Approaches to Anti-Glaucoma Medication Nonadherence

William C. Stewart, MD

Treatment nonadherence is an entrenched challenge in glaucoma care. Failure to identify and remedy nonadherence can mean suboptimal IOP suppression for vulnerable patients.

Glaucoma affects about 3 million individuals worldwide and is a leading cause of vision loss and blindness. Topical ocular anti-glaucoma medication has been shown to slow the progression of glaucoma in clinical trials and represents the mainstay of pharmacologic treatment. However, nonadherence—prevalent among glaucoma patients—undercuts clinical efforts to control the disease. In effect, a patient who discontinues treatment is in the same boat as a patient who goes untreated, something good clinicians strive vigorously to avoid. As such, nonadherence—and the factors that contribute to it—merits greater clinical attention and discussion within the medical community than it receives.

Deficient focus on this vexing problem is, in one sense, understandable. Clinicians generally prefer to operate from a place of firm knowledge; and nonadherence is shrouded in some fundamental unknowns. First, it can be difficult to detect. Doctors rely on patients (or caregivers) to be forthcoming about medication issues, including adherence difficulties; however, studies show that patients tend to report greater adherence than that demonstrated on objective measures (Figure 1). Further, doctors also tend to overestimate adherence and therefore have little success predicting it accurately.

A second problem is a lack of proven strategies to change patient behavior and remedy nonadherence once it has been uncovered. Third, it’s unknown whether or not better adherence makes for better outcomes although several small studies have found increased IOP and visual field loss among patients with poor compliance. However, no major prospective studies (to my knowledge) have correlated improved medication...
adherence with better patient outcomes.

To sum up, we appreciate that some level of medication adherence is probably important to help maintain visual function, but we do not know exactly how much or how. And taking on nonadherence requires that eye care providers wade into the murky waters of human behavior. However, if we are intent on giving patients the best shot possible to maintain long term vision, we must not overlook adherence issues; in fact, we should look squarely at them, look for underlying influences, and provide support and strategies for patients.

**SCOPE OF THE PROBLEM**

Proper adherence to topical ocular medication requires that patients fill their prescriptions and instill the proper dosage into the ocular cul-de-sac at the appropriate time every day. Anything that interferes with the medication contacting the eye can be thought of as nonadherence, including not filling the prescription, taking a drug holiday, missing doses, or allowing for too little (compressing) or too much (spreading) time between doses. Patients with arthritis or other physical comorbidities may have trouble steadying their hand or squeezing the dropper, resulting in the drop missing the eye.

Studies across a range of populations show that medication nonadherence and dosing errors are widespread among patients being treated for glaucoma. A 2005 literature review showed that up to 80% of patients deviate significantly from their prescribed antiglaucoma treatment regimen. Self-report rates of nonadherence are generally lower but also range widely, from 28% to 59%. Roughly 1 in 13 newly diagnosed patients never filled their first anti-glaucoma prescription. Among newly diagnosed patients who fill their prescriptions, persistence (defined as starting and continuing therapy as prescribed for a certain period of time) has been estimated at 50% at 6 months and about 31% at 12 months. Other estimates suggest that about 50% are adherent at 12 months.

Successful therapy initiation and persistence in the early months may be quite important toward successful adherence long term. According to one study, patients with “persistently good adherence” (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 study.
subsequent three years. Conversely, patients with persistently “very poor” or “declining” adherence in year one rarely achieved good adherence in later years.¹⁰

NONADHERENCE INFLUENCES

Barriers to adherence are highly variable in type and number. In one survey, 61% of glaucoma patients reported multiple barriers to adherence.¹⁴ In contrast, types of medication adherence in glaucoma comprise four categories: the disease, the medication, patients, and prescribers.

