

Adherence and barriers to glaucoma topical medication

Albert Saladrigas¹, Valeria Opazo², Elena Milla²

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¹Department of Ophthalmology, Hospital de la Santa Creu i Sant Pau, Barcelona 08041, Spain; ²Instituto Clínic d' Oftalmologia, Hospital Clínic de Barcelona, Barcelona 08036, Spain

Correspondence to: Albert Saladrigas. albertsaladrigas@gmail.com

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青光眼局部用药的依从性及其障碍

Albert Saladrigas¹, Valeria Opazo², Elena Milla²

作者单位:¹(08041)西班牙巴塞罗那,圣十字圣保罗医院眼科;

²(08036)西班牙巴塞罗那临床医院临床眼科研究所

通讯作者:Albert Saladrigas. albertsaladrigas@gmail.com

摘要

目的:评估接受局部眼内压(IOP)降低治疗患者的药物依从性,并确定接受青光眼专家治疗的患者与接受普通眼科医生随访患者之间的药物依从性是否存在差异及导致依从性差的多个障碍。

方法:横断面调查研究。纳入 2020-10/2021-02 共 54 名患者行局部降眼压药物,且受试者完成了一份定制调查问卷,评估药物依从性及其障碍。

结果:约 60% 受试者未完全依从局部治疗。Pearson 检验表明,依从性与是否接受青光眼专家的随访之间无显著关联($\chi^2=1.2468, P=0.5361$)。其次,43% 的受试者排斥滴眼液,Logistic 回归分析显示,受试者表现出低依从性($\beta_1=3.168, P=0.0367$)。

结论:问卷可有效评估对局部降 IOP 治疗的药物依从性及其障碍。本研究药物依从率非常低,因此必须实施策略应对影响依从性最常见的障碍。

关键词:药物依从性;局部治疗;滴眼液;障碍;青光眼

Abstract

• **AIM:** To evaluate medication adherence among patients taking topical intraocular pressure (IOP) lowering treatment and ascertain if there are differences in medication adherence between patients treated by a glaucoma specialist and those who are followed up by a general ophthalmologist. Furthermore, to identify multiple obstacles contributing to poor adherence.

• **METHODS:** Cross-sectional survey study was conducted among a total of 54 patients, recruited from October 2020 to February 2021, who were using topical

ocular hypotensive medication. Subjects completed a personalized questionnaire which was developed to evaluate medication adherence and its barriers.

• **RESULTS:** Approximately 60% of our subject population were not completely adherent to topical treatment. Pearson's Chi-squared test demonstrated that there was no significant association between adherence and being followed up by a glaucoma specialist or not ($\chi^2=1.2468, P=0.5361$). Furthermore, 43% of participants expressed having problems with eyedrop instillation and Logistic regression analysis revealed that those subjects were significantly more likely to be low adherent to treatment ($\beta_1=3.168, P=0.0367$).

• **CONCLUSION:** The questionnaire was effective to evaluate medication adherence to topical IOP lowering treatment and its barriers. The medication adherence rate found in this study was remarkably low, so several strategies must be put into practice to deal with the most common obstacles related to poor adherence.

• **KEYWORDS:** medication adherence; topical treatment; eye drops; barriers; glaucoma

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INTRODUCTION

Glaucoma is a worldwide leading cause of irreversible vision loss, affecting over 70 million people^[1]. Glaucoma is a group of progressive optic neuropathies characterized by slow progressive degeneration of retinal ganglion cells^[2]. Primary open-angle glaucoma (POAG) is the most common form of glaucoma in Western countries^[3].

Reaching an adequate intraocular pressure (IOP) level is the only proven method of minimizing both the development and progression of glaucoma^[4]. The most common manner in which patients with glaucoma control their IOP is with administration of daily topical ocular hypotensive drugs^[5].

Eye drop medications can preserve visual function long term, but poor adherence is a major issue with reported rates of non-adherence ranging from 30%-80%. Poor adherence has been shown to be associated with disease progression and blindness^[4].

Multiple obstacles to adherence have been identified, including: medication side effects, difficulty with eye drop administration, psychological attributes (such as lack of motivation, depression or anxiety), complex medication

regimens, difficulty with opening or squeezing the eyedrop containers, limitation of physical capacities in elderly patients with tremor or arthritis, low socioeconomic status and poor knowledge or skepticism about the disease^[6-7].

