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The Impact of the Coronavirus Disease 2019 Pandemic on Adherence to Ocular Hypotensive Medication in Patients with Primary Open-Angle Glaucoma

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Purpose: Emerging evidence suggests that the coronavirus disease 2019 (COVID-19) pandemic is disrupting health behaviors such as medication adherence. The objective of this study was to determine whether adherence to ocular hypotensive medication was affected by the pandemic and to identify factors associated with this change.

Design: In this cohort study, we used a controlled interrupted time series design in which the interruption was the declaration of the COVID-19 pandemic in the United States on March 13, 2020. The 300-day monitoring period, which evenly bracketed this declaration, started on October 16, 2019, and ended on August 10, 2020.

Participants: Patients with primary open-angle glaucoma enrolled in an ongoing longitudinal National Institutes of Health-funded study initiated before the onset of the pandemic were selected if they were prescribed ocular hypotensive medication and had adherence data spanning the 300-day period.

Methods: We applied segmented regression analysis using a "slope change following a lag" impact model to obtain the adherence slopes in the periods before and after the segmentation. We compared the 2 slopes using the Davies test.

Main Outcome Measures: The main outcome measure was daily adherence to ocular hypotensive medication, defined as the number of doses taken divided by the number of doses prescribed, expressed in percent. Adherence was measured objectively using Medication Event Monitoring System caps. We assessed the associations between change in adherence and demographic, clinical, and psychosocial factors.

Results: The sample included 79 patients (mean age, 71 years [standard deviation, 8 years]). Segmented regression identified a breakpoint at day 28 after the declaration of the pandemic. The slope in the period after the breakpoint (−0.04%/day) was significantly different from zero ($P < 0.001$) and from the slope in the period before the breakpoint (0.006%/day; $P < 0.001$). Mean adherence in the period before the segmentation breakpoint was significantly worse in Black patients (median, IQR: 80.6%, 36.2%) compared with White patients (median, IQR: 97.2%, 8.7%; chi-square, 15.4; $P = 0.0004$). A significant positive association was observed between the Connor-Davidson resilience score and the change in slope between the periods before and after the breakpoint ($P = 0.002$).

Conclusions: Adherence to ocular hypotensive medication worsened during the COVID-19 pandemic and seems to be related to patient resilience. This collateral consequence of the pandemic may translate into vision loss that may manifest beyond its containment. *Ophthalmology 2022;129:258-266 © 2021 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.aaojournal.org.

Emerging evidence suggests that the coronavirus disease 2019 (COVID-19) pandemic is disrupting behaviors such as physical activity, sleep, and alcohol consumption. In previous seasonal and pandemic influenzas, poorer adherence to antiviral treatment was reported.[1] During the COVID-19 pandemic, changes in medication adherence—a critical health behavior in the management of chronic diseases—also have been reported.[2–4] Only 1 of the 3 studies assessing medication adherence with objective measurements reported improved adherence during the pandemic. Patients with asthma and chronic obstructive pulmonary disease showed a 14.5% increase in adherence to daily controller medications between January and March 2020.[4] This improvement likely reflects an understanding of the importance of controlling these diseases in the midst of a pandemic of respiratory illness. Of the other 2 studies, 1 reported a 10% decrease in the number of long acting antipsychotic injections administered within an ambulatory clinic located in

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Pittsburgh, Pennsylvania.[3] The other study analyzed administrative databases and reported higher failed refill rates for chronic disease medications in Italian clinical practice settings from April through May 2020.[2] Together, these findings suggest that adherence behavior was affected during the pandemic. These findings also raise concern for medication adherence in glaucoma patients, specifically because adherence to prescribed ocular hypotensive therapy was found previously to be poorer compared with adherence to other medications.[5]

Primary open-angle glaucoma (POAG), a chronic age-related optic neuropathy that is asymptomatic in the early stages, can lead to irreversible blindness if left untreated. Hypotensive eye drops are prescribed as a first-line treatment to control intraocular pressure, the only known modifiable risk factor for glaucoma progression. Although efficacious,[6] adherence to this treatment is challenging for patients, who are required to instill eye drops every day for the duration of their lives.[7] Given the strong association between nonadherence and visual field progression,[8] the primary goal of this study was to assess the impact of the COVID-19 pandemic on adherence to ocular hypotensive therapy in patients with POAG. Adherence, conceptualized as a dynamic process,[9] is likely to fluctuate in response to stressful situations or changes in personal circumstances. As a result, a secondary goal of this study was to identify factors associated with medication adherence during the pandemic. We assessed the association between demographic, clinical, and psychosocial factors and adherence in the periods before and after the onset of the pandemic. Psychosocial factors included resilience,[10] coping styles,[11] illness perception,[12] and self-efficacy,[13] which have been associated with adherence and visual function.

