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ORIGINAL RESEARCH ARTICLE

Patient Medication Preferences for Managing Dry Eye Disease: The Importance of Medication Side Effects

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Abstract

Objectives The side effects of dry eye medications can lead to medication non-adherence and, eventually, to poor outcomes. This study aimed to quantify to what extent the side effects of dry eye disease (DED) medications (burning/stinging sensation and blurring) are important to patients compared to medication benefits or costs.

Methods Patients diagnosed with DED were recruited at a referral eye center in Singapore ($n = 139$). This study utilized a Discrete Choice Experiment where patients were presented with 10 choice tasks where they were asked to choose between their current medication (or no medication), and two hypothetical medications that varied based on five attributes: duration of burning/stinging, duration of blurring, time to medication effectiveness, medication frequency, and out-of-pocket cost. The main outcomes were relative attribute importance and predicted uptake.

Results Latent class logistic regressions found two groups with distinct preferences. For both classes, duration of burning/stinging (Class 1 = 23%, Class 2 = 29%) and cost (Class 1 = 24%, Class 2 = 27%) were the most important attributes while duration of blurring (Class 1 = 15%, Class 2 = 9%) was the least important. The predicted uptake of a medication increased 18 percentage-points when burning/stinging duration decreased from 2 h to a few minutes. The predicted uptake for new medications was lowest for those on medication with well-controlled symptoms and highest for those who were not on medication and could not control their symptoms effectively.

Conclusion This study showed that duration of burning/stinging was an important factor when choosing medications. Incorporating patient preferences in medication decisions can potentially improve patient acceptance of a treatment regimen.

Key Points for Decision Makers

Duration of burning sensation and out-of-pocket costs were the most important attributes while duration of blurring was the least important attribute when choosing DED medications.

The predicted uptake for new medications was lowest for those on medication with well-controlled symptoms and highest for those who were not on medication and could not control their symptoms effectively.

Development of medications that minimize burning/stinging sensation can help improve uptake of and/or adherence to treatment regimens.

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1 Introduction

Dry eye disease (DED) is the loss of homeostasis of the tear film [1]. World prevalence of DED ranges between 4.3 and 52.4% [2]. Dry eye disease is more prevalent among people of Asian descent, older individuals, and females [2–4]. In terms of disease severity, about 50% of the DED patients experience mild disease, while 42% and 8% are estimated to experience moderate and severe DED, respectively [5]. Common patient-reported symptoms include dryness, grittiness, itching, redness, fluctuating visual disturbances, and ocular fatigue [6]. These symptoms are likely to cause a negative impact on patient's visual function and abilities to perform daily visual activities and can lead to depression and reduced quality of life [7–9]. If left untreated, patients may experience continued discomfort and impaired vision. In severe cases, DED can result in permanent vision loss [10].

While the less severe symptoms of DED are typically treated with over-the-counter eye drops, prescription medications are often recommended for moderate and severe symptoms. For the management of DED (and eye diseases in general), off-label medications, such as certain cancer medications, or on-label medications can be modified to reach optimal effectiveness and tolerance for side effects [11]. However, medications used for DED may take several months of continued daily use to become effective [12]. In addition, side effects experienced immediately after medication use such as blurred vision and burning sensation are quite common [12, 13]. The delayed long-term benefits but immediate side effects following treatment can lead to treatment non-adherence [14, 15]. Patients may discontinue their medication, or they may not adhere to the prescribed frequency and dose, resulting in lower frequency of medication administration. For optimal management of DED, an improved formulation with tolerable side effects while not compromising its effectiveness is required.

The direct costs (e.g., therapeutic management and consultation visits) and indirect costs (e.g., productivity loss) of DED pose a high economic burden to both patients and society. In the USA alone, societal disease burden was estimated to be US$55 billion [16]. When choosing a medication, affordability of medications can also be a concern to the patients in health care systems where out-of-pocket payments remain a significant percentage of total health spending [17]. It is thus necessary for clinicians and pharmaceutical companies to understand patient medication preferences, and the trade-offs that patients are willing to make when selecting DED medications [18–21]. To the best of our knowledge, no study has investigated how patient preferences for DED medications are affected by side effects as opposed to the benefits and costs of medications.

