be the best combination to lower IOP. The pair synergistically reduces IOP with minimal systemic risk. My own primary choice of drug is a PGA, followed by a topical CAI. After that I would add either an alpha-agonist or a beta-blocker. If three medications cannot bring the patient to target IOP, the patient should probably be referred for laser or surgical intervention.

Patient compliance is critically important to the success of chronic medical therapy for glaucoma. Patients must understand that glaucoma is a lifetime disease, that the damage from open-angle glaucoma is usually imperceptible from one day to the next, and that the success of therapy requires commitment to the medication regimen and continuing assessment. In addition to teaching the importance of adherence, clinicians can help patients by choosing a simpler medication regimen with as few doses per day as possible, and by selecting agents that are safe and comfortable to use.

Most glaucoma eye drops, especially preserved ones, can cause minor disruptions in the ocular surface and can exacerbate dry eye signs and symptoms. Treating pre-existing dry eye and other ocular surface conditions may help improve tolerability and prevent noncompliance. Of course, if a topical lubricant is used at the same time as glaucoma medications, it should be applied last and at least 5 minutes after any glaucoma medication.

OCULAR PERFUSION PRESSURE

Recent clinical studies have provided strong evidence that low perfusion pressure is connected to glaucoma damage and progression. A reflection of vascular status at the optic disc, ocular perfusion pressure is defined as the difference between the mean arterial blood pressure and IOP. It is believed that perfusion pressures lower than 50 to 55 mm Hg are associated with increased risk of glaucoma progression.

Maintaining ocular perfusion pressure at appropriate levels may be beneficial in the treatment of glaucoma. By definition, the perfusion pressure increases as blood pressure increases and as IOP drops. The PGAs and CAIs, with little effect on blood pressure or cardiac output, may enhance perfusion pressure by lowering IOP alone. The alpha-agonists and beta-blockers, on the other hand, have a greater potential to reduce blood pressure and cardiac output. As a result, they may lower perfusion pressure and thus increase the risk of progression, which may to some degree undermine their IOP-lowering effect.

One new agent, latanoprostene bunod, which is not approved in the US but is in phase III clinical trials,
combines the PGA latanoprost with a nitric acid donating moiety and may have a positive impact on perfusion pressure as well as on IOP.

At present, blood pressure is not routinely measured in patients with glaucoma. Including this parameter in glaucoma management will allow us to evaluate the perfusion pressure at follow-up visits and perhaps improve the efficacy of glaucoma treatment. In cases where a glaucoma patient is also being treated for high blood pressure, IOP reduction may be helped by a discussion with the primary care physician of the possibility of lowering the dose of blood pressure medication or changing the dosing schedule from the evening to the morning.

The clinical significance of ocular perfusion pressure, though in need of further elucidation, highlights the impact of other factors on the disease process of glaucoma. In the end, medical management of glaucoma is not just about pharmacology. It is also about our knowledge of all the variables that contribute to the onset and progression of the disease.

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REFERENCES
Improving Adherence to Glaucoma Medications

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Medication nonadherence is one of the most important issues in glaucoma care. Understanding its complex origins is the first step in helping steer patients toward greater control of their disease.

As eyecare providers, our most diligent efforts to identify and treat patients with glaucoma are thwarted when patients fail to take their medications. Proper adherence requires that patients fill their prescriptions, instill the drops with appropriate technique and timing, and do so with daily consistency.1 A breakdown in any step compromises adherence and threatens efficacy.

Improving adherence requires that we acknowledge glaucoma patients’ central role in their disease management and use the most effective means available for supporting them. Good communication is key to uncovering barriers to adherence and providing practical strategies for eliminating or reducing those barriers.

