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Modeling Patterns of Medication Adherence in Primary Open-Angle Glaucoma

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Objective: To use group-based trajectory modeling to identify patterns of medication adherence in patients with primary open-angle glaucoma (POAG) and to identify factors associated with each pattern.

Design: Prospective cohort study.

Participants: Seventy-two patients with POAG who were enrolled in a National Institutes of Health–funded progression study at the University of Alabama at Birmingham were included in this study. Patients were required to be >18 years of age, have a diagnosis of POAG, and be prescribed hypotensive eye drops to treat their glaucoma.

Methods: Fifty-two weeks of mean weekly medication adherence data were collected using Medication Event Monitoring Systems. Group-based trajectory modeling was used to estimate models with 2, 3, 4, 5, and 6 medication adherence trajectory groups. Self-reported race and illness perception were included as covariates. The model with the lowest Bayesian information criterion (which provides a measure of the trade-off between model fit and model complexity) and the highest number of clinically relevant trajectory groups was deemed optimal.

Main Outcome Measures: Medication adherence trajectory groups.

Results: The Bayesian information criterion was −1041.1 for the 2-group model, −755.9 for the 3-group model, −643.8 for the 4-group model, −590.4 for the 5-group model, and −559.0 for the 6-group model. We identified the 4-group model as the most optimal. The 4 trajectory groups estimated by this model were near-perfect adherence (51.8% of participants), good adherence (23.2% of participants), declining adherence (18.1% of participants), and poor adherence (6.9% of participants). Compared with the poor adherence group, a higher illness perception score predicted a lower probability of membership in the good (B = −0.276, $P = 0.042$) and declining (B = −0.303, $P = 0.028$) adherence groups.

Conclusions: Medication adherence is an important clinical outcome that is associated with disease severity and disease progression in POAG. Further investigation of this important topic may reveal other shared clinical characteristics that can be used to identify patients who may be at risk for adverse clinical outcomes such as glaucoma progression.

Financial Disclosure(s): Proprietary or commercial disclosure may be found in the Footnotes and Disclosures at the end of this article. *Ophthalmology Science 2025;5:100706 © 2025 by the American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).*

Supplemental material available at www.ophthalmologyscience.org.

Primary open-angle glaucoma (POAG) is the leading cause of irreversible blindness worldwide.[1] For many patients, eye drops that lower intraocular pressure and delay disease progression[2] are the preferred treatment modality. Medication adherence, which describes the degree to which patients use their medication as prescribed, is important for preventing vision loss in POAG, yet it is notably poor. Although studies have reported medication adherence rates as high as 97%,[3–5] as many as 80% of patients fail to use their medication as prescribed.[6] As an important clinical outcome that is associated with POAG progression, it is important to thoroughly investigate medication adherence. However, research is complicated by the use of summary metrics such as the mean and median, which mask periods of poor adherence. Instead, analyzing patients' patterns of medication adherence—which delineate their medication use over extended periods of time—may be more informative.

Group-based trajectory modeling (GBTM) is a statistical procedure for clustering individuals who follow similar physiological, clinical, or behavioral trajectories over time.[7–11] In POAG, GBTM has been applied to pharmacy claims data to identify long-term patterns of medication adherence.[12] However, pharmacy claims data are not very granular because the summary metric employed—the medication possession ratio—provides only 1 mean value of medication adherence every 3 months. On the other hand, electronic monitors capture each individual eye drop instillation and more faithfully delineate medication adherence over time. In this study, we used GBTM to identify patterns of medication adherence in POAG patients with 12 months of electronically monitored data. We included clinical, demographic, and psychological variables in the GBTM procedure to determine their association with each medication adherence pattern.

