Adherence and Persistence: The Challenges for Glaucoma Medical Therapy

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Abstract: Suboptimal adherence and persistence to therapy are major challenges for patients treated with ocular hypotensive medications. The problem affects 5% to 80% of glaucoma patients from all nations, ethnicities, socioeconomic backgrounds, and education levels. Although health care providers are generally poor at detecting suboptimal or poor adherence in the clinical setting, several strategies to systematically assess adherence and persistence rates are available. One strategy involves electronic monitoring of patient dosing, which provides useful insights into specific patterns of adherence behavior among glaucoma patients. Adherence behavior is complex with multiple interrelated determinants; these can be broadly grouped into provider factors, environmental factors, medication factors, and patient factors. Targeted patient education strategies, counseling, electronic monitors, alarms, and reminders have all been used in efforts to improve adherence. These interventions probably work best in combination. Identifying tangible barriers to adherence and simple strategies to overcome these through an open, discursive relationship between clinician and patient is key to optimizing adherence.

Key Words: adherence, persistence, glaucoma, topical ocular hypotensive medications


The global disease burden due to glaucoma is large and will continue to rise.¹ In 2010, 60.5 million people worldwide had glaucoma; by 2020, this will reach 79.6 million.² In the United States, glaucoma is the leading cause of preventable, irreversible vision loss and will affect 3 million people by 2020.²³ India in 2010 had 8.2 million people with open-angle glaucoma and 3.7 million with angle-closure glaucoma.²⁴ In China today, 0.7% of the adult population has primary open-angle glaucoma; 1.2% have angle-closure glaucoma.²⁵ Elevated intraocular pressure is the major risk factor for glaucomatous progression; multiple clinical trials have demonstrated that lowering intraocular pressure reduces glaucomatous visual loss in patients with ocular hypertension or glaucoma.⁶–⁸

Despite advances in laser and surgical therapies,⁹¹³ topical hypotensive medications are the mainstay of treatment for most forms of glaucoma today and will continue to be in the foreseeable future.¹⁴¹⁵ Most patients and clinicians prefer topical agents as first-line treatment as they are effective, generally safe, widely available, and relatively simple to administer. However, they have their limitations, including ocular and systemic adverse effects, preservative-related drop toxicity, and difficulty with self-administration for some individuals. These can dampen a patient’s enthusiasm for using eye drops regularly. Critically, the success of these medications in preventing glaucomatous visual loss depends on patient adherence to and persistence with fixed treatment regimens.¹⁶

Sustained and consistent patient adherence to treatment regimens with ocular hypotensive agents would significantly delay glaucomatous disease progression for most patients.¹⁷ Yet, as diagnostic techniques continue to improve,¹⁸¹⁹ poor adherence and persistence remain significant barriers to effective treatment.²⁰²¹

Poor adherence also impairs effective treatment for chronic diseases such as diabetes, asthma, and hypertension.²²²³ For these conditions, a direct association exists between poor patient adherence and negative clinical outcomes.²²²³ Similarly, for glaucoma, poor adherence is associated with severity of glaucomatous visual loss.²⁴²⁵ Like many chronic systemic conditions, glaucoma is initially asymptomatic or provokes only vague symptoms and progresses slowly, while treatment can be uncomfortable, cumbersome, intrusive to patients’ lifestyle, and costly. All of these factors can contribute to poor patient motivation for regular adherence to treatment regimens.²⁶

Terminology

The first step in understanding the problem is to clarify the terminology. “Persistence,” “compliance,” and “adherence” are frequently used with various meanings.²⁶²⁷ One working group defined persistence as “the act of continuing the treatment for the prescribed duration” or “time from initiation to discontinuation of therapy.”²⁷ It considered compliance and adherence to be synonyms, defined as the “extent of conformity to the recommendations about day-to-day treatment by the provider with respect to the timing, dosage, and frequency.”²⁷ Other authors would suggest there is an important difference between “compliance” and “adherence”; the term “adherence” implies an open discursive therapeutic relationship between the informed patient and physician, whereas “compliance” suggests that the patient passively follows the doctors’ orders.²⁸ A therapeutic alliance based on trust and open dialogue using treatment tailored to suit the individual is pivotal to optimize patient participation in treatment regimens; hence, “adherence” is the preferred term.