The data examined in this study were obtained from an ongoing longitudinal National Institutes of Health-funded study (referred to as the parent study elsewhere in this article) that fortuitously began before the onset of the COVID-19 pandemic. Although the primary goal of the parent study was to reduce the time to detection of progression through the development of a joint structure−function model,[14] objective measurements of adherence as well as psychosocial data were obtained as ancillary data. This afforded a unique opportunity to examine the effects of the pandemic on objectively measured medication adherence in patients with POAG.

Methods

We used a controlled interrupted time series design in which the date of the COVID-19 emergency declaration in the United States—March 13, 2020—served as the interruption. We selected data from the parent study, in which patients were monitored over a 3-year period. Information on all demographic variables was obtained by self-report. Eligibility criteria at baseline included the presence of the following in at least 1 eye: a confirmed diagnosis of POAG, open anterior chamber angle, best-corrected visual acuity of 20/40 or better, spherical correction of less than 5 diopters (D), cylinder correction of less than 3 D, and at least 1 reliable visual field test result. All patients were at least 18 years of age. Participants with a history of intraocular surgery (except uncomplicated cataract or glaucoma surgery), secondary glaucoma, other ocular and systemic diseases that affect the visual field, cognitive impairment, inability to perform visual field tests reliably, and severe visual field loss defined as mean deviation of −12 decibels (dB) or worse on a reliable static automated perimetry test were not eligible. Visual field tests were performed with the Humphrey Field Analyzer (Carl Zeiss Meditec) using the 24-2 pattern and the Swedish Interactive Thresholding Algorithm. Institutional review board approval was obtained from the University of Alabama at Birmingham.

Participants

Patients were selected from the parent study if they had been prescribed ocular hypotensive medication throughout the 300 days of the study, which covered the period of October 16, 2019 (150 days before the interruption), through August 10, 2020 (150 days after the interruption). Patients were excluded if they had incomplete adherence data, which could have happened, for example, if a clinical decision was made to undergo surgery or if the patient reported not using the Medication Event Monitoring System (MEMS) for a given period while continuing to use eye drops. The study conformed with the principles and guidelines for the protection of human subjects in biomedical research, adhered to the Health Insurance Portability and Accountability Act, and followed the tenets of the Declaration of Helsinki. Written consent was obtained from each participant.

Medication Adherence

Daily medication adherence was measured using MEMS caps (Aardex), which electronically registered the date and time at which the bottle was opened. The MEMS caps recorded data during the implementation phase of adherence,[15] which follows treatment initiation and describes the extent to which actual dosing corresponded to prescribed dosing. Patients were given 1 MEMS device for each prescribed ocular hypotensive medication and were instructed to place the eye drop bottle in the MEMS bottle after each instillation. This method was used previously to assess adherence in patients with glaucoma.[13,16] We labelled the MEMS devices with the name of each medication, and the research coordinator verified that the correct medication was in the correct MEMS device at each study visit. Patients were told that the MEMS caps recorded the date and time at which the bottle was opened and were instructed to use the eye drops as usual. The MEMS caps were not equipped with a liquid crystal display, and patients did not receive daily feedback on adherence. The data were downloaded from the MEMS caps at each study visit using a MEMS universal serial bus near-field communication reader, which allows for seamless data transfer from the MEMS caps to the secure web-based MedAmigo platform. When a study visit was missed, the MEMS device continued to monitor adherence and the data were downloaded at the next study visit. Although study visits were missed during the pandemic, all but 4 patients had returned for a visit when the dataset used in this study was assembled.

For each patient, a profile was created in MedAmigo that included the number of MEMS caps assigned, the medication regimen associated with each cap, and regimen changes. This information allowed MedAmigo to translate the raw data downloaded from the MEMS caps into percent adherence. Only 2 patients underwent a change in regimen during the study period. One patient was excluded because of a clinical decision to stop ocular hypotensive therapy in favor of surgery. The other patient underwent a change in medication class and was excluded to avoid introducing regimen change as a confounding variable. Daily adherence was defined as

$$\frac{\text{Number of doses taken}}{\text{Number of doses prescribed}} \times 100.$$

The 24-hour period that defined 1 day was set arbitrarily to start at 3 AM and to end at 2:59 AM to minimize the impact of variability in bedtime hour (e.g., if a patient instilled a bedtime dose at 12:25 AM, this dose would be counted even though it was technically obtained on the next day). Additional instillations were excluded from the calculation, but no penalty was applied. Penalties also were not applied for doses obtained outside the prescribed time frame (e.g., we did not apply any penalization for an eye drop instilled at 3 PM that was prescribed to be taken in the morning). When 2 or more medications were prescribed, an overall percent adherence score was calculated by averaging the mean adherence for each medication.

