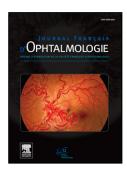


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Evaluation of Medication Adherence of Glaucoma Patients During the Covid-19 Pandemic

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Evaluation of Medication Adherence of Glaucoma Patients During the Covid-19 Pandemic Evaluation of Medication Adherence of Glaucoma Patients During the Covid-19 Pandemic

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Abstract

Purpose: To evaluate changes in the medication adherence of glaucoma patients during the Covid-19 pandemic and the factors influencing medication adherence.

Materials-Methods: This cross-sectional study included a total of 197 glaucoma patients who were followed for at least six months in the Glaucoma Unit of the Ophthalmology Department of Inonu University, Faculty of Medicine. Patients were given a 28-item questionnaire, including the eight-item Morisky Medication Adherence Questionnaire, to evaluate medication adherence. Demographic and clinical data were recorded. p<0.05 was considered statistically significant. **Results:** Interruption of glaucoma clinic visits during the pandemic was reported by 82 (41.6%) patients. Non-adherence was reported by 56 patients (28.4%) (95% confidence interval: 22.1–34.7). For these patients, the most common reasons for nonadherence were forgetfulness (50%), the inability to receive a prescription for the drug (10.7%) and being busy (10.7%). Factors influencing non-adherence were determined to be younger age, female gender, interruption of glaucoma clinic visits and high-income levels (p<0.05).

Conclusion: Interruption of glaucoma clinic visits during the Covid-19 pandemic and the resulting inability to have medications prescribed resulted in patient nonadherence with medication use.

Abstract

Objectif : évaluer les changements dans l'adhésion aux médicaments des patients atteints de glaucome pendant la pandémie de Covid-19 et les facteurs influençant l'adhésion aux médicaments.

Matériaux-Méthodes : Cette étude transversale a inclus un total de 197 patients atteints de glaucome qui ont été suivis pendant au moins six mois dans l'unité de glaucome du service d'ophtalmologie de l'université Inonu, faculté de médecine. Les patients ont reçu un questionnaire en 28 points, dont le questionnaire de Morisky sur l'adhésion aux médicaments en huit points, pour évaluer l'adhésion aux médicaments. Les données démographiques et cliniques ont été enregistrées. p<0,05 a été considéré comme statistiquement significatif.

Résultats : 82 patients (41,6 %) ont déclaré avoir interrompu leurs visites à la clinique du glaucome pendant la pandémie. Le non-respect du traitement a été signalé par 56 patients (28,4 %) (intervalle de confiance à 95 % : 22,1-34,7). Pour ces patients, les raisons les plus courantes de la non-observance étaient l'oubli (50 %), l'impossibilité de recevoir une ordonnance pour le médicament (10,7 %) et le fait d'être occupé (10,7 %). Les facteurs influençant la non-

observance ont été déterminés comme étant un âge plus jeune, le sexe féminin, l'interruption des visites à la clinique du glaucome et les niveaux de revenus élevés (p<0,05).

Conclusion : L'interruption des visites dans les cliniques de glaucome pendant la pandémie de Covid-19 et l'impossibilité qui en a résulté de se faire prescrire des médicaments ont entraîné la non-observance de la médication par les patients.

Key Words: glaucoma, adherence, compliance, questionnaire, medication **Mots-clefs :** glaucome, adhésion, conformité, questionnaire, médicaments

Introduction

Among the previous epidemics of coronaviruses (CoV), which are enveloped positive-sense RNA viruses that primarily target the human respiratory system, are Severe Acute Respiratory Syndrome (SARS-CoV) and Middle East Respiratory Syndrome (MERS-CoV)¹. Following the emergence of an unprecedented outbreak of pneumonia of unknown etiology in the Wuhan province of China in December 2019, the causative pathogen was identified as a novel coronavirus in January 2020. This virus, which was named as COVID-19 by the World Health Organization (WHO), is a betacoronavirus termed as SARS-CoV-2 that involves the lower respiratory tract and presents as pneumonia in humans^{2,3}. On January 30, 2020, the WHO declared the COVID-19 epidemic in China to be a Public Health Emergency of International Concern that poses a high risk for countries with vulnerable health systems⁴. Despite stringent global containment and quarantine efforts, Covid-19 evolved into a global pandemic and continues to claim thousands of lives.