https://doi.org/10.1016/j.xops.2025.100706
ISSN 2666-9145/25

Methods

Participants

In this study, we analyzed medication adherence data collected from patients enrolled in a National Institutes of Health-funded study on POAG progression (EY025756) at the University of Alabama at Birmingham—henceforth referred to as the parent study. Study approval was obtained from the University of Alabama at Birmingham Institutional Review Board, and all participants provided informed consent. All aspects of this study followed Health Insurance Portability and Accountability Act regulations and adhered to the tenets of the Declaration of Helsinki. At the baseline visit of the parent study, patients were required to be above age 18, have a diagnosis of POAG, have visual acuity better than 20/40, and have a mean deviation better than −12 decibels on a reliable visual field test. To be included in the current analysis, patients also had to have ≥14 months of electronically monitored medication adherence data. Patients with a history of secondary POAG, diseases other than POAG affecting the visual field, intraocular surgery (except uncomplicated cataract or POAG surgery), or conditions that prevented completion of study assessments were excluded.

Medication Adherence

Medication Event Monitoring System (MEMS) combined with the MEMS Adherence Software (MEMS AS), AARDEX Group, Belgium, is an integrated system that was used in this study to measure and/or to manage patients' adherence to medications.[13] We measured adherence during the implementation phase, which describes the period between patients' first prescription fill (initiation) and their last use of the prescribed medication (discontinuation).[13] Participants were given 1 MEMS bottle for each prescribed eye drop medication. Participants were then instructed to use their eye drops as prescribed and to store them inside the MEMS bottles. Over 365 days, each opening of the MEMS bottles was recorded by the MEMS caps, and each recorded event served as a proxy for an instilled eye drop. Medication Event Monitoring System–recorded events have been found to closely correspond with patient dosing using this bottle-in-bottle approach.[14]

All medication adherence data were collected between July 2018 and June 2021. For each participant, the first 2 months of data were excluded in order to minimize the Hawthorne effect among participants and allow them to revert to their usual patterns of medication use.[15,16] For each eye drop medication, daily medication adherence was calculated using the formula: $\frac{\textit{Number of doses taken}}{\textit{Number of doses prescribed}}$ X 100%. Extra doses were excluded. Daily medication adherence was then averaged over the total number of eye drop medications to calculate mean daily medication adherence. Lastly, mean daily medication adherence was averaged over every 7 days to yield 52 values of mean weekly medication adherence.

Trajectory Modeling

In the GBTM procedure, participants are assigned to the trajectory group to which they have the highest probability of belonging.[9] This probability is modeled as a multinomial logistic regression using the *traj* command (copyright 2023),[7] which was downloaded from traj: group-based modeling of longitudinal data (cmu.edu) through the 3-Clause Berkeley Software Development License (Open-Source Initiative). Using the *traj* command in Stata 18.0, quadratic polynomial functions were applied to mean weekly medication adherence data to estimate trajectory models with 2, 3, 4, 5, and 6 groups. A censored normal (cnorm) trajectory model was deemed to be most appropriate as our data were continuous and limited by minima (0% adherence) and maxima (100% adherence). We also estimated a logit model in which each value for mean weekly medication adherence was coded as a binary variable: 1 (≥80%) or 0 (<80%).[17] As researchers and clinicians often dichotomize patients as being adherent or nonadherent,[18] we estimated 2 trajectory groups in this model. All coding used in the GBTM procedure, as well as the logit and cnorm datasets, are included in the Supplementary Appendix (available at www.ophthalmologyscience.org).

The Bayesian information criterion (BIC) is a measure of the trade-off between model fit and complexity and was used to identify the model with the optimal number of trajectory groups. Lower BIC absolute values indicate more optimal models.[8] Because the BIC favors parsimonious models, model selection was also based on having an average posterior probability (AvePP) above 0.7 for each trajectory group (AvePPs close to 1 suggest little ambiguity in group assignment),[19] having odds of correct classification (OCCs) >1 for each trajectory group (OCC >1 indicates that the OCCs are greater than random chance),[19] having ≥5% of participants in each trajectory group,[8] having no overlap in the confidence intervals for the estimated trajectories,[20] and having the highest number of clinically relevant trajectory groups.[11]