This study aimed to quantify the importance of duration of burning/stinging sensation and blurring upon medication administration to patients, in relation to time to effectiveness, medication frequency, and out-of-pocket costs when choosing a DED medication. The findings of this study will inform drug formulations with the goal to enhance patients' acceptance of and adherence to the medications. To address this aim, we developed a discrete choice experiment (DCE), a survey research method that has been used extensively to quantify preferences for healthcare services and products [22]. The survey was conducted with DED patients in Singapore, where the prevalence of DED is 12.3% [3].

2 Methods

2.1 Study Setting

The cross-sectional survey was administered face-to-face by trained interviewers between August 2019 and October 2020 at the Singapore National Eye Centre (SNEC). Data collection was halted temporarily between February 2020 and June 2020 due to COVID-19 restrictions. Eligibility criteria were having received outpatient prescription medicated eye drops (e.g., cyclosporine, dexamethasone, and tacrolimus) for at least 3 months, or to have used them in the past year. All patients who attended the dry eye specialty clinic at SNEC were screened for eligibility. Eligible patients were then invited to participate in the study when they were in the clinic for regular consultations. Of the 142 eligible patients identified, two declined participation. The remaining 140 patients provided written informed consent. One patient withdrew from the study as they found the hypothetical survey questions challenging. A total of 139 patients completed the survey, which was administered on tablets via Qualtrics platform in English or Mandarin based on the patient's preference. The study was approved by the SingHealth Centralised Institutional Review Board (CIRB Ref. No.: 2018/2022).

2.2 Survey Development

Discrete Choice Experiment is a research methodology which uses a series of choice tasks where individuals select the preferred alternative from two or more scenarios. This allows researchers to assess individual preferences and trade-offs for medications with selected attributes [23]. These attributes are characterized by their levels and the utility that the individuals achieve is determined by the different attribute level combinations.

The selected attributes were informed by the research question, existing evidence from literature, and input from clinicians who provided consultations to patients with DED

at the study site. Delayed benefit of DED medications was reported as one of the main concerns of non-adherence or suboptimal medication use [15]. We thus framed the 'benefit' attribute in terms of time taken to achieve a noticeable improvement in symptoms. Frequency of eye drop applications may affect medication adherence as higher dosing frequency has been found to be associated with non-adherence [24–26], especially when patients experience side effects [25]. Through a literature review, we identified 12 studies with DED patients. From these articles, we identified the potential side effects associated with DED medications. We shortlisted burning/stinging sensation and vision blurring after medication use as the most commonly reported distinctive side effects that the patients complain about [12, 13]. Lastly, in Singapore, DED medications are not subsidized by the government and most common health insurance plans do not cover them. Thus, patients pay the medical expenses associated with DED out of their pocket.

The survey instrument was pretested with ten patients by following the "think-aloud" protocol [27] to examine if all relevant attributes were included and if patients were able to understand the questions. Participants recruited during pretesting did not mention any other medication attribute or feature that was missing and should be included in the study. Editorial changes were made based on the feedback from the pretest interviews. For example, "eye drop regimen" was revised to "medicated eye drops". We also added more questions to assess patients' experience with the side effects of their current medication. Responses gathered from the ten participants during pretesting were not included in the final analysis.

The final list included five attributes: (1) time taken to achieve a noticeable improvement in symptoms, (2) frequency of eye drop applications, (3) duration of vision blurring after medication use, (4) duration of experiencing burning/stinging sensation after medication use and (5) monthly out-of-pocket medication cost. The levels for the attributes were selected based on clinical evidence and discussions with clinicians. Cost levels were selected based on the current medication (both subsidized and unsubsidized) costs at the local hospitals (Table 1).

The survey first provided information pertinent to DED and the attributes used in the study. A sample DCE task was then presented with instructions. In each DCE task, respondents were asked to choose between two hypothetical eye drops (A and B) with differing levels of the five attributes. This was followed by a question on whether respondents would choose their selection (Eye Drops A/B) or their current medication, if they had any, or no medication if they were not using any medication at the time of the survey (Fig. 1). The survey also included questions about patient demographics, their experience with current or past medicated eye drops, and affordability of medications.