Glaucoma is one of the leading causes of irreversible blindness worldwide. The prevalence of glaucoma is gradually increasing; 76 million individuals globally were affected in 2020 and 111.8 million individuals are expected to be affected by 2040⁵. Reduction of intraocular pressure (IOP) with medical or surgical treatment is a proven treatment for slowing or stopping the progression of glaucoma^{6,7}. Medical therapy is the most common approach in the treatment⁸. The treatment of glaucoma, a chronic progressive disorder, requires adherence with a long-term treatment, which is a difficult task for the patient. However, rates of using the prescribed medication are quite low among these patients in the long term. A retrospective cohort study including 1234 recently diagnosed open-angled glaucoma patients revealed that only 15% of the patients showed good adherence with the treatment permanently over a 4-year follow-up period⁹. Due to the covid-19 pandemic, certain limitations are in effect in Turkey as are throughout the world, and routine polyclinic examinations has been limited in this period due to both the risk of transmission and the overcrowding in hospitals. This study aimed to evaluate the changes in the medication adherence of glaucoma patients during the Covid-19 pandemic and the factors influencing medication adherence.

Materials and Method:

This study was approved by the local Institutional Review Board (IRB number: 2020/849, date: 06/16/2020) and written informed consent was obtained from each subject. The study was performed in adherence to the Declaration of Helsinki.

Participants and Sample Selection

This cross-sectional study included 197 glaucoma patients who were followed up for at least 6 months in the Glaucoma Unit of the Ophthalmology Department of Inonu University, Faculty of Medicine. All patients who reported receiving medications (\geq 1) to reduce IOP and who volunteered to participate in the study between July-September 2020 were given a questionnaire form in the clinic waiting room. Trained personnel were present to assist the subject in completing the questionnaire form where necessary. The sample size of the research needed to assess adherence to topical glaucoma medications was calculated to be 188 using the single population proportion formula by considering 95% confidence interval (CI), marginal error (w) = 7%, p = 0.4 (prevalence of non-adherence at Gulhane Medical School in Turkey)¹⁰ and z value of 1.96.

The primary outcome of this study was medication adherence during the Covid-19 pandemic. The secondary outcomes were interruption of glaucoma clinic visits during the pandemic, the progression of vision loss and visual field loss, the factors influencing medication adherence.

Questionnaire

The printed questionnaire consisted of 28 item and its completion took approximately 20 minutes. The questionnaire was composed of four sections: 1) demographic information; 2) questions regarding the Covid-19 pandemic; 3) the 8-item Morisky Medication Adherence Scale (MMAS)¹¹; and 4) barriers to medication adherence. Demographic information included age, gender, education level, the presence of social support, monthly income levels and whether the patients have social security. The second section of the questionnaire asked patients if they or their relatives had been infected with Covid-19 and if their glaucoma clinic visits had been interrupted during the Covid-19 pandemic. In the third section of the questionnaire, the subjects completed the 8-item MMAS, which is a validated tool assessing self-reported adherence¹². The MMAS has been used to measure adherence in a wide variety of chronic conditions by being adapted for use with the relevant disease (generally including asymptomatic conditions such as diabetes and osteoporosis)^{13,14}. It was applied for glaucoma in this study. The reliability of the

Turkish-translated form of the scale was previously evaluated and confirmed by another study¹⁵. The fourth section of the questionnaire probed the causes of medication nonadherence. Clinical data of the patients was evaluated by the same researcher (Dr. AC). Patients' best corrected visual acuity (BCVA), IOP, visual field assessment and mean deviation (MD) values at the last visit, glaucoma type, length of glaucoma diagnosis, number of glaucoma medications, concomitant systemic diseases were recorded. Visual acuity was evaluated using the Snellen chart and the data were converted into logMAR for statistical analysis. Visual field was evaluated using Humphrey standard automated perimetry (Carl Zeiss Humphrey 750i Field Analyzer Perimeter, Germany).

A multivariate logistic regression analysis was conducted to evaluate the relationship between non-adherence with glaucoma medication and the variables predicted to be important. The predictor variables evaluated in this study included age, gender, length of glaucoma diagnosis, the presence of concomitant systemic diseases, interruption of glaucoma visits and monthly income levels.