Medication adherence may also have a genetic background, related to personality traits. Seo *et al*^[8] identified four loci that were suggestively associated with medication adherence.

It is well known that the ophthalmologist's ability to judge adherence is poor. Newman-Casey *et al*^[4] found out that only the 26.5% of the subjects were supposed to be non-adherent by self-report while in recent meta-analysis these rates reach 80.0%. Self-reported non-adherence has been shown to be lower than rates of non-adherence measured with electronic dosing monitors. Okeke *et al*^[9] also reported a marked increase in adherence just a few days previous to their ophthalmologist appointment. Furthermore, the percentage of patients expressing non-adherence in front of their physicians is low^[7].

Several methods have been utilized in efforts to assess adherence in patients. However, there is no available standardized, validated questionnaire, specifically designed to assess adherence to topical medication^[10].

The primary objective of our study is to evaluate medication adherence among patients taking topical IOP lowering treatment in our population. Secondary objectives are to ascertain if there are differences in medication adherence between patients treated by a glaucoma specialist and those who are followed up by a general eye care doctor, identify barriers contributing to poor adherence, and examine/propose several strategies to improve adherence.

SUBJECTS AND METHODS

Participants A cross-sectional survey study was conducted among a total of 54 patients who were using topical ocular hypotensive medication on a daily basis. Consecutive patients were recruited from October 2020 to February 2021 in outpatient clinic rooms of the Institut Clínic d'Oftalmologia (ICOF), Hospital Clínic de Barcelona. Half of the patients were recruited by approaching them during their glaucoma specialist appointment. The other half were recruited during their general ophthalmologist appointment.

Inclusion criteria All patients over 18 years old who were taking at least one topical IOP lowering medication and were interested in completing the survey were included in the study. Verbal authorization was obtained from all survey subjects. The study was approved by the ethics committee of the Hospital Clinic and University of Barcelona.

Exclusion criteria Elderly patients with cognitive decline who were not able to answer the questions properly or whose answers could not be corroborated by someone else were excluded from the study.

Methodology A research assistant (AS) interviewed the selected patients immediately after their medical appointment in a next-door room so they could complete the questionnaire privately. Patients received assurance that all responses would remain anonymous and that their ophthalmologist would not

know the information provided.

Questionnaire A personalized questionnaire was developed to evaluate topical IOP lowering medication adherence (Table 1). To assess exclusively medication adherence, the questionnaire included four questions adapted from the Morisky, Green and Levine Medication Adherence Questionnaire (MGL)^[11]. These four questions required a yes/no answer; a "yes" was given a score of 1 and a "no" 0. The adherence scores were calculated, and the adherence categories were established as: MGL = 0 representing high adherence, MGL = 1 representing moderate adherence and MGL = 2 or more representing low adherence. More questions were included in the survey to assess other relevant information such as demographics, living status, problems when putting eyedrops or knowledge about glaucoma. Hoddap-Parrish-Anderson criteria was used to classify POAG functional damage in our patients^[12]. Participants were classified into early (mean deviation, MD, < -6 dB), moderate (MD > -6 and < -12 dB) and severe defect (MD > -12 dB).

Data Analysis Data was analyzed using RStudio with R version 4.0.3 from 10th October 2020. Logistic regression analysis using Wald statistic test and its significance was performed to assess which patient characteristics, obtained with the questionnaire, were associated with "high adherence" and "low adherence" to topical IOP lowering treatment. The statistical confidence was set at 90%. Non-parametric Chi-squared and Fisher's exact test analyses were employed to assess adherence between patients who were followed up by their glaucoma specialist and those who were followed up by another physician.

RESULTS

Table 2 includes the characteristics of study subjects and all the questionnaire responses, categorized as having low, moderate or high adherence to topical POAG medication. Most participants (41%) had an early defect, while 16% had moderate and 15% severe defects. The remaining 28% had ocular hypertension (OHT).

Adherence and follow up Approximately 60% of our subject population were not completely adherent to topical treatment. 39% of the patients in the study were categorized as "high adherent" by self-report on the MGL questionnaire. "Moderate adherence" was illustrated by 41% and "low adherence" by 20%.