The Size of the Problem

A substantial proportion of patients treated for glaucoma or ocular hypertension have poor or suboptimal adherence and/or persistence with therapy. This applies to patients from all nations, communities, socioeconomic backgrounds, and education levels.²⁶²⁹³⁰ On average, patients with chronic medical conditions take 30% to 70% of prescribed medication doses, and up to half discontinue medications in the first few months of therapy.³¹³² The adherence and persistence figures for glaucoma are similar, with adherence reported to range anywhere from 5% to 80%.³³

Measuring Adherence

Reported rates of adherence vary widely, partly because adherence is difficult to quantify. Several measurement techniques

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have been used producing varying results; each has its own advantages and limitations. These include clinical interview, self-report surveys, pharmacy claims data analysis, electronic monitoring systems, and direct observation of drop-installation technique.26,28,29,34–39

Clinical Interview

Discussion between the health care provider and patient regarding adherence, persistence, and practical aspects of drop administration should be encouraged. It may yield useful information regarding factors influencing administration of glaucoma medication and may reveal obstacles to effective treatment. However, health care providers in general are poor at distinguishing more adherent from less adherent patients and tend to overestimate adherence.34,40,41 It can be difficult for patients to discuss the extent of their adherence behavior as they commonly want to “please” their clinicians and wish to give the impression that they are looking after themselves well. However, clinicians can use clues from physical examination, including signs of drug-related effects such as lash changes from prostaglandin analogs.

Self-report Surveys

Formal self-assessment questionnaires may be slightly more accurate than clinical interview.42 Sleath et al17,43 devised questionnaires to reflect eye-drop self-instillation efficacy and instillation technique; these correlate with objective markers of adherence and eye-drop technique, respectively. However, self-report surveys are subjective and influenced by personality, recall bias, mood, memory, and white-coat syndrome.44 Like clinical interview, self-report surveys often overestimate adherence.34,41

Pharmacy Claims Data Analysis

Pharmacy claims data analysis compares the number of scripts written by clinicians with bottles dispensed at pharmacies. These provide important insights into adherence rates.20,30,35,45–47 According to a systematic literature review, patients had access to glaucoma medications for 56% (range, 37%–92%) of days in the first year of prescription, and 31% (range, 10%–68%) were persistent after 1 year.26

Pharmacy claims data analysis studies have demonstrated that adherence is greatest for simpler routines with daily dosing drops. In general, it is greatest for monotherapy, in particular with prostaglandin analogs.20 Pharmacy claims analysis has the advantage of evaluating real-world data retrospectively, outside clinical studies; as such, all patients are evaluated, not just those enrolled in studies and completing follow-up. Furthermore, patients are unaware they are being monitored, which otherwise could inflate adherence rates artificially. However, pharmacy claims analysis has several inherent inaccuracies in measurement. Some patients receive free drop samples or receive unnecessary script duplicates from 1 or several health care providers. Added medications can be misclassified as switched medications, and patients previously on medication can be misidentified as new to treatment.48 Furthermore, bottles dispensed are measured, not drops administered, and probably adherence and persistence are overestimated.

Electronic Monitoring Systems

With proper patient training and instruction, electronic dose monitoring devices reliably and accurately record the number, time, and date of eye-drop administration.34,49,50 These involve sensors in medication bottles that are activated when the medication is administered, for example, a lever that is pushed on a dosing aid to dispense the drop, as in the Travatan Dosing Aid (Travalert; Alcon Inc, Fort Worth, Tex). Electronic monitoring directly measures the patterns of drop-administration behavior and is probably the most direct and accurate means available to evaluate adherence.40,51 Electronic monitoring additionally provides useful information on the time and date of each dose to better assess patterns of drop administration. Weaknesses include selection bias, as poorly adherent patients may drop out of the study before completion, and measurement bias, as patients are generally aware that their medication usage is being assessed, known as the Hawthorne effect.52 These can lead to overestimation of real-life adherence rates.

Electronic monitoring studies for glaucoma have identified 4 broad types of adherence behavior: early discontinued usage, good adherence (>80% of doses), poor adherence (<80%) with drug holidays, and poor adherence (<80%) with frequently missed doses.53,54 Drug holidays are defined as substantial periods of time (often 7 days) without any drop administration; frequently missed doses include shorter periods of inconsistent or erratic usage. A significant proportion of patients with suboptimal drop usage improve adherence after the office visit and just before the return visit.34 The proportion of patients with each type of adherence behavior was recently evaluated in 2 UK electronic monitoring studies. Cate et al57 followed up 88 of an original 98 patients with primary open-angle glaucoma over 2 months. Ajit et al56 followed up 37 of an original 53 patients with chronic open-angle or narrow angle glaucoma over 3 months. The proportion of patients with each type of adherence behavior type is outlined in Table 1.