Statistical Analysis

Two metrics of medication adherence were assessed to capture both its static and dynamic components. Mean adherence was used to provide a summary of adherence over a period of time, and the slope was used to quantify the extent to which adherence changed over time. The breakpoint identified using the segmented regression (described below) was used as a cutoff point in all analyses.

Change in Adherence Slope Using Segmented Regression Analysis. We performed segmented regression analyses to determine whether the COVID-19 pandemic impacted the slope of adherence over time using the segmented package in R (R Foundation for Statistical Computing, Vienna, Austria).[17,18] We selected a "slope change following a lag" impact model,[19] which is suitable when a delayed change occurs after an event. In this study, we assumed a priori that a delay would occur between the declaration of the pandemic and its resulting impact on medication adherence. We used ordinary least square linear regression because mean adherence—the outcome variable—is continuous. A 2-tailed Davies test[20] was performed to determine whether the slopes of the segments before and after the onset of the pandemic were significantly different from each other. Autocorrelations in the data were assessed using the Durbin-Watson test. The output of this test ranges from 0 to 4, and values between 1.5 and 2.5 are considered normal.

Change in Percent Mean Adherence. Mean adherence was calculated for each patient in the period before and after the declaration of the pandemic. The percent change in adherence was calculated as

$$\frac{\%\text{ Mean adherence after the COVID declaration} - \%\text{ Mean adherence before the COVID declaration}}{\%\text{ Mean adherence before the COVID declaration}} \times 100.$$

Negative values indicated a worsening of adherence in the 150 days after the onset of the pandemic. We compared the percent change in adherence between these periods using the Wilcoxon signed-rank test. This analysis was performed using JMP statistical software version 15.2.0 (SAS Institute, Inc).

Factors Associated with Change in Adherence. We assessed the association between demographic, clinical, and psychosocial factors and change in percent mean adherence, as well as change in adherence slope, defined as the difference between the slopes in the period before and after the segmentation point. The demographic factors included age, race, sex, educational level, marital status, employment, and household income (patients who declined to answer this question were excluded from this analysis). Race was self-reported based on the categories of the United States Office of Management and Budget's Revisions to the Standards for the Classification of Federal Data on Race and Ethnicity. In addition, patients could select "unknown," "other (specify)," and "decline to answer."

Clinical factors included mean adherence in the period before the segmentation point, as well as regimen complexity, operationalized as the number of daily eye drop instillations multiplied by the number of prescribed ocular hypotensive medications.[21] The number of comorbidities was also included. Psychosocial factors included resilience, illness perception, coping, and self-efficacy for adherence. The 25-item Connor-Davidson resilience scale was used to measure psychological resilience.[22] Coping was assessed using the 66-item Ways of Coping questionnaire,[23] which provides a total score as well as raw scores (frequency of effort) and relative scores (percentage of effort) for the following 8 subscales: confrontive coping, distancing, self-controlling, seeking social support, accepting responsibility, escape-avoidance, planful problem solving, and positive reappraisal. Each subscale represents a specific coping strategy. Illness perception was assessed with the 9-item Brief Illness Perception questionnaire.[24] Each question is a subscale that assesses a specific dimension of illness perception: consequences, timeline, personal control, treatment control, identity, coherence, emotional representation, and illness concern. Self-efficacy was measured using the 10-item Glaucoma Medication Adherence Self-Efficacy scale,[25] which assesses patients' confidence in their ability to adhere to their prescribed ocular hypotensive medications. The data from each questionnaire were examined carefully, and when response sets were identified, these data were excluded from the analyses. Response sets refer to the tendency of some participants to use a pattern of responses regardless of the question asked (e.g., circling 0 for all questions on a questionnaire) and affect the validity of the results because the answers do not reflect the views of the respondents.

Results

Demographic and clinical data for the 79 participants included in the study are presented in Table 1. Seventy-one patients (90%) had glaucoma in both eyes and 43 patients (54%) were prescribed only 1 glaucoma medication. One patient selected "other (specify)" for race and reported being Indian. This participant was excluded from the analyses on race.

