Adherence in Glaucoma: Objective Measurements of Once-Daily and Adjunctive Medication Use

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• PURPOSE: To determine with electronic monitoring an objective measurement of adherence in two populations of subjects: those using once-daily prostaglandin analogs as sole ocular hypotensive therapy (one-drug group) and those requiring an adjunctive medicine to the prostaglandin analog (two-drug group).

• DESIGN: Single-site, open-label, nonrandomized, parallel design of 60 days.

• METHODS: Sixty-two consecutive adult subjects with a diagnosis of open-angle glaucoma (OAG) or ocular hypertension: 31 were taking one drug and 31 were taking two drugs. An electronic event medication monitoring device was used to record each bottle opening. The main outcome measures were dosing errors (number of under-adherence or over-adherence events) and coverage (proportion of pharmacologic duration covered by dosing) relative to the ophthalmologist-prescribed regimen.

• RESULTS: Adherence to the prostaglandins once daily was good in both groups by all measures (≤10% of subjects with more than five dosing errors and mean coverage of 97.2% ± 6.1%). Adherence to the second medication in the two-drug group was poorer (37% of subjects with more than five dosing errors and mean coverage of 85.6% ± 12.6%). For the subjects using β-adrenoceptor antagonists, 24.8% ± 18.4% of doses were taken at less than 10-hour intervals (over-adherence).

• CONCLUSIONS: The incorporation of a time component in electronic monitoring provides more information than prescription refill rate or other methods. We found that more complex dosing regimens result in poorer adherence, although once-daily drugs in a complex dosing regimen were found to have good adherence. (Am J Ophthalmol 2007;144:533–540. © 2007 by Elsevier Inc. All rights reserved.)

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PATIENT ADHERENCE IS NOW WIDELY RECOGNIZED AS a critical link to effective treatment and successful management of a broad array of acute and chronic diseases. At best, treatment adherence in chronic diseases is estimated to be 75%.[1] Even in symptomatic diseases where lapses in therapy may result in clinically significant symptoms (e.g., epilepsy and oncology), treatment adherence remains a problem.[2,3] In glaucoma, the lack of overt symptoms, in theory, may tend to decrease the adherence of the patient to pharmacotherapy requiring frequent self-treatment.[4] Increasing the complexity of the medical regimen also is associated with decreasing patient adherence.[5]

Various multicenter studies have found that consistent IOP lowering is related to minimizing the risk of both developing optic nerve damage and preventing its progression.[6–9] Although adherence often is discussed in chronic glaucoma therapy, there are few studies wherein patient dosing is actually measured. Kass and associates found in tandem studies that patients self-reported almost 100% adherence using only one glaucoma medication, whereas an electronic monitor documented the actual mean percent of doses taken to be 65% for pilocarpine four times daily and 73% for timolol taken twice daily.[10,11] Since the studies of Kass and associates, once-daily prostaglandin analogs have become the mainstay of topical ocular hypotensive therapy in the United States, and the concept of target pressure has gained acceptance. Recent studies of electronic monitoring of glaucoma medications have focused on the accuracy of a new recording device[12] and adherence with brimonidine (Hermann MM, et al. IOVS 2006;47:ARVO E-Abstract 3388). However, several prostaglandin analogs are being used as primary therapy, and a relatively large proportion of patients require more than one ocular hypotensive medication (e.g., 40% of ocular hypertensive patients at five years).[6] Thus, we wanted to explore the impact of a more complex dosing regimen as well. To our knowledge, no published studies have evaluated objectively the adherence of a once-daily glaucoma medication, nor that of two glaucoma medications. Unlike requirements for the purity and stability of pharmaceuticals, and for their efficacy and safety, there is no gold standard for adherence, and arbitrary bifurcation into "good" and "bad" is of limited use.[13,14] Thus, we calculated several objective measures of adherence.