The DCE tasks were created using an experimental design based on optimal D-efficiency using the SAS 9.4 software, which resulted in 32 choice tasks [28]. The choice tasks were divided into four blocks with eight tasks to reduce cognitive burden. Each respondent was randomly assigned to one of the blocks. In addition, two manually prepared choice tasks were added to each block. The first task had one alternative that was strictly better than the other one on all the attributes. This task was intended to determine the

Table 1 Attributes and levels used in the DCE tasks

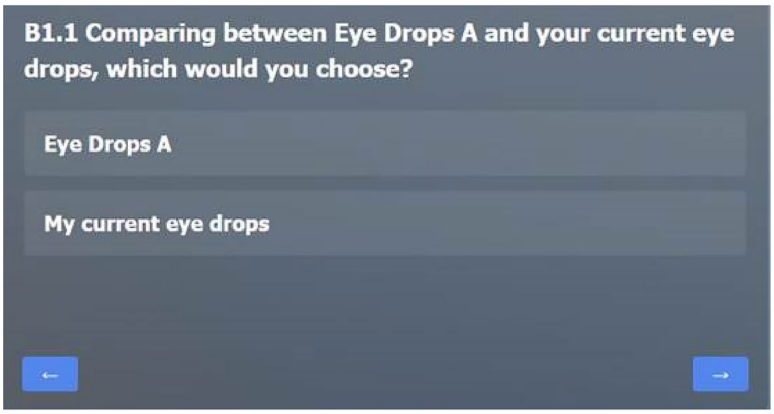
Attributes	Levels
Time taken to achieve a noticeable improvement in symptoms	1 day 1 week 1 month 2 months
Frequency of administering the eye drops	Once a week Every other day Once a day Three times a day
Duration of experiencing vision blurring after using the eye drops	A few minutes 15 min 1 h 2 h
Duration of experiencing burning/stinging sensation after using the eye drops	A few minutes 15 min 1 h 2 h
Out-of-pocket cost of eye drops per month	SGD 50 (USD 37.3) SGD 100 (USD 74.5) SGD 200 (USD 149.0) SGD 300 (USD 223.5)

DCE discrete choice experiment, *SGD* Singapore dollar, *USD* US dollar

If you had to choose one of these eye drops, which would you choose?

	Eye Drops A	Eye Drops B
Time taken to achieve a **noticeable improvement** in symptoms	1 month	1 week
How often do you need to apply the eye drops	Once a week	3 times a day
Duration of experiencing **vision blurring** after using the eye drops	15 minutes	A few minutes
Duration of experiencing **burning/stinging** sensation after using the eye drops	2 hours	15 minutes
Out-of-pocket cost of eye drops per month	$50	$200
If you had to choose one of these eye drops, which would you choose?	**Eye Drops A** ○	**Eye Drops B** ○

[If patients were using medicated eye drops at the time of the survey]



[If patients were **not** using medicated eye drops at the time of the survey]

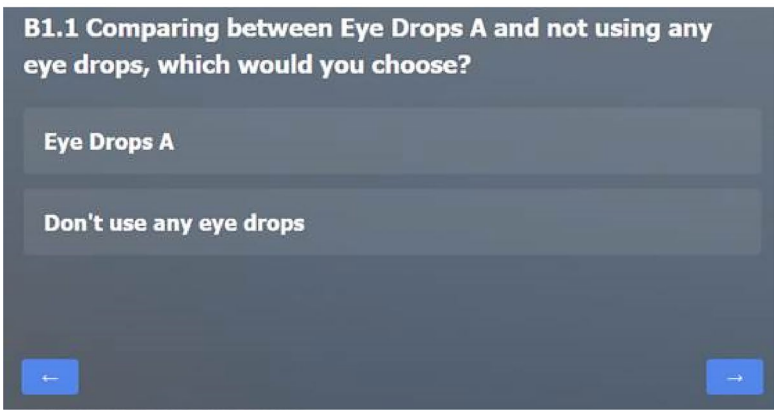


Fig. 1 Sample discrete choice experiment (DCE) task

respondent's attentiveness. Any utility maximizing individual is expected to choose the better alternative regardless of their individual preferences [29]. The second was a holdout task that was used to test the accuracy of model prediction. This choice task was excluded from the analysis. The results of the model using data from the other tasks were compared to choice data from the holdout task [30]. Levels for the holdout task were chosen according to the characteristics of the current available medications (i.e., cyclosporine and corticosteroid formulations) (Fig. 1 presents the holdout task). Each respondent was shown ten tasks in total. The full survey is provided as Supplementary Material 1.

2.3 Statistical Analysis

According to Orme and Johnson [31, 32], the minimum sample size required depends on the number of choice tasks ($t = 8$), the number of alternatives ($a = 2$), and the largest number of levels for any attributes ($c = 4$): $N \geq \frac{500c}{a \times t} = 125$. We recruited more patients to enhance precision. Our analytical sample consisted of 139 participants.