Change in Adherence Slope Using Segmented Regression Analysis

Figure 1 shows the segmented regression analysis applied to the daily mean adherence data. The optimal segmentation point was at 28 days after the declaration of the pandemic, April 10, 2020. The slope before the segmentation was 0.006%/day ($P = 0.116$) compared with −0.041%/day ($P < 0.001$) after the segmentation.

Table 1. Summary of the Demographic, Clinical, and Psychosocial Data for the Participants Included in This Study

Variable	Data
Demographic data	
Age, (yrs)	71 ± 8
Race	
White	41 (52)
Black	37 (47)
Other	1 (1)
Gender	
Women	43 (54)
Men	36 (46)
Education	
High school or less	7 (9)
Higher than high school	72 (91)
Marital status	
Married	52 (66)
Not married	27 (34)
Employment	
Employed full-time	4 (5)
Not employed full-time	75 (95)
Household income	
≤$60 000	30 (38)
>$60 000	21 (27)
Declined to answer or unknown	28 (35)
Clinical data	
Comorbidities	
≤2	46 (58)
≥3	33 (42)
No. of prescribed glaucoma medications, median (IQR)	1 (1)
No. of prescribed eye drops per day, median (IQR)	2 (2)
Regimen complexity, median (IQR)	2 (5)
Psychosocial data	
Resilience, median (IQR)	88 (14)
Coping, median (IQR)	59.5 (87.25)
Coping (response sets excluded; n = 58)	71.8 (64.3−79.3)
Glaucoma illness perception	28.5 (25.9−31.2)
Glaucoma medication self-efficacy (n = 75), median (IQR)	30 (3)

IQR = interquartile range.
Data are presented as no. (%), mean ± standard deviation, or mean (95% confidence interval), unless otherwise indicated.

The Davies test showed that the difference between these slopes (−0.047) was significant ($P < 0.001$). The Durbin-Watson test yielded a value of 1.6, indicating that adjustments for autocorrelations were not needed.

Percent Change in Mean Adherence

Figure 2 shows the percent change in mean adherence in the period after the breakpoint compared with the period before this breakpoint. Compared with baseline adherence, the median percent change in mean adherence (median, interquartile range [IQR]: 0%, 5.1%) was not significantly different from zero (P = 0.17). The outliers indicate that on the individual level, some patients showed marked improvement, whereas others showed marked worsening. One patient, for example, improved by 72%, with a mean adherence of 32% in the period before the breakpoint increasing to 55% in the period after the breakpoint. Adherence worsened in 38 patients (48%), improved in 38 patients (48%), and remained at the same level in 3 patients (4%).

Factors Associated with Change in Mean Adherence

Table 2 shows the P values for the univariate associations between adherence and each of the demographic, clinical, and psychosocial factors. Mean adherence in the period before the segmentation breakpoint was significantly worse in Black patients (median, IQR: 80.6%, 36.2%) compared with White patients (median, IQR: 97.2%, 8.7%; chi-square, 15.4; P = 0.0004). Mean adherence in this period also was positively associated with resilience (Spearman $\rho = 0.25$; P = 0.03) and negatively associated with glaucoma illness perception (Spearman $\rho = -0.32$; P = 0.006). This suggests that lower resilience and having a more threatening view of glaucoma were associated with poorer adherence. None of the factors were associated with the slope in adherence before the breakpoint.

Factors Associated with Change in Adherence Slope

Change in adherence slope was positively associated with resilience (Spearman $\rho = 0.34$; P = 0.002) and negatively associated with the raw scores (Spearman $\rho = -0.36$; P = 0.006) and relative scores (Spearman $\rho = -0.35$; P = 0.008) for confrontive coping (Table 3). In contrast, change in slope was positively associated with the relative score of the planful problem solving (Spearman $\rho = 0.30$; P = 0.02). Coping data were available for 58 of the 79 patients included in this study. The results for each subscale of illness perception are presented in Table S4 (available at www.aaojournal.org) and show no associations with pandemic-related change in adherence. Similarly, glaucoma medication self-efficacy was not associated with change in adherence.

Discussion

This study documents an adverse impact of the COVID-19 pandemic on adherence to ocular hypotensive medication in patients with POAG. Similar reports have emerged in other nonrespiratory diseases,[2,3] whereas an improvement in adherence was reported in patients with chronic obstructive pulmonary disease.[4] Deterioration of other health behaviors has also been observed during the pandemic. For example, using cell phone data from more than 1.5 million people from 10 large United States cities, Hunter at al[26] identified a large reduction in both walking frequency and walking distance during the first 3 months of the pandemic. Such changes are important because they compound the negative impact of the pandemic on overall health and may persist beyond the pandemic.