First among the four categories is the disease itself. Glaucoma is a chronic disease for which no definitive cure is available at present. Thus, patients must cope with the prospect of taking medication every day, and sometimes multiple medications, to control the disease. The seeming endlessness of treatment can feel tiring or even defeating to patients, especially when there are side effects or doubts about treatment efficacy or importance. Since no symptoms are associated with glaucoma in its early and intermediate stages, patients may be frustrated by the lack of identifiable payoff to taking their drops.¹⁵ Research also shows that when glaucoma is upstaged by what the patient perceives to be a more pressing comorbid condition, adherence is reduced.¹⁶

Second, factors associated with the medication and medication regimen may contribute to nonadherence. Studies show that being on multiple medications, or complex regimens, may contribute to nonadherence.³ Higher frequency dosing is also thought to contribute to nonadherence, the common wisdom being that once or twice is superior to three or four times daily dosing in the treatment of glaucoma. Via a series of studies in the 1980s utilizing an eye drop medication monitor in bottle caps, Kass and coworkers demonstrated that patients dosed twice daily had higher compliance compared with those dosed three or four times daily.⁴,¹⁷ A study that used Travalert® dosing aid (Alcon, Ft. Worth, TX) to measure adherence electronically revealed that patients on travoprost monotherapy had greater medication adherence compared with those on a combined drop (travoprost plus timolol), possibly a reflection of more advanced age and polypharmacy in the latter group.¹⁸

The patient is a pivotal third factor. Patient factors that may contribute to nonadherence are wide-ranging and include factors that are psychological (eg, denial, passive-aggressive behavior), mental (eg, dementia, forgetfulness), physical (eg, arthritis), and circumstantial (being over-busy, lacking social support, difficulty with time management). In a recent, sizeable, well-designed anti-glaucoma medication adherence study, Spleth and coworkers found that higher rates of patient self-efficacy (ie, sense of confidence and control over their disease) significantly correlated with high adherence.¹⁹

It is important that physicians resist any notion to pin all blame for nonadherence on the patient.²⁰ A fourth key influence on medication adherence is the relationship between patient and eye care provider. 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 focus group surveys, patients cite deficient knowledge about glaucoma as a leading barrier to optimal management.²¹

Patients may achieve greater adherence when their physicians show interest in their well-being. Taking the time to provide disease education, address patient concerns, and answer questions will likely enhance rapport and increase the likelihood that patients will adopt a positive-minded, proactive stance toward their disease.²² In the adherence study cited above, teaching patients how to instill the drops in their eyes was the most important patient education intervention that increased adherence.¹⁹

IDENTIFYING NONADHERENCE

Nonadherence is on the differential diagnosis when IOP does not respond to treatment as expected; in cases of progressed disease, especially when the IOP is measured in the normal range; and when previously controlled IOP begins to creep back up. In the latter case, waning medication effectiveness should also be considered. Normal IOP during an office visit may fool the physician into assuming good adherence, as it may reflect “white-coat adherence” or good adherence for the period just before the clinic visit.²² Therefore it is worth inquiring about adherence regardless of IOP and clinical findings.

Physician-patient communication likely plays a significant role in identifying and addressing nonadherence. Doctors often use closed-ended questions when speaking with patients, meaning answerable by yes or no, rather than open-ended questions that invite patients to talk more broadly about their experience.²³ In a study that videotaped clinic interactions, 94% of questions doctors asked when discussing glaucoma with patients
were closed-ended and was associated with missed opportunities to identify nonadherence. In contrast, patients asked open-ended questions may be more likely to disclose nonadherence. In one study, doctors who took a brief (under 2 hours) course in communication skills—that included open-ended questioning—were able to identify 78% of nonadherent patients compared with 25% before the instruction.

**TOPICS IN GLAUCOMA**

Physicians might improve medication adherence by staying aware of its importance, talking with and educating patients, and providing tools that help patients stick with their regimens. Listen for implied and explicitly stated barriers to success so that a solution tailored to patients’ circumstances and lifestyle can be proposed. Also listen for and correct fatalistic language that suggest a patient feels resigned to a bad outcome. Good communication can help patients maintain a positive outlook and sense of self-efficacy about their disease.

Asking patients to complete a self-efficacy scale—noted in one study to correlate with adherence—while in the waiting room is an efficient way to uncover specific opportunities to improve adherence. Training patients in the correct method for instilling eye drops can be well worth the time; in one study, it was the facet of glaucoma patient education that improved adherence the most.