When analyzing the DCE choice data, we combined answers to the two types of the questions and the choice was indicated as the one chosen among the three options (Eye Drops A, Eye Drops B or patient's current medication/no medication). For example, if someone chose Eye Drops A over Eye Drops B but then their current medication over Eye Drops A, then current medication was indicated as the chosen alternative among the three options.

A latent class logistic model (LCM) was chosen as it allowed preference heterogeneity between mutually exclusive and exhaustive groups/classes [33]. This allows preferences to be different across classes. We also investigated predictors of class membership. Potential predictors included variables related to patient-reported experiences with their disease and medications. We hypothesized that patients who had good experiences with their current medication (i.e., control their symptoms well, have no adherence issues or side effects) would be more likely to be in a class with positive preference for the status quo (i.e., current or no medication). Those who are on medicated eye drops (hereafter, 'on medication') and are not on medicated eye drops (hereafter, 'not on medication') may also have different preferences. Since not being on medication can be due to either managing DED symptoms well without medication or due to not being satisfied with the existing medications, we created dummy variables indicating: (1) not on medication and controlling symptoms well, (2) not on medication and controlling symptoms neutrally or poorly, and (3) on medication and controlling symptoms neutrally or poorly, where the reference level was being on medication and controlling symptoms well. We also included variables indicating experiencing severe medication-related side effects and having adherence issues. Since the number of different eye drops a patient uses may be correlated with preferences for medications and financial ability to cover DED-related medical costs may affect preferences regarding cost, we also investigated these variables as predictors. We used NLOGIT 5.0 to analyze choice data and STATA 16 for the other types of analyses.

All the attribute levels were effects coded. The worst level of each attribute was set as the reference level. The coefficients (β) were interpreted as preference weights for each attribute level. The model also had an alternative specific constant (ASC) for the current/no medication reflecting the utility gained associated with the current/no medication over the hypothetical eye drops. We calculated the relative attribute importance (RAI) for each class, informing the extent to which one attribute is important compared to the other attributes used in the design [34]. For each attribute, we took the difference between the best and worst coefficients of an attribute and normalized it to the sum of all attribute differences. We then scaled RAI to present it as a proportion out of 100 for each class.

We also calculated the predicted uptake as the probability of choosing a hypothetical medication at certain levels of each attribute compared to the current/no medication. We first calculated the conditional probability of choosing the new medication for each class. We then calculated the probability of each individual choosing the new treatment by weighting the conditional probability of choosing a medication by individual-specific class membership probabilities. The individual-specific uptake predictions were then used to calculate the predicted uptake for the full sample and different subsamples based on medication use and symptom control (See Supplementary Material 2 for details).

3 Results

3.1 Patient Characteristics

Patient characteristics are presented in Table 2. The mean (standard deviation [SD]) age of the patients was 63 (13) years. Most were females ($n = 124$, 89%). This is consistent with the higher prevalence of DED among females. Most patients were Chinese ($n = 133$, 96%) and the median monthly household income was SGD3000–3999 (US$2264–3019).

Close to half ($n = 61$, 44%) of the patients were diagnosed with DED less than five years ago. Most of the patients ($n = 114$, 82%) were on medication while the rest were not on medicated eye drops ($n = 25$, 18%) at the time of the survey. Patients who reported well or very well-controlled symptoms made up 41% ($n = 57$) of the sample and 52 of these patients were on medication. Among patients who reported neutral or poorly controlled symptoms (59%, $n = 82$), 62

Table 2 Patient characteristics ($N = 139$)