The rate of decline in adherence observed in this study translates to a nontrivial reduction of 15% over the course of 1 year, moving overall mean adherence from 83.6% (before the pandemic) to 68% 1 year later. This level, well below the commonly accepted 80% threshold for good adherence, places patients at risk of vision loss. Given that ocular hypotensive medications are the first line of treatment for POAG, many patients are likely to have experienced a reduction in medication coverage during the pandemic. The long-term implications are concerning because poor adherence has been associated with visual field progression.[8] By modeling self-reported data obtained from the Collaborative Initial Glaucoma Treatment Study, Newman-Casey et al[8]

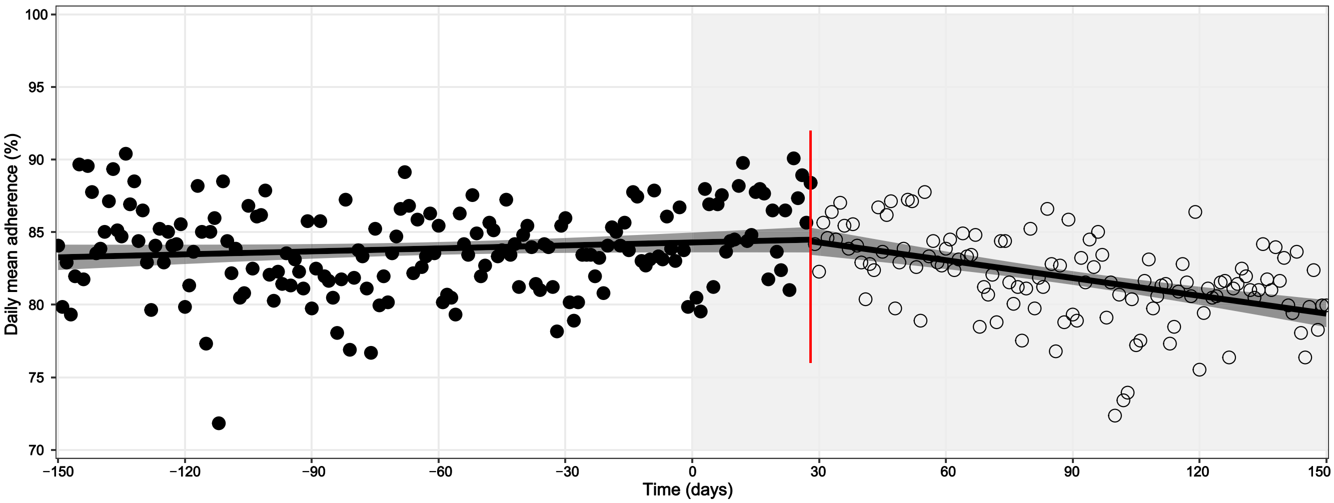

Figure 1. Segmented regression analyses performed on daily mean adherence data. The segmented regression and 95% confidence interval are presented for the periods before (solid circles) and after (open circles) the segmentation (red vertical line). Mean adherence for each of the 300 days included in the study is represented by 1 data point (circle) on the graph. Time 0 represents the day of the coronavirus disease 2019 declaration in the United States. The segmentation occurred at 28 days after time 0. The difference in slopes before and after the segmentation was significant.

showed an increasingly steeper slope for mean deviation over time for patients who reported missing medication doses at 0%, 33%, 50%, and 66% of the Collaborative Initial Glaucoma Treatment Study visits.

Associations between resilience—defined as the process of positive adaptation to adversity—and medication adherence were reported previously in some chronic diseases,[10,27,28] but not in glaucoma. The positive association we observed between resilience and medication adherence in the period before the pandemic provides evidence for a protective role of resilience against nonadherence to ocular hypotensive medication. The pandemic offered an opportunity to assess whether higher resilience would allow patients to maintain the baseline level of adherence in the face of the adversity imposed by the pandemic. We also found a positive association between resilience and the change in adherence slope. These associations suggest that resilience may be a promising target for improving adherence. We found that higher levels of planful problem solving also enhanced patients' ability to maintain their medication regimen during the pandemic. In contrast, we found that confrontive coping, defined as taking aggressive efforts to change a situation, to the point of being risky and antagonistic, was negatively associated with change in adherence slope. In the context of the pandemic, individuals whose most frequent and predominant style was confrontive coping may have had diminished ability to focus on the medication regimen.