Our patients' adherence was also assessed according to the ophthalmologist who was following up their POAG. Half of the patients, 27, were followed up by their glaucoma specialist and the other half by a general ophthalmologist. "Moderate adherence" was demonstrated by 41% in both groups.

The differences are observed in "high adherence" and "low adherence" categories. Out of the patients followed up by their glaucoma specialist, 44% of them were found in the "high adherence" category, whereas out of those followed up by a general ophthalmologist, only 33% were "high adherent" (Figure 1).

Table 1 Topical intraocular pressure lowering medication adherence questionnaire

Questions	Answers
Age;	
Sex;	Male/Female
Educational level;	Without studies/High school/Vocational training/College education
Who do you live with?	Alone/Family/Carer/Other
Do they help you with drop instillation?	No/Sometimes/Always
How many eyedrops are you taking per day (one eye only)?	1/2/3 or more
MGL	
Do you ever forget to put your eyedrops?	Yes/No
Are you careless at times when putting your eyedrops?	Yes/No
When you feel better do you sometimes stop taking your medicine?	Yes/No
Sometimes if you feel worse when you take the medicine, do you stop taking it?	Yes/No
Have you experienced any side effect from your medication?	Yes/No
If so, which ones?	
Do you have problems with opening or squeezing the eyedrop container?	Yes/No
Do you have problems with drop insertion?	Yes/No
Have you ever been taught how to put your eyedrops properly?	Yes/No
If glaucoma could be treated with oral medication, would you prefer it?	Yes/No
Would you prefer surgery rather than continuing taking eyedrop medication?	Yes/No
How much do you know about glaucoma?	Very little/Fair amount/A lot
Do you think it is important to follow the treatment every single day?	Yes/No
Do you think that this treatment is hard to follow?	No/Sometimes could be difficult/Yes
How would you describe your current vision?	Really good/Good/Inadequate/Bad

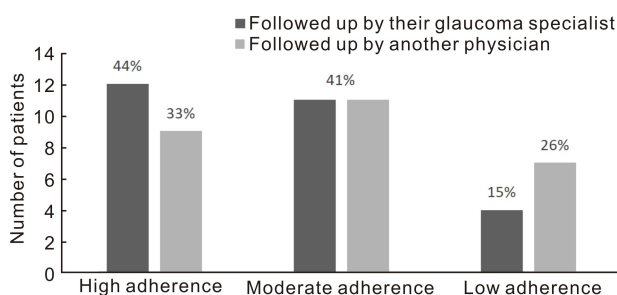


Figure 1 Medication adherence between patients who were followed up by their glaucoma specialist and those who were followed up by another physician.

Despite the fact that within our subject population adherence was higher for those patients followed up by their glaucoma specialist, Pearson’s Chi-squared test demonstrated that being followed up by a glaucoma specialist or not and medication adherence are independent variables ($\chi^2 = 1.2468, P = 0.5361$). Also, no significant associations were observed when Fisher’s exact test was used to verify these results ($P = 0.6061$).

Side Effects Most patients (78%) reported that they had never experienced any medication side effects. Among those who did have adverse events, the most common one was eye pruritus, followed by conjunctival hyperemia. Some patients also reported foreign body sensation in the eye and blurred vision during the following morning when eyedrop medication was taken at night. There was no significant association noted between medication adherence and experiencing side effects ($\beta_i = 0.411, P = 0.688$).

Only 15% of participants reported having problems with

opening or squeezing the eyedrop container. Nonetheless, 43% of subjects reported having problems with eyedrop instillation, that is, with the drop hitting the eye correctly. Most participants, nearly 80%, reported that they had never been taught how to instill their eyedrops properly by their physician.

Patient characteristics related to adherence The results of the logistic regression analysis (Table 3) revealed that being a woman may be associated with “high adherence” to medication ($\beta_i = 1.086, P = 0.279$). Patients with high educational level, including vocational training or college education, appear to be more adherent ($\beta_i = 1.269, P = 0.159$). Also, being taught how to instill eyedrops properly may increase adherence to treatment ($\beta_i = 0.969, P = 0.349$). However, none of these attributes reached statistical significance. Patients with early glaucomatous defects were significantly associated with “high adherence” to topical treatment ($\beta_i = 2.484, P = 0.059$).