Patient characteristics	Mean ± SD/*N* (%)
Demographics	
Age	62.7 ± 13.4
Ethnicity	
Chinese	133 (95.7%)
Malay/Indian/others	6 (4.3%)
Female	124 (89.2%)
Employment status	
Employed full-time	44 (31.7%)
Employed part-time	21 (15.1%)
Unemployed	3 (2.1%)
Housewife	22 (15.7%)
Retired	49 (35.2%)
Monthly household income (SGD)	
Less than SGD1000	26 (18.7%)
SGD 1000–SGD 1999	13 (9.3%)
SGD 2000–SGD 2999	13 (9.3%)
SGD 3000–SGD 3999	25 (18.0%)
SGD 4000–SGD 4999	7 (5.0%)
SGD 5000–SGD 5999	11 (7.9%)
SGD 6000–SGD 6999	7 (5.0%)
SGD 7000–SGD 9999	15 (10.8%)
SGD 10,000 and over	22 (15.8%)
Time since diagnosis of DED	
Less than 3 months	2 (1.4%)
More than 3 months < 1 year	5 (3.6%)
More than 1 year but < 5 years	54 (38.9%)
More than 5 years but < 10 years	40 (28.8%)
More than 10 years but < 20 years	24 (17.3%)
More than 20 years	14 (10.1%)
Self-reported DED symptom control	
Very well controlled	4 (2.9%)
Well controlled	53 (38.1%)
Neutral	60 (43.1%)
Poorly controlled	19 (13.7%)
Very poorly controlled	3 (2.2%)
Status of using medicated eye drops prescribed by doctor	
Current users	114 (82.0%)
Not current users, but have used the medicated eye drops in the past	25 (18.0%)
Self-reported experience with current eye drops	
Time taken to achieve a noticeable improvement	
Less than 1 day	4 (3.5%)
More than 1 day but < 1 week	8 (7.0%)
More than 1 week but < 1 month	9 (7.9%)
More than 1 month but < 2 months	13 (11.4%)
More than 2 months but < 3 months	10 (8.8%)
More than 3 months but < 6 months	10 (8.8%)
More than 6 months	10 (8.8%)
I have not experienced symptom relief yet	23 (20.2%)
I am not sure	27 (23.7%)
Frequency of experiencing vision blurring after medication use	
Yes, every time	18 (15.8%)

Table 2 (continued)

Patient characteristics	Mean ± SD/*N* (%)
Yes, sometimes	23 (20.2%)
No	73 (64.0%)
Duration of vision blurring after medication use	
About a few minutes	30 (73.2%)
More than a few minutes but < 15 min	8 (19.5%)
More than 15 min but < 30 min	3 (7.3%)
More than 30 min but <1 h	0 (0%)
More than 1 h but < 2 h	0 (0%)
More than 2 h	0 (0%)
Frequency of experiencing burning/stinging sensation after medication use	
Yes, every time	38 (33.3%)
Yes, sometimes	41 (36.0%)
No	35 (30.7%)
Duration of burning/stinging sensation after medication use	
About a few minutes	60 (75.9%)
More than a few minutes but < 15 min	9 (11.4%)
More than 15 min but < 30 min	5 (6.3%)
More than 30 min but < 1 h	1 (1.3%)
More than 1 h but < 2 h	1 (1.3%)
More than 2 h	3 (3.8%)
Frequency of eye drops application	
5-times daily	0 (0%)
4-times daily	18 (15.8%)
3-times daily	2 (1.7%)
Twice daily	22 (19.3%)
Once daily	72 (63.2%)
Once every 2 days	0 (0%)
Once a week	0 (0%)
Ability to manage the out-of-pocket costs of current eye drops	
Very well	19 (16.7%)
Fairly well	58 (50.9%)
Poorly	15 (13.2%)
Don't pay for eye drops	22 (19.3%)

DED dry eye disease, *SD* standard deviation, *SGD* Singapore dollar

were on medication. Among patients on medication (n = 114), about one-third (n = 41, 36%) reported experiencing vision blurring after medication use while more than two-thirds (n = 79, 69%) reported experiencing burning/stinging sensation. Most of the patients on medication (n = 72, 63%) applied their eye drops once a day and the remainder applied them multiple times a day.

3.2 Patient Medication Preferences

Among 2-, 3-, and 4-class LCMs, the 2-class model was chosen based on the significance of estimates, the number of low prevalence classes, and how well the model predicted the holdout task (Supplementary Material 3). The estimated prior probabilities for class membership were 62% for Class 1 and 38% for Class 2 (Table 3); 94% of the individual probabilities were either smaller than 0.1 or greater than 0.9 showing that respondents were well assigned to the two classes. The 2-class model predicted that 18%, 16%, and 67% of the sample would choose Eye Drops A, Eye Drops B, and current/no medication, respectively in the holdout task, which was highly similar to the actual data of 18%, 17%, and 65% for Eye Drops A, Eye Drops B, and current/no medication, respectively. We did the same comparison for those on medication and not on medication separately. For those on medication, the model predicted 15%, 13%, and 71% for the alternatives in the hold-out task and the actual choices among this subsample were 15%, 16%, and 69%. For those not on medication, the model predicted 28%, 27%, and 45% for the alternatives in the hold-out task and the actual

Table 3 Latent class logistic regression results (2-class) ($N = 139$)

