• Investigation •

# A cross-sectional study on compliance with topical glaucoma medication and its associated socioeconomic burden for a Chinese population

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## Abstract

● **AIM:** To estimate the overall drug compliance for local Chinese glaucoma patients on long-term topical treatment.
● **METHODS:** This was a retrospective cross-sectional study. Fifty-seven primary glaucoma patients from the subspecialty clinic of a publicly-funded tertiary care hospital in Hong Kong completed a questionnaire on compliance with topical glaucoma medication, attitude towards glaucoma and therapy and vision related quality of life. Noncompliance was defined as reporting missing more than or equal to 10% of the prescribed topical glaucoma medication during the 2wk immediately prior to the consultation. Relationships between noncompliance and demographics, attitude, disease and treatment status was studied. Cost was estimated with quality of life and direct medical cost involved with noncompliance. Multivariable logistic regression on noncompliance was performed on selected factors.
● **RESULTS:** Compliance was calculated as 75% (95% CI: 64%-87%) among 57 subjects (mean age 69y, female 51%). No statistical significant relationship was established between noncompliance and any single factors or outcomes. Age (*P*=0.048) and forgetfulness (*P*=0.064) were found to be marginally significant predictive factors on noncompliance in multivariable logistic regression. Noncompliance might be related (*P*=0.130) to poorer self-

rated vision-associated quality of life. The societal cost of noncompliance was estimated to be over 2510 life-years and US$ 3.7 million territory-wide.
● **CONCLUSION:** The compliance of Chinese glaucoma patients in Hong Kong is comparable to other parts in the world, and carries detrimental impacts on individual and societal levels. Age and forgetfulness are two possible independent predictors for noncompliance.
● **KEYWORDS:** glaucoma; eye drop; compliance; quality of life

## INTRODUCTION

Glaucoma is the leading cause of irreversible visual impairment globally, with number of affected individual expected to reach 111.8 million in 2040[1-2]. Currently, topical intraocular pressure (IOP)-lowering therapy remains the universally accepted first line management of this emerging pandemic.

As in other chronic diseases, patient compliance is of paramount importance in disease management; noncompliance towards treatment often leads to treatment failure and disease progression. In particular, forgetfulness, lack of understanding of glaucoma, attitudes towards the disease and misbeliefs about the drug effect have been shown in previous studies as significant contributors to noncompliance[3-5].

On top of deteriorating quality of life of individual patients, disease progression resulted from noncompliance incurs direct and indirect societal costs as drug cost, need of advanced therapeutics, and productivity lost[6-7]. A four-fold increase in economic burden from the mildest to the most severe stage of glaucoma in US and in Europe has been reported[8-9].

Despite the high prevalence of glaucoma in Asia and significance of treatment compliance, characteristics of compliance

among Chinese glaucoma populations is to be explored. Therefore, a comprehensive study on drug compliance in glaucoma in Hong Kong will be essential in identifying the extent of the problem, its effect on individuals and society, as well as potential management options.

## OBJECTIVES

The aim of our study is to estimate the overall drug compliance for Chinese glaucoma patients towards long-term topical treatment in a subspecialty clinic of a publicly funded tertiary care hospital in Hong Kong. Secondary objectives involve identifying factors affecting compliance, effects of poor compliance on disease progression and the associated economic burden to the public health care system.

## PATIENTS

This was a retrospective cross-sectional study approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (HKU/HA HKW IRB). Questionnaires were distributed to patients with a diagnosis of glaucoma and were on long-term topical IOP-lowering medication. Parameters regarding the respondents' disease status, including visual acuity (VA), visual field and treatment regimen, were reviewed from their electronic medical records.

