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Glaucoma Medication Adherence:

Room for Improvement in Both Performance and Measurement

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Glaucoma is the leading cause of irreversible blindness worldwide^{1,2} and the number of Americans with glaucoma is expected to increase by 50% in the next 15 years.³ Multiple clinical trials have shown that with effective medical treatment, much (but not all) vision loss can be prevented.^{4–6} Whether measured by pharmacy data,⁷ self-report,^{8,9} or medication monitor,¹⁰ adherence to glaucoma medication is often poor. Investigators studying medication adherence have identified multiple factors related to poor adherence, including more frequent¹¹ and complex¹² dosing and situational factors, such as competing activities¹² and forgetfulness,⁸ as well as patient-centered factors, such as poor disease knowledge,¹³ poor health literacy,¹⁴ and a passive learning style.¹³ This information is important because the identification of barriers to adherence facilitates a better understanding of the problems and possible interventions to reduce these barriers. However, to critique the success or failure of such interventions, we need to use comprehensive and accurate measurements of adherence. In this editorial, we have attempted to construct a framework for the components of medication adherence and review the metrics available for quantifying adherence.

ADHERENCE, PERSISTENCE, AND COMPLIANCE

Medication adherence is generally defined as how well a patient takes his or her prescribed medication according to the recommended dosing schedule. The term *persistence* is used to describe whether or not a patient stops taking the medication completely. For example, a patient who missed his or her dose and a patient who took a sample medication as prescribed but never filled the prescription for the medication when the sample ran out would be nonpersistent. Previously, the term *compliance* was often used to describe how well a patient followed physician instructions. The terms *adherence* and *persistence* have largely replaced *compliance* as more specific terms for describing the often complex relationship between prescribed and actual medication use.

COMPONENTS OF MEDICATION ADHERENCE

Once a patient accepts that medical therapy is indicated, proper adherence to a prescribed glaucoma medication regimen involves at least 4 steps: patients must obtain the medication; successfully instill the drop into the eye; use the medication at the appropriate time; and do so each day. These 4 steps can be conceptualized into 2 domains: the tasks of acquiring the medication and proper dosing and the more physical task of instilling a drop into the eye (Table).

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Obtaining a medicine involves navigating an increasingly complex health care system, which may be particularly difficult for elderly individuals or those with poor health literacy skills. In most circumstances, patients must also pay, at least in part, for their medication, creating a sometimes insurmountable obstacle.

Proper medication adherence requires taking the prescribed medication each day, without gaps in therapy. As measured by pharmacy data of almost 14 000 subjects in the Glaucoma Adherence and Persistency Study, only 10% of those prescribed glaucoma drops were persistent with therapy without gaps over the following year.⁷ Although it remains unclear if fluctuation of intraocular pressure or peaks of intraocular pressure are more harmful, the results of the Advanced Glaucoma Intervention Study suggest that greater long-term fluctuation in intraocular pressure (variation in intraocular pressure from clinic visit to clinic visit) may be associated with greater visual field loss over time.⁵ As such, it is likely that gaps in treatment adherence are associated with worse clinical outcomes.

For patients taking medications with shorter half-lives, taking the prescribed medication at the appropriate time of the day may reduce short-term fluctuation in intraocular pressure. Recent work with medication monitors suggests that one cannot assume that if a medication is taken on a given day that it is taken at the appropriate time. For example, in 1 study, most subjects prescribed 2 glaucoma medications took the appropriate number of doses of the second medication, but time-appropriate dosing was significantly worse compared with patients who took only 1 medication.¹⁵ Determining whether time-appropriate dosing is clinically important depends on accurate measurement.

Even experienced drop users struggle with the successful instillation of glaucoma drops. In a study involving direct observation, although 93% of experienced drop users reported no problems instilling eye drops, only 31% were able to correctly instill an eyedrop.¹⁶ Approximately 20% of patients with glaucoma depend on another person to instill their eyedrops,¹⁷ but the success of assisted dosing compared with self-dosing has not been studied.