	Class 1			Class 2		
	β	SE	p value	β	SE	p value
Time taken to achieve noticeable improvement in symptoms						
1 day	0.696**	0.301	0.021	0.705***	0.138	0.000
1 week	0.274	0.408	0.501	0.123	0.128	0.334
1 month	0.033	0.398	0.933	− 0.206	0.152	0.175
2 months (Ref)	− 1.003**	0.426	0.019	− 0.622***	0.144	0.000
Frequency of eye drops to treat dry eye symptoms						
Once a week	0.741**	0.323	0.022	0.340*	0.194	0.079
Every other day	0.306	0.424	0.470	0.188	0.192	0.327
Once a day	− 0.021	0.390	0.957	0.023	0.194	0.905
3 times/day (Ref)	− 1.026*	0.526	0.051	− 0.551***	0.169	0.001
Duration of experiencing blurring sensation after using the eye drop						
A few minutes	0.732**	0.326	0.025	0.133	0.145	0.359
15 min	0.000	0.251	0.999	0.036	0.148	0.811
1 h	− 0.069	0.321	0.829	0.239*	0.137	0.082
2 h (Ref)	− 0.662**	0.323	0.040	− 0.407***	0.147	0.006
Duration of experiencing burning/stinging sensation after using the eye drop						
A few minutes	1.063***	0.299	0.000	0.835***	0.167	0.000
15 min	0.837***	0.300	0.005	0.317**	0.130	0.014
1 h	− 0.809*	0.473	0.087	− 0.194	0.154	0.207
2 h (Ref)	− 1.091**	0.527	0.038	− 0.958***	0.171	0.000
Out-of-pocket cost of medication per month						
SGD50	1.308***	0.370	0.000	0.709***	0.148	0.000
SGD100	0.179	0.328	0.585	0.401***	0.141	0.004
SGD200	− 0.619	0.501	0.217	− 0.129	0.151	0.391
SGD300 (Ref)	− 0.869**	0.382	0.023	− 0.980***	0.149	0.000
ASC for current/no treatment						
ASC	4.140***	0.426	0.000	− 0.673***	0.207	0.001
Class probabilities	0.62			0.38		
Class 1 membership predictors						
Constant	1.630***	0.507	0.001			
On medication and not well-controlled symptoms	− 1.396**	0.633	0.028			
Not on medication and well-controlled symptoms	− 1.224	1.364	0.369			
Not on medication and not well-controlled symptoms	− 2.765**	1.133	0.015			
(Ref: On medication and well-controlled symptoms)						
Akaike information criterion	1337.5					

ASC alternative specific constant, β coefficient, *CI* confidence interval, *SE* standard error, *SGD* Singapore dollar

*,**,***Significance at the 10%, 5%, and 1% levels, respectively

choices among this subsample were 32%, 24%, and 44%. Only two respondents failed the attention task. These were kept for subsequent analyses as excluding them did not affect the findings.

As expected, both classes preferred shorter duration of time to achieve improvement, lower frequency of eye drop applications, shorter duration of burning/stinging sensation, as well as lower out-of-pocket cost (Table 3). Patients in Class 1 also preferred shorter duration of vision blurring. For those in Class 2, there was disordering between 15 min and 1 h of blurring, but the coefficient estimates were not significantly different from each other (p value = 0.376).

For both classes, duration of burning/stinging sensation (Class 1 = 23%, Class 2 = 29%) and out-of-pocket cost (Class 1 = 24%, Class 2 = 27%) were the most important attributes followed by time to achieve improvement (Class 1 = 19%, Class 2 = 21%) and application frequency (Class 1 = 19%, Class 2 = 14%) (Fig. 2). Duration of blurring (Class

