Adherence and Persistence with Glaucoma Therapy
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Abstract. Adherence and persistence with chronic therapies is crucial to prevent disease progression, such as in glaucoma. Patients report high rates of adherence, which are not supported by pharmacy claims analysis. This article reviews the literature regarding methods to assess adherence and persistence and the patient behaviors that pose challenges to proper treatment. Rates for persistence are generally below 50% at 1 year. Differentiating efficacy of eyedrops from lack of adherence presently confounds ophthalmic treatment. Additionally, as intraocular pressure (IOP) can appear controlled by short-term adherence, the physician can be fooled into believing the patient’s glaucoma is well-controlled. Likewise, when progressive worsening is noted despite good IOP control, it can be problematic whether the patient’s target pressure needs to be lowered or adherence needs to be improved. White-coat adherence is common, in which patient adherence rises sharply 1 week before the appointment with the physician, then declines rapidly following the appointment. White-coat adherence may make it difficult to assess IOP control over the longer term; cycling behavior with medication use is well-documented. Adherence and persistence rates differ by class of drug, with higher rates associated with prostaglandin use. We review findings from The Glaucoma Adherence and Persistency Study that identified behaviors associated with poor adherence. Greater physician awareness of adherence and persistence issues is necessary in order to help the patient become more adherent. (Surv Ophthalmol 53:S57–S68, 2008. © 2008 Elsevier Inc. All rights reserved.)

Key words. adherence • compliance • glaucoma • persistence

Patient cooperation with chronic medical therapy is now known to be far from ideal. Successful treatment outcomes for chronic diseases like glaucoma usually require daily use of medication to minimize disease progression. Diseases that are asymptomatic are more prone to poor patient adherence and persistence.10 Patients with poor glaucoma medication adherence had a higher rate of visual loss in one series.48 Not only does poor adherence lead to worse outcomes, it can increase health care costs.19,52 The scope of the issue is enormous throughout medicine. Approximately 9% of all prescriptions written are never filled29 with many remaining unclaimed across all therapeutic areas, and especially at initial stage of treatment.26

The terms that denote patient behavior in medication use have become more precise over time. The term compliance has been abandoned for more specific metrics. Adherence is a measure of the degree to which patient follows prescribed instructions during a defined time period. If pills are prescribed twice daily and over 30 days the patient takes 20 pills, adherence is defined as 33%. By contrast, persistence is a criterion that evaluates the time until the patient first discontinues use of medication. A patient prescribed drug X on January 1, who fills the first two monthly prescriptions, but does not fill one for March is persistent for 2 months (even if it is restarted in June). Thus, adherence allows the patient to have lapses in perfect drug taking, and summarizes the percent of days on which the patient has drug to use (e.g., when pharmacy refill data are used in its calculation). Persistence is a measure of the time to discontinuation. Both measurements provide meaningful information. For
example, if twice daily pills are taken once every other day and the patient continues to refill the prescription each month (generating a stockpile), the patient is persistent, but with an adherence rate of 25%. Recent research brings the unwelcome conclusion that persistence with initial glaucoma medication is as low as 33–39% at 1 year. In U.S. studies of prostaglandin analogs, the adherence rate for glaucoma eyedrops is similar to that for hypertension pills, a disturbing 70% over time.

To measure adherence and persistence, we can look to large insurance claims databases that are now available to gauge patient behavior. These provide huge national samples of information, and have been generally confirmed as validly indicating imperfect adherence and low persistence with glaucoma drugs. However, pharmacy refill data have difficulty capturing the difference between added medication or switches from one drug to another when their information is correlated with chart review and/or patient interviews. Interestingly, minor adverse events, such as patient spontaneous reports of stinging and burning, appear to correlate with better adherence (those who take the drops have the side effects). By contrast, hyperemia from eyedrops is associated with poorer adherence and drug discontinuation.