Patients 1) having a diagnosis of glaucoma and 2) on at least 1 topical IOP lowering medication for at least 3mo were eligible for the study. They were receiving specialist care, which was based on the same service standard, from attending ophthalmologists under the glaucoma subspecialty clinic of the Department of Ophthalmology, Queen Mary Hospital. Consecutive patients fulfilling these criteria were identified and recruited from the clinic between the 1st of February 2014 and the 31st of July 2014. Subjects had to reach at least 18y of age and be capable to give written informed consent for the study. To be classified as glaucomatous, eyes needed to have at least 2 consecutive reliable standard automated perimetry examinations with either a pattern standard deviation outside the 95% confidence limits or a glaucoma hemifield test result outside the 99% confidence limits. Reliability was defined as less than 30% fixation losses, less than 30% false-positive rates, and less than 30% false-negative rates. Due to the altered disease course, patients with a diagnosis of secondary glaucoma were excluded. Other exclusion criteria included: receiving ocular surgery within 1mo, inability to apply their own topical IOP lowering medication and inability to communicate effectively. Subjects were allowed to withdraw at any point upon their wish.

## METHODS

**Questionnaire** The questionnaire consisted of 79 questions and was developed with reference to a number of reported questionnaires on glaucoma compliance and quality of life[7,10-15], with inputs from 2 local ophthalmologists working in the public out-patient clinic. It was divided into six parts, namely demographics, disease status, attitude and efficacy, knowledge on glaucoma, quality of life and disease particulars. Each respondent was required to complete the first 5 sections of the questionnaire, while the researchers completed the final section on disease particulars with medical records. The questionnaire was available in both English and traditional Chinese, and assistance in completion was given when necessary, for example, for illiterate patients and patients with severely impaired vision. It took, on average, 20min to complete the whole questionnaire.

**Compliance** Noncompliance was defined as reporting missing at least 10% of the prescribed topical glaucoma medication during the 2wk immediately prior to the consultation.

**Quality of Life** Quality of life was assessed *via* a numerical scale in general, and 15 questions focusing on specific activities and functions associated with vision adopted from Glaucoma Quality of Life-15 (GQL-15)[7].

**Knowledge on Glaucoma** Ten true or false questions were selected from a previous described questionnaire on knowledge of glaucoma, with coverage of pathogenesis, diagnosis, treatment, and patient-doctor interaction[11]. Knowledge was expressed as percentage of correct response.

**Visual Acuity** All VA measurements were recorded as pinhole distant VA and measured by a registered optometrist at the Department of Ophthalmology, Queen Mary Hospital. Count fingers (CF), hand movement (HM) and light perception (LP) were regarded as VA of 0.0 in analysis.

**Intraocular Pressure** IOP was measured with non-contact tonometry (NCT). Values >21 mm Hg were confirmed with Goldmann applanation tonometry (GAT).

**Visual Field** All visual field tests were performed using an automated visual field analyzer (Humphrey Field Analyzer; Carl Zeiss Ophthalmic Systems Inc.) with a 24-2 test pattern, size III white stimulus with the Swedish Interactive Threshold Algorithm standard strategy.

**Statistical Analysis** All continuous variables and categorical variables were expressed as mean±standard deviation and frequencies or percentages, respectively. They were compared between noncompliant and compliant patients. Continuous variables were compared using independent Student's *t*-test. Categorical variables were compared using Pearson's Chi-square test, or Fisher's exact test if more than 10% of the cells had expected count less than 5.

Regarding the targeted sample size, the primary objective of the current study is determination of noncompliance in local population. We estimated the local drug compliance being 75% according to results from literature reviews, and we targeted an interval of 15% wide. One hundred and twenty-eight patients would be needed to reach such interval at a level of confidence of 95%.

Questions adopted from GQL-15 and Eye-Drop Satisfaction Questionnaire (EDSQ) were analysed in structures previously reported[7,10,13].

To estimate the costs of noncompliance to individual patients, quality of life in relation to visual impairment and disability was calculated and compared between groups. The difference in their self-rated quality of life is attributed to drug noncompliance. In addition, drugs belonging to noncompliant patients were deemed improperly used. To calculate the direct drug costs of noncompliance to the public health care system, the cost of topical glaucomatous prescription was calculated for noncompliant subjects and estimated for the population of Hong Kong. All costs were expressed in US dollars.

Logistic regression was done to examine the associations between compliance and individual predictors shortlisted from preceding studies. The factors have been tested for correlations among themselves for their independence, and univariable analysis with compliance before entering into multivariable analysis by the forced entry approach.