In the evaluations, BCVA and MD values were determined based on the affected eye in those with unilateral disease or the better-seeing eye in those with bilateral disease. BCVA is classified according to the International Council of Ophthalmology's classification of visual acuity; normal vision: 6/6—6/18, low vision: 6/24—counting finger (CF) @1 m, and blindness: CF @0.5 m— no light perception (NLP)¹⁶.

Statistical Analysis

The analyses were performed using the IBM SPSS Statistics 22.0 software. Normality of distribution was tested using the Kolmogorov-Smirnov test. Continuous data were reported as mean \pm standard deviation (SD) or median (min-max) values. Categorical data were reported as count (n) and percentage (%). Statistical analyses used the following tests where appropriate: Mann-Whitney U test, Pearson chi-square test, Yates' corrected chi-square test, Fisher's exact chi-square test. For odds ratio estimates, multivariate logistic regression analysis was performed. p<0.05 was considered statistically significant.

The preliminary results of this study were presented at the 55th Turkish Ophthalmology Society National Congress, 3-7 November 2021, Antalya/Turkey as a poster presentation.

Results:

This study enrolled 197 patients in total, of whom 108 (54.8%) were male and 89 (45.2%) were female. Most of the patients (173 patients, 87.8%) had good vision of 6/18 or better in at least one eye. One-hundred and sixty-one of the cases (81.7%) used medications for both eyes. Of the patients, 69.03% (136 patients) used two or more medications. One-hundred and fifty-two patients (77.2%) had primary open angle glaucoma (POAG), 28 patients (14.2%) had pseudoexfoliation glaucoma and 17 patients (8.6%) had other (congenital, uveitic, traumatic, neovascular, etc) types. Ninety-nine patients (50.3%) reported having adequate knowledge about glaucoma while 98 (49.7%) reported not having adequate knowledge. Concomitant systemic diseases (often diabetes and hypertension) were reported by 125 patients (63.5%) and these patients reported having to use medications regularly. Only two patients (1%) had been infected with Covid 19. Compliance with social isolation was reported by 194 (98.5%) patients. Interruption of glaucoma polyclinic visits during pandemic was reported by 82 patients (41.6%). Table 1 shows the comparison of the responses of patients adherent to glaucoma treatment versus those nonadherent to questions regarding the Covid-19 pandemic.

Of the patients, 163 (82.8%) were married and 34 (17.2%) were single. Ten patients (5.1%) lived alone while 187 patients (94.9%) lived with family. The education level was reported as no education for 26 patients (13.2%), elementary school for 108 patients (54.8%), middle school-high school graduate for 38 patients (19.3%) and university graduate for 25 patients (12.7%). Thirty-seven patients (18.8%) were actively employed, 111 patients (56.3%) were retired, and 49 patients (24.9%) were unemployed. Twenty-eight patients (14.2%) had a monthly income lower than 1000TL (Turkish Lira), 155 (78.7%) had a monthly income of 1000-5000TL, 8 patients (4.1%) had a monthly income higher than 5000TL. Six patients (3.0%) did not provide a response to the item regarding monthly income. Of the patients (26%) visited our clinic for follow-up from other cities. Presence of social security was reported by 185 patients (93.9%) while 12 patients (6.1%) did not have social security. Table 2 and 3 show demographic and clinical characteristics of adherent and nonadherent patients.

Of the patients, 56 (28.4%) (95% CI: 22.1–34.7) were nonadherent based on the self-reported MMAS (morisky score≥2 higher likelihood). Forgetfulness (28 patients, 50%) was the most common reason reported by nonadherent patients. The reason for nonadherence was reported as

the inability to receive a prescription for the drug by six patients (10.7%); busy work schedule by six patients (10.7%); not obtaining the expected benefit from the drug by three patients (5.3%); negligence by three patients (5.3%); unavailability of the drug, being outside home, using too many medications by two patients (3.6%) each; cost, avoiding the side effects associated with the medications, belief that medical treatment will not be helpful and not knowing the importance of regular medication use by one patient (1.8%) each (Table 4).