Patients routinely overestimate their adherence with eyedrops. In fact, 95% of patients claimed they never missed taking one study (Glaucoma Adherence and Persistency Study; GAPS) that they never missed taking glaucoma drugs. However, pharmacy refill data have difficulty capturing the difference between added medication or switches from one drug to another when their information is correlated with chart review and/or patient interviews. Interestingly, minor adverse events, such as patient spontaneous reports of stinging and burning, appear to correlate with better adherence (those who take the drops have the side effects). By contrast, hyperemia from eyedrops is associated with poorer adherence and drug discontinuation.

Cost was a significant barrier to adherence in GAPS. The majority of studies of adherence have evaluated only patients who had third-party pharmacy benefits. Interestingly, few differences were noted between patients in a Blue Cross pharmacy benefit plan compared to those enrolled in either Medicaid or a health maintenance organization. One study found better adherence and persistence with prostaglandin analogs versus other classes despite a higher copay, yet others, which include patient interviewing, report cost as a barrier. A willingness-to-pay analysis targeted patients’ perceived value of different drop characteristics.

Patient demographics as related to adherence have been variable by study. Patients residing in the southeast U.S. and younger patients had poorer adherence and persistence. Black patients were found to have lower adherence rates than whites, particularly males, independent of education and socioeconomic status.

### Adherence

Assessing adherence accurately poses a significant challenge. The methodology used to measure adherence has typically followed one of three techniques: patient self-report, electronic monitoring, or pharmacy refill data assessed by an index called Medication Possession Ratio (MPR). Patient self-report, although simple and inexpensive, tends to overestimate adherence, whether assessed by self-administered questionnaire or interview by trained personnel, and it is subject to both recall bias and the desire to please the physician. Self-report may also be affected by white-coat syndrome. Additionally, a selection bias of patients who are willing to complete a questionnaire or participate in an interview may demonstrate higher rates of compliance. Patients with poor compliance may not have returned for follow-up, and thus be unable to participate. Self-report tends to be variable, but overall high. In a recent study of 230 patients from a glaucoma subspecialty practice, 85% of patients reported never or almost never missing a medication dose. Another study, of persons in the United Kingdom, found a 77% reported rate of compliance, but only 55% of patients could correctly name their medication and frequency of use, suggesting that patients overestimate their own behavior. In the 2 weeks prior to a visit with a glaucoma subspecialist in an academic practice, 92% (n = 48) of patients reported not missing a dose.

Even in self-reported adherence data, studies do indicate poor cooperation with therapy when
patients are given an opportunity to admit to their failure to perform ideally. In a focus group setting of 21 patients on at least two ocular hypertensive medications who had been seen by at least two ophthalmologists, all members acknowledged some nonadherence. A study of patients on timolol therapy found that 24% of patients missed doses occasionally or frequently. Claxton performed a review of the systemic medical literature, noting fewer doses per day correlated significantly with better compliance. With regard to ocular dosing frequency, 59% of glaucoma clinic patients admitted some rate of noncompliance, with 49% of patients reporting compliance with qd or bid dosing, and 39% complying with more than bid dosing. Another study found 44% of patients admitting to missing more than two doses per week.

Problems with eyedrop-taking and the complex regimens that are prescribed can play a role in poor adherence. Sixty-two percent of patients who were specifically questioned about side effects reported one or more problems with their glaucoma medication in the previous week, including difficulties with drop administration (44%), cost (41%), and side effects (16%). Thirteen percent of patients reported someone else administering their drops. Patients with adjunctive therapy commonly reported more problems with medication use than those on monotherapy. A study of adjunctive therapy suggested that patients prescribed a second ocular hypertensive medication refilled their first-prescribed medication less regularly. Busche and Gramer also reported decreased adherence when multiple medications were used. It is not clear whether complex regimens lead to poor adherence, or if poorly adherent patients are more likely to engender second and third prescriptions, due to physicians recording poor IOP control and adding medications, when the target was not attained due to poor adherence with the initial drug. Rates in a randomized, observer-masked, 12-week comparative beta-blocker study self-reported compliance of 98% and 96%, but in such a clinical trial, the patient may have self-selected for high cooperation (being willing to do an “experiment”), visit attendance is heavily enforced, and medication is often provided free and without the bother of going to a pharmacy. The accuracy of self-report/patient recall may decline also as the time period in question becomes longer. One area of interest for future research could be the role of patient personality; do more compulsive individuals have higher rates of adherence?