SCOPE OF THE PROBLEM

Medication nonadherence is highly prevalent among patients being treated for glaucoma.2-4 A 2005 literature review showed that up to 80% of patients deviate significantly from their prescribed antihypertensive treatment regimen. Roughly one in 13 newly diagnosed patients never fills their first prescription for anti-glaucoma medication.5 Among newly diagnosed patients who fill their prescriptions, persistence (defined as possessing the correct amount of medication at least 80% of the time) within the first 12 months of ocular hypotensive therapy continued to have at least moderately good persistence over the course of the subsequent 3 years. Conversely, patients with persistently “very poor” or “declining” adherence in year 1 rarely achieved good adherence in later years.9

Barriers to adherence vary widely, and most patients have multiple barriers. In one survey, 10% of glaucoma patients reported a single barrier to adherence, and 61% reported multiple barriers.7 Common barriers to medication adherence include polypharmacy/simple regimens, forgetfulness, cost, and difficulty instilling drops due to arthritis or other physical comorbidities. Poor health literacy—for example, poor understanding of what is required for appropriate disease management—may lower patient engagement and medication adherence.1 In focus groups, patients cite insufficient knowledge of glaucoma as a leading barrier to optimal adherence to glaucoma treatment.8 Even patients with a good understanding of their disease and strong motivation may be frustrated by the lack of identifiable payoff to taking their drops.

Patients’ perceptions and beliefs directly affect their willingness to engage meaningfully in their care.9 Patients who are not aware that their condition is serious or do not believe that their medications will help are less likely to adhere to therapy, particularly if they are experiencing side effects or have other justification for stopping. In contrast, believing that you have control over your disease—called “self-efficacy”—increases engagement and likelihood of success.9

IDENTIFYING NONADHERENCE

Patients often report much higher adherence than found when electronic monitoring is used in studies.1 In general, physicians are poor predictors of patient adherence.10 A useful way to gain better insight into patient prac-
system, pharmacy data is accessible to clinicians, providing a useful means for uncovering discrepancies between patient reporting of medication usage and refill frequency. In most instances, though, refill information is not available to providers, and we depend on patients to tell us the truth.

COMMUNICATION MATTERS TO PATIENTS

Managing glaucoma can be frustrating for both patient and doctor. Rather than performing a clearly positive function for patients, like alleviating suffering or restoring lost vision, ocular hypotensive medications typically counter a silent process. In some ways, patients are taking a leap of faith when they follow our recommendation for lifelong medication.

Considering the level of trust required, it is not surprising that many patients place a high value on the quality (and quantity) of interactions they have with their eye care provider. One of the simplest and most meaningful things we can do to build trust with patients is to listen. In one survey, when patients were asked about perceived barriers to effective glaucoma control, the most common responses related to pitfalls in the doctor–patient relationship. Specifically, patients lamented doctors not taking time to talk with them, ask questions, or listen to their concerns.7

One study showed that, in a 16-minute office visit, only 49 seconds were devoted to proper use of medications. That’s clearly inadequate! A separate study showed that physicians who communicate well have 19% higher adherence rates compared with those who communicate poorly.11

ADHERENCE STRATEGIES

Another strategy to help patients stay on track is to keep medication regimens as simple and as convenient as possible. A well-known tenet of prescribing, one that is particularly important to glaucoma care, is to use once-a-day medication whenever possible.

At the time of diagnosis, patients should be counseled on what to expect from their disease and its treatment, including side effects. When prescribing prostaglandin analogs, for example, an upfront conversation about the potential for lash lengthening, iris changes, or loss of periorbital fat can prepare patients, should any of these occur. Also, providing guidelines for notifying the office can help patients keep minor side effects in perspective: for example, explain to patients that a bit of stinging with medication is normal, but anything worse should prompt a phone call.

To assess their understanding, sometimes asking surprise questions is helpful—for example, saying to the patient, “You tell me: what is glaucoma?” A surprising number of patients confuse glaucoma with cataracts. When they do, they are less inclined to worry about it because they wrongly presume that an outpatient surgery will fix it down the road. By simply asking the question, misunderstandings that may be contributing to nonadherence have a chance to surface, providing an opportunity to remedy that by educating the patient on the spot.

CAREFUL LISTENING

Listen for implied or explicitly stated barriers to success so that you can tailor a solution. For example, a patient who forgets to take her medication needs a way to remember, such as a visual reminder or linking her bedtime dose to an already ingrained habit such as brushing their teeth. By contrast, a patient who holds the belief that his medication is of no importance will not benefit from a discussion about reminder systems. Rather, this patient needs to be invited to express the underlying reasons for his cynicism so they can be addressed.