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METHODS

THIS WAS AN OPEN-LABEL, NONRANDOMIZED STUDY IN which we invited the following consecutive subjects to participate: those who were currently using either a topical prostaglandin as sole ocular hypotensive medical therapy once daily and those who were currently using a topical prostaglandin plus an adjunctive topical ocular hypotensive-marketed product either once daily, twice daily, or thrice daily in the same eye(s) for 30 days or more. Subjects continued to receive their medications in a container that electronically records dosing. All subjects were clinical patients of a private, subspecialty glaucoma practice. All individuals with whom the study was discussed opted to participate.

To participate in the study, individuals were required to be 18 years of age or older, to have a diagnosis of open-angle glaucoma (OAG) or ocular hypertension (OHT) in one or both eye(s). Allowed were diagnoses of exfoliation syndrome with glaucoma or pigmentary glaucoma and previous laser surgery (including laser trabeculoplasty) or intraocular surgery (including cataract extraction or glaucoma filtering procedures). Additionally, acceptable for enrollment were subjects with chronic or subacute angle-closure disease, as long as their medication regimen was stable and at least six months had elapsed since a laser iridotomy. Subjects were required to be using—and have stable IOPs as a result—a constant topical ocular hypotensive treatment in one or both eyes for 30 days or more as either: 1) a once-daily marketed prostaglandin analog (2.5-ml bottle) as monotherapy (referred to as one-drug subjects) or 2) a once-daily marketed prostaglandin analog (2.5-ml bottle) and a topical ocular hypotensive-marketed product either once daily, twice daily, or thrice daily in the same eye(s) in any size bottles (referred to as two-drug subjects). Excluded from the study were individuals with known hypersensitivity to any component of the formulation or to topical anesthetics, known lack of ocular hypotensive response to the currently used ocular hypotensive medication(s), and—other than ocular hypotensive medications—ocular medication of any kind (with the exception of lubricating drops for dry eye) within 30 days of the screening visit. Also excluded were subjects with unstable IOP control, those using systemic medications used to lower IOP, or those with known contraindications to the currently used ocular hypotensive medication(s), clinically significant systemic disease (e.g., uncontrolled diabetes, myasthenia gravis, or hepatic, renal, cardiovascular, or endocrine disorders) that may interfere with the study, participation in any study involving an investigational new drug within the previous 30 days, or changes in systemic medication within 30 days before screening that could have a substantial effect on IOP or anticipated changes during the study.

Subjects were explicitly told on multiple occasions that their behavior in using their ocular hypotensive medication(s) was being monitored. At the screening visit, we measured best-corrected distance visual acuity and IOP by Goldmann applanation tonometry and performed a slit-lamp biomicroscopy and nondilated ophthalmoscopic evaluation. Visual fields and dilated ophthalmoscopy could have been performed up to six months before this visit. An electronic event medication monitoring device, the Medication Event Monitoring System (MEMS 6 SmartCap; Aardex, Union City, California, USA), was used to record the time and date of each opening of the bottle containing the ocular hypotensive medication (Figure 1). Patients were advised orally and in writing that they were being monitored. This device provides a passive mnemonic aid for the subject (i.e., clock showing last dose and number of doses taken within the last 24 hours) and has been used in more than 300 studies measuring adherence to oral dosing regimens.[15,16] The use of a bottle within a bottle has been used previously for topical ocular therapy (Bartlett J, et al. IOVS 2003;44:ARVO E-Abstract 1930).[17,18] The device records the time of each cap opening and does not require inversion. Additional openings within a 15-minute period are not counted. The LCD bottle top displays a number beginning with zero during each 24-hour period. With each bottle opening, the number advances. In this way, a subject knew if and how many times the bottle had been opened during the current 24-hour period. A representation of a 24-hour clock also is seen around the rim of the bottle top, helping to let subject know how long until their next dose. Color-coded labels that corresponded to the color of the eye drops bottle top also were placed on the outside of the MEMS 6 container to avoid confusion. The placement of the ocular hypotensive medication in the bottle(s) and the color coding were demonstrated by the office staff, and the subject was educated in the use of these bottles. Subjects returned at

FIGURE 1. Photograph showing prostaglandin bottle in standard pharmacy bottle with MEMS cap (Aardex, Union City, California, USA) to measure patient use of medication electronically. The "2" on the cap indicates two openings within the previous 24 hours.