Patients who attend their clinic visits are more likely to adhere to treatment. A reminder system for upcoming appointments might be useful to get patients into the clinic. Barriers to attending commonly include transportation issues or difficulty getting time off of work and should be addressed.

Patients who have difficulty remembering to use their medication might benefit from linking dosing to mealtime or other predictable event in their routine. Smartphone apps that prompt patients to take their medications—including at least one that is specific to eye drops—are available and might help certain patients, particularly younger patients (Figure 2).

**FIGURE 2 Technology-based dosing reminders may be useful for some patients.**

Even for patients who are not expressly forgetful, reminders might 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. The intervention was inexpensive, about $20 per patient per year, and was well received by patients.

Opting for longer-acting anti-glaucoma agents may reduce therapeutic burden and might improve medication adherence. Prostaglandin analogues (eg, latanoprost, travoprost, tafluprost, bimatoprost) and some beta-adrenergic antagonists (eg, levobunolol) are formulated for once-daily dosing. Combination agents (beta blocker plus carbonic anhydrase inhibitor, beta blocker plus alpha agonist, or carbonic anhydrase inhibitor plus alpha agonist) help simplify regimens for patients who require more than one drug for IOP control.

**CONCLUSION**

As eye care providers, our most diligent efforts to identify and treat patients with glaucoma are thwarted when patients fail to take their medications as prescribed. To optimize care, we must address nonadherence head on, with compassion and skill, and work diligently with patients to find the medication regimen and reminder system that is best for them.

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**REFERENCES**


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Glaucoma Drug Delivery: New Advances

James D. Brandt, MD

Patient-independent, sustained-release drugs will be a much needed and welcome addition to the medical armamentarium of glaucoma treatment. Successful adoption of the new therapies, however, will largely depend upon physicians’ and patients’ evaluation and perception of risks and therapeutic benefits.

Medication nonadherence remains an enduring challenge in glaucoma management. Like patients with hypertension, diabetes, hyperlipidemia and other chronic conditions requiring long-term therapies, glaucoma patients often do not comply with their eye drop regimens. The problem has been recognized for decades and is well-documented in the literature. Some studies suggest that perhaps half of patients stop using their glaucoma eye drops one year following the initial prescription. Even when they know they are being electronically monitored, nearly half of patients use their drops less than 75% of the time. As the lowering of IOP is the only therapeutic benefit, glaucoma patients often do not comply with their eye drop regimens. We are now beginning to understand why glaucoma patients do not adhere to eye drop regimens. Recent clinical studies point to multiple contributing factors, the most common ones being decreased self-efficacy, forgetfulness, difficulty with eye drop instillation, and difficulty with medication schedule. Given these barriers to self-treatment, perhaps the best strategy is to develop drug delivery systems that achieve efficient drug delivery without relying on patient behavior between office visits.

SUSTAINED-RELEASE THERAPY: THE NEW DIRECTION

The Ocusert™ pilocarpine system, a tiny reservoir that provided continuous delivery of pilocarpine for a week when placed in the conjunctival sac, was the first and only product approved (in the 1970s) as a long-acting, controlled drug delivery system for glaucoma. The product caused discomfort in some cases due to a large bolus release of drug when first inserted, and pilocarpine has an unfavorable side-effect profile. However, as an alternative to daily eye drops, the Ocusert system was the first successful “proof of concept.”

Over the past decade, there has been increasing interest and effort to create drug delivery platforms that support slow release of glaucoma medications over time—preferably months or more, with a single application. It is clear that sustained-release systems, when they finally arrive on the market, will profoundly enhance our ability to help our patients with glaucoma.

One underappreciated aspect of sustained-release platforms is that they open up the potential to revisit drug candidates abandoned in the past during early development. Many compounds in the pipeline fail not due to poor efficacy, but because they have unacceptable side effects (eg, stinging, taste) or require instillation too frequently. Sustained-release platforms open up the possibility that highly effective molecules discarded in the past can be successfully commercialized.