In theory, the most accurate method of assessing adherence would be electronic monitoring of dosing. Whereas devices that record the patient using the bottle are more direct measures than self-report, they cannot, of course, prove that a drop was truly instilled in the patient’s eye (as opposed to the cheek or the floor). Rates of compliance using two different electronic monitors were 76–86% in three studies, although these studies were initially performed with pilocarpine and were conducted over 20 years ago. Kass et al. evaluated four methods of assessing compliance over 30 days in a single group of patients. Patient interview reported a 97% rate of compliance and medication log indicated a 99% rate of compliance. However, the electronic eye drop monitor revealed a rate of 76% compliance. Fifty-five percent of patients overstated compliance by more than 10% as determined by the monitor. After the data were available to determine which patients overstated compliance, physicians had not been able to predict which patients were non-compliant.

The TRAVATAN dosing aid (Alcon Labs, Ft. Worth, TX) is a recently developed electronic reminder/monitoring device. The device records the majority of doses administered and 70% of patients found the device relatively easy to use, although proper handling of the device is important for proper recording. The device records drop dispensation, but does not confirm placement in the eye. Although one need not inform the patient that the device is recording behavior, it is possible that even patients who are studied under stealth conditions do guess that they are being monitored. There is evidence that this affects their behavior, although sometimes in perverse ways. Possibly it improves adherence in some patients, but is thought not to affect overall adherence when carried on for months. And, some studies have shown that patients who are aware that their adherence is being monitored (for example, by weighing the bottle) will dump medication just prior to a visit to appear more adherent than they are.

A third method to estimate adherence and persistence is the evaluation of large claims database information. Data from these can be used to estimate MPR, defined as the number of days during a defined period of time when the patient had the drug available to use at the prescribed frequency. MPR has the advantage of adjusting for combination therapy and may be more comprehensive for patients who cycle off and back on drops than is survival analysis (whose principal outcome is persistence estimation). MPR does not provide insight into timeliness and consistency of refilling. In addition, the provision of free samples to some patients may artificially decrease the measured adherence when MPR is calculated from claims data. Gurwitz et al. used MPR to calculate adherence in two studies. In 2,440 Medicaid senior
citizens who had initiated glaucoma therapy, the MPR was 69% (253 days with therapy available in a year).\(^\text{17}\) Twenty-three percent of patients had not filled a second glaucoma prescription in the 12 months after the initiation of therapy. A second group of patients in a managed-care setting averaged 103 days without therapy over 12 months. The most highly correlated factor with low MPR was the patients’ age at the time of therapy, separating categories that were termed involuntary, such as forgetfulness or difficulty instilling the medication, and voluntary, in which they included medication side effects.

Patient perceptions of risk of vision loss and means of gaining information regarding glaucoma also impact adherence. Patients who stated that they did not believe that failure to take eyedrops for glaucoma would lead to vision loss had lower mean MPR, than those who believed that poor adherence could lead to blindness. Furthermore, adherence was lower in patients who depended completely on the physician for all that they knew about glaucoma, was lower in patients who depended completely on the physician for all that they knew about glaucoma medicine, seeking the reasons as related to adherence. GAPS analyzed MPR correlated with patient charts, finding patients with lower MPR were likely to have negative comments regarding drop use noted by their physicians in the clinical chart as well as a lower rate of keeping follow-up visits.

Reasons for non-compliance were studied by Tsai et al,\(^\text{51}\) using patient interviews. They created a taxonomy of reasons for poor adherence; 71 distinct obstacles to compliance were identified. The majority (80%) were situational/environmental or in some way related to the medication itself, such as side effects or difficulty with the regimen. Konstas\(^\text{27}\) also reported patient cooperation with therapy, separating categories that were termed involuntary, such as forgetfulness or difficulty instilling the medication, and voluntary, in which they included medication side effects.