All the data analyses were performed using the commercially available statistical software SPSS for window (Version 21.0). All $P$ values reported were 2-sided for consistency. A $P$ value <0.05 was considered to be statistically significant.

### RESULTS

Seventy-six patients were recruited in the study. Among these patients, 19 patients were excluded from the final analysis, either due to missing or incomplete record ($n$=3), or satisfying any exclusion criteria upon analysis of medical record: secondary glaucoma in at least one eye ($n$=8), not currently on topical anti-glaucoma treatment ($n$=4) and receiving eye surgery within 1mo ($n$=4) respectively. Analyses were based on information from remaining 57 patients. Figure 1 illustrates the exclusion process. Compared to included subjects, the excluded subjects were in general younger, as half of excluded subjects had secondary glaucoma (comparison not shown).

**Basic Demographics** Table 1 presents the demographics of enrolled subjects. The study included 57 valid Chinese patients, comprising 29 females (51%) and 28 males (49%). Their ages ranged from 34 to 91, with mean at 69±14y. The majority of patients lived with family or caretaker ($n$=49, 86%) and were retired ($n$=44, 77%).

**Clinical Features** Table 1 also presents the basic clinical characteristics and ophthalmic diagnoses of subjects. The mean duration of glaucoma among our subjects was 7.8±7.0y. Most patients were diagnosed with primary open angle glaucoma ($n$=28, 49%) or normal tension glaucoma ($n$=17, 30%). The majority of patients had glaucoma affecting both eyes ($n$=46, 81%). The worse affected eye had a mean IOP of 17.1±5.8 mm Hg and a VA of 0.53±0.28. On average, the patients were receiving 1.8±0.9 glaucoma eye drops, which resulted in 2.2±0.8 instillations of eye drops per day.
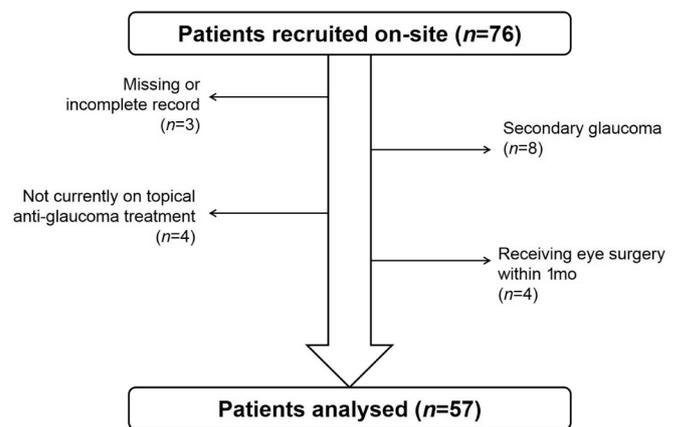


**Figure 1 Illustration on exclusion process.**

**Table 1 Demographical and disease characteristics of patients** $n$(%)

| Demographics | Results ($n$=57) |
| --- | --- |
| Age (a) | |
| $\bar{x} \pm s$ | 69±14 |
| Range | 34 to 91 |
| Sex | |
| F | 29 (51) |
| Ethnicity (Chinese) | 57 (100) |
| Education level | |
| Secondary | 23 (40) |
| Working status | |
| Retired | 44 (77) |
| Living condition | |
| Live with family/caretaker | 49 (86) |
| Monthly household income | |
| $ 0-645 | 25 (44) |
| Requiring external help in instillation | 8 (14) |
| Disease status (a) | |
| Duration of glaucoma | 7.8±7.0 |
| Duration of eye drop treatment | 7.5±7.1 |
| Diagnosis | |
| Bilateral glaucoma | 46 (81) |
| Primary open angle glaucoma | 28 (49) |
| Primary angle-closure glaucoma | 13 (23) |
| Normal tension glaucoma | 17 (30) |
| Positive family history | 10 (18) |
| Visual function of worse affected eye ($\bar{x} \pm s$) | |
| Intraocular pressure ( mm Hg) | 17.1±5.8 |
| Visual acuity | 0.53±0.28 |
| Treatment ($\bar{x} \pm s$) | |
| No. of glaucomatous eye drops prescribed | 1.8±0.9 |
| No. of instillations, times per day | 2.2±0.8 |

**Comparisons Between Compliant and Noncompliant Groups** Fourteen reported noncompliance among 57 patients analysed, based on the mentioned criteria. The self-reported compliance is 75% (95%CI: 64%-87%). Subsequent analyses between compliant ($n$=43) and noncompliant ($n$=14) groups were based on this self-reported compliance.