After selecting the optimal model, we used existing literature to identify variables in our dataset that were reasonably supported to have an influence on medication adherence. We identified age,[21] self-reported race,[22] number of comorbidities,[23] number of ocular medications/regimen complexity,[24] education level,[25] income level,[25] self-efficacy,[26] and illness perception.[27] In the parent study, self-efficacy was measured using the Glaucoma Medication Self-Efficacy Scale,[28] and illness perception was measured with the Brief Illness Perception Questionnaire.[29] In our study, regimen complexity was operationalized as the number of daily eye drop instillations multiplied by the number of prescribed eye drop medications.[30] Based on the findings of a previous publication that also used medication adherence data collected during the parent study,[31] we refined our list of risk factors to include self-reported race and illness perception. We fit 1 logit multivariate trajectory model and 1 cnorm multivariate trajectory model with these variables as risk factors.

Results

A total of 72 participants were included in this analysis. Participants' baseline characteristics are reported in Table 1. Mean (standard deviation [SD]) age was 70.0 (7.8) years. Approximately 53% of participants were female and 52% self-reported as White. Mean (SD) medication adherence was 86.7% (18.1), and the mean number of comorbidities was 2.6 (1.5), among which hypertension (71%), hyperlipidemia (51%), and type 2 diabetes (28%) were most common. The mean (SD) [max] eye drop self-efficacy score was 17.0 (1.6) [18], and the mean medication self-efficacy score was 23.6 (6.9) [30]. Higher scores indicate higher perceived ability. The mean illness perception score was 29.3 (10.0) [80]. Higher scores indicate a more daunting outlook on POAG.

Table 2 provides BICs for each model, and Figure 1 shows the estimated trajectory groups. All models had trajectory groups with memberships >5%, OCC >1, and AvePPs >0.70. After considering each model's parameters

Table 1. Participant Demographic and Clinical Characteristics

Study Variable	Distribution N (%)
Sex	
Female	38 (52.8)
Male	34 (47.2)
Race	
Asian	1 (1.4)
Black	33 (45.8)
White	38 (52.8)
Highest education level	
High school or less	8 (11.2)
Technical or vocational	11 (15.2)
Some college	37 (51.4)
College degree	12 (16.6)
Graduate or professional degree	4 (5.6)
Employment level	
Employed	21 (29.2)
Unemployed	1 (1.4)
Retired	50 (69.4)
Marital status	
Unmarried	29 (40.3)
Married	2 (59.7)
Household income	
<$40,000	16 (22.2)
$40–$80,000	20 (27.8)
$80–$99,000	7 (9.8)
>$100,000	5 (6.9)
Not reported	24 (33.3)

Clinical variables	Mean (SD), median [IQR]
Age (yrs)	70.0 (7.8)
Number of ocular medications	1.5 (0.6)
Regimen complexity	4.1 (4.1)
Number of comorbidities	2.6 (1.5)
Medication self-efficacy score	23.6 (6.9), 26.5 [10.8]
Eye drop self-efficacy score	17.0 (1.6), 18 [1.0]
Illness perception score	29.3 (10.1), 29 [12.0]
Mean medication adherence	86.7 (18.1), 96.6 [15.5]

IQR = interquartile range; SD = standard deviation.

and research literature indicating the existence of 4 to 5 medication adherence groups in POAG,[3,12,32] the 4-group model (BIC = −643.8) was considered most in line with research findings and most clinically relevant. The 5- and 6-group models had lower BICs (−590.4 and −559.0). However, these models estimated 2 trajectory groups that were indistinguishable from each other and had crossover in the confidence interval bands, which brought their clinical utility into question. The 4-group model estimated the following trajectories: group 4 (near-perfect adherence [51.8% of participants], group 3 (good adherence [23.2%]), group 2 (declining adherence [18.1%]), and group 1 (poor adherence [6.9%]).