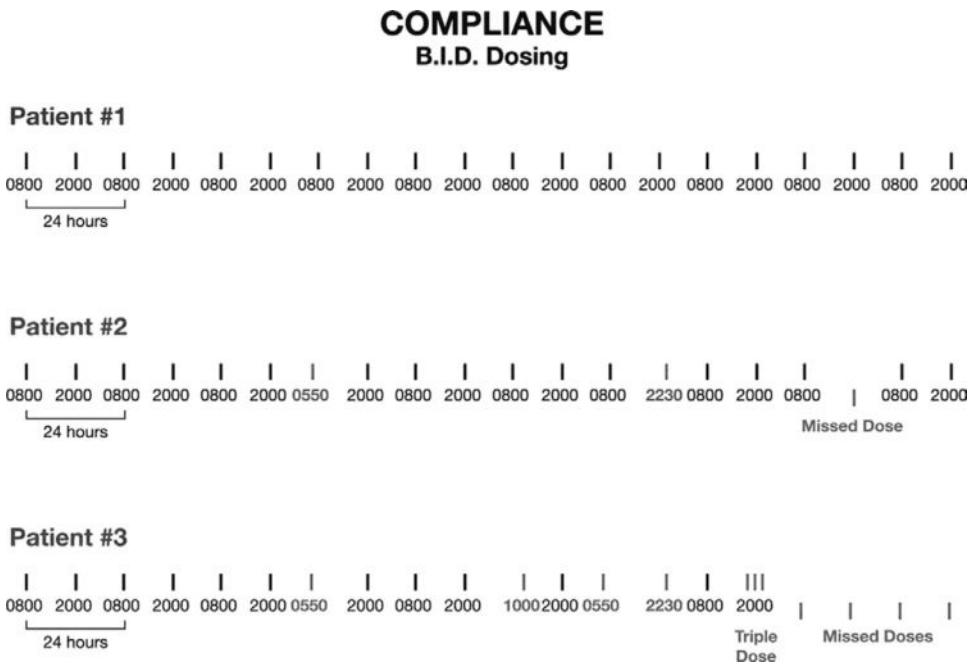

FIGURE 2. Schematic of examples of treatment adherence patterns. Patient 1 has had perfect adherence; Patient 2 has had early, late, and missed doses; and Patient 3 has had early, late, missed doses, and overdosing.

TABLE 1. Description of Adherence Measures Used in This Study of Topical Ocular Hypotensive Medications

Measure	Description	Example
Dosing errors	Overadherence or underadherence of the number of doses per 24-hour period (3:00 AM to 2:59 AM) as determined by the PowerView program compared with the nominal dosing.	Subject using timolol twice daily who takes a dose at 8:00 AM, 3:00 PM, and 11:00 PM would be counted as one dosing error.
Coverage	Proportion of time during the study for which the interval between doses was no more than two hours more than the nominal dosing interval. Makes no adjustment for overdosing.	Subject who took 60 planned once-daily doses, 30 at 20-hour intervals and 30 at 28-hour intervals, would have 88% coverage (1260/1440 hours covered).
Interdose interval	Interval between doses.	Subject who took twice-daily doses half of the time at 10.5-hour intervals and half the time at 13.5-hour intervals would have a mean interdose interval of 12 hours.
Percent of doses taken	Number of doses divided by the number of days in the study times the prescribed dosing frequency.	Subject who took 55 of 60 planned doses would have taken 92% percent of doses.