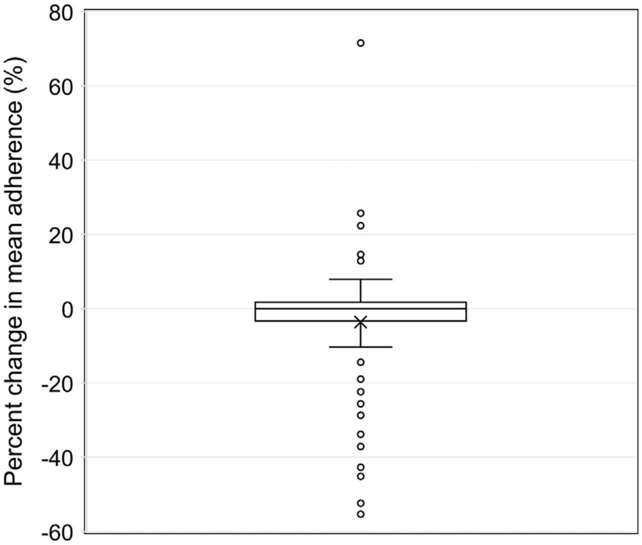

Figure 2. Percent change in mean adherence in the period following the onset of the pandemic. Box-and-whisker plot depicting the percent change in mean adherence after the breakpoint identified by the segmented regression. The top and bottom of the boxes show the 25th (first quartile) and 75th (third quartile) percentiles, respectively. The line inside the box indicates the location of the median (second quartile). The X inside the box indicates the location of the mean. The whiskers represent the minimum and maximum values, after excluding the outliers. The dots represent outliers.

Self-described race was not associated with percent change in mean adherence, nor with the decline in adherence observed during the pandemic. However, consistent with previous reports both in glaucoma[29] and other chronic diseases,[30] mean adherence was significantly lower in this group before the pandemic (74.3% compared with 92% in White patients; chi-square, 14.4; $P = 0.0001$). This difference may be the result of factors such as the stress generated by the experience of systemic or individual racial bias.[31] Other social determinants of health, such as demographic factors, health status, out-of-pocket costs, convenience of refilling prescriptions, and socioeconomic status, that are captured by the construct of race, also may be involved,[32] although a large study of privately insured patients with type 2 diabetes, hypertension, and hyperlipidemia showed

Table 2. Associations between Demographic, Clinical, and Psychosocial Factors and Mean Adherence and Slope before the Pandemic and 2 Metrics of Change in Adherence after the Onset of the Pandemic

	Adherence before Breakpoint				Change in Adherence			
	Mean Adherence		Slope		% Change in Mean Adherence		Slope	
Variable	Coefficient	P Value	Coefficient	P Value	Coefficient	P Value	Coefficient	P Value
Demographic factors								
Age	0.14	0.21*	−0.10	0.40*	0.04	0.73	0.17	0.14*
Race (n = 78)	14.43	**0.0001**†	3.56	0.06†	1.59	0.21†	1.14	0.29†
Sex	0.35	0.55†	3.34	0.07†	1.51	0.28†	0.26	0.61†
Education	0.002	0.97†	0.15	0.70†	1.50	0.22†	0.11	0.74†
Marital status	0.70	0.40†	0.06	0.81†	0.81	0.37†	0.11	0.74†
Employment	0.12	0.73†	0.67	0.41†	0.18	0.67†	1.12	0.29†
Household income (n = 51)	0.74	0.39†	1.13	0.29†	0.23	0.63†	0.50	0.48†
Clinical factors								
Mean adherence before breakpoint	1.00	<0.001	0.03	0.77*	0.03	0.81*	0.14	0.21*
Regimen complexity	0.03	0.79*	−0.16	0.15*	−0.07	0.55*	0.05	0.62*
Comorbidities	2.52	0.11†	0.44	0.51†	2.45	0.12†	0.13	0.72†
Psychosocial factors								
Resilience	0.25	**0.03***	0.06	0.59*	−0.09	0.43*	0.34	**0.002***
Coping (n = 58)	−0.21	0.12*	0.002	0.99*	−0.08	0.56*	−0.26	0.05*
Glaucoma illness perception	−0.32	**0.006***	0.06	0.62*	−0.04	0.75*	−0.09	0.46*
Glaucoma medication self-efficacy	0.17	0.14*	0.14	0.23*	0.14	0.23*	0.13	0.27*