METHODS OF MEASURING MEDICATION ADHERENCE

Glaucoma medication adherence can be queried by self-report, physician report, direct observation, electronic medication monitors, and pharmacy data. Without a biologic metabolite to measure, no “gold standard” for quantifying glaucoma medication adherence exists.

Self-reported adherence is probably the most commonly employed measure of adherence used in the clinical care of patients. Self-report, however, overestimates adherence compared with the results of an electronic monitor.^{10,18}

Direct observation of how a patient is able (or unable) to instill eyedrops captures an element of adherence not well described by other measures: whether the drop successfully reached the eye. Like self-report, direct observation is a practical method for assessing adherence in the clinic, although it may not represent what happens outside of the clinic. Until recently, direct observation has not been used frequently in ophthalmic research.¹⁶

Pharmacy records offer a wealth of information from a single source. For example, the medication possession ratio is defined as the days of prescription supply dispensed by the pharmacy divided by the number of days between the first and last prescription refill.⁷ Medication possession ratio incorporates the adherence of 1 or more medications over a period into one number that is useful for comparing adherence between patients who are prescribed multiple drops. Pharmacy records can also be used to describe gaps in therapy.¹⁹

Gaps in therapy can be quantified in terms of number and lengths of gaps over a given period. Although both medication possession ratio and gap analysis are very useful metrics, it is quite possible that a patient might appear highly adherent by 1 measure and nonadherent by the other. For example, a patient who struggles to properly instill an eye-drop and uses more drops than prescribed in the effort may request multiple bottles in the early months of therapy, leading to a high medication possession ratio. If the same patient then becomes frustrated with failed attempts to use the medication properly, he or she may not refill the medication again for some time, leading to a gap in therapy. Additionally, pharmacy records are only accurate in a closed pharmacy system and do not account for sample medications. In the Glaucoma Adherence and Persistence Study, approximately 20% of patients reported routinely receiving samples.⁷

Electronic medication monitors provide detail not available in pharmacy records, but monitors are subject to observation bias. Subjects using an electronic monitor may be more adherent than they would be if they did not know that their actions were being recorded. Electronic monitors, however, provide information about timing of dosing and underdosing and overdosing that cannot be obtained by other methods.

In one of the few studies that measures adherence by more than 1 metric, self-reported medication adherence was associated with adherence as measured by an electronic monitor, but the association was not significant in multivariable analyses.²⁰ Such disparity suggests that various metrics for quantifying adherence capture different elements of successful medication use. Adherence as measured by self-report, electronic monitoring, and pharmacy claims data may all be important to clinical outcomes yet not well correlated with each other.

SIGNIFICANCE

Despite the many recent advances in quantifying glaucoma medication adherence, we still lack a way to tie various measures of adherence together into an inclusive description of effective medication use. Additionally, much of the work in medication adherence is limited by relatively short-term follow-up. As we move forward with research in the arena of adherence and trials investigating novel medical treatment for glaucoma, we have the opportunity to and should at all possible times include multiple methods of measuring adherence over longer periods. With such measures, information about short-term and long-term adherence patterns can be compared with clinical outcomes to develop a robust and clinically meaningful index of truly effective glaucoma medication use.

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Table

Quantifying Medication Adherence

Method of Measuring Adherence	Example Metrics	Steps in Proper Medication Adherence ^a			
		Domain 1		Domain 2: Instilling Medication Into Eye	
		Obtaining Medication	Using Medication Each Day	Timing Dose Appropriately	
Self-report		Poor	Poor	Poor	Poor
Electronic medication monitor	Therapeutic coverage	Good	Good	Good	
	Percentage of doses taken	Good	Good		
Pharmacy records	Days without medication	Good	Fair		
	Medication possession ratio	Good	Fair		
Observation					Good

^aHow well the step in adherence is captured by the metric (empirical grading system).