Table 3 presents participant characteristics for each trajectory group. Mean medication adherence was 98.2% (1.0) in the near-perfect adherence group, 90.4% (5.0) in the good adherence group, 68.1% (6.0) in the declining adherence group, and 37.2% (11.5) in the poor adherence group. Table 4 shows each predictor's contribution to trajectory group membership. Compared with the poor adherence group, a higher illness perception score predicted a lower probability of membership in the good (B = −0.276, P = 0.042) and declining (B = −0.303, P = 0.028) adherence groups. This relationship did not hold for the near-perfect adherence group (B = −0.251, P = 0.062). The logit model estimated the following trajectories: group 1 (adherent [75.7% of participants]) and group 2 (nonadherent [24.3% of participants]). Black race predicted a greater likelihood of membership in the nonadherent group (B = 2.126, P = 0.003) compared with the adherent group.

Discussion

We used GBTM to identify the following patterns of medication adherence: near-perfect, good, declining, and poor adherence. Our finding that higher illness perception score predicted a greater likelihood of membership in the poor adherence group parallels research by Jiang et al,[33] who reported that higher illness perception score was associated with worse adherence. It is possible that a more daunting view of POAG may be indicative of greater psychological stress, which may negatively affect adherence. Similarly, our finding that Black race predicted lower adherence parallels research identifying Black race as a predictor of nonadherence.[25] As a pseudo-variable representing the interplay of socioeconomic and cultural factors, the effect of race can likely be attributed to the impact of these factors within the current social context. For example, Shen et al[34] found that Black patients experienced poorer communication quality with clinicians and were less involved in decision-making compared with White patients.

Group-based trajectory modeling is an excellent tool for identifying patients with shared characteristics. However, as a mathematical technique, it has the potential to shift the context away from clinical relevance. To address this concern, we sampled a panel of 8 ophthalmologists and optometrists with 18.5 ± 9.5 years of experience treating POAG to assess their perspectives on the optimal trajectory model. Overall, 5 of 8 clinicians indicated a preference for the 3-group model, followed by 2 of 8 for the 4-group model and 1 of 8 for the 5-group model. Thus, our selection of the 4-group model appeared to parallel clinical preferences. The only other GBTM study in POAG identified the following trajectory groups after analyzing 4 years of pharmacy claims data: *good*, *moderate*, *declining*, *poor*, and *nonadherence* (after index prescription).[12] Compared with this study, we did not identify a *moderate adherence* group, which may be due to the subjective nature of trajectory group nomenclature. We also did not identify a *nonadherent after index prescription* trajectory group, as newly diagnosed patients were not included in our study. In GBTM, it is important to note that researchers caution against the quixotic quest of identifying the "true" number of groups because trajectories are simply approximations of more complex realities.[7]

In POAG, poor medication adherence is associated with worse disease severity[26] and disease progression.[35] Compounding this issue is a report by Curtis et al[36]

Table 2. Trajectory Group Parameters

Number of Groups	BIC	Group Proportions (%)					
		Group 1	*Group 2*	*Group 3*	*Group 4*	*Group 5*	*Group 6*
2*	−1112.6	25.0	75.0	-	-	-	-
2	−1041.1	34.7	65.3	-	-	-	-
3	−755.9	9.7	26.3	64.0	-	-	-
4	−643.8	6.9	18.1	23.2	51.8	-	-
5	−590.4	6.9	18.0	12.4	26.4	36.3	-
6	−559.0	6.9	12.5	7.3	10.4	26.5	36.4

BIC = Bayesian information criterion.
*Logit model.

showing that medication adherence in newly diagnosed POAG patients declined more sharply than medication adherence in patients with other chronic conditions. In POAG, interventions for improving medication adherence range from community-based education[37] to medication rebates.[38] Although some have demonstrated success, there is a lack of compelling evidence for the recommendation of any particular strategies.[39] This may be due to their "one size fits all" nature, as they may not be equally relevant to patients. Our finding that illness perception score predicted trajectory group membership could be used to identify patients who may be at risk for poor medication adherence and glaucoma progression. The results of a meta-analysis across 188 studies support this