Failure to maintain follow-up visits has been correlated in several studies with lower adherence.\(^\text{13,18,28,35,38,43}\) Kosoko et al\(^\text{28}\) compared glaucoma patients in an eye clinic setting who kept follow-up appointments at least every 6 months with those who had lapses in follow-up of more than 6 months. Patients in each group participated in a telephone interview, and the patients who did not keep appointments more often admitted to not taking their eyedrops than those who kept appointments regularly. The GAPS papers showed that patients who admitted to any non-adherence were truly much lower in MPR than the vast majority who claimed to be perfect. Thus, it is possible to conclude that interviewed patients who admit to any non-adherence are, in fact, much more likely not to be following drop instructions. Friedman et al\(^\text{14}\) evaluated glaucoma patient care and follow-up of those enrolled in a comprehensive health insurance plan with pharmacy benefits. Lower adherence was associated with fewer follow-up visits.

In GAPS, patients seen by physicians who send them reminders to come back for visits had higher MPR.\(^\text{13}\) It is tempting to conclude that physicians who try to assure that patients return for care are increasing MPR, either directly or indirectly. It is not possible to know without further research into physician effects on adherence whether this derives simply from more frequent contact, or is a surrogate for a range of beneficial behavior by reminding physicians.

Table 1 summarizes the ophthalmic literature with regard to adherence studies.

### Persistence

Persistence with glaucoma medication has been found to be low in several studies (Table 2), varying from 20%\(^\text{47}\) to 64%.\(^\text{7}\) Glaucoma suspects beginning latanoprost or a beta-blocker drop had persistency rates of 39% and 25%, retrospectively, at 1 year.\(^\text{44}\) Another study of patients who began one of seven ocular hypotensive therapies found rates of persistence at 1 year of 33% for the prostaglandin group compared to 19% for the six other classes.\(^\text{38}\) In a study of 2,850 patients prescribed an ocular hypotensive medication, only 61% persisted with the index medication within 21 months.\(^\text{37}\)