The median age of the patients was 63 (18-88) and 58 (22-93) years, the median duration of glaucoma was 6 (0.5-40), 6 (1-20) years in adherent and non-adherent groups, respectively. The median BCVA of the eyes was 0 (0-1.92) logMAR and 0 (0-1.52) logMAR, the median MD value of the patients was -2.49 (-31-5.19) and -1.71 (-30.33-1.05), the median number of glaucoma medications used was 2 (1-4) and 2 (1-3) in adherent and non-adherent groups, respectively (Table 2).

Factors influencing medication nonadherence were determined as age, gender, monthly income levels and interruption of glaucoma clinic visits. Nonadherent patients were significantly younger than adherent patients (p<0.05). Females were more nonadherent compared with males (p<0.05). Those with an income higher than 5000TL were more nonadherent than those with an income level between 1000-5000TL (p<0.05). Patients whose glaucoma visits were interrupted once or more were more nonadherent that those whose visits were not interrupted, with statistical significance (p<0.05). Number of glaucoma medications, length of glaucoma diagnosis, presence of concomitant systemic diseases, BCVA, educational status and living alone were not found to influence medication adherence.

The multivariate logistic regression model demonstrated a good fit to the mentioned data (age, gender, interruption of glaucoma visits, monthly income levels, length of glaucoma diagnosis and the presence of concomitant systemic diseases) (Hosmer and Lemeshow Test; p=0.498). According to the results of the multivariate logistic regression, female gender, younger age, high monthly income levels and interruption of glaucoma visits were determined to be significantly correlated with nonadherence. The likelihood of nonadherence was found to be 2.75 times higher for females compared with males (AOR=2.75, (%95 CI: 1.32-5.71)) and 1.03 times higher for younger patients compared with older patients (AOR=1.03, (%95 CI:0.94-0.99)). The likelihood of nonadherence was determined to be 6.38 times higher for patients with an income higher than 5000TL compared with patients with an income level between 1000-5000TL (AOR=6.38, (%95

CI:1.01-40.39)) and 2.38 times higher for patients with interrupted glaucoma visits compared with patients without interrupted visits (AOR=2.38, (%95 CI:0.21-0.85)). Table 5 shows the results of multivariate logistic regression analysis of factors influencing medication nonadherence.

Discussion

SARS-CoV-2 infections, the coronavirus disease 2019 (Covid-19) outbreak, have spread to millions of individuals worldwide and were accepted as a global medical emergency. The global impact of this viral infection continues to be a cause for concern as the number of confirmed cases continue to increase internationally^{3,4}. The COVID-19 pandemic has radically changed the lives of individuals. Since the detection of the first Covid-19 case in Turkey in March 2020, quarantine has been used as a tool in the battle against Covid-19. At times, routine polyclinic examinations at hospitals were limited to urgent and symptomatic patients. Unfortunately, routine polyclinic examinations of patients with chronic diseases were also interrupted in this period.

Increased medication adherence is considered as an important factor for better management of glaucoma, which is a chronic and progressive disease. However, patients have trouble in adhering to the prescribed glaucoma treatments and non-adherence is probably the most significant factor contributing to glaucoma-related vision loss. A meta-analysis reported that nonadherence with medical treatment varied between 5-80%¹⁷. One of the reasons underlying such high variability in the reported rates of nonadherence is that different methods were used in the assessment of nonadherence. It was shown in a study that self-reported nonadherence rates are lower than those measured with electronic dosage monitors¹⁸. In the present study, which used the MMAS, a self-reported assessment of nonadherence, the rate of nonadherence was found as 28.4%. This rate is consistent with the rates reported in the studies using self-reported tests before the pandemic^{11,17,19-21}. In a study conducted in a single center in Turkey before the pandemic, the rate of nonadherence was quite low compared to this study. This may be because the patients we were able to include in this study were the group that tried not to interrupt their glaucoma clinic visits even during the pandemic.

In the study we conducted, 41.6% of the subjects expressed that their glaucoma clinic visits were interrupted during the pandemic. Cases whose glaucoma visits were interrupted showed significantly higher nonadherence with medication and that the likelihood of nonadherence was 2.38 times higher for patients with interrupted glaucoma visits compared to patients without interrupted visits. This result appears to be linked to the second most common cause of nonadherence reported in our study, which was the inability to receive a prescription. This result also reveals the importance of regular polyclinic visits in improving medication adherence in those with glaucoma. It was reported in a study that patients who visited the clinic every two months showed better adherence with the treatment compared with those whose visits were less frequent²².