**Table 2 Comparison on demographic characteristics between compliant and noncompliant groups**

| Demographics | Compliant (*n*=43) | Non-compliant (*n*=14) | *P* |
|---|---|---|---|
| Sex (F) | 51% | 50% | 0.941 |
| Age (a) | 71 | 63 | 0.072 |
| Duration of treatment (a) | 8.0 | 5.9 | 0.329 |
| No. of instillations, times per day | 2.2 | 2.3 | 0.670 |
| Requiring external help in instillation | 16% | 7% | 0.664 |

**Table 3 Comparison of attitude and knowledge between compliant and noncompliant groups**   %

| Patient parameters | Compliant (*n*=43) | Non-compliant (*n*=14) | *P* |
|---|---|---|---|
| Concern over treatment | 35 | 40 | 0.393 |
| Concern over disease | 54 | 56 | 0.800 |
| Satisfaction with patient-clinician relationship | 65 | 63 | 0.668 |
| Positive beliefs | 79 | 80 | 0.804 |
| Treatment convenience | 47 | 47 | 0.979 |
| Often forget taking eye drops | 24 | 43 | 0.107 |
| Correctness of usage of eye drops | 66 | 55 | 0.090 |
| Knowledge on glaucoma | 54 | 56 | 0.707 |

Up to 10 questions were grouped under each above-named category for analysis.

The demographics, attitude and knowledge towards various aspects of glaucoma are compared between compliant and noncompliant groups in Tables 2 and 3. All factors in this part lacked statistical significance, but some items may deserve further analysis with a larger sample size, such as the item "often forgetting eye drops" (*P*=0.107). Table 3 also presents the knowledge on glaucoma by compliant and noncompliant patients. Both groups had similar correct response rate (54% and 56%) regarding their knowledge of the disease overall. However, a potentially noteworthy difference between the two groups was noticed on correctness of usage of eye drops (66% *vs* 55%, *P*=0.090).

Table 4 shows the vision-associated quality of life with GQL-15 and numerical scale between the two groups, with a breakdown of component scores in GQL-15. The compliant group had less self-rated functional impairment than noncompliant group in each factor in GQL-15, but the trend was not statistically significant.

Comparisons on disease and treatment between the two groups are presented in Tables 5 and 6. Average IOP of the worse effected eye was 4 mm Hg higher than that in the noncompliant group, but the difference was not statistically significant (*P*=0.177). Difference in VA and disease progression was not substantial. There was no difference between the number of glaucoma medications and frequency of drops between the compliant and noncompliant groups (Table 6).

Based on the prescription received, the average daily cost of topical glaucoma treatment of the groups was computed (calculation not shown), which was $ 0.71 and $ 0.72 per day per patient, in the noncompliant group and compliant group respectively. This serves as an estimation of direct drug cost involved in noncompliance.

**Table 4 Comparison on vision-associated quality of life between compliant and noncompliant groups**   %

| Patient parameters | Compliant (*n*=43) | Non-compliant (*n*=14) | *P* |
|---|---|---|---|
| GQL-15 | | | |
| Overall | 28 | 37 | 0.252 |
| Central and near vision | 29 | 38 | 0.294 |
| Peripheral vision | 25 | 33 | 0.340 |
| Glare and dark adaptation | 34 | 42 | 0.287 |
| Outdoor mobility | 16 | 25 | 0.275 |
| Numerical scale | | | |
| Current quality of life | 64 | 61 | 0.685 |
| Quality of life without glaucoma | 78 | 84 | 0.171 |
| Quality of life attenuated by glaucoma | 14.4 | 22.9 | 0.130 |

GQL-15 score represents perceived difficulties in performing vision-related activities.