The most common method to measure persistence has been survival analysis (Cox regression) performed retrospectively on pharmacy claims databases, but there is no standardization of the methods used.\(^\text{21,45}\) Survival analysis does not point to the reasons for discontinuation or switching of a medication, nor does it take free samples into account.\(^\text{36}\) It also does not give any credit to patients who cycle off drops but later restart, which is a frequent finding in every study of claims databases that report the behavior. Schwartz et al\(^\text{43}\) evaluated rates of patients who discontinued then restarted prostaglandin monotherapy after a gap in therapy of longer than 6 months. Of the 65% of patients who discontinued (and were defined...
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<td>Jampel et al\textsuperscript{20}</td>
<td>Methods: Standardized questionnaire administered by interview (U.S.)</td>
<td>Patient report of how often they forgot to instill their eye drops</td>
<td>Never or almost never missed a dose: 87%</td>
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<td>Tsai et al\textsuperscript{51}</td>
<td>Methods: Structured interview; hierarchical cluster analysis of reasons for noncompliance (U.S.)</td>
<td>Patient report of missed doses and barriers to medication compliance</td>
<td>Never missed a dose in previous 14 days: 92% Identified 71 distinct barriers to compliance; 49%: situational/environmental factors 32%: medication regimen factors 16%: patient factors 3%: provider factors</td>
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<tr>
<td>Taylor et al\textsuperscript{50}</td>
<td>Methods: Focus groups and in-depth interviews (U.S.)</td>
<td>Patient report of noncompliance and reasons for noncompliance</td>
<td>All patients in focus group reported some level of noncompliance Forgetfulness the main reason for noncompliance Few noncompliant due to side effects Cost not a reported factor in noncompliance Many patients instilled eye drops incorrectly Some patients want regimens to be easier Clinically significant noncompliance: 44% Voluntary noncompliance: 29% Involuntary noncompliance: 15% Reasons for noncompliance: Lack of visual symptoms w/o treatment and/or blurring of vision with treatment: 34% Forgetfulness: 28% Inconvenient frequency: 16% Medication unavailable: 15% No one available to instill drops: 5% Noncompliance more frequent in: Those using drops up to 2 times/day vs. those using drops &gt; 4 times/day Men vs. women Judged very capable of instilling eye drops accurately: 53%</td>
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<tr>
<td>Konstas et al\textsuperscript{27}</td>
<td>Methods: Prospective study; open questionnaire administered by interview (Greece)</td>
<td>Patient report of frequency of missed doses of eye drops and reason(s) for missing doses</td>
<td>Clinically significant noncompliance: missed &gt; 2 doses/week</td>
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<td>Schenker et al42</td>
<td>Methods: 12-week, randomized, observer-masked, crossover study of two formulations of a topical beta-blocker; standardized patient-preference questionnaire administered by interview (U.S.) Sample: POAG or OH; n = 202</td>
<td>Patient report of frequency of missed doses of ocular hypotensive medication</td>
<td>Never forgot medication: 78%, 68% Never or rarely forgot medication: 98%, 96%</td>
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<td>Kosoko et al28</td>
<td>Methods: Computer records review; structured telephone interview; compared cases (noncompliant patients) and controls (compliant patients) (U.S.) Time frame: 2 years Sample: Patients with ICD-9 code for glaucoma or glaucoma suspect; n = 438 interviewed</td>
<td>Follow-up visit compliance: Compliant: seen at least every 6 ± 2.5 months</td>
<td>Visit noncompliance associated with: Being a glaucoma suspect vs. a defined glaucoma case Dissatisfaction with waiting time in clinic Not having been prescribed an ocular hypotensive drug Not taking an ocular hypotensive medication as prescribed</td>
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<td>Rotchford et al40</td>
<td>Methods: Mailed questionnaire; hospital and practice dispensing data for subset of patients (UK) Time period: 12 months for dispensing data Sample: Patients &gt;55 years of age with repeat prescriptions for a topical beta-blocker in 3 clinical practices; n = 86 reports; n = 55 pharmacy dispensing records</td>
<td>Patient report of frequency of missed drops</td>
<td>Frequently or occasionally missing drops: 24% Reports of never missing drops associated with belief that drops were “vital” as opposed to “important” Insufficient eye drops for 51% (of 55 with dispensing data) Average shortfall in noncompliant patients: 85 days out of a maximum of 165 days</td>
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<td>Gurwitz et al18</td>
<td>Methods: Retrospective cohort study (U.S. health maintenance organization) Time frame: 12 months following the index prescription Sample: Patients newly initiated on any topical ocular hypotensive medication to treat OAG; n = 616</td>