Those patients who did not need any help with eyedrop instillation were significantly less likely to be adherent to medication ($\beta_i = -3.045, P = 0.0491$) than those who needed it. Participants who expressed having problems with the drop hitting the eye correctly while instilling the eyedrops were significantly more likely to be “low adherent” to treatment ($\beta_i = 3.168, P = 0.0367$).

DISCUSSION

The questionnaire that was developed has been effective to evaluate medication adherence to topical IOP lowering treatment. Only 39% of patients affirmed being completely

Table 2 Characteristics of subjects, and all the questionnaire responses, categorized as having low, moderate or high adherence to topical primary open-angle glaucoma medication

Responses	Total	Low	Moderate	High
Sex				
Male	48% (n=26)	19% (n=5)	46% (n=12)	35% (n=9)
Female	52% (n=28)	21% (n=6)	36% (n=10)	43% (n=12)
Age				
≤70	30% (n=16)	19% (n=3)	50% (n=8)	31% (n=5)
71-80	44% (n=24)	29% (n=7)	21% (n=5)	50% (n=12)
>80	26% (n=14)	7% (n=1)	64% (n=9)	29% (n=4)
Studies				
Without	20% (n=11)	28% (n=3)	36% (n=4)	36% (n=4)
High school	54% (n=29)	21% (n=6)	45% (n=13)	34% (n=10)
Vocational training	19% (n=10)	0% (n=0)	40% (n=4)	60% (n=6)
College	7% (n=4)	50% (n=2)	25% (n=1)	25% (n=1)
Living status				
Alone	28% (n=15)	7% (n=1)	53% (n=8)	40% (n=6)
Family	70% (n=38)	26% (n=10)	34% (n=13)	40% (n=15)
Carer	0% (n=0)	0% (n=0)	0% (n=0)	0% (n=0)
Others	2% (n=1)	0% (n=0)	100% (n=1)	0% (n=0)
Help				
No	78% (n=42)	24% (n=10)	43% (n=18)	33% (n=14)
Sometimes	9% (n=5)	20% (n=1)	20% (n=1)	60% (n=3)
Always	13% (n=7)	0% (n=0)	43% (n=3)	57% (n=4)
N° eyedrops				
1	56% (n=30)	23% (n=7)	37% (n=11)	40% (n=12)
2	33% (n=18)	22% (n=4)	39% (n=7)	39% (n=7)
3 or more	11% (n=6)	0% (n=0)	67% (n=4)	33% (n=2)
Side effects				
Yes	22% (n=12)	16% (n=2)	42% (n=5)	42% (n=5)
No	78% (n=42)	21% (n=9)	41% (n=17)	38% (n=16)
Open				
Yes	15% (n=8)	0% (n=0)	50% (n=4)	50% (n=4)
No	85% (n=46)	24% (n=11)	39% (n=18)	37% (n=17)
Drop insertion				
Yes	43% (n=23)	26% (n=6)	30% (n=7)	44% (n=10)
No	57% (n=31)	16% (n=5)	48% (n=15)	36% (n=11)
Taught properly				
Yes	20% (n=11)	0% (n=0)	45% (n=5)	55% (n=6)
No	80% (n=43)	26% (n=11)	39% (n=17)	35% (n=15)
Oral treatment				
Yes	31% (n=17)	12% (n=2)	35% (n=6)	53% (n=9)
No	69% (n=37)	24% (n=9)	43% (n=16)	33% (n=12)
Surgery				
Yes	30% (n=16)	31% (n=5)	38% (n=6)	31% (n=5)
No	70% (n=38)	16% (n=6)	42% (n=16)	42% (n=16)
Knowledge				
Little	55% (n=30)	20% (n=6)	47% (n=14)	33% (n=10)
Fair amount	43% (n=23)	17% (n=4)	35% (n=8)	48% (n=11)
A lot	2% (n=1)	100% (n=1)	0% (n=0)	0% (n=0)
Important				
Yes	91% (n=49)	18% (n=9)	39% (n=19)	43% (n=21)
No	9% (n=5)	40% (n=2)	60% (n=3)	0% (n=0)

Table 2 Characteristics of subjects, and all the questionnaire responses, categorized as having low, moderate or high adherence to topical primary open-angle glaucoma medication(continued)