A positive correlation was established between GQL-15 score and duration of disease or treatment (*P*<0.01 for both), which indicates self-rated impairment increases with the duration of disease. Scatter plots for the correlation are presented in Figures 2 and 3.

A logistic regression analysis is presented in Table 7 on effects of several factors and responses towards noncompliance. Age was established as an independent predictive factor of compliance in the multivariable logistic regression model (adjusted OR=0.95 per year of age, *P*=0.048), with advanced age linked to better self-rated compliance.

## DISCUSSION

**Compliance**   Regarding the primary objective, the overall self-reported compliance to topical glaucoma medication was 75% (95% CI: 64%-87%) among the subjects. The rate was

**Table 5 Comparison on disease status between compliant and noncompliant groups**

| Patient parameters | Compliant (*n*=43) | Non-compliant (*n*=14) | *P* | Odds ratio (95%CI) |
|---|---|---|---|---|
| IOP of the worse affected eye (mm Hg) | 16 | 20 | 0.177 | |
| VA of the worse affected eye | 0.56 | 0.46 | 0.259 | |
| Disease progression (by visual field) | 7/43 (16.3%) | 2/14 (14.3%) | | 0.86 (0.16-4.70) |

**Table 6 Comparison on treatment status between compliant and noncompliant groups**

| Patient Parameters | Compliant (*n*=43) | Non-compliant (*n*=14) | *P* |
|---|---|---|---|
| No. of glaucomatous eye drops prescribed | 1.9 | 1.8 | 0.781 |
| No. of instillations, times per day | 2.2 | 2.3 | 0.670 |

**Table 7 Logistic Regression of demographic factors and responses on noncompliance**

| Patient parameters | Univariable | | Multivariable | |
|---|---|---|---|---|
| | Odds ratio (95%CI) | *P* | Odds ratio (95%CI) | *P* |
| Age (a) | 0.96 (0.92-1.01) | 0.079 | 0.95 (0.91-1.00) | 0.048[b] |
| Duration of treatment (a) | 0.94 (0.84-1.06) | 0.331 | 0.91 (0.79-1.05) | 0.180 |
| GQL-15[a] | 1.01 (0.99-1.04) | 0.251 | - | - |
| Often forget taking eye drops[a] | 1.02 (1.00-1.04) | 0.061 | 1.02 (1.00-1.04) | 0.064 |

[a]On a scale from 0 to 100; [b]$P<0.05$.



**Figure 2 Correlation between GQL-15 (on a scale from 0 to 100) and duration of glaucoma (in years).**
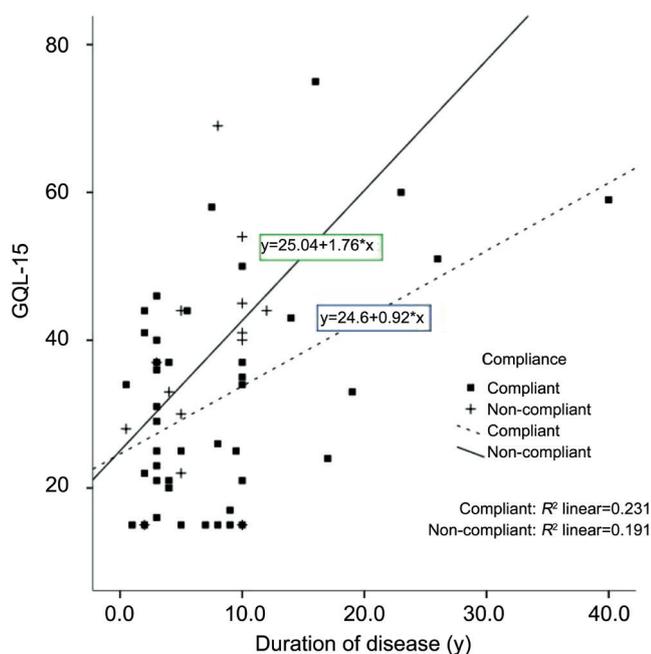