THE PIPELINE

A variety of novel sustained-release products are being developed for glaucoma, including injectable depots, punctal plugs, and inserts placed into the fornices. Fundamentally, these represent two different approaches to glaucoma drug delivery: intraocular delivery (eg, injectable depots to the intravitreal, intracameral or subconjunctival space) and extraocular delivery (eg, conjunctival insert, punctual plugs).

Two injectable depots are currently in clinical evaluation. Bimatoprost Sustained-Release (Bimatoprost SR, Allergan) is a biodegradable intracameral depot implant in Phase 3 clinical trials. Interim results from Phase 2 trials of the implant were encouraging, with significant, sustained reduction of intraocular pressure (IOP) over 6 months. Another biodegradable intracameral depot implant is ENV515 (travoprost XR, Envisia Therapeutics), an extended-release formulation of travoprost based on the proprietary PRINT® (Particle Replication in Nonwetting Templates)

To obtain CME credit for this activity, go to http://cme.ufl.edu/ed/self-study/tig/
technology platform. ENV515 demonstrated comparable IOP-lowering efficacy to once-daily travoprost eye drops in a 28-day phase 2 trial; a second 12-month phase 2 study designed to evaluate its long-term IOP-lowering effect is currently underway.10

Unlike injectable depot implants, the external sustained-release products never enter the eye. The bimatoprost ring (Bimatoprost ocular insert, ForSight Vision5) is a silicone ring impregnated with bimatoprost. Designed to be replaced by a physician every 6 months, the ring rests under the upper and lower eyelids, in the fornices (Figure 1). In a Phase 2 study, the bimatoprost ring sustained an IOP reduction of 4 to 6 mmHg from baseline over the course of six months.11 This level of IOP-lowering was slightly less than timolol drops, but the study was underpowered to compare treatment effects—a much larger Phase 3 program is planned to start this year.

Another approach to external drug delivery currently in clinical development for glaucoma are punctal plugs, which are designed to release drugs into the tear film in a controlled fashion from the nasolacrimal punctum. Sustained-release travoprost (OTX-TP; Ocular Therapeutix), an intracanalicular depot that dissolves over time, produced clinically meaningful IOP reduction for up to three months in phase 2 clinical studies.12 Ocular Therapeutix is planning to advance to phase 3 trials.13 Phase 2 studies of the latanoprost-punctal plug delivery system (L-PPDS, Mati Therapeutics), a non-dissolving superficial drug-eluting punctal plug, are ongoing. Results of past trials showed a 20% IOP reduction at 12 weeks.14

FIGURE 1 Photographs showing placement of a bimatoprost ring in a patient’s eye. (Courtesy Dr. Brandt.)

THE CHALLENGES

Perhaps the most important issue around these novel sustained-release platforms will be the balancing of efficacy with safety, comfort, and practicality. An ideal sustained-release product would be one that offers maximal benefit with minimal risk: highly effective, totally safe, and lasting at least six months or longer after a single application. In the real world, however, each platform will require some tradeoffs. How physicians and patients choose to balance among these considerations when deciding on a sustained-release platform remains to be seen.

One example of such tradeoffs for an external sustained-release product is its ability to maintain itself in place following initial placement. Unlike injectable depots, external devices can become dislodged and lost. In such a case, the patient may or may not be aware that the product has fallen out, especially if it is a product as small as a punctal plug. Such a patient may have a false sense of security when in fact the product has fallen out and he or she is at risk of going several months without any medication on board. In contrast, the bimatoprost ring has the advantage of being very visible; its presence or absence is easy for patients or family members to notice (Figure 1). Indeed, in clinical studies of the bimatoprost ring, we saw no cases of dislodgment in which a patient was unaware that the insert had been lost.11 Another example of a tradeoff is reversibility. Note that all drugs have side-effects: when (not if) a side effect occurs, the externally applied systems—both the punctal plug and the ring—can simply be removed, whereas the injectable platforms would leave the patient between a rock and a hard place: reversing the side effect would involve removing the drug from inside the eye or waiting until the drug wears out.