Responses	Total	Low	Moderate	High
Difficult				
No	89% (n=48)	21% (n=10)	42% (n=20)	37% (n=18)
Sometimes	7% (n=4)	25% (n=1)	50% (n=2)	25% (n=1)
Yes	4% (n=2)	0% (n=0)	0% (n=0)	100% (n=2)
Vision				
Really good	13% (n=7)	43% (n=3)	57% (n=4)	0% (n=0)
Good	61% (n=33)	12% (n=4)	42% (n=14)	46% (n=15)
Inadequate	20% (n=11)	28% (n=3)	36% (n=4)	36% (n=4)
Bad	6% (n=3)	33% (n=1)	0% (n=0)	67% (n=2)
Grade				
Ocular hypertension	28% (n=15)	27% (n=4)	40% (n=6)	33% (n=5)
Early defect	41% (n=22)	27% (n=6)	23% (n=5)	50% (n=11)
Moderate defect	16% (n=9)	11% (n=1)	56% (n=5)	33% (n=3)
Severe defect	15% (n=8)	0% (n=0)	75% (n=6)	25% (n=2)

Table 3 Patient characteristics and adherence logistic regression analysis

Characteristics	Estimate	Std. Error	Z	P (> z)
Sex	1.08580	1.00291	1.083	0.2790
Educational level	1.26868	0.90096	1.408	0.1591
Living status	-0.70006	1.24591	-0.562	0.5742
Number of eyedrops	-0.10253	0.61062	-0.168	0.8667
Adverse events	0.41100	1.02467	0.401	0.6883
Problems opening and squeezing	0.22898	1.46695	0.156	0.8760
Problems with instillation	0.32535	0.89765	0.362	0.7170
Being taught properly	0.96975	1.03596	0.936	0.3492
Knowledge about glaucoma	0.18325	0.93711	0.196	0.8450
Current vision	-0.05214	0.91119	-0.057	0.9544
Help always	-0.98865	1.97308	-0.501	0.6163
Help never	-3.04503	1.54725	-1.968	0.0491
Not difficult to follow	1.57301	1.51672	1.037	0.2997
Difficult to follow	18.33184	1678.92	0.011	0.9913
Ocular hypertension	1.22297	1.44819	0.844	0.3984
Early defects	2.48382	1.32034	1.881	0.0599
Moderate defects	1.62653	1.43610	1.133	0.2574

Null deviance = 72.171 on 53 degrees of freedom
 Residual deviance = 54.415 on 35 degrees of freedom
 AIC = 92.415

adherent to medication. This adherence rate is remarkably low although it is greatly similar to the one in McClelland *et al's*^[10] study, in which adherence was also assessed by self-report. To minimize the patients' anxiety that might be caused by talking about adherence medication with their physician, a research assistant was the one who interviewed the patients. This approach might have encouraged patients to tell the truth about medication adherence.

Most patients (41%) were categorized in the "moderate adherence" group (MGL = 1 score). In those "moderately-adherent" patients the most frequent cause for not being completely adherent was forgetfulness. Prior research has found out that forgetfulness was the number-one reason for

poor adherence^[3-4].

Participants followed by a glaucoma specialist were 10% more likely to be completely adherent than those who were not. It might seem that being followed up by a glaucoma specialist physician could be related to better adherence. Nevertheless, this did not reach statistical significance although a tendency towards this statement was found. Further studies with a larger number of participants should be carried out to clear up if patients would benefit from only being followed up by a glaucoma specialist. It has been described that, despite being a glaucoma specialist or not, ophthalmologists need to improve communication with patients, and better observe and instruct patients instilling eyedrop treatment, especially if it is

suspected they may be getting worse despite medical treatment^[13]. One fifth of patients in our study reported having experienced local side effects from their eyedrop medication, being pruritus and hyperemia the most frequent ones.

Adverse effects of topical hypotensive medication for glaucoma are a leading cause of non-adherence. An analysis of 36 randomized controlled trials that included 17 511 patients identified adverse effects as the most common cause of withdrawals^[14]. Zimmerman *et al*^[15] reported that hyperemia was the most common adverse effect noted and one out of ten patients in their study with red eye admitted to skipping medication because of this reason.