30 and 60 days, at which time we again measured best-corrected visual acuity and IOP and performed slit-lamp biomicroscopy and an ophthalmoscopic examination. At the final visit, each MEMS cap was queried electronically, and the data were transferred to a computer. By design, we gave no feedback to the subjects as to their adherence.

Shown in Figure 2 is a schematic of three theoretical patients: Patient 1 has perfect adherence, Patient 2 has early, late, and missed doses, and Patient 3 additionally overdosed. To quantify such dosing behavior, we calculated dosing errors, coverage, interdose interval, and percent of doses taken, as shown in Table 1 (PC-SAS version 9.1.3; SAS Institute, Cary, North Carolina, USA; and PowerView program; Aardex, Union City, California, USA). We arbitrarily divided adherence as measured by dosing errors into good (missing fewer than two doses in the two-month study period), adequate (missing two to five doses), or poor (missing more than five doses).

For two-drug subjects, criteria were used requiring appropriate dosing for both the prostaglandin and adjunctive

TABLE 2. Pre-study Characteristics of Patients in This Ocular Hypotensive Medication Adherence Study

	One Medication	Two Medications	Overall
Age			
No.	31	31	62
Mean ± SD	66.6 ± 13.1	62.8 ± 15.0	64.7 ± 14.1
Minimum, maximum	40, 90	36, 87	36, 90
Gender			
Male	18 (58.06%)	14 (45.16%)	32 (51.61%)
Female	13 (41.94%)	17 (54.84%)	30 (48.39%)
Race			
White	22 (70.97%)	21 (67.74%)	43 (69.35%)
Black	8 (25.81%)	9 (29.03%)	17 (27.42%)
Asian	—	1 (3.23%)	1 (1.61%)
Hispanic	1 (3.23%)	—	1 (1.61%)
Iris color			
Brown	19 (61.29%)	17 (54.84%)	36 (58.06%)
Hazel	2 (6.45%)	4 (12.90%)	6 (9.68%)
Blue	10 (32.26%)	8 (25.81%)	18 (29.03%)
Other	—	2 (6.45%)	2 (3.23%)
Diagnosis			
Open-angle glaucoma, right eye	26 (86.67%)	25 (80.65%)	51 (83.61%)
Open-angle glaucoma, left eye	26 (86.67%)	26 (83.87%)	52 (85.25%)
Pseudoexfoliation	1 (3.33%)	0	1 (1.64%)
Lens opacity, mean ± SD			
Right eye	1.6 ± 1.5	1.6 ± 1.6	1.6 ± 1.5
Left eye	1.7 ± 1.5	1.8 ± 1.7	1.8 ± 1.6
Cup-to-disk ratio, mean ± SD			
Right eye	0.7 ± 0.3	0.8 ± 0.2	0.7 ± 0.2
Left eye	0.7 ± 0.3	0.8 ± 0.2	0.8 ± 0.2
Glaucoma field severity (Hodapp and associates),[28] mean ± SD			
Right eye	1.3 ± 0.7	1.6 ± 0.8	1.5 ± 0.7
Left eye	1.5 ± 0.8	1.7 ± 0.9	1.6 ± 0.8
Glaucoma surgery			
Laser trabeculoplasty	19 (30.7%)	5 (16.1%)	14 (45.2%)
Trabeculectomy	11 (17.7%)	7 (22.6%)	4 (12.9%)
No. of systemic medications, mean ± SD	4.2 ± 3.3	3.6 ± 3.1	3.9 ± 3.2

SD = standard deviation.

therapy (combined criteria). At the time this study was designed, there were no glaucoma studies using the intended adherence monitor, nor were there studies using a once-daily medication. Thus, a sample size of 30 per group (the one-drug group and the two-drug group) for a total of 60 subjects was selected arbitrarily to allow for descriptive statistics.

RESULTS

• **DISPOSITION AND DEMOGRAPHICS:** We conducted this study between January 2006 and April 2006. All subjects invited to participate were enrolled in the study. Two subjects (one in each group) withdrew consent (day six and day 33) and were replaced, resulting in 62 subjects entered. All analyses were conducted on the intent-to-treat population (n = 62), with the exception of the dosing errors analysis (n = 60 completing subjects). Pre-study characteristics are shown in Table 2.