Previous studies have reported various reasons for non-adherence with medical treatment such as forgetfulness, preoccupation, suspicion regarding the association of glaucoma with vision loss or the effectiveness of glaucoma medication, poor knowledge about glaucoma, poor self-efficacy, cost, certain difficulties associated with the medication schedule, side effects, difficulty in administering eye drops and lack of trust in the doctor^{10,23}. In our study, the most common cause of nonadherence was determined to be forgetfulness (50%), in congruence with various studies conducted before the pandemic that reported forgetfulness as one of the leading causes of nonadherence^{24,25}. Other causes for nonadherence we identified in our study were the inability to receive a prescription for the drug by six patients (10.7%); busy work schedule by six patients (10.7%); not obtaining the expected benefit from the drug by three patients (5.3%); negligence by three patients (5.3%); unavailability of the drug, being outside home, using too many medications by two patients (3.6%) each; cost, avoiding the side effects associated with the medications, belief that medical treatment will not be helpful and not knowing the importance of regular medication use by one patient (1.8%) each. The point that draws attention here is that inconsistent with the pre-Covid-19 pandemic studies, the inability to receive a prescription for the drug is a prominent reason.

In the literature, different results were reported regarding adherence with glaucoma medication in males and females^{21,26}. In our study, females were determined to be more nonadherent than males with statistical significance and the likelihood of nonadherence was 2.74 times higher for females compared with males. Our study also determined that younger patients were more nonadherent, in line with a previous study¹⁹. This result may be associated with the fact that

younger patients have a more active lifestyle and spend less time at home. During the pandemic, our country implemented more stringent curfew measures for individuals aged 65 and older. However, in our study, the categorization of the patients into age groups did not result in statistically significant differences between the groups. While non-adherence is a risk factor for the progression of glaucoma, reduced vision in those with advanced glaucoma may also be a factor hampering adherence with the application of eye drops^{22,27}. Our study did not identify a statistically significant relationship among BCVA, the severity of glaucoma, length of glaucoma diagnosis, and nonadherence.

Generally, financial status of the patients is among the core limiting factors for access to health services. There are studies in the literature that report cost as an effective factor in medication nonadherence in patients with glaucoma^{22,28}. In our study, only one patient reported cost as a reason for nonadherence. However, our study determined that the likelihood of nonadherence was 6.38 times higher for patients with an income higher than 5000TL compared with patients with an income 1000-5000TL (AOR=6.38, (%95 CI:1.01-40.39)). This result may be linked to the fact that this group of patients have a busier work schedule. Despite the measures taken in Turkey during the pandemic, unemployment has increased especially among low-income ones. Certain studies have reported that living alone is associated with lower adherence compared with being married^{18,21,29}. Although social support of individuals has decreased because of the quarantine imposed due to the pandemic, in our study, we found that living alone was not associated with medication adherence. There are publications reporting better adherence in those living in cities²¹. Despite the quarantine due to the pandemic in our study, no statistically significant difference was found between patients living in the city or the countryside and patients from other cities who visited our clinic in terms of nonadherence. The majority of the patients in our study had social security and their medications were covered by the social security institution. No statistically significant difference was determined between patients with and without social security in our study.

This study has certain limitations. This study used a self-reporting adherence test that relies on the responses of the patients and is therefore associated with a risk of recall bias. Another potential limitation of our study is that it was conducted on patients who visited the clinic during the pandemic. Some individuals follow social isolation more diligently and it is possible that adherence rates are poorer in these patients who do not visit the clinic for this reason. In

conclusion, patients' medication adherence is reduced due to the interruption of polyclinic visits during the pandemic and, as a consequent reason that draws attention, due to the inability to receive a prescription. This should be taken into consideration by ophthalmologists and necessary measures should be taken where possible during Covid-19 pandemic.

Conflict of interest

All authors have no conflict of interest to declare. No funding. Compliance with ethical standards.

Ethical approval

All procedures performed in the studies involving human participants were in accordance with the ethical standarts of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standarts.

Informed consent

Informed consent was obtained from all individual participants included in the study.