The preservatives and the excipients in glaucoma medication may have an important role in the occurrence of these local adverse effects. For example, benzalkonium chloride (BAK) is commonly used as a preservative in multidose bottles and it has been linked to toxic effect on human conjunctival cells. Preservative-free solutions should be considered when available to minimize patient discomfort and increase adherence^[6].

It was surprising that most patients mentioned that they had never been taught how to instill their eyedrops properly. Sayner *et al*^[16] in a large observational study, where the medical visit was videotaped, revealed that only 16% of patients received instructions about eye drop administration. This percentage in our study is not that different (20%). Zimmerman *et al*^[17] demonstrated that nasolacrimal occlusion and eyelid closure are simple techniques that not only improve efficacy of topically applied ocular medication, increasing ocular bioavailability, but also reduce the probability of adverse systemic effects. More than half of the patients (56%) mentioned that their knowledge about glaucoma was poor.

Friedman *et al*^[18], in the GAPS study, found out that adherence was significantly lower in those who stated that they did not believe that nonadherence to glaucoma medication would put them at risk for reduced vision. GAPS data also suggested that doctor-patient communication plays a role in patient concern about glaucoma. Comprehension of the disease generates commitment, which in turn produces adherence to treatment^[6]. It is remarkable that nearly half of the subjects reported having problems with the drop hitting the eye correctly. And this has reached significance in our study in being related to “low adherence” to medication. In addition, the percentage of people with problems with drop insertion might be higher because prior research has detected that older patients overestimate their physical ability to properly perform the self-application of eyedrops^[19].

Hennessy *et al*^[13], in a study in which patients with glaucoma were videotaped to evaluate eyedrop instillation, reported that one third of the subjects could not instill a drop onto the surface of the eye, and of those who could, used multiple

drops and possibly contaminated the bottle tip. Another important data in their study is that the rate of successfully applied eyedrops was significantly higher among elderly patients using an eyedrop bottle than among those using single-use containers. The use of a standard eyedrop bottle might be a solution to increase self-application comfort in elderly patients and may improve adherence.

It is also curious that patients who did not need any help with eyedrop instillation were significantly less likely to be completely adherent. This could be related to the fact that receiving help or supervision might increase adherence by reducing the odds of forgetting to take the medication.

Being between 71 and 80 years old was significantly related to “high adherence” to medication compared to the other age groups. However, prior research has shown that older glaucoma patients are convinced that they forget their medication very rarely compared to younger patients^[19].

Patients with mild glaucomatous defects were significantly associated to great adherence to medication. This might be interesting because it is difficult to discern if patients tend to be more adherent in order to maintain their good vision or if having low defects is the consequence of being high adherent to topical treatment.

There are several limitations to this study. First, the sample of patients was recruited from only one clinic (ICOF) so the results may not be representative of patients followed in other hospitals. Furthermore, being a self-reported research, patients may not have told the whole truth in expressing poor adherence when answering the questionnaire. In addition, it would be interesting to perform this same study or similar with a larger number of patients, to increase statistical significance and establish more variables associated with medication adherence. Finally, the risk of volunteer bias is present, in which patients who participated in the study might tend to be more aware of health care.

There are several strategies that should be implemented to improve patient adherence. It was mentioned previously that some measures such as selecting preservative-free medication, simplified drug regimens or standard eyedrop bottles in elderly people may increase patient satisfaction just as adherence. Prior research has also found out that patients would benefit from educational interventions^[20]. Another important target should be reducing forgetfulness. Smartphone technology could help to set an alarm or to receive regular reminders to use their glaucoma drops. It would also be helpful to raise awareness within their family if it were possible.

Various novel medication delivery systems such as surgically implanted programmable mini-pumps^[6] or drug-eluting contact lenses^[2] are in development to improve pharmacokinetics as well as adherence. Bimatoprost intracameral implant 10 μm (Durysta®) is the only sustained-release glaucoma therapy approved by the FDA in

March 2020 for the lowering of IOP^[21-22].

In conclusion, the questionnaire we have designed is a useful instrument even though a validated standard one should be created to assess adherence in a universal manner. Several strategies must be put into practice to deal with the most common barriers related to poor adherence that have been found. Improving doctor – patient communication, patient comprehension of the disease and understanding the importance of the treatment might be the key to reduce the low rate of adherence to glaucoma medication.

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