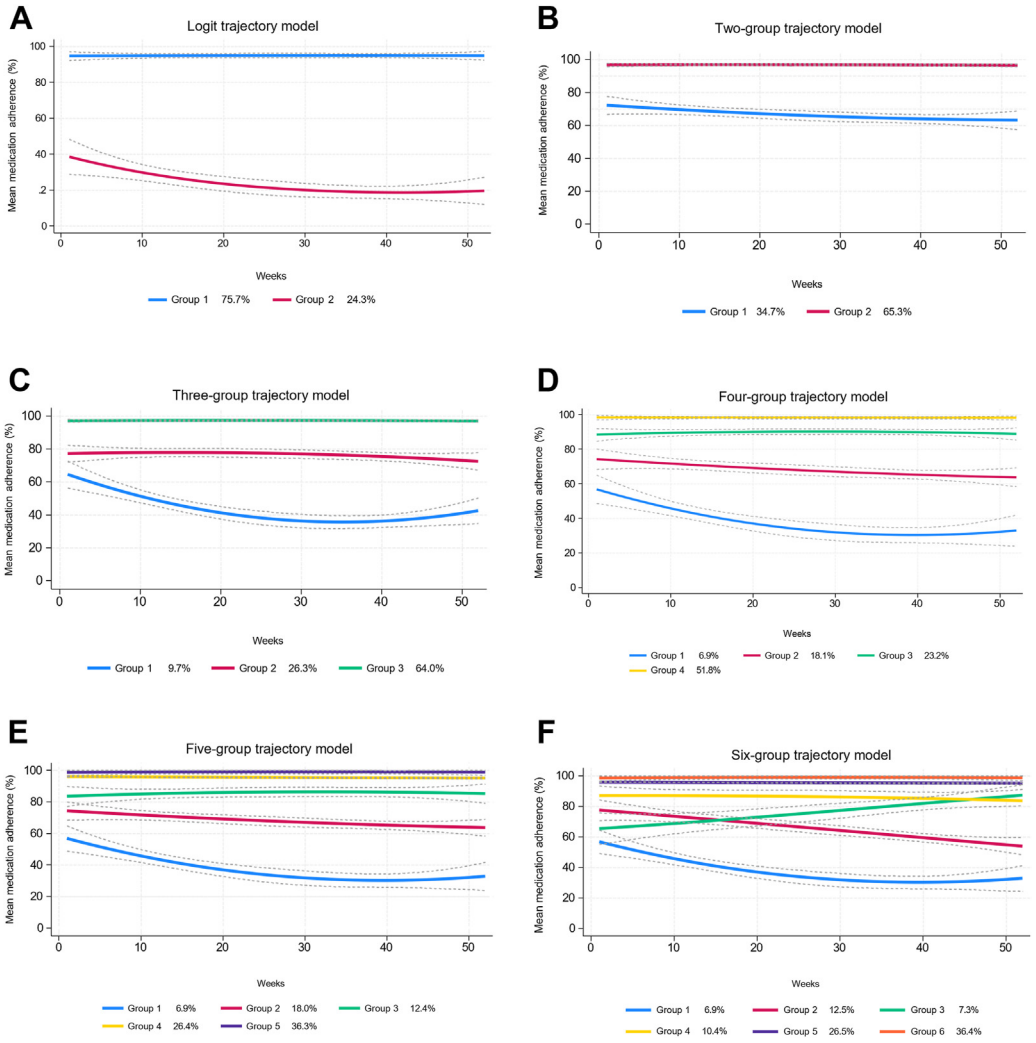

Figure 1. Trajectories identified over 52 weeks using GBTM. **A,** Logit model; 1 = adherent, 2 = nonadherent. **B**–**F,** 2, 3, 4, 5, and 6-group cnorm models. Four-group model: 4 = near-perfect adherence, 3 = good adherence, 2 = declining adherence, 1 = poor adherence. Percentages indicate group prevalence. cnorm = censored normal; GBTM = group-based trajectory modeling.