Boldface indicates statistical significance.
*Spearman ρ.
†Wilcoxon test.

that the difference in adherence between Black and White patients was not eliminated after adjusting for these factors.[33] Regardless, in the context of the COVID-19 pandemic in glaucoma, further reductions in suboptimal baseline levels of adherence portend higher rates of disease progression in Black patients. This is particularly concerning in this population, which is disproportionately affected by POAG and is more likely to experience POAG-related visual impairment.[34] As can be appreciated in Figure S3 (available at www.aaojournal.org), which shows

Table 3. Associations between Each of the Subscales of the Ways of Coping Questionnaire and Mean Adherence and Slope before the Pandemic and 2 Metrics of Change in Adherence after the Onset of the Pandemic

	Adherence before Breakpoint				Change in Adherence			
	Mean Adherence		Slope		% Change in Mean Adherence		Slope	
Variable	Coefficient	P Value	Coefficient	P Value	Coefficient	P Value	Coefficient	P Value
Raw scores								
Confrontive	−0.27	**0.04***	0.03	0.84*	−0.11	0.42*	−0.36	**0.006***
Distancing	0.06	0.67*	0.15	0.27*	0.26	0.05*	−0.006	0.96*
Self-controlling	−0.21	0.12*	0.02	0.85*	−0.09	0.49†	−0.06	0.65*
Seeking social support	−0.18	0.18*	0.08	0.54*	0.03	0.83*	−0.23	0.09*
Accepting responsibility	−0.20	0.13*	−0.12	0.38*	−0.10	0.44*	−0.23	0.09*
Escape-avoidance	−0.23	0.08*	0.05	0.69*	−0.18	0.19*	−0.25	0.06*
Planful problem solving	−0.20	0.13*	0.07	0.58*	0.02	0.87*	0.12	0.36*
Positive reappraisal	−0.21	0.11*	−0.22	0.10*	−0.18	0.19*	−0.16	0.23*
Relative scores								
Confrontive	−0.16	0.22*	0.08	0.54*	−0.03	0.80*	−0.35	**0.008***
Distancing	0.29	**0.02***	0.09	0.52*	0.19	0.16*	0.21	0.12*
Self-controlling	0.14	0.29*	−0.005	0.97*	−0.10	0.46*	0.22	0.10*
Seeking social support	−0.03	0.81*	0.09	0.52*	0.10	0.47*	−0.10	0.45*
Accepting responsibility	−0.10	0.48*	−0.15	0.27*	−0.08	0.58*	−0.17	0.21*
Escape-avoidance	−0.09	0.50*	0.10	0.47*	−0.11	0.43*	−0.20	0.14*
Planful problem solving	−0.002	0.99*	0.08	0.56*	−0.02	0.87*	0.30	**0.02***
Positive reappraisal	−0.09	0.51*	−0.27	**0.04***	−0.17	0.21*	−0.07	0.61*

Boldface indicates statistical significance.
*Spearman ρ.
†Wilcoxon test.

segmented regressions performed in Black and White patients separately, the levels of adherence observed in Black patients are likely sufficiently low to threaten sight over time. Resilience, which was positively associated with change in slope, was significantly lower in Black patients (median, 82; IQR, 16) compared with White patients (median, 90; IQR, 13; chi-square, 7.05; $P = 0.03$).

Although global crises are relatively rare, national emergencies and local crises occur more frequently. The development of effective approaches to ensure stable levels of access to medications would have special impact in these instances. The segmented regression identified a lag of 28 days in this study, suggesting that the decline in adherence began approximately 1 month after the declaration of the pandemic. This lag is important because it may provide a critical intervention window during which clinicians can reach out to patients and provide alternative ways to obtain medications to minimize nonadherence in future crises.[35] In a recent *Journal of the American Medical Association* viewpoint article, Alexander and Qato[36] proposed several strategies that could be implemented to ensure continued access to medication, including expanding the capacity for mail-order and home delivery. Newman-Casey et al[37] reported that patients who used mail orders and pharmacy pick-ups were 90% more likely to maintain good adherence over a 4-year period, emphasizing the potential benefit of expanding this type of access to medication. Until such improvements are made, providers should maintain awareness of the negative impact of the pandemic on adherence and should highlight this during clinic visits. The patient–provider relationship was previously described as a facilitator of good adherence[38] and is a promising vehicle for identifying barriers as they arise in patients, as well as for developing individualized solutions.