Assessment of Drop-Instillation Technique

Assessment of eye-drop-instillation technique provides useful insights into barriers against good adherence. Although self-assessment questionnaires can be useful, more fruitful analysis can be provided by objective patient demonstrations of drop-instillation technique. A recent video analysis of patients on regular topical medication has demonstrated that 62% have imperfect technique; either the drops miss the conjunctiva;

<table>
<thead>
<tr>
<th>Adherence Behavior Type</th>
<th>Description</th>
<th>Percentage (n) of Patients (Cate et al57)</th>
<th>Percentage (n) of Patients (Ajit et al56)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Early discontinuation</td>
<td>10% (9)</td>
<td>8% (3)</td>
</tr>
<tr>
<td>2</td>
<td>Good adherence: &gt;80% adherence rate</td>
<td>56% (49)</td>
<td>62% (23)</td>
</tr>
<tr>
<td>3</td>
<td>&lt;80% adherence rate with frequent drug holidays</td>
<td>10% (9)</td>
<td>11% (4)</td>
</tr>
<tr>
<td>4</td>
<td>&lt;80% adherence rate with variable and frequent missed doses</td>
<td>24% (21)</td>
<td>19% (7)</td>
</tr>
</tbody>
</table>

TABLE 1. Patterns of Adherence Behavior in Patients Treated With Topical Hypotensive Medication56,57

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the bottle touches the lashes, eye, or face; or too many drops are instilled at once.24 Similar studies have demonstrated an alarmingly high prevalence of poor drop technique.39 However, technique is probably a less important predictor of glaucomatous progression than adherence as measured by electronic monitoring.24

**DETERMINANTS OF ADHERENCE**

Treatment adherence is a complex behavior23 that is influenced by multiple interrelated factors.58,59 Personality, beliefs, culture, motivation, age, and health literacy are all important determinants, as are drop-related blurriness, redness or stinging, and frequency or complexity of the administration regimen. Furthermore, many patients’ physical ability to self-administer drops can be limited by comorbidities that influence cognition or dexterity.4,60

Because of its chronicity, the lack of specific symptoms in early to moderate disease stages, and the lack of immediately perceived consequences if medications are not used, by its very nature glaucoma promotes nonadherence and nonperseverance. Specific determinants of a patient’s adherence and persistence to glaucoma treatment can be broadly divided into 4 categories: provider factors, environmental factors, medication factors, and patient factors.61

**Provider Factors**

Communication and trust in the relationship between health care provider and patient influence adherence.38,55 In a study, adherence was highest among patients who felt that their clinicians had time to explain the condition and treatment and that they could ask health care providers or pharmacists questions regarding treatment.29

**Environmental Factors**

Major life events, travel, and changes in routine (e.g., moving residence) can reduce adherence.62 Some factors are simply distracting, whereas others impair a patient’s ability to administer drops on a very practical level, for example, loss of a partner who always reminded/aided the patient in drop administration, or admission to a hospital for an intercurrent illness where the drops are temporarily omitted or unavailable.

**Medication Factors**

Adherence and persistence are influenced by drop adverse effects, local discomfort, and exacerbation of ocular surface disease,29,63 which is an important cause of morbidity in glaucoma patients.64 Adherence and persistence are substantially reduced by medication regimen complexity,29,63 in particular the number of medications, the number of doses of each medication, and differences between the eyes.30 More than 2 drop administrations per day are associated with significantly reduced glaucoma medication adherence,33,65 perhaps due to the complexity of the regime or perhaps due to exacerbation of ocular surface disease.66,67 Cost and availability of medication also influence adherence and persistence.38,58,68

**Patient Factors**

Poor or suboptimal adherence and low persistence are common irrespective of background, ethnicity, socioeconomic status, education, and sex; these factors are not consistently predictive of adherence behavior.17,29,30,33,69 Some US studies found that nonwhite people had a higher rate of nonadherence, but these findings are limited by confounding factors.17,24,36,68–70

Poor adherence is more common in older patients,70,71 which can be influenced by comprehension, memory,18,59,68 difficulty reading bottle labels and instructions,36,38,60 coordination, and dexterity.4,60,72 In addition, younger (<50 years) patients are at increased risk of poor adherence and persistence.17,30,70

Poor vision, due to reduced acuity or field loss, is associated with reduced adherence.29,38,60. This is a particular challenge for patients with advanced glaucoma.

Cognitive factors are important; the most influential is forgetfulness.29 This is not limited to those with cognitive impairment; a busy schedule, low priority for health care issues, and multiple life distractors all contribute.29,38,65,68,73 Poor comprehension of the disease process and treatment, lack of perceived benefit from treatment, or satisfaction with treatment commonly contribute to poor adherence.29,59,74 Depression, which is more common in patients with increasing glaucoma severity,29 has been associated with self-report of nonadherence, as are stress and certain personality traits.58,76,77 Attitudes, beliefs, and social supports can all influence treatment adherence and persistence.29,61

**INTERVENTIONS TO IMPROVE ADHERENCE AND PERSISTENCE**

Efforts to improve adherence and persistence rates among glaucoma patients are critically important to optimize medical treatment and prevent progressive field loss.16,24,25 Interventions that address the issues listed above are likely to improve adherence and persistence rates and should be considered and/or discussed at every clinical interview with a high priority.