Table 3. Participant Demographic and Clinical Characteristics per Trajectory Group

Variable	Group 4	Group 3	Group 2	Group 1
Proportions (N, %)	37 (51.8)	17 (23.2)	13 (18.1)	5 (6.9)
Demographic Variables	**N (%)**	**N (%)**	**N (%)**	**N (%)**
Sex				
Female	19 (51.4)	7 (41.1)	9 (69.2)	3 (60.0)
Male	18 (48.6)	10 (58.8)	4 (30.7)	2 (40.0)
Race				
Asian	1 (2.7)	0 (0.0)	0 (0.0)	0 (0.0)
Black	9 (24.3)	9 (52.9)	10 (76.9)	5 (100.0)
White	27 (73.0)	8 (47.1)	3 (23.1)	0 (0.0)
Highest education level				
High school or less	6 (18.2)	0 (0.0)	0 (0.0)	2 (40.0)
Technical or vocational	6 (18.2)	1 (5.9)	2 (15.4)	2 (40.0)
Some college	18 (48.7)	11 (64.7)	7 (53.8)	1 (20.0)
College degree	7 (18.9)	2 (11.8)	3 (23.1)	0 (0.0)
Graduate or professional degree	0 (0.0)	3 (17.6)	1 (7.7)	0 (0.0)
Employment level				
Employed	9 (24.3)	4 (23.5)	5 (38.5)	3 (60.0)
Unemployed	1 (2.7)	0 (0.0)	0 (0.0)	0 (0.0)
Retired	27 (73.0)	76.5	8 (61.5)	2 (40.0)
Marital status				
Unmarried	13 (35.1)	5 (29.4)	7 (53.8)	4 (80.0)
Married	24 (59.7)	12 (70.5)	6 (46.2)	1 (20.0)
Household income				
<$40,000	7 (18.9)	3 (17.7)	4 (30.7)	2 (40.0)
$40–$80,000	11 (29.7)	4 (23.5)	4 (30.7)	1 (20.0)
$80–$99,000	3 (8.1)	3 (17.7)	1 (7.7)	0 (0.0)
>$100,000	3 (8.1)	1 (5.9)	1 (7.7)	0 (0.0)
Not reported	13 (35.1)	6 (35.3)	3 (23.2)	2 (40.0)
Clinical Variables	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**
Age (yrs)	71.0 (7.9)	69.2 (6.4)	69.6 (8.6)	67.2 (10.7)
Number of ocular medications	1.5 (0.6)	1.7 (0.8)	1.5 (0.5)	1.4 (0.9)
Regimen complexity	3.9 (3.8)	5.2 (5.2)	3.0 (2.1)	4.2 (6.1)
Number of comorbidities	2.3 (1.5)	2.6 (1.2)	2.6 (1.6)	4.4 (1.3)
Medication self-efficacy score	24.0 (7.2)	23.5 (6.8)	23.4 (6.8)	21.8 (6.8)
Eye drop self-efficacy score	16.9 (1.7)	17.2 (1.3)	17.2 (0.9)	16.5 (3.0)
Illness perception score	28.8 (8.8)	27.8 (10.6)	26.8 (6.4)	47.0 (14.4)
Mean medication adherence	98.2 (1.0)	90.4 (5.0)	68.1 (6.0)	37.2 (11.5)

SD = standard deviation.
Group 4—near-perfect adherence, Group 3—good adherence, Group 2—declining adherence, Group 1—poor adherence.