**Figure 3 Correlation between GQL-15 (on a scale from 0 to 100) and duration of eye drop treatment (in years).**

comparable to some reported findings in other populations[3], but was much higher than that reported by a similar local research (37%) a decade ago[16]. It is proposed that difference in definitions of noncompliance, advancement in drug delivery, improvements in patient consultations and knowledge, *etc*. may explain the gap. With continuous patient recruitment and representative demographics among respondents, the subjects are representative of the local glaucoma population in the public sector in the current era. Hence, our study shows that the compliance in the public sector in Hong Kong is comparable to that in other parts of world.

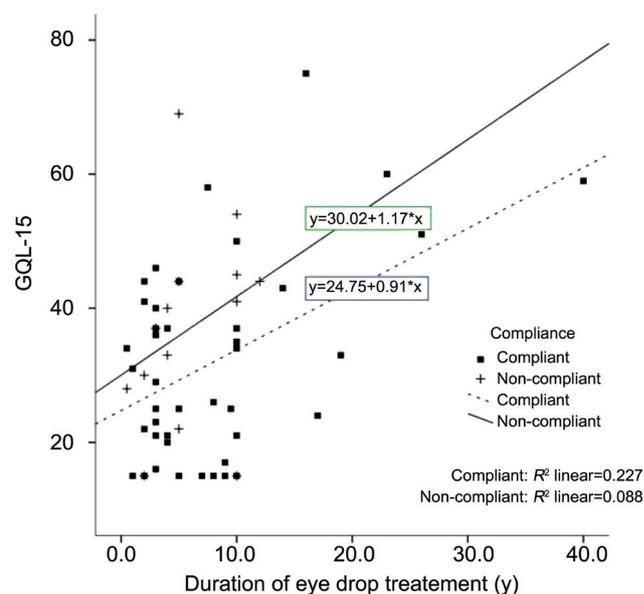**Quality of Life**　A statistically significant correlation ($P<0.01$

overall) was found between GQL-15 score and duration of disease or treatment. This indicates vision-related quality of life deteriorates with disease course, despite the use of long-term glaucoma treatment. The finding matches with the consensus that topical IOP lowering treatment slows down disease progression, but does not provide a cure to chronic glaucoma.

**Predictive Factors of Noncompliance**　The study falls short in establishing any statistically significant relationship between compliance and demographics, attitude, knowledge or quality of life (represented by GQL-15 or numerical scale).

For subjective components, the factor "correctness of usage of eye drops" showed some positive but statistically insignificant

relationship with compliance at $P=0.090$. This observation was in-line with many described studies that forgetfulness is a central component in noncompliance[3-4,14]. Regarding knowledge, a study showed ability to describe the disease correctly in own words was a protective factor[3]. However, our study, making use of objective questions, failed to establish any significant overall relationship between factual knowledge towards glaucoma and their compliance, as in the study the questions adopted from[11]. A possible reason was that the scope of knowledge we covered was too broad. Items bore varied clinical significance to different patients, so the knowledge tested was of comparatively less relevance to patients' recognition of the disease.

Evidence was conflicting on the significance of objective predictors (such as demographics and regimen complexity) on compliance[3-5,14,17], but a systematic review has drawn a rather pessimistic conclusion to this question[18]. We therefore decided to search for possible independent predictive factors, with a focus on objective factors, of compliance among our subjects. Eventually 4 factors, namely age, duration of treatment, quality of life (as GQL-15 score) and forgetfulness, were selected for logistic regressions. The choice was based on a previous report[17] and for the significance in local clinical settings. However, quality of life was not entered in multivariable logistic regression for its significant correlation with on duration of treatment. On the final multivariable logistic regression model, patient age was noted to be an independent protective factor of noncompliance (OR=0.95 per year of age, $P=0.048$). The observation was in line with previous reported findings in other countries[17]. In the locality, this finding may be a result of younger individuals being too busy or perceiving the disease as a less concern in their lives. Forgetfulness was a marginally significant ($P=0.064$) predictor of noncompliance. Its positive relationship with noncompliance may well explain the cause of latter.