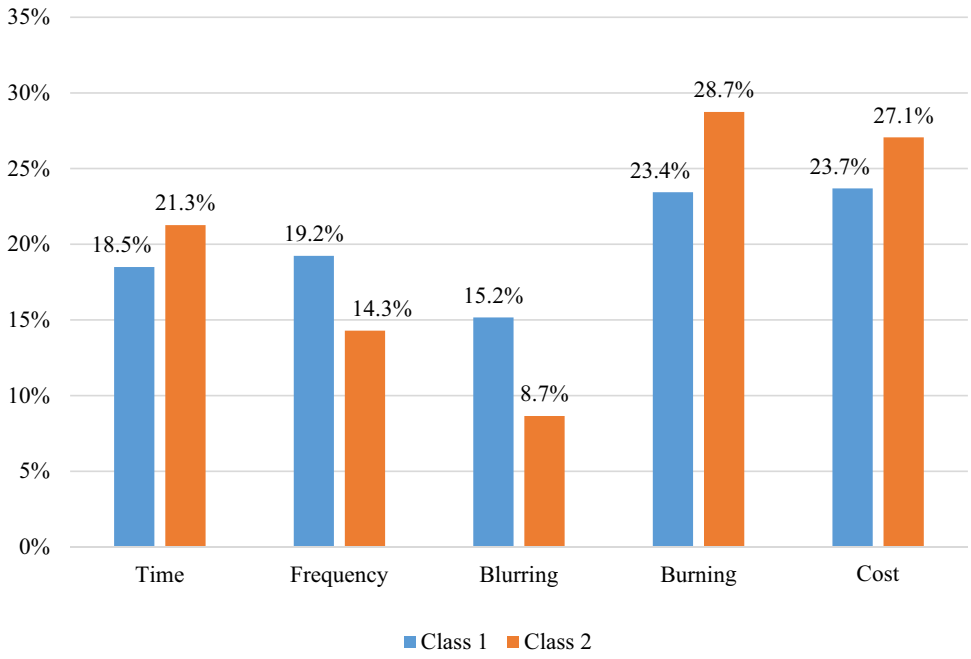


Fig. 2 Relative attribute importance (out of 100%)

1 = 15%, Class 2 = 9%) was the least important attribute for both classes.

Patients in Class 1 had positive preferences ($\beta = 4.140$, p value <0.01) for the current/no medication while those in Class 2 had negative preferences for it ($\beta = -0.673$, p value < 0.01). Patients were less likely to be in Class 1 (vs Class 2) if they were on medication and reported that their symptoms were not well controlled ($\beta = -1.40$, p value = 0.028) or not on medication and reported that their symptoms were not well controlled ($\beta = -2.76$, p value = 0.015) as opposed to those who were on medication and reported well-controlled symptoms. Covariates related to adherence, current medication side-effects, number of eye drops and financial ability to cover medication costs were found to be not significant (p value > 0.5 for all) and dropped from the final model.

Figure 3 shows the predicted uptake for the overall sample based on changes in the duration of burning/stinging sensation and blurring, respectively. We set the other attributes to fixed levels that were commonly seen in current DED medications (time-to-effectiveness: 1 month, frequency: 3 times a day, out-of-pocket cost: SGD100/month). At a few minutes of burning/stinging sensation and a few minutes of blurring, the predicted uptake for a new medication was 32%. As the duration of these side effects increased from a few minutes to 2 h, the predicted uptake decreased. The decrease was larger for burning/

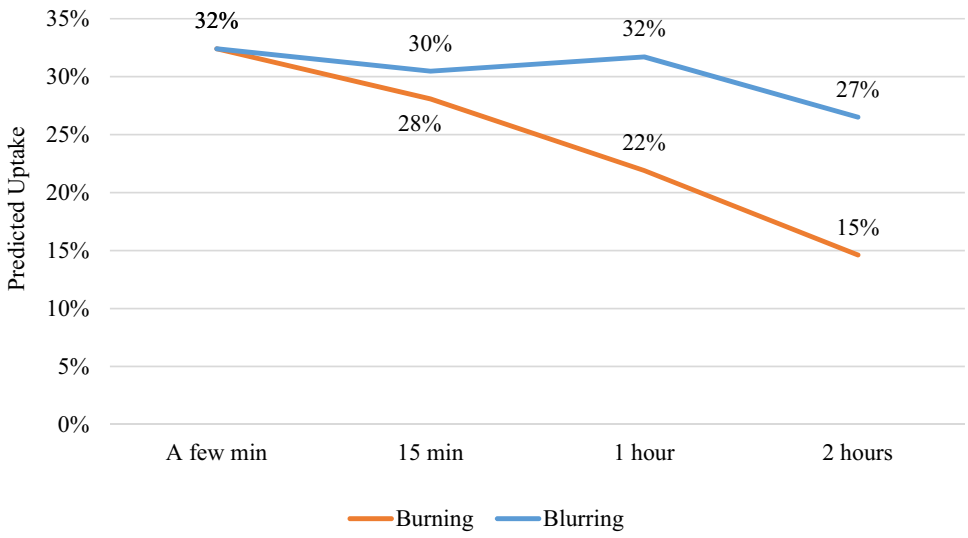


Fig. 3 Predicted uptake based on duration of burning/stinging sensation and duration of vision blurring (against current/no medication). *Other attributes were set to fixed levels: time taken to achieve improvement: 1 month, Frequency of eye drops: 3 times a day, Out-of-pocket cost: SGD 100/month

stinging sensation (from 32 to 15%) than blurring (from 32 to 27%).