Table 4. Predictors of Adherence Trajectories in the 4-Group Cnorm Model

Group	Covariate	Estimate	Standard Error	T-Value	P-Value
4 — Near-perfect adherence	Race	18.649	4003.911	0.005	0.996
	Illness perception score	−0.251	0.135	−1.865	0.062
3 — Good adherence	Race	17.367	4003.911	0.004	0.997
	Illness perception score	**−0.276**	**0.136**	**−2.035**	**0.042**
2 — Declining adherence	Race	16.188	4003.911	0.004	0.997
	Illness perception score	**−0.303**	**0.138**	**−2.199**	**0.028**

Cnorm = censored normal.
Group 1 (poor adherence) is the reference group. Bolded items are significant predictors.

proposition by reporting that illness perceptions were closely associated with treatment outcomes such as depression and risk of hospitalization.[40] Thus, other interventions aiming to medication adherence can improve their relevance and effectiveness by selecting for shared patient characteristics.

This study has several strengths, including the use of electronic monitors, which provide a more objective measure of medication adherence compared with pharmacy claims or self-report. Another strength is the long duration of the monitoring period given the use of electronic monitoring. A final strength is the inclusion of clinical, demographic, and psychological covariates to determine their association with patterns of medication adherence. Limitations of this study include the relatively small sample size, the exclusion of patients with severe visual field damage, and the exclusion of newly diagnosed patients. Although larger samples allow for better detection of trajectory groups, GBTM has been reliably performed in sample sizes ranging from 41 to 25 000.[10,11,41,42] However, exclusion of patients with severe visual field damage may have influenced our findings because worse visual field damage has been associated with worse adherence.[26] The absence of newly diagnosed patients may also have affected our findings, as we were unable to identify medication adherence patterns that may have been exhibited by this population. Lastly, a drawback of our use of MEMS is the Hawthorne effect,[15] although this was likely minimized by the exclusion of the first 2 months of data.

We identified the 4-trajectory group model as being the most optimal. In this model, a higher illness perception score predicted membership in the poor adherence group. In the logit model, Black race was associated with nonadherence. As a key predictor of clinical outcomes in POAG, it is important to carefully characterize medication adherence. Further research in this area may reveal other shared characteristics that can be leveraged to identify patients who may be at risk for poor medication adherence and, by extension, worse treatment outcomes.

Acknowledgments

The authors would like to acknowledge Miss Tracy Thomas for her role in collecting and curating the data analyzed in this study.

Footnotes and Disclosures

Originally received: February 16, 2024.
Final revision: January 6, 2025.
Accepted: January 7, 2025.
Available online: January 13, 2025. Manuscript no. XOPS-D-24-00054.

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Disclosures:

All authors have completed and submitted the ICMJE disclosures form.

The authors made the following disclosures:

L.R.: Stock options − Olleyes, Inc.

This research was supported by the Vision Science Graduate Program, School of Optometry, University of Alabama at Birmingham (UAB), NIH Grant EY025756, P30 grant (EY003039), and an unrestricted grant from Research to Prevent Blindness.

Support for Open Access publication was provided by the Department of Ophthalmology and Visual Sciences, Heersink School of Medicine, University of Alabama at Birmingham.

HUMAN SUBJECTS: Human subjects were included in this study. Study approval was obtained from the University of Alabama at Birmingham Institutional Review Board. All aspects of this study followed Health Insurance Portability and Accountability Act regulations and adhered to the tenets of the Declaration of Helsinki, and all participants provided informed consent.

No animal subjects were used in this study.

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Data collection: Poleon, Racette

Analysis and interpretation: Poleon, Racette

Obtained funding: Twa, Racette

Overall responsibility: Poleon, Twa, Schoenberger-Godwin, Fifolt, Racette

Abbreviations and Acronyms:
AvePP = average posterior probability; **BIC** = Bayesian information criterion; **GBTM** = group-based trajectory modeling; **MEMS** = medication event monitoring system; **OCC** = odds of correct classification; **POAG** = primary open-angle glaucoma; **SD** = standard deviation.

Keywords:
Glaucoma, Medication adherence, GBTM, Modeling.

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