Clinically, we suggested ophthalmologists and other allied professionals to have a higher index of suspicion on the compliance of younger and forgetful patients towards glaucoma treatment. Their compliance and difficulties in drug usage, if any, should be explored. Strategies such as educational class and reducing frequency of dosing, visual cues, as well as reminders by family, may be adopted to improve the compliance. Unfortunately, evidence is currently inconclusive, and there is still insufficient evidence to recommend any single strategy over others on efficacy or economic grounds[18-19]. Hence, a case-by-case approach should be adopted to cater the specific needs and difficulties of each patient.

**Costs and Impacts** Despite not reaching statistical significance, certain trends were observed in cost on individual patient in terms of vision-related quality of life. The score in all 4 factors of GQL-15 is higher in noncompliant group, suggesting

greater visual impairment in the group. In addition, attenuation of quality of life by glaucoma was more profound in the noncompliant group (14.4% *vs* 22.9%, *i.e.* an extra 8.5% attenuation in noncompliant group), suggesting they may be aware of faster deterioration and greater disruption of life due to improper management.

On a societal level, with an estimated prevalence of glaucoma of 3% in Chinese population aged 40 or above, glaucoma affects about 118 000 individuals in Hong Kong[20]. We may here attempt estimating the quality-adjusted life year lost due to noncompliance. On a territory basis, by multiplying the additional 8.5% of quality of life attenuated with 25% (estimated noncompliance) of 118 000 (estimated glaucomatous population), it was projected that 2510 quality-adjusted life years were potentially salvageable by improvement in compliance.

The extra economic burden of noncompliance on the public health care system was estimated. For simplicity, here we only provide an account for the direct drug cost involved. The average daily cost for topical glaucoma medication was $ 0.71 per noncompliant patient. Assuming half of all the local glaucoma patients were followed up by the public system, daily expenditure on prescriptions to noncompliant glaucoma patients would be over $ 10 000. Annually, over $ 3.7 million is spent by the public system on medications bearing questionable efficacy due to improper usage. The drug cost involved is significant even when additional cost involved in extra surgery and indirect cost are yet to be included. Thus, introduction of extra measures to improve compliance should be considered by administrators on economic ground.

**Limitation** There were some limitations to this study. First, it involved only a small sample size ($n=76$) and in which a significant proportion ($n=19$, 25%) had to be excluded. On particular findings, with a *post-hoc* analysis, the study's power in detecting a statistically significant difference in forgetfulness (24% *vs* 43%, $P=0.107$) and correctness of eye drop usage (66% *vs* 55%, $P=0.090$) of such size are both 40%. The study was therefore underpowered for a number of outcomes, which rendered type II errors easier to be committed. Moreover, there could be potential recall bias since most information used in the study was obtained from patients' recall of their behaviour over past few months. Some patients also required frequent assistance in interpreting individual questions. This could pose a potential flaw in the reliability of results. Furthermore, self-reporting nature of the study predisposed patients, especially those requiring interpretation by researchers, to give socially standardised answers. This could lead to an overestimation of drug compliance.

**Implications** Despite being statistically insignificant, patterns and trends observed in the current study suggest larger scale studies on similar topic should be done in future. To improve the quality of the evidence, a prospective cohort study should

be designed; with objective drug compliance measured using electronic devices recording usage and volume. This will eliminate recall bias, and the data generated may be cross-checked with the self-reported compliance. Information on general health could be controlled to reduce confounding.

Drug compliance has always been a big issue in outpatient management of chronic diseases. Extra challenges are involved in glaucoma due to unique dosage form and long disease course. Yet, the issue is largely ignored despite presence of extensive researches on its prevalence and consequences. This study once again highlights the decisive outcomes brought about by noncompliance, reminding us the severity and prevalence of this hidden obstacle to management. For the sake of patients and the public system, clinicians should pay more attention to assess and explore drug compliance of their patients; and most importantly, look for ways of improvement.

## ACKNOWLEDGEMENTS

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