Several interventions have been proposed and tested; not all have been consistently successful. Education about glaucoma, counseling, electronic reminders, and medication alarm devices have been evaluated systematically.35,77

Educational interventions to improve general health literacy and knowledge about glaucoma have a small but significant impact on improving adherence.77–80 In general, such interventions are most useful in populations with low health literacy levels and low background adherence rates.

Counseling regarding drop technique, the importance of daily adherence, and strategies to overcome barriers to adherence may lead to increased adherence.79,81

Automated telephone reminders have been evaluated in the context of treatment adherence for other systemic chronic diseases, and many studies show they have a positive impact on health outcomes.82 Regular automated text messaging has been shown to improve medication adherence in asthma and may also be useful in glaucoma.83 Telephone and text reminders appear to be most beneficial if they are frequent (e.g., daily) as opposed to infrequent (e.g., monthly).77,79,83 One current clinical trial is evaluating the effectiveness of e-monitoring and electronic text messaging for children with asthma treated with regular aerosols. Tailored text messages are sent only when e-monitoring detects a dose at risk of omission.84 Perhaps such tailored use of available social media and e-monitoring will help improve adherence rates for glaucoma patients.85 In particular, midappointment interventions can be used to prevent the rapid decline in adherence in the weeks following 1 medical appointment and preceding the next.54,49,77 New smartphone or tablet computer technology may see the introduction of applications to remind patients to use their medications; at least 1 such “app” has been introduced (MyEyedrops 1.9; Singapore National Eye Centre Pte Ltd; http://www.snecn.com.sg). These may improve adherence rates.

Lim et al77 recently evaluated the efficacy of monthly automated telephone calls and an educational intervention by the physician at month 3; these did not improve adherence rates after 5 months. A similar study by Okeke et al79 involving patients with a low background adherence rate used multiple
intervention types including watching an educational video, reviewing current barriers to adherence and possible solutions, regular telephone call reminder, and audible and visible reminders on dosing aid devices. In contrast to the study of Lim et al., this resulted in a significant improvement in adherence during the 3 months of intervention. Perhaps the most effective solution will involve multiple strategies simultaneously, as demonstrated by Okeke et al. Alternatively, the contradictions in the literature may reflect the complex nature of adherence behavior, which is influenced by multiple determinants. Accordingly, strategies to improve a patient’s involvement in their own care program need to be flexible, adapting to an individual’s specific requirements and expectations.

**SUMMARY**

Suboptimal adherence and persistence to treatment for patients with glaucoma or ocular hypertension can be difficult to detect and treat. These problems account for a large proportion of progression in known glaucoma patients from all backgrounds. Directly questioning patients regarding adherence may not be productive; however, indirect methods may be useful. For example, stating “some people may have difficulty remembering their drops” or instilling their drops—what is your experience?” or asking “Do you have any particular challenges when instilling your drops?” may yield more clinically relevant information than “Do you ever forget?” Holistic approaches to identifying tangible barriers to adherence and simple strategies to overcome these are important. Optimizing the ocular surface, inquiring about drop-related adverse effects, simplifying the drop regimen, and discussing drop-instillation technique are some strategies that may improve adherence rates. Discussing ways of remembering drops, creating daily routines or drop diaries, or taking advantage of emerging smartphone technologies can be helpful for some patients, whereas others may benefit from a discussion involving relatives or carers as to who will be able to help or supervise drop administration. Patient education, counseling, and appropriate access to information and resources from health care providers are important. A tight network with open communication avenues between physician, practice nurse, optician, pharmacist, general practitioner, and patient results in improved drop adherence and persistence. Electronic monitoring offers useful insights into adherence and persistence rates and patterns of adherence behavior and may be used in combination with tailored digital alarm systems to optimize adherence. A broad array of strategies to improve adherence, including education, counseling, electronic monitors, and alarm devices, is probably most useful when used in combination. Above all, clinicians should strive to maintain an open, discursive relationship with the patient in a therapeutic alliance against the disease.

**REFERENCES**


26. Reardon G, Kotak S, Schwartz GF. Objective assessment of compliance and persistence among patients treated for glaucoma and ocular


71. Rossi GC, Pasinetti GM, Scudeller L, et al. Monitoring adherence rates in glaucoma patients using the Travatan Dosing Aid. A 6-month study comparing patients on Travoprost 0.004% and patients on Travoprost 0.004%/timolol 0.5% fixed combination. *Expert Opin Pharmacother*. 2010;11:499–504.


"Only in the eyes of love you can find infinity." — Sorin Cerin, *Wisdom Collection: The Book of Wisdom*