For two-drug subjects, adjunctive therapy was β-adrenoceptor antagonists, α-adrenoceptor agonists, topical carbonic anhydrase inhibitors, or cholinergic agonists. The prescribed frequency of the second medication ranged from once daily to thrice daily, with most subjects (71.0% [22/31]) prescribed the second medication on a twice-daily basis, consistent with common usage patterns for β-adrenoceptor antagonists, topical carbonic anhydrase inhibitors, and α-adrenoceptor agonists. All dosing was in both eyes.

Mean IOP in the one-drug group was 16.7 ± 3.6 mm Hg at entry, 16.3 ± 3.7 mm Hg at one month, and 16.2 ± 3.4

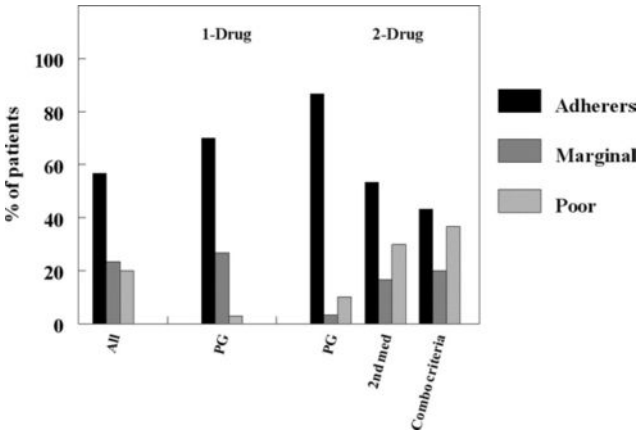

FIGURE 3. Graph showing categorical analysis of dosing errors by patients. Dosing errors are over-adherence or underadherence of the number of doses per 24-hour period. All = all patients; PG = prostaglandin; 2nd med = adjunctive therapy; Combo criteria = meeting both prostaglandin and adjunctive therapy criteria; adherers = zero to two errors; marginal = three to five errors; poor = more than five errors.

mm Hg at two months. Mean IOP In the two-drug group was 15.8 ± 3.6 mm Hg, 16.0 ± 4.1 mm Hg, and 15.0 ± 3.8 mm Hg at the same visits.

• **DOSING ERRORS:** Shown in Figure 3 is the proportion of subjects in three categories of dosing errors (under-adherence and over-adherence): adherers (zero to two errors), marginal (three to five errors), and poor (more than five errors). Overall, 20% (12/60) of subjects were in the poor category. For subjects in the one-drug group, only 3.3% (1/30) were in the poor category. For subjects in the two-drug group, 10.0% (3/30) were in the poor category for prostaglandins and 30.0% (9/30) were in the poor category for adjunctive therapy. Using combined criteria, 36.7% (11/30) of subjects were in the poor category.

• **COVERAGE:** For the prostaglandin users, the mean coverage was 97.2% ± 6.1% (range, 73.7% to 100.0%). It was similar in both the one-drug group (97.5% ± 3.9%) and the two-drug group (96.8% ± 6.2%). For the second medication, the mean coverage was slightly less: 93.0% ± 8.3% (93.4% ± 3.4% for once-daily dosing, 91.6% ± 9.1% for twice-daily dosing, and 99.5% ± 0.7% for thrice-daily dosing). For two-drug patients using combined criteria, coverage was much lower than either drug alone: 85.6% ± 12.6% (Table 3).

• **INTERDOSING INTERVALS:** With respect to the first drug (prostaglandin analog), the mean interval between doses was 24.4 ± 1.2 hours (range, 22.5 to 29.8 hours). This mean was 101.5% ± 6.1% of perfect once-daily dosing (i.e., 24 hours). When stratified by the number of medications, the two groups were similar (24.3 ± 1.2 hours for the one-drug group and 24.4 ± 1.3 hours for the two-drug group). With respect to the adjunctive medications, the mean interval between doses was 22.7 ± 2.1 for once-daily dosing, 12.4 ± 1.4 for twice-daily dosing, and 8.2 ± 0.2 hours for thrice-daily dosing. This mean was very near to perfect dosing, which is 24, 12, and eight hours, respectively. Overall, the subjects dosed themselves at 101.9% ± 10.7% of their nominal dosing interval (Table 4). Using combined criteria, for the two-drug group, the

TABLE 3. Coverage (Percent) of Patients in This Ocular Hypotensive Medication Adherence Study

Category	Mean ± SD
Prostaglandins (once daily)	
All patients	97.2 ± 6.1
One-drug patients	97.5 ± 3.9
Two-drug patients	96.8 ± 6.2
Adjunctive medications	
All patients	93.0 ± 8.3
Once daily (n = 5)	93.4 ± 3.4
Twice daily (n = 22)	91.6 ± 9.1
Thrice daily (n = 3)	99.5 ± 0.7
Adjunctive medications (combined criteria*)	
All patients	85.6 ± 12.6
Once daily (n = 5)	87.3 ± 16.2
Twice daily (n = 22)	85.1 ± 12.8
Thrice daily (n = 3)	86.4 ± 6.5

SD = standard deviation.

Coverage is the proportion of time during the study for which the interval between doses was no more than two hours more than the nominal dosing interval. N = 62 for all patients, n = 31 for one-drug patients and n = 31 for two-drug patients.

*Appropriate dosing for both the prostaglandin and adjunctive therapy.

TABLE 4. Interdose Interval of Patients in This Ocular Hypotensive Medication Adherence Study

Category	Hours (Mean ± SD)	Percent of Nominal (Mean ± SD)
Prostaglandins (once daily)		
All patients	24.4 ± 1.2	101.5 ± 6.1
One-drug patients	24.3 ± 1.2	101.4 ± 4.8
Two-drug patients	24.4 ± 1.3	101.7 ± 5.5
Adjunctive medications		
All patients	14.0 ± 4.7	101.9 ± 10.7
Once daily (n = 5)	22.7 ± 2.1	94.7 ± 8.5
Twice daily (n = 22)	12.4 ± 1.4	103.7 ± 11.3
Thrice daily (n = 3)	8.2 ± 0.2	102.5 ± 2.8

SD = standard deviation.

Interval is the time between doses of the same medication (hours and percent of nominal). N = 62 for all patients, n = 31 for one-drug patients, and n = 31 for two-drug patients.

TABLE 5. Percent of Ocular Hypotensive Doses Taken by Patients in This Ocular Hypotensive Medication Adherence Study

Category	Mean ± SD
Prostaglandins (once daily)	
All patients	97.0 ± 6.7
One-drug patients	96.5 ± 4.7
Two-drug patients	97.5 ± 8.2
Adjunctive medications	
All patients	99.9 ± 13.0
Once daily (n = 5)	110.2 ± 28.0
Twice daily (n = 22)	97.6 ± 4.1
Thrice daily (n = 3)	96.0 ± 3.0

SD = standard deviation.
N = 62 for all patients, n = 31 for one-drug patients, and n = 31 for two-drug patients.

subjects dosed at 101.8% ± 6.1% of their nominal dosing interval.

• **PROPORTION OF DOSES TAKEN:** With respect to the first drug (prostaglandin analog), subjects took 97.0% ± 6.7% of doses prescribed (range, 78.5% to 130.7%). The proportion of doses taken was similar when stratified by one-drug or two-drug subjects (96.5% ± 4.7% and 97.5% ± 8.2%, respectively). With respect to the adjunctive medications (two-drug subjects only), subjects took 99.9% ± 13.0% of doses prescribed. When stratified by dosing frequency, the mean proportion of doses taken was 110.2% ± 28.0%, 97.6% ± 4.09%, and 96.0% ± 3.0% for once daily, twice daily, and thrice daily dosing, respectively (Table 5).

• **OVER-ADHERENCE:** Nearly all subjects (96.8% [60/62]) had at least one interdosing drug interval for prostaglandin of less than 20 hours (nominal once-daily dosing is 24 hours). The proportion of interdosing intervals meeting this criterion was approximately 5%, with no apparent effect of stratification by one-drug or two-drug subjects. With respect to the adjunctive medication, nearly all subjects using twice-daily or once-daily dosing (92.9% [26/28]) had a least one interdosing drug interval for the second drug of less than 10 hours (nominal twice-daily dosing is 12 hours). Calculated for 20 subjects using products containing β-adrenoceptor antagonists (a potential safety issue), the proportion of interdosing intervals meeting this criterion was 24.8% ± 18.4%.

• **STRATIFICATION BY PRE-STUDY CHARACTERISTICS:** There was no apparent effect of stratification by pre-study characteristics on adherence measures (age, race, gender, number of systemic medications, severity of glaucoma, and glaucoma surgery).

DISCUSSION

WE USED ELECTRONIC MONITORING TO MEASURE PATIENT adherence with various current glaucoma dosing regimens and calculated adherence in multiple ways. We were able to use the commercially available MEMS caps and a bottle-in-a-bottle method with minimal logistical issues. Depending on the definition of adherence (Table 1), we had a range of adherence results.

Our main finding is that although adherence with once-daily prostaglandin analogs was excellent in both the one-drug and two-drug patients, time-appropriate adherence with the adjunctive medication in the two-drug patients was not, even in a situation where subjects knew they were being monitored. Adjunctive therapies were taken in approximately the correct number (i.e., percent of doses taken) and at a correct interval on average (i.e., interdose interval). However, appropriate ocular hypotensive coverage was achieved only 86% of the time. Dosing errors showed that 37% of patients were in the poor adherence category (more than five errors). The relatively poor adherence in the two-drug patients was despite: 1) patients being frequently advised by the investigators that their dosing behavior was being monitored and 2) the MEMS cap displaying the number of doses within the previous 24 hours. Recent large, multicenter studies emphasize the importance of IOP in progression of visual field loss.[6–9] This gives greater import to continual control of IOP, which, with pharmacologic therapy, requires good patient adherence. Our study provides valuable time-stamped data as to how patients adhere to their ocular hypotensive medication dosing regimen.

Also of interest was that approximately one quarter of doses with β-adrenoceptor antagonists were taken with fewer than 10 hours in between doses. In the study by Kass and associates, for those taking timolol, 65% of patients administered at least three doses per day at least once, and 13% of patients administered three doses per day for at least one week during the four- to six-week monitoring period.[11] This is a major safety concern, given that systemic β-adrenoceptor antagonism may occur, leading to serious untoward effects. This finding is surprising, given that the MEMS cap displayed recently administered doses and may be expected to eliminate overdosing. Notable is that both the efficacy and safety issues typically are occult to the clinician and are uncovered only by electronic adherence monitoring. As well, even if patients perceive the safety issue, they may not associate systemic symptoms with their eye drops.

The finding of poorer adherence with more complex regimens is consistent with theory,[4] as well as with previous reports. For example, in a study evaluating prescription refills of 1,784 patients who were taking a prostaglandin for at least one year, had a second medication added, and were followed up for an additional year, the mean interval between refills increased by 6.7 days for the prostaglandin after the second medication was added.[19] In the present, relatively short,

two-month study, we did not see any issues with poor persistence, that is, patients who stop using therapy.[20–22] We also did not see the reported increased adherence just before a planned visit to the physician, a phenomenon known as the toothbrush or white coat effect.[23] As in most adherence studies, all patients in the present study stated that they took all of the doses. Electronic monitoring bore out that this was true; however, the patients did not take their medications at the correct time.

Adherence, as measured by the percent of doses taken, regardless of time, was much higher in this study than in the prior studies by Kass and associates.[10,11] This may be because of differences in our studies or physicians' attitudes, as well as the changes in ocular hypotensive therapies in the intervening two decades. The patients in this study were patients in a private practice of a glaucoma specialist, rather than that of a comprehensive ophthalmologist or a research university center. As well, patients in the present study were advised in the consent process that their use of their ocular hypotensive medications would be monitored, whereas those in the studies by Kass and associates were not advised that they were being monitored. In the case of patients using two bottles of ocular hypotensive mediation, we monitored both bottles. The study duration and visit schedules also had some differences. Unlike requirements for the purity and stability of pharmaceuticals and for their efficacy and safety, there is no gold standard for adherence, and arbitrary bifurcation into good and bad is of limited use.[13,14]

To our knowledge, ours is the first study that objectively monitors patient adherence to all ocular hypotensive medications in those using a once-daily monotherapy and in those using two different medications. Electronic monitoring provides a time-stamp of subjects' use of the medication. Although this study used the bottle-in-a-bottle method with MEMS caps, other designs have been used. The Travatan™ Dosing Aid is a mnemonic device designed to use with travoprost. It includes a handle, the depression of which records an event.[24,25] Using another microprocessor-controlled device to measure vertical position and pressure, Hermann and associates found that patients took 75% of brimonidine twice daily doses and 90% of brimonidine thrice-daily doses. In a second study, they found that 47% of postoperative anti-inflammatory treatments were taken (Hermann MM, et al. IOVS 2005;46:ARVO E-Abstract 3832).

As an initial study, our report has several limitations. Although we know when a MEMS container was opened, we do not know if the inner bottle was used. However, in previous ophthalmic studies using this bottle-in-a-bottle method in which patients stored the medication bottle in the larger, monitored bottle, it appeared that recorded events corresponded with dosing (Bartlett J, et al. IOVS 2003;44: ARVO E-Abstract 1930).[17,18] An additional issue, common to all electronic monitoring studies, is whether the patients actually used the medication. Adherence, at least for the once-daily medications, was much higher in this patient population than previously reported for patients using either oral or topical drugs.[1,26] The adherence of patients aware of being monitored may be greater than that in typical, unmonitored conditions. Additionally, patients being treated by a glaucoma subspecialist in private practice also may be different than those in other university clinical settings. The duration of the study, two months, also was relatively short compared with the lifetime of glaucoma therapy typically required. Although we did document other medications used by the patients (e.g., cardiovascular therapies), we did not monitor their use. Finally, patients continued to receive their current therapies; they were not randomized to the one-drug and two-drug treatment groups. Thus, our findings may be explored further in a study in which there is randomization with regard to the complexity of the ocular hypotensive dosing regimens. As well, the role of intervention in improving patient adherence should be explored in glaucoma, as it has in other diseases.[27]

A substantial portion of patients with elevated IOP eventually may require more than one glaucoma medication to reach target pressures.[6] One study found that between 39% and 51% of established patients switching to a prostaglandin require an additional glaucoma medication, depending on the prostaglandin, and it takes only approximately 85 days for that to occur.[28] Thus, it is likely a large number of patients with glaucoma will use a more complex dosing regimen, and our finding of apparent poorer adherence with adjunctive therapy needs to be considered in managing these patients. One may conjecture as to whether physician feedback on poor adherence may enhance adherence in the long-term. However, it may be that poor adherers need alternative therapies to complex patient-instilled medication such as combination drugs, laser surgery, or incisional surgery.

In conclusion, the use of electronic monitoring provides more information than simple pill counting, bottle weighing methods, or prescription refill rate, because it incorporates a time component. We found that more complex dosing regimens result in poorer adherence, although once-daily drugs in a complex dosing regimen were found to have good adherence.

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Biosketch

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