<td>Noncompliant: did not fill sufficient prescriptions for ≥ 80% of days Days without therapy: cumulative number of days during which ocular hypotensive therapy was not available</td>
<td>Average days without therapy in noncompliant group: 104 days Average days without therapy in compliant group: 7 days Noncompliance most strongly related to &lt;2 visits with an ophthalmologist during the study period</td>
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<td>Patel and Spaeth34</td>
<td>Methods: Patient interview (U.S.) Sample: Clinic patients taking eye drops for glaucoma; n = 100</td>
<td>Patient report of whether doses ever missed, reasons for missing, and whether ever stopped taking drug</td>
<td>Not strictly compliant: 59% Increasing daily frequency of eye drops associated with increasing rate of noncompliance Reasons for noncompliance: Forgetfulness Away from home Inconvenient timing/frequency Side effects</td>
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<td>Gurwitz et al17</td>
<td>Methods: Retrospective cohort study (New Jersey Medicaid Program) Time frame: 12 months Sample: Patients newly initiated on any topical ocular hypotensive medication; n = 2,440</td>
<td>Total noncompliance: absence of a filled prescription for any ocular hypotensive medication in the 12 months following the index prescription Days without therapy: cumulative number of days during which ocular hypotensive medication was not available in the 12 months following the index prescription</td>
<td>Total noncompliance: 23% Average days without therapy in overall sample: 112 days Noncompliance most strongly related to use of medication requiring &gt; 2 instillations/day, initial therapy with a single ocular hypotensive agent, and presence of multiple other drugs in the patient's overall regimen</td>
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<td>Kass et al23</td>
<td>Methods: Prospective observational study; electronic eye drop medication monitors for beta-blocker and cholinergic agonist if a used concomitantly (U.S.) Time frame: 4 to 6 weeks Sample: Quota sample of patients seen in private ophthalmology practice and prescribed the index medication (topical beta-blocker); n = 110</td>
<td>Compliant: % of prescribed doses taken as recorded by the monitor</td>
<td>Compliant: Beta-blocker alone: 79% Beta-blocker with 1+ other ocular hypotensives: 86% 47% had ≥ 1 day/month with no beta-blocker Compliance in subgroup taking beta-blocker + cholinergic agonist (n = 45): Beta-blocker: 84% Cholinergic agonist: 78% Compliant by eye drop monitor: 76% Compliant by patient interview: 97% Compliant by patient log (n = 32): 99% Estimated compliance by physician: 79% Physicians unable to distinguish patients with low versus higher compliance rates; accuracy of predictions not affected by how well they knew the patients</td>
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<tr>
<td>Kass et al24</td>
<td>Methods: Prospective observational study; electronic eye drop medication monitor; patient interview; patient medication log; physician subjective impression of patient compliance (U.S.) Sample: Quota sample of patients seen in a private ophthalmology practice and prescribed the index medication (topical cholinergic agonist); n = 184</td>
<td>Compliant by eye drop monitor: % of prescribed doses taken as recorded by the monitor over 30 days Compliant by patient log: number of doses they were unable to take over 30 days Physician estimation of number of doses patient would omit over 30 days</td>
<td>Patient report of missed doses and reasons for missing doses Never missed: 58% Missed occasional dose/week: 21% Took at least half doses: 12% Used some but &lt; half of doses: 2% Did not use medication: 6% Main reasons for noncompliance: Forgetfulness Inconvenience</td>
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<tr>
<td>MacKean et al30</td>
<td>Methods: Structured questionnaire administered in patient's home (UK) Sample: Chronic OAG patients seen at 2 hospitals; n = 188</td>
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<td>Alward and Wilensky1</td>
<td>Methods: Prospective (U.S.) Sample: Glaucoma patients receiving a carbonic anhydrase inhibitor; n = 87</td>
<td>Compliant: CO2 ≤20 mEq/L Noncompliant: CO2 ≥25 mEq/L Partially compliant: 20 mEq/L &lt; CO2 &lt; 25 mEq/L</td>
<td>Patient report of missed doses and reasons for missing doses Never missed: 58% Missed occasional dose/week: 21% Took at least half doses: 12% Used some but &lt; half of doses: 2% Did not use medication: 6% Main reasons for noncompliance: Forgetfulness Inconvenience</td>
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as non-persistent), then used no drug for 6 months, 49% resumed therapy, and in 32% of these, they resumed the originally prescribed medication. Fifty-one percent of patients failed to resume any topical therapy after an extended gap in treatment. Forty-two percent of patients had not obtained a glaucoma follow-up visit in the 180 days preceding the index date. This type of cycling behavior was also seen in GAPS. Other techniques, such as chart review and decision-analysis, have likewise demonstrated poor persistence in glaucoma patients.