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	Adherent (n)	Non-Adherent (n)	p-value
Having Covid-19 infection			
Yes	2	0	0.50
No	139	56	
Having Covid-19 infection in relati	ves		
Yes	3	2	0.35
No	138	54	
Adherence to social distancing reco	mmendations		
Yes	139	55	0.32
No	2	1	
Interruption of glaucoma clinic vis	its during Covid-19 pande	mic	•
Yes	50	32	0.01
No	91	24	

Table 1: Comparison of the responses of patients adherent to glaucoma treatment versus those

 nonadherent to questions regarding the Covid-19 pandemic.

	Adherent (n)	Non-Adherent (n)	p-value
F/M	56/85	33/23	0.02
Age, years (median (MinMax)	63 (18-88)	58 (22-93)	0.02
BCVA, logMAR (median (Min	0 (0-1.92)	0 (0-1.52)	0.79
Max)	, , , , , , , , , , , , , , , , , , ,	· · · ·	
MD (median (MinMax)	-2.49 (-31.0-5.19)	-1.71 (-30.3-1.05)	0.25
Number of glaucoma medications	2 (1-4)	2 (1-3)	0.42
(median (MinMax)	, , , , , , , , , , , , , , , , , , ,	· · ·	
Marriage status			
Married	119	44	0.27
Single	22	12	
Living alone	1		4
Yes	6	4	0.48
No	135	52	-
Occupation	1		
Unemployed	34	15	0.36
Active	24	13	
Retired	83	28	-
Monthly income levels			1
<1000tl	18	10	0.01
1000-5000tl	117	38	0.01
≥5000tl	3	5	
Residence		5	
Rural	21	12	0.51
Urban	117	42	0.51
Another city	3	2	-
Social security	5	2	
Yes	134	51	0.20
No	7	5	0.20
Educational attainment	1	5	
No education	21	5	0.47
Elementary school graduate	76	32	0.77
Middle school-high school graduate	25	13	-
University graduate	19	6	-
Concomitant systemic diseases	17	U	
Yes	85	40	0.11
No	56	16	0.11
Enough knowledge about glaucoma	50	10	
Yes	69	30	0.53
No	72	26	0.55
Bilaterality	12	20	
Unilateral	19	4	0.07
Bilateral	19	52	0.07
	122	52	
Glaucoma type	105	47	0.20
POAG DEV alauseme	105	47	0.20
PEX glaucoma	24	4	

Other				12	5			
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Table 2: Comparison of demographic and clinical characteristics of patients adherent and nonadherent to glaucoma treatment.

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	Adherent (n)	Non-Adherent (n)	p-value	
Age (years)				
18-45	15	12	0.21	
46-64	73	30		
≥65	53	14		
Length of glaucoma diagnosis (years)				
<u>≤5</u>	58	25	0.05	
5-10	56	14		
≥10	27	17		
BCVA	·			
6/6 - 6/18	122	51	0.53	
6/24 – CF (1m)	16	-5		
CF (1/2m) - NLP	3	0		
Number of glaucoma medications				
One	46	15	0.73	
Two or more	95	41		
MD			•	
>-6	104	43	0.30	
-7-(-12)	22	4		
<-13	15	9		

Table 3: Comparison of some categorical demographic and clinical data of patients adherent and nonadherent to glaucoma treatment.

	n	%
Forgetfulness	28	50
Inability to receive a prescription for the drug	6	10.7
Being busy	6	10.7
Not obtaining the expected benefit from the drug	3	5.3
Negligence	3	5.3
Unavailability of the drug	2	3.6
Being outside home	2	3.6
Using too many medications	2	3.6
Cost	1	1.8
Avoiding the side effects associated with the	1	1.8
medications		
Belief that medical treatment will not be helpful	1	1.8
Not knowing the importance of regular medication use	1	1.8

Table 4: The reasons for medication nonadherence reported by nonadherent patients.

Table 5: The multivariate logistic regression analysis of factors influencing medication

	OR	%95 CI	р
Age	1.03	0.94-0.99	0.024
Gender	2.74	1.32-5.71	0.007
Interruption of glaucoma clinic visits	2.38	0.21-0.85	0.016
Monthly income levels	6.38	1.01-40.39	0.049
Length of glaucoma diagnosis	1.73	0.72-4.13	0.215
Concomitant systemic diseases	1.56	0.28-1.44	0.285

nonadherence.