As I see it, when the data from the ongoing regulatory trials are available for us to compare, the injectable platforms currently in development are likely to have slightly more efficacy than the external platforms—but at the cost of more invasiveness and a small but real risk of infection. In contrast, the external delivery approaches prioritize safety.

In the US, the largest group of patients treated for glaucoma have either very early disease or just ocular hypertension. Many will not develop significant visual impairment in their lifetimes even without treatment because their disease is progressing at an extremely slow rate or not progressing at all. In my view, these are patients in whom safety should take priority over efficacy, for whom the incremental efficacy benefits of injected drug platforms do not outweigh the associated risks. Indeed, the risk of blindness from glaucoma in some of these patients is likely as small as the risk of infection following injection.

Intravitreal injection of anti-vascular endothelial growth factor (VEGF)
agents has become the mainstay treatment for neovascular age-related macular degeneration (AMD). Despite a great safety record of anti-VEGF injections, there remains an underlying rate of injection-related infection and endophthalmitis that remains acceptable: neovascular AMD is a rapidly blinding disease in which the infection risk of multiple injections is offset by the very real risk of rapid, irreversible blindness. The risk-benefit balance in neovascular AMD is clearly different than for ocular hypertension or early glaucoma.

**WHAT LIES AHEAD**

The sustained-release drug products, once approved, will markedly expand the therapeutic options for the treatment of glaucoma. New iterations of sustained-release platforms and the drugs delivered will undoubtedly follow over the next decade. The conjunctival insert, for instance, has sufficient volume to carry more than one drug, one day perhaps allowing customization of a sustained-release platform for an individual patient. I envision being able to order a ring that contains a combination of drugs: a prostaglandin analogue plus a beta blocker, perhaps, or a prostaglandin analogue plus beta blocker plus alpha agonist, etc.

We know that nonadherence among glaucoma patients means that many are not receiving proper medical treatment and are at risk for disease progression. The emerging platforms described here open up entirely new options for this large group of patients.

**REFERENCES**

1. According to Dr. Brandt, which glaucoma patients may not be appropriate candidates for injectable sustained-release therapies that target the anterior chamber or vitreous cavity?
   A. Patients with early glaucoma
   B. Patients with advanced glaucoma
   C. Patient with ocular hypertension
   D. Both A and C

2. The term self-efficacy refers to:
   A. Patients’ sense of control over their disease
   B. Patients’ ability to select their medication
   C. Study participants who are lost to follow-up
   D. Study design based on self-report

3. Which of the following is an unavoidable risk associated with injectable approaches to sustained drug release?
   A. Device dislodgment
   B. Intraocular infection
   C. Cataract
   D. Hypotony

4. Which of the following is NOT a potential barrier to ocular hypotensive adherence?
   A. Sourcing information from the Internet
   B. Not understanding the disease
   C. Distrusting the provider
   D. Leading a busy life

5. According to the 2015 study by Sleath and colleagues, which educational lesson had the greatest impact on adherence to anti-glaucoma medication?
   A. Disease education
   B. Outcomes education
   C. Medication mechanism education
   D. Instillation technique

6. Which of the following is a common cause of treatment nonadherence in glaucoma patients?
   A. Forgetfulness
   B. Difficulty with self-administering eye drops
   C. Difficulty with medication schedule
   D. All of the above

7. Which of the following may improve anti-glaucoma treatment adherence?
   A. Reminder systems
   B. Tailoring medication regimen to the patient
   C. Teaching patient how to instill drops
   D. All may improve adherence

8. Through which of the following are sustained-release therapies expected to improve the treatment of glaucoma?
   A. Greater IOP-lowering efficacy
   B. Less cost
   C. Improved patient adherence
   D. Combination of multiple medications

9. Which of the following questions is open-ended?
   A. Did you take your medications this month?
   B. Any difficulty taking your eyedrops?
   C. How did it go adding the new medication?
   D. All may improve adherence

10. Which of the following sustained-release drug delivery platforms has the potential to be customized for the individual patient by combining different glaucoma medications?
    A. The silicone conjunctival ring
    B. The punctal plugs
    C. The intracameral depot implant
    D. The Ocusert system