Table 2 summarizes the ophthalmic literature with regard to persistence studies.

Variability by Drug Class

Several studies have found differences in adherence and persistence by class of ocular hypotensive medication. Separating adverse events/tolerability from frequency of dosing cannot be conclusively determined from retrospective pharmacy claims analyses in the absence of chart review or patient interview. Cost may also play a role; however, the majority of studies evaluating class differences were performed in a setting of pharmacy benefit coverage. Prostaglandins have been found to have higher rates of persistence than other classes. Nordstrom et al analyzed prescription claims data by survival analysis in a large health insurance company database looking at adherence and persistence with glaucoma medication by class in glaucoma patients (n = 3,623) and glaucoma suspects (n = 1,677). Patients were newly initiated to glaucoma monotherapy. Nearly half of patients who had filled a prescription discontinued all ocular hypotensive therapy within 6 months. By 3 years after the initial prescription, only 37% of patients had recently refilled the prescription. Patients with glaucoma were found to have somewhat better rates of adherence and persistence than glaucoma suspects, although percentages were poor overall.

Clinical Implications and Techniques for Improving Adherence and Persistence

Determining, maintaining, and adjusting a target pressure range for patients is important parts of glaucoma care. A patient who resumes medication shortly before an office visit after a gap in therapy may appear to be at an optimal pressure, yet visual field progression may have occurred. It becomes impossible to sort out if the pressure goal needs to be further lowered, typically requiring additional therapy, or if the pressure goal is appropriate, but the patient is progressing because of nonadherence with therapy,
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<td>Reardon et al&lt;sup&gt;38&lt;/sup&gt;</td>
<td>Methods: Retrospective cohort study (U.S. managed care plan pharmacy claims data)</td>
<td>Initial treatment with any of 7 ocular hypotensive agents</td>
<td>Prostaglandin vs. other drugs: No discontinuation: 33% vs. 19% No discontinuation or change: 23% vs. 13%</td>
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<td>Schwartz et al&lt;sup&gt;44&lt;/sup&gt;</td>
<td>Methods: Retrospective cohort study (U.S. managed care plan pharmacy claims data)</td>
<td>Initial treatment with a beta-blocker or a prostaglandin</td>
<td>Prostaglandin vs. beta-blocker: No discontinuation: 39% vs. 25% No discontinuation or change: 30% vs. 18%</td>
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<td>Rouland et al&lt;sup&gt;41&lt;/sup&gt;</td>
<td>Methods: Naturalistic, prospective study (France)</td>
<td>Second-line therapy with a beta-blocker or a prostaglandin as monotherapy or as part of combination therapy</td>
<td>Monotherapy prostaglandin vs. beta-blocker: No discontinuation: 84% vs. 69% Mean time on therapy: 326 days vs. 292 days Combination therapy, with prostaglandin vs. without prostaglandin: No discontinuation: 80% vs. 44% Mean time on therapy: 340 days vs. 237 days</td>
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<td>Diestelhorst et al&lt;sup&gt;9&lt;/sup&gt;</td>
<td>Methods: Retrospective chart review (Europe)</td>
<td>Initial treatment with a beta-blocker or a prostaglandin</td>
<td>Prostaglandin vs. beta-blocker: Median time on therapy: 21.8 months vs. 10.8 months</td>
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<td>Bernard et al&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Methods: Decision-analytic model (European chart review; French costs)</td>
<td>Initial treatment with beta-blocker or a prostaglandin</td>
<td>Prostaglandin vs. beta-blocker: Mean time on therapy: 20.5 months vs. 13.4 months</td>
</tr>
<tr>
<td>Reardon et al&lt;sup&gt;37&lt;/sup&gt;</td>
<td>Methods: Retrospective cohort study (U.S. managed care plan pharmacy claims data)</td>
<td>Initial treatment with any of 5 ocular hypotensive agents</td>
<td>Overall: No discontinuation: 61% No discontinuation or change: 43%</td>
</tr>
<tr>
<td>Zimmerman et al&lt;sup&gt;54&lt;/sup&gt;</td>
<td>Methods: Prospective, multicenter, historical controlled trial (U.S.)</td>
<td>Initial monotherapy with any of 18 ocular hypotensives; switch to a prostaglandin</td>
<td>No discontinuation of prostaglandin after switch: 78%</td>
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so that the IOP is above goal for the period of nonadherence. The physician needs to address nonadherence and inquire openly in all patients, not just those in whom it is suspected. Patients may still not admit to poor compliance, even with open-ended questioning. This may result in addition or switching of medication or recommendation for a procedure. Although physicians may not be able to identify all nonadherent patients, improving physician care by following the recommendations of the preferred practice patterns (PPP) established by the American Academy of Ophthalmology may better identify patients who are progressing. Increasing the frequency of visual field testing and optic nerve evaluation with documentation of appearance, among other measures, serves as an objective means of measuring glaucomatous progression, and may raise the level of suspicion for noncompliance in a patient who is worsening despite apparent good IOP control. Additional methods to improved adherence include writing down directions for medication use, providing resources for the patient to read about glaucoma and therapy, and tailoring drop use to match the patient’s schedule. Research is needed into which aspects of physician behavior with glaucoma patients leads to improved persistence and adherence. Such research is hampered by the lack of valid outcome measurement, because electronic monitoring is not yet practical for most glaucoma drugs.