When time is limited, it is valuable to have a staff member—such as a nurse, nurse practitioner, technician, or coach—available to counsel patients who are at risk for nonadherence. Adjunctive communications such as pamphlets (eg, containing disease and treatment information as well as answers to commonly asked questions) and/or waiting room videos can be useful in reinforcing verbal messages. Using point-of-care tools to help patients visualize their disease can help ground conversations and make abstract ideas more real to patients.

Even for patients who are not very forgetful, reminders may improve adherence. One study showed that the use of telephone and text reminders significantly improved medication adherence among patients on once-daily medical treatment for glaucoma.13 The intervention was inexpensive, about $20 per patient per year, and was well received by patients. However, not all patients stand to benefit from technology-based reminders. One survey of glaucoma patients concluded that email or text-based reminder systems were generally best suited to the under-40 demographic.14

Smartphone apps that remind patients to take their medications may also be useful. Dozens of phone and tablet apps are available for help-
ing patients stay on course with their therapies, including several specifically for managing eye drop regimens.

**FUTURE STUDIES**

Surprisingly, no studies show conclusively that improved adherence improves outcomes in glaucoma. As providers, we may agree that adherence is important, but we do not fully understand how the degree of adherence (eg, taking 50% of doses vs 70%) affects visual function. Are different levels of adherence needed at different stages of disease? Research in these and related areas will help us advise patients more effectively.

The impact of nonadherence will be easier to study as IOP-monitoring technology evolves. In addition, I look forward to the day we can prescribe drug-eluting contact lenses, punctal plugs, and other devices that not only improve adherence, but improve drug delivery as well. Effortless adherence plus continuous IOP monitoring will usher in a new era in the medical treatment of glaucoma and render nonadherence a nonissue.

**CONCLUSION**

The doctor–patient relationship can be the difference between adherence and nonadherence. Spending more time with patients, nonjudgmental listening, recruiting help from staff and caregivers, and employing patient-specific strategies for overcoming barriers and incorporating eye drops into daily life all can help improve adherence.

**REFERENCES**


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1. Which of the following is NOT a potential contraindication to topical beta blocker use?  
   A. Asthma  
   B. Rheumatoid arthritis  
   C. Chronic obstructive pulmonary disease  
   D. Bradycardia

2. Which of the following characteristics of prostaglandin analogs is most likely to support adherence?  
   A. High efficacy  
   B. Once-daily dosing  
   C. Potential for iris color change  
   D. Over-the-counter availability

3. Which of the following is NOT a potential barrier to adherence?  
   A. Sourcing accurate information about glaucoma from the Internet  
   B. Not understanding the disease  
   C. Distrusting the provider  
   D. Leading a very busy life

4. Which of the following is NOT a potential side effect of PGAs?  
   A. Change of eye color  
   B. Growth of lashes  
   C. Hyperemia  
   D. Sulfonamide allergy

5. Among newly diagnosed glaucoma patients who fill their first prescription, the percentage who remain on the medication at 6 months is approximately:  
   A. 95%  
   B. 80%  
   C. 50%  
   D. 15%

6. In addition to IOP, which one of the following measurements is required to determine ocular perfusion pressure?  
   A. Blood pressure  
   B. Trabecular meshwork status  
   C. Aqueous humor prostaglandin level  
   D. None of the above, perfusion pressure is measured directly

7. Which of the following factors can potentially compromise compliance in glaucoma treatment?  
   A. Failure to communicate the importance of treatment and follow-up visits  
   B. Side effects of glaucoma eye drops  
   C. Ocular surface conditions  
   D. All of the above

8. Effective communication helps achieve which of the following glaucoma-care objectives?  
   A. Identifying medication nonadherence  
   B. Identifying barriers to adherence  
   C. Preventing nonadherence  
   D. All of the above

9. Glaucoma drugs from which class may mask hypoglycemic signs and symptoms in diabetics?  
   A. PGAs  
   B. Beta-blockers  
   C. CAIs  
   D. Alpha-agonists

10. The term “self-efficacy” refers to:  
    A. Patients’ sense of control over their disease  
    B. Patients’ ability to select their medication  
    C. Patients’ ability to instill eye drops properly  
    D. Study design based on self-report