In some patients, we observed a change in the timing of eye drop instillations in the periods before and after the onset of the pandemic. Figure S4A (available at www.aaojournal.org) shows an example of a patient whose adherence was stable during the study period, changing from 62% to 59%. However, the instillation timing of this patient became starkly less consistent after the onset of the pandemic. This irregularity may translate into poorer medication coverage, which may impact visual outcomes in the future. Figure S4B presents the data for the patient whose adherence improved by 72% (the outlier observed in Fig 2). Although adherence greatly improved in this patient after the pandemic was declared, only approximately half of the prescribed medication was taken, and at irregular times. Taken together, these anecdotal examples illustrate that the impact of the pandemic on medication adherence is complex and that its manifestation varies considerably among patients.

This study allowed us to assess the impact of the pandemic on adherence to ocular hypotensive medication and has several strengths. The use of a controlled interrupted time series design in which measurement of the outcome variable—adherence—remained stable throughout the study period is an important strength of the study. Patients were using a MEMS device before the start of the study, which provided an excellent baseline, and no new protocols were initiated during the pandemic. Another strength includes the use of MEMS devices as objective surrogate measures of medication adherence. Although direct observation of medication adherence, either in person or wirelessly, would be ideal, these approaches are more intrusive and alert patients to the fact that their adherence is monitored. This may introduce reactivity bias that can impact patient behavior and can translate into higher levels of adherence.[39] The use of MEMS devices is less invasive than direct observation, provides more accurate estimates than self-report, and provides finer granularity compared with medication possession ratio. Additionally, evidence shows that the Hawthorne effect, another type of reactivity bias in which patient adherence initially improves when electronic monitoring is used, decreases after approximately 2 months of using the devices.[40] In this study, adherence was monitored for at least 2 months before study onset in 89% of the patients and was monitored for at least 1 month before study onset in all patients.

This study also has several limitations. First, the interrupted time series design is vulnerable to the co-occurrence of other events that can impact the outcome variable. For example, in the 150 days after the declaration of the COVID-19 pandemic, racial tension that rose in the United States may have contributed to the decline in adherence. Second, the presence of a ceiling effect in some patients precluded the identification of a possible improvement in adherence after the onset of the pandemic. Third, we did not perform an assessment of seasonality, which is recommended in interrupted time series designs.[41] This study did not span a full year, and the typical activities associated with each season were affected drastically during the pandemic. Fourth, the data on the demographic and psychosocial variables were collected at the baseline visit of the parent study. Fifth, the study was not powered to identify covariates associated with a change in adherence. Therefore, it is possible that some of variables included in this study did not reach statistical significance because of insufficient statistical power. Sixth, the study relied on self-report to obtain demographic variable data, which is a method frequently used in clinical studies, but also one that can introduce bias. Seventh, this was a single-site study performed in Jefferson County, Alabama, which was the county most impacted by the pandemic statewide and had 13 530 cumulative cases of COVID-19 and 246 deaths by August 10, 2020, the last day included in this study. During the study period, the maximum number of new cases recorded was 285 on July 18, 2020. The intensity of the COVID-19 pandemic varied across the United States over time and the pattern of infection rates must be taken into consideration when interpreting our results and their generalizability. Our study, unfortunately, is not powered to assess changes in adherence associated with spikes and troughs in the number of cases, hospitalizations, or deaths. Eighth, although 2 patients received diagnoses of COVID-19 during the study period, no significant change in slope was observed in either patient. This suggests that the observed decline in adherence was not a result of the COVID-19 diagnoses. Finally, the results of the study may not generalize to patients with advanced glaucoma because these patients were not represented in this study.

In conclusion, our findings suggest that medication adherence was affected adversely by the COVID-19 pandemic. This reduction was associated with lower psychometric measures of resilience and more confrontational coping strategies. This may translate into ocular complications and poorer visual outcomes in the months and years after the pandemic. Although the timing and speed of the eventual reversal to the levels of adherence observed before the pandemic is difficult to predict, the recent surge of the Delta variant suggests an extended recovery period. Therefore, clinicians, in glaucoma and other nonrespiratory specialties, should have a raised awareness of this collateral consequence and should consider placing greater emphasis on medication adherence, providing information to patients about alternate ways to ensure continued access to medications, and recognizing the additional burden placed on patients because of the COVID-19 pandemic.

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Abbreviations and Acronyms:
COVID-19 = coronavirus disease 2019; **D** = diopter; **dB** = decibels; **IQR** = interquartile range; **MEMS** = Medication Event Monitoring System; **POAG** = primary open-angle glaucoma.

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