For a new medication with a few minutes of burning/stinging sensation and a few minutes of blurring, the predicted uptake was, on average, lowest for those on medication with well-controlled symptoms (16% [95% confidence interval = 10–24%]). The predicted uptake was 34% (4–63%) for those not on medication with well-controlled symptoms, and 37% (28–45%) for those on medication having not well-controlled symptoms. The predicted uptake was the highest at 60% (46–72%) for those not on medication and experiencing not well-controlled symptoms.

4 Discussion

We used a DCE survey to quantify how important side effects such as burning/stinging sensation and vision blurring were to patients when choosing a DED medication. We found two groups of patients with distinct preferences. The estimated prior probabilities for class membership were 62% for Class 1 and 38% for Class 2. The differences between these groups were mainly driven by their preference towards current/no medication. Patients who reported well-controlled symptoms were more likely to have a positive preference for current/no medication (Class 1), while those who could not control their symptoms effectively were more likely to have a negative preference for the status quo (i.e., current/no medication) (Class 2).

Regardless of being on or not on medication, symptom control was one of the key factors affecting uptake. These findings are consistent with reports in studies involving patients with eye diseases. Chance of medication discontinuation due to medication side effects was found to be low when patients were satisfied with the medication [35]. Similarly, lack of efficacy and poor local tolerance were the main reasons for medication switching [36].

It was not surprising that cost was a major concern to Singaporean patients as, at the time of the survey, no prescription DED medications were subsidized by the government, with 80% of our sample reportedly paying for their medication out of pocket. In addition, the use of non-pharmacological treatments such as punctum plug, punctum cautery and tarsorrhaphy, eye masks, omega-3 fatty acids, humidifiers and frequent replacement of contact lenses contribute to the financial burden [37, 38]. Any increase in the cost of prescription eye drops will increase the total out-of-pocket spending for DED management, imposing additional burden on patients.

Our findings support past literature demonstrating that burning/stinging sensation was the most important consideration for all patients [39, 40] and indicate that mitigating burning/stinging sensation could potentially increase patient satisfaction and medication adherence. We also found that patients did not consider vision blurring a major concern. This may be because most (63%) reported using medication only once a day. Vision blurring may have also been managed by using eye drops before sleep to limit interference with daily living. This strategy, however, would not help prevent burning/stinging sensation.

Our study had several limitations. First, although the selection of attributes was informed by the research question, clinician input, and extensive evidence from the existing studies on DED medications, patients were not directly involved in selecting the attributes. In addition, other clinicians might have suggested different attributes to be used in this study and this could affect the findings. Second, we did not include patients with mucomimetics such as diquafosol as these medications were not available in Singapore at the time of the survey. Third, we also used a convenience sample of patients, so our findings may not be applicable to other healthcare systems, especially those where medication costs may be covered by third-party payers. The mean age of the sample was close to the official retirement age (65 years) in Singapore, which may affect the generalizability to younger and potentially more financially independent participants. Fourth, the potential for increasing ocular pressure of corticosteroids was not included in the DCE design, but this is usually discussed between physician and patient at the time of prescription of these eye drops. If patients required long-term corticosteroids, the dosage would have been toned down to once a day to minimize the risk. Fifth, disease severity as perceived by patients or subjectively assessed by physicians could affect patients' medication preferences. However, disease severity was not recorded as part of this study. Sixth, although we used a dual-response choice format, our modelling technique assumes that individuals were shown Medication A, Medication B, and Current/No Medication all at the same time in a choice set. However, using a latent-class logit model allowed us to account for "current/no medication" option as well as to investigate taste heterogeneity. Lastly, we used the term "predicted uptake" to estimate the potential stated demand or preference share for specific medications. However, decision-making is very complex and is affected by many factors not included in this study design. Thus, uptake in the real world may differ from the estimates presented here in unknown directions.

To the best of our knowledge, this is the first study to systematically quantify patient medication preferences for controlling DED symptoms. Using a DCE allowed us to predict the uptake of a specific novel treatment with known attributes of duration of blurring and burning/stinging sensation, time to effectiveness, frequency of medication and out-of-pocