The Effect of an Educational Intervention on Adherence to Intraocular Pressure-Lowering Medications in a Large Cohort of Older Adults with Glaucoma

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ABSTRACT

BACKGROUND: Glaucoma is a progressive, irreversible disease that can lead to vision loss and lower quality of life if treatment is not optimized. Effective glaucoma therapies are available to lower intraocular pressure (IOP) and minimize or delay disease progression. Nonetheless, adherence to treatment remains suboptimal for many patients.

OBJECTIVE: To identify potentially nonadherent patients and evaluate the effect of patient- and physician-centric educational interventions on adherence by using a validated predictive model of nonadherence to glaucoma medication.

METHODS: This prospective, randomized, controlled, and interventional study included Humana Medicare Advantage Prescription Drug plan patients with a glaucoma diagnosis between May and October 2014, ≥ 1 pharmacy claim for glaucoma medication, and $\geq 50\%$ likelihood of nonadherence. Patients and physicians were randomized to cohorts A (no interventions), B (physician intervention), or C (patient and physician interventions). Physicians in cohorts B and C received information on the model, adherence, and patient profiles at baseline and months 3, 6, and 9. Patients in cohort C received educational materials on glaucoma and adherence (same schedule). The primary outcome was the proportion of days covered (PDC) with medication over 12 months. Adherence was defined as $PDC \geq 0.80$.

RESULTS: Overall, 23,306 patients and 2,955 physicians were eligible. After excluding physicians with < 3 nonadherent patients, each cohort included 200 physicians and 600 patients. Mean PDC was 0.54-0.56 across cohorts. At 12 months, $\geq 90.5\%$ of physicians and $\geq 75.5\%$ of patients remained in the study; mean PDC was 0.53-0.54 across cohorts. No statistically significant between-cohort differences in PDC and adherence were observed.

CONCLUSIONS: Intensive educational mailings to patients and their physicians did not improve PDC or adherence in this large population of potentially nonadherent patients with glaucoma. Findings highlight the difficulty of improving adherence in a disease that requires lifelong therapy despite being largely asymptomatic and can inform development of future interventions aimed at improving adherence to glaucoma therapy.

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What is already known about this subject

- Interventions aimed at improving adherence to glaucoma therapy, such as daily voice or text messages reminding patients to take their medication, or combination of educational videos, regular phone calls, and dosing-aid activated reminders, have been shown to be effective in small ($n \leq 70$) randomized studies of patients with glaucoma set in university subspecialty clinics or eye institutes.
- From a physician's perspective, however, such interventions may be impractical given the prevalence of the disease.

What this study adds

- Using a validated and peer-reviewed predictive model of nonadherence to glaucoma medication to identify potentially nonadherent patients enrolled in a large U.S.-based health care company, this study shows that a multifaceted approach that included repeated mailings of educational materials specifically adapted for patients and their physicians over a 12-month period did not significantly improve adherence to treatment.
- Study findings illustrate the difficulty of improving adherence to treatment using interventions designed to be practical and applicable in large populations when the disease is chronic and typically asymptomatic until late stages.

Although effective glaucoma treatment approaches are available to lower intraocular pressure (IOP) and minimize disease progression that can otherwise lead to vision loss and lower quality of life, adherence to medications remains suboptimal for many patients, and its negative effect on visual field has been reported.¹⁻⁸ Numerous factors have been implicated in nonadherence, such as older age, the cost of medication, inconvenience of frequent administration, and lack of symptoms until late disease stage.²⁻⁷ Interventions aimed at improving adherence have been shown to be effective in randomized studies of patients with glaucoma ($n \leq 256$) set in university subspecialty clinics or eye institutes in the United States.⁹⁻¹¹ These interventions have included single approaches, such as daily voice or text messages reminding patients to take their medication; multifaceted ones, such as a combination of

educational videos, regular phone calls, and dosing-aid-activated reminders; or a customized letter and personal telephone call from the researcher.⁹⁻¹¹ From a physician's perspective, however, interventions such as sending daily texts to all patients who are prescribed IOP-lowering medication (or having to keep track of the information generated by those interventions up to 3 times a day, if automated) may be impractical given the incidence and prevalence of the disease.^{12,13} Moreover, nonadherence is a multifactorial issue, and although automated reminders would be expected to help address barriers to adherence such as forgetfulness and difficulty with the treatment schedule, other important barriers (e.g., poor knowledge and difficulty with drop administration) are likely to benefit more from educational information and/or interaction with the health care providers (as suggested by the American Academy of Ophthalmology).^{1,14} Identification of potentially nonadherent patients is thus an important issue; however, identifying potentially nonadherent patients based on demographic or clinical factors, which may be more easily accessed and measured than behavioral and psychological factors, remains a challenge.

Using claims data from a large U.S.-based health care company, a study was recently conducted to identify demographic and clinical factors associated with nonadherence to glaucoma medication in elderly patients. A predictive model was developed (using multivariable logistic regression, a significance level of 0.01, and a patient sample of 48,840/73,256) as a tool to help physicians and payers identify elderly patients at risk of nonadherence.¹⁵ Baseline variables incorporated in the initial model included demographics (age, gender, race, and geographic region); plan type; low-income subsidy; Rx-Risk-V composite risk score (a pharmacy claims-based comorbidity measure that assesses medical condition burden¹⁶); conditions present (hypertension, hyperlipidemia, diabetes, congestive heart failure, joint disorders, muscle weakness/movement disorders, mental disorders, or glaucoma); glaucoma surgery, glaucoma-related eye exam, or open-angle glaucoma diagnosed by an ophthalmologist; number of physicians seen and pharmacies used; new versus continuing users of IOP-lowering medications; source of prescription (mail order vs. retail, formulary tier, prescriber gender, and prescriber specialty for the index IOP-lowering prescriptions); and preindex medical and pharmacy costs. Of those, 10 factors that were significantly related to nonadherence were incorporated in the final model; 4 significantly increased the likelihood of nonadherence (i.e., index IOP-lowering prescription filled through mail order [available to all individuals with a pharmacy benefit], higher overall medical costs before the study period, being a new user of IOP-lowering medication, and being male), while 6 significantly decreased it (i.e., advanced age, higher pharmacy costs before the study period, receiving low-income subsidy, residing in the southern U.S. Census Bureau region,

a previous diagnosis of open-angle glaucoma, and a history of glaucoma surgery). The final model was then validated using the remaining patient sample (i.e., 24,416/73,256) and was shown to perform equally well in the development and validation patient samples (area under the curve = 0.71), suggesting a robust model.¹⁵ The objective of the present study was to apply this validated, predictive model in a large population of older adults with glaucoma to identify those at risk for nonadherence to IOP-lowering therapy and to evaluate the effect of patient- and physician-centric informational and educational interventions on adherence to treatment in this population.

Methods

Study Design and Participant Selection

This was a prospective, controlled, and cluster-randomized study (i.e., randomized by treating physician) conducted among patients with glaucoma within a large U.S. health care company. The study protocol was approved by an independent institutional review board (IRB) before study initiation.

The administrative claims database used for this study included enrollment files, medical claims, and outpatient pharmacy claims data from Humana, a U.S.-based health care company that provides Medicare Advantage Prescription Drug (MAPD) plan, standalone Medicare Prescription Drug plan, and commercial health plan offerings. The Humana research database was screened to identify patients with MAPD coverage, aged 65-89 years, who had ≥ 1 diagnosis of glaucoma (*International Classification of Diseases, Ninth Revision, Clinical Modification* [ICD-9-CM] code 365.xx [i.e., any type]) and ≥ 1 pharmacy claim for an IOP-lowering medication between May 1, 2014, and October 31, 2014. For inclusion in the study, patients were also required to be continuously enrolled in the MAPD plan during the 6-month identification period and the preceding 12 months. In addition, during the identification period, all patients and all physicians prescribing the most recent IOP-lowering medication were required to have a valid mailing address. MAPD plan patients in long-term care and elderly patients with a standalone prescription drug plan only were excluded from the study.

From this eligible study sample, patients considered likely to be nonadherent to IOP-lowering medication were selected using the validated predictive nonadherence model described in the Introduction.¹⁵ The model was fitted with enrollment and medical/pharmacy data from the 6-month identification period to identify potentially nonadherent patients (defined as those with a $\geq 50\%$ probability of having medication supply for $< 80\%$ of study days).

Patients included in the study were linked to the physician who prescribed their most recent IOP-lowering medication, and physicians were categorized according to their number of study-eligible patients. In accordance with the planned study inclusion ratio (3 patients per physician), physician selection

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FIGURE 1 Randomization of Patients and Physicians to the Study Interventions

was limited to those treating at least 3 potentially nonadherent patients with glaucoma. Nonadherent patients for whom the patient-to-physician ratio was lower than 3:1 were excluded at this stage. In the event a physician was treating more than 3 potentially nonadherent patients, 3 were randomly selected for that physician to maintain the 3:1 patient-to-physician ratio.

Randomization and Interventions

From the selected physician and patient populations, 600 physicians were randomly assigned to 1 of 3 cohorts, together with their associated 1,800 patients (Figure 1): cohort A (“usual care” control group in which neither physicians nor patients received interventions), cohort B (interventions directed at physicians only), and cohort C (patients and physicians received interventions). A waiver of consent and authorization for use of administrative data were granted by an independent IRB.

Patients were automatically included in the same cohort as their physician. Physicians assigned to cohorts B and C received (a) a cover letter explaining that they were contacted because a prior study conducted at Humana identified that the physicians had prescribed glaucoma medications for patients who were at high risk of being nonadherent to those medications; (b) a 2-page brochure (“Glaucoma Adherence in Humana’s Medicare Population”) containing information on adherence to glaucoma medications in the Humana Medicare population, background information on the predictive model (including the predictors of nonadherence), and relevance to clinical practice; and (c) patient-specific clinical and medication profiles (i.e., medication refill history, outpatient visits and procedures, and comorbid conditions). These materials were mailed at baseline and months 3, 6, and 9 for a total of 4 interventions. On the same schedule, patients in cohort C received a cover letter describing the potential effect of glaucoma on their vision and the importance of continued use of IOP-lowering eye drops to prevent disease progression, and a 2-page

educational brochure on glaucoma that discussed the importance of adherence to therapy and provided such tips as how to keep track of the treatment schedule, what to do if a dose is missed, how glaucoma medications work, and potential side effects. The content of the materials (“Treating Glaucoma,” from the “Understanding and Living with Glaucoma” brochure developed by the Glaucoma Research Foundation¹⁷) was adapted by Comprehensive Health Insights (with permission) for the patients enrolled in Humana’s health care programs, and graphic design elements were added to ensure ease of reading and compliance with Humana and Medicare material guidelines.

Study Outcomes

The primary outcome measure was the proportion of days covered (PDC) with ≥ 1 IOP-lowering medication (including alpha-agonists [brimonidine, apraclonidine]; beta-blockers [betaxolol, carteolol, levobunolol, metipranolol, timolol]; carbonic anhydrase inhibitors [brinzolamide, dorzolamide]; miotics [carbachol, pilocarpine], prostaglandin analogs/prostamide [bimatoprost, latanoprost, tafluprost, unoprostone]; combinations [brimonidine/timolol, brinzolamide/brimonidine, dorzolamide/timolol]; and others [phospholine iodide, Propine], identified by brand name and generic National Drug Code number) over the 12 months following the date of dispatch of the initial (baseline) intervention (index date: March 26, 2015). The 12-month PDC was calculated by summing the total days’ supply of IOP-lowering medication during the first 365-day post-index period and dividing that by 365 days. The interim 6-month PDC was also measured and reported.

For comparison, the PDC with ≥ 1 IOP-lowering medication over the 12 months immediately preceding the index date (i.e., baseline PDC) was also estimated. The days supply of IOP-lowering medication (days covered) was accessed from prescription fill claims data for each patient. The number of

days ophthalmic drug supply provided by each prescription fill was determined from published medication drop-count studies that measured the number of drops of drug solution dispensed from commercially available bottles of IOP-lowering medication, together with recommended dose and dosing frequency data.¹⁸⁻²⁰ Patients were deemed to be adherent if they had ≥ 144 and ≥ 292 days with IOP-lowering medication supply over the 180-day and 365-day assessment periods, respectively (equivalent to a PDC ≥ 0.80).

Covariates and Other Measures

Demographic characteristics (age, sex, race, and geographic region of residence) and health plan characteristics (e.g., plan type, low-income subsidy status) were reported based on enrollment data available at the identification date.

Clinical characteristics and glaucoma measures were also described in the baseline period, including Rx-Risk-V score,¹⁶ the proportion of patients with common comorbidities identified by Rx-Risk-V categories (e.g., hypertension, hyperlipidemia, diabetes, congestive heart failure), and comorbidities that may interfere with application of topical glaucoma medications (e.g., joint disorders, movement disorders, mental disorders). Additionally, whether the patient had a documented diagnosis of open-angle glaucoma by an ophthalmologist, an eye exam (by any physician), a glaucoma-related eye exam, and evidence of any type of glaucoma surgery were recorded.

Prescription utilization measures (e.g., new IOP-lowering medication user [i.e., no claims for an IOP-lowering medication in the previous 12 months], distribution channel of medications [i.e., mail order or retail], and number of unique medications), health care costs (total, medical, and pharmacy [plan- and patient-paid]), and predicted adherence to IOP-lowering medication were also reported.

Statistical Analyses

Demographic and clinical characteristics obtained at baseline (Table 1) were as defined in the previous publication,¹⁵ reported using descriptive statistics, and compared across cohorts using a chi-square test (categorical variables) or 1-way analysis of variance (ANOVA; continuous variables). Mean PDC over the 6- and 12-month post-index periods was analyzed using 1-way ANOVA (intercohort comparisons). Post hoc analyses of the change in pre- to post-index mean PDC were compared using Student's paired t-test (intracohort comparisons). Intercohort comparisons of adherence were performed using a chi-square test. A *P* value < 0.05 was considered statistically significant.

Sample Size Calculations

A sample size of 400 patients per cohort was determined using a 2-sided t-test with 80% power, a significance level of 0.05 (*P* value), and an expected mean adherence improvement of 10% over a 12-month time frame.^{3,10} To account for an

estimated 30% loss of study participants over time and ensure that the claims data analysis at the end of the observation period would include at least 400 patients per arm with continuous post-index enrollment, the sample size was set at 600 patients per intervention arm.

Results

Patient Flow

Of 60,621 patients who met the inclusion and exclusion criteria, 23,306 patients identified as potentially nonadherent, together with 2,955 physicians, were eligible for randomization (Figure 2). All patients sampled where the ratio of nonadherent patients to physician did not equal 3:1 were then excluded. Of the 6,675 and 2,225 remaining patients and physicians, respectively, 600 physicians in total (200 in each cohort) were randomly assigned to cohorts A, B, or C, and 1,800 patients in total (600 in each cohort) of those physicians were automatically included in the same cohort without crossover.

Across cohorts, patient attrition rates at 6 months (i.e., after the second mailing) and 12 months post-index were 12.3% and 20.3%, respectively, primarily due to disenrollment and removal after their physician was excluded due to an invalid address. Consistent with these data, physician attrition rates at 6 and 12 months post-index were 4.0% and 6.3%, respectively, primarily due to undeliverable or returned mailings. At 12 months post-index, the numbers of patients and physicians remaining in each cohort were 502 and 199 (cohort A), 480 and 182 (cohort B), and 453 and 181 (cohort C), respectively.

Patient Demographics and Characteristics

At baseline, the majority of patients were female and Caucasian, lived in the South, and had a preferred provider organization (PPO) health plan (Table 1); average age was 75 years. All demographic and clinical variables were balanced across cohorts, except for geographic region, hyperlipidemia, and diagnosis of open-angle glaucoma by an ophthalmologist (Table 1). The physicians prescribing the most recent IOP-lowering medication in the identification period were primarily ophthalmologists (76.5%-79.0% across cohorts) and male (78.5%-84.5% across cohorts). At 12 months post-index, the characteristics of the remaining patient sample were comparable to those of the entire study cohort at baseline and comparable across cohorts; only 1 variable, geographic region, remained unbalanced across cohorts (*P* < 0.001). Physicians' characteristics also remained similar at 12 months post-index and across cohorts.

PDC and Adherence

No statistically significant differences in PDC were demonstrated across cohorts over the 12-month post-index period (Table 2). Consistent with this finding, there were no statistically significant differences in the proportion of adherent patients (characterized by a PDC ≥ 0.80) across cohorts (Table 2).

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TABLE 1 Baseline Demographics and Clinical- and Prescription-Related Characteristics of Study Patients

	Cohort A (n = 600)		Cohort B (n = 600)		Cohort C (n = 600)		P Value
Demographics							
Mean age (SD), years	75.5	(5.9)	75.6	(6.2)	75.5	(6.0)	0.876
Sex, n (%)							0.239
Male	252	(42.0)	280	(46.7)	273	(45.5)	
Female	348	(58.0)	320	(53.3)	327	(54.5)	
Race, n (%)							0.936
Caucasian	472	(78.7)	460	(76.7)	477	(79.5)	
African American	107	(17.8)	114	(19.0)	101	(16.8)	
Other	21	(3.5)	26	(4.3)	22	(3.7)	
Geographic region, n (%)							<0.0001
Northeast	15	(2.5)	12	(2.0)	18	(3.0)	
Midwest	210	(35.0)	135	(22.5)	187	(31.2)	
South	308	(51.3)	388	(64.7)	323	(53.8)	
West	67	(11.2)	65	(10.8)	72	(12.0)	
Health plan type, n (%)							0.115
Health maintenance organization	202	(33.7)	218	(36.3)	226	(37.7)	
Preferred provider organization	324	(54.0)	333	(55.5)	319	(53.2)	
Other	74	(12.3)	49	(8.2)	55	(9.2)	
Low-income subsidy status, n (%) ^a	61	(10.2)	58	(9.7)	59	(9.8)	0.957
Clinical characteristics							
Chronic conditions, n (%)							
Hypertension	465	(77.5)	479	(79.8)	465	(77.5)	0.527
Hyperlipidemia	439	(73.2)	440	(73.3)	474	(79.0)	0.029
Diabetes	198	(33.0)	190	(31.7)	222	(37.0)	0.127
Congestive heart failure	53	(8.8)	47	(7.8)	43	(7.2)	0.561
Joint disorders	126	(21.0)	135	(22.5)	124	(20.7)	0.712
Mental disorders	76	(12.7)	68	(11.3)	68	(11.3)	0.710
Muscle weakness/neuropathy/movement disorders	78	(13.0)	87	(14.5)	72	(12.0)	0.436
Glaucoma-related variables, n (%)							
Eye exam ^b	558	(93.0)	546	(91.0)	547	(91.2)	0.378
Glaucoma-related eye exam ^c	401	(66.8)	377	(62.8)	402	(67.0)	0.228
Glaucoma surgery ^d	19	(3.2)	11	(1.8)	16	(2.7)	0.335
Open-angle glaucoma diagnosis ^e	358	(59.7)	373	(62.2)	402	(67.0)	0.030
Prescription-related characteristics							
New prescription users, n (%)	110	(18.3)	124	(20.7)	118	(19.7)	0.593
Used mail order for first IOP-lowering medication in identification period, n (%)	513	(85.5)	518	(86.3)	520	(86.7)	0.834
Number of unique medications, mean (SD)	10.5	(6.1)	10.6	(5.6)	10.9	(6.0)	0.378
Rx-Risk-V score, mean (SD) ^f	6.0	(3.2)	6.1	(2.8)	6.1	(3.0)	0.751
Medical costs (\$), mean (SD)	6,466	(10,335)	6,928	(10,857)	7,778	(13,968)	0.150
Prescription costs (\$), mean (SD)	2,145	(3,831)	2,005	(3,189)	2,216	(4,627)	0.637
Probability of patients being nonadherent, mean % (SD) ^g	63	(8)	63	(9)	63	(9)	0.629

^aRefers to older adults who have an income that does not exceed 150% of the federal poverty level and are eligible for additional premium and cost-share assistance for prescription drugs under the Medicare Part D program.

^bIncluded CPT codes 92002, 92004, 92012, 92014, 92019, 92081, 92082, 92083, and 92140.

^cIncluded CPT codes 92081, 92082, 92083, and 92140.

^dIncluded CPT codes 65850, 65855, 66170, 66172, 66180, and 66185.

^eICD-9-CM code 365.1x, diagnosed by an ophthalmologist.

^fPharmacy claims-based comorbidity measure used to assess medical condition burden. The unweighted version of the Rx-Risk-V provides a summary count of the number of unique medical condition categories for a patient based on medication proxy. Rx-Risk-V summary score and the prevalence of select Rx-Risk-V components were determined for each patient based on prescription claims adjudicated during the identification period. Comorbidities included hypertension, hyperlipidemia, diabetes, and congestive heart failure. The Rx-Risk-V categories and associated medication classes were adapted from Sloan et al.¹⁶

^gBased on the predictive model.¹⁵ The probability of nonadherence represents the likelihood of PDC < 0.80 based on the factors specified in the model.

CPT = Current Procedural Terminology; ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification; IOP = intraocular pressure; PDC = proportion of days covered; SD = standard deviation.

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FIGURE 2 Patient Selection Flow Diagram

^aThis identification period was later modified to May 1, 2014–October 31, 2014, to capture patients with the most recent IOP prescription closer to the time of the intervention. It was also required that patients have continuous enrollment for 18 months before the identification date (October 31, 2014), which allowed for a full 12 months of claims data for each patient before the most recent IOP medication claim in the modified identification period.

^bModified criteria.

^cThese are patients who were identified by the predictive model as having a ≥50% likelihood of being nonadherent (PDC < 0.80) based on the specified factors.

ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification; IOP = intraocular pressure; MAPD = Medicare Advantage Prescription Drug plan; PDC = proportion of days covered.

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TABLE 2 PDC and Adherence over the Baseline Period and 6-Month and 12-Month Post-Index Periods

Cohorts	Baseline Period ^a			6-Month/12-Month Post-Index Period			PDC Change Mean (SD)	P Value	
	N	PDC Mean (SD)	Adherence ^b n (%)	N	PDC Mean (SD)	Adherence ^b n (%)		Intercohort Comparison (Post-Index)	
								PDC	Adherence ^b
6-month post-index period									
A	545	0.56 (0.30)	141 (25.9)	545	0.52 (0.32)	134 (24.6)	-0.04 (0.29)	0.636 ^c	0.870 ^c
B	522	0.55 (0.31)	132 (25.3)	522	0.52 (0.33)	128 (24.5)	-0.03 (0.29)		
C	512	0.54 (0.31)	128 (25.0)	512	0.54 (0.32)	132 (25.8)	-0.02 (0.27)		
12-month post-index period									
A	502	0.56 (0.26)	110 (21.9)	502	0.54 (0.30)	128 (25.5)	-0.02 (0.26)	0.921 ^c	0.773 ^c
B	480	0.55 (0.26)	100 (20.8)	480	0.53 (0.30)	114 (23.8)	-0.02 (0.27)		
C	453	0.55 (0.26)	98 (21.6)	453	0.54 (0.29)	108 (23.8)	-0.01 (0.23)		

^aDefined as the 12-month period immediately preceding the baseline intervention mailing (March 25, 2014-March 26, 2015).

^bDefined as PDC ≥ 0.80.

^cComparison across all 3 cohorts.

PDC = proportion of days covered; SD = standard deviation.

Additional analyses comparing pre- to post-index changes in PDC did not reveal any statistically significant differences across cohorts ($P > 0.05$ in all cases; Table 2) or within cohorts.

Discussion

The primary objectives of this study were to identify older adults who were potentially nonadherent to prescribed IOP-lowering therapy and to evaluate the effect of patient- and physician-centric interventions on patient adherence to treatment in this population based on prescription fill data. The study used a multifaceted approach specifically adapted for patients and their physicians (mostly ophthalmologists) and intended to promote patient education and involvement of treating physicians, the effect of which on adherence has been reported in other studies.^{21,22} However, despite provision of written educational materials to both audiences and patient-specific clinical and prescribing information to physicians over a 12-month period in an at-risk population, adherence to treatment did not significantly change. Our findings illustrate the difficulty of improving adherence to treatment using interventions designed to be practical and applicable in a large health plan when the disease is chronic and typically asymptomatic until late stages.

Other published investigations of various patient-centric strategies aimed at improving adherence in glaucoma have yielded mixed results, although they included considerably fewer patients ($n = 11$ to 805) than the present study ($n = 1,800$).^{9-11,23-34} Two studies employed automated telecommunications such as texts and voice messages to send reminders, for example, about taking medications or upcoming appointments.^{9,29} In other studies, print materials and letters were also included as part of the patient-centric intervention, but poor

health literacy about glaucoma and the importance of adherence to treatment may have lessened their effect, as discussed by other groups.^{11,26,29,35,36} The interventions that reportedly had the greatest effect on adherence to IOP-lowering treatment utilized interactive approaches such as telephone calls or face-to-face meetings, along with coaching or visual education materials (e.g., demonstrations and videos).^{10,11,23,24,33} Regardless, adherence to treatment increased by only ≤ 16% compared with the respective baseline or control group.

Consistent with observations reported in studies of patient-centric interventions, studies that included a physician-centric intervention to improve patient adherence to treatment have also produced mixed results.³⁷⁻⁴⁰ These interventions comprised, for example, faxing prescribing physicians to alert them of patients with gaps of > 10 days in their prescription refill, and educational materials ± patient-specific computerized alerts.^{37,38} The intervention evaluated herein provided physicians with clinical and prescription information that was patient-specific and could be used for individual patient counseling or follow-up, as well as educational materials on glaucoma for both patients and physicians. Although 1 of the previously published studies was similar to ours in terms of the type of intervention (educational mailings) and being directed at both patients and physicians, it incorporated additional improvement initiatives (disease management programs), thereby complicating attempts to determine the contribution of the educational intervention to the observed improvement in adherence.³⁹

Whether our patient-centric intervention would have benefited from inclusion of a more interactive component is unclear. However, the feasibility and cost-effectiveness of extending the use of interactive, adherence-fostering approaches to all

patients who are potentially nonadherent to their glaucoma medication (23,306 with 2,995 physicians in this study alone) should be taken into consideration. Even if automated, texts, emails, and/or voicemails sent 1, 2, or 3 times daily (depending on the medication class) to remind patients to use their IOP-lowering medication would require tracking (potentially making it impractical in large populations) and would not be expected to help alleviate the instillation-related component of nonadherence (for example).¹⁴ Moreover, adherence to ocular treatment in elderly populations is often further compromised by the concomitant use of systemic medications or comorbidities such as arthritis. These constraints highlight the need for effective, longer-term glaucoma therapies with improved tolerability profiles that do not need to rely on the patients' compliance or physicians' reminders to ensure adherence. The development of sustained-release drug delivery systems and minimally invasive glaucoma surgery devices thus has the potential to overcome issues related to nonadherence to a prescribed dosing regimen.⁴¹⁻⁵³

It is also possible that interventions involving a team approach and collaboration between physicians and pharmacists might have a greater effect on adherence to medication. Such interventions could include emails, texts, or voicemails from the pharmacist alerting patients with gaps of >10 days in their prescription refill (which could be more effective than alerting providers of patients with such gap)³⁷ and/or encouraging patients to sign up for auto-refills. Educational materials such as those used in this study could be emailed to patients, which (compared with print versions) would allow those with potential visual impairment (glaucoma-related or not) to adjust the font size, brightness, and/or contrast as needed and facilitate reading of the information. It should also be noted, however, that if patients do not see well enough to read written information (or have co-conditions such as arthritis), instillation of eye drops could be an issue. In such cases, designating a family member to help foster adherence behavior may be helpful.^{54,55} Patients could also be asked to provide a reason for their nonadherence to treatment before their prescriptions are released, based on a recent study in which adherence to guidelines improved if health care practitioners had to provide a reason for nonadherence.⁵⁶ Results from a study investigating the effects of incentives on adherence to glaucoma treatment (i.e., 50% or 25% rebate on glaucoma-related health care costs for adherence over at least 90% or 75% of days, respectively, based on a medication event monitoring system) should be very informative as well.⁵⁷ Future studies might benefit from investigating combinations of the aforementioned interventions.

Limitations

This study has some limitations to consider. The effect of clustering was not evaluated, and identification of potentially nonadherent patients was based on a predictive model.¹⁵ Although

the model was developed and validated in a population of patients with glaucoma from the same Humana research database as this study population, differences in demographics and clinical- and/or prescription-related characteristics of the 2 populations due to variations in patient populations over time may have affected its discriminative ability. For example, approximately 35%, 54%, and 10% of patients had a health maintenance organization, PPO, or other plan in this study compared with 54%, 28%, and 18% in the previous study, respectively.¹⁵ Similarly, the proportions of new prescription users and mail orders for the first IOP-lowering prescription were approximately 20% and 86% in this study compared with 31% and 35% in the previous study, respectively.¹⁵ It should be noted, however, that these numerical differences have not been tested for statistical significance.

Although most large Medicare providers offer some type of mail order benefit to patients, there may be some that do not, which could also affect the discriminative ability of the model in other studies. Moreover, patients were eligible for intervention if their probability of nonadherence was $\geq 50\%$; while this value was selected to capture varying levels of potential nonadherence, a narrower range might have produced statistically significant differences across cohorts.

It is also worth noting that the intervention materials were sent by mail (although there was no means of verifying whether patients and physicians received or read them) and that, compared with the PDC, a medication event monitoring system might have been better suited to measure adherence. The cost-effectiveness of the latter approach in a real-world clinical setting, however, should be determined. In addition, the actions of physicians in cohorts B and C were not recorded, which may have contributed to the lack of statistically significantly different results between those cohorts.

Although the modified identification time frame spanned May 1, 2014–October 31, 2014, data extraction did not occur until early 2015 because of the lag in enrollment and medical claims data. Therefore, after data extraction, patient/physician identification, and preparation of the mailings, there was a gap between the dates used for identification of nonadherent patients and the baseline mailing, during which adherence could have changed. However, nonadherence across cohorts was measured and verified by utilizing baseline data in the 12 months immediately preceding the first intervention (i.e., April 2014–March 2015), mitigating this limitation's effect on the findings.

This study included a variety of patients with glaucoma and set no conditions on the time since diagnosis, time on treatment, or type of IOP-lowering medication; it may be useful, however, to investigate these subsets of patients in future studies. New users of IOP-lowering medication constituted approximately 20% of the patient sample, leaving 80% with previous or continuing treatment. Since adherence to IOP-lowering

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medication has been reported to decrease to 56%-57% within the first year of treatment, patients may have already reached a point at which the effect of any intervention would have been limited.^{5,58,59} Differences in adherence to IOP-lowering drugs of the same class have also been reported,⁶⁰ but this factor was not considered in this study. Likewise, the study did not take into account behavioral or psychological factors that may affect adherence.^{61,62}

Finally, limitations common to studies using administrative claims data apply to this case, such as potential errors in claims coding. In addition, the data used were from patients enrolled with a single health care company and, as such, results may not be generalizable to other populations; however, Humana is a large national health care company with broad geographic representation.

Conclusions

Findings from this prospective, randomized, and controlled study show that patient- and physician-centric multifaceted informational and educational mailings were not effective in improving adherence to IOP-lowering treatment in this population of elderly patients with glaucoma, underscoring the challenge of finding novel mechanisms for improving adherence in glaucoma, an irreversible disease that requires early and lifelong therapy despite being asymptomatic until late stages.

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DISCLOSURES

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