**Summary**

Medications only work for patients who take them. Glaucoma patients may have variable clinical

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<td>Stewart et al⁴⁹</td>
<td>Methods: Prospective chart review (U.S.) Time frame: 1 year Sample: POAG or OH patients switching from or adding to beta-blocker therapy; n = 148</td>
<td>Initial treatment with a beta-blocker; switched to a prostaglandin, or added a prostaglandin or alpha-adrenergic agonist</td>
<td>Prostaglandin + beta-blocker vs. alpha-agonist + beta-blocker: Mean time on therapy after switch/add (range): 11.2 months vs. 9.4 months</td>
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<tr>
<td>Dasgupta et al⁷</td>
<td>Methods: Retrospective cohort study (U.S. managed care plan pharmacy claims data) Time frame: 2 years Sample: Patients dispensed any index drug; n = 1,330</td>
<td>Initial treatment with any of 7 topical hypotensive agents</td>
<td>Prostaglandin vs. alphablocker: No discontinuation or change: 64% vs. 37% Prostaglandin vs. carbonic anhydrase inhibitor</td>
</tr>
<tr>
<td>Spooner et al¹⁷</td>
<td>Methods: Retrospective cohort study (U.S. managed care plan pharmacy claims data) Time frame: 18 months Sample: Patients dispensed any index drug; n = 1,006</td>
<td>Initial treatment with any of 6 topical hypotensive agents</td>
<td>Prostaglandin vs. beta-blocker: Mean time to discontinuation: 216 days vs. 183 days Mean time to discontinuation or change: 193 days vs. 176 days</td>
</tr>
<tr>
<td>Schwartz⁴₃</td>
<td>Methods: Retrospective cohort study (U.S. managed care plan pharmacy claims data) After drug discontinuation, evaluated percent of patients who resumed medication after a 180 day or more gap in treatment</td>
<td>Initial treatment with any of 3 prostaglandin analogs</td>
<td>Persisted with initial prostaglandin: 35% Failed to restart any therapy: 51%</td>
</tr>
</tbody>
</table>

courses based on the disease itself, but this is further confounded by improper or irregular medication use. Greater awareness by the physician of the widespread nature of nonadherence is a very important component of patient care. Tracking of patients who fail to follow-up is crucial; this can be improved with the use of telephone reminder calls for appointments.\(^3\) Discussion with patients should include open-ended questioning regarding medication use and recommendations by the physician for how to best fit the medication into the patient’s life and address any barriers that can be identified.

### Method of Literature Search

Database used: www.pubmed.com. Years searched: 1970–present. Search terms: **compliance, persistence, adherence, glaucoma, glaucoma medication**. Additionally used references cited in the reference lists of other articles. Busche and Gramer\(^3\) is the only non-English reference used, for which the English translation was used.

### References

49. Stewart WC, Leech J, Sharpe ED, et al: An economic analysis of switching to latanoprost from a beta-blocker or adding brimonidine or latanoprost to a beta-blocker in open-angle glaucoma or ocular hypertension. Am J Manag Care 8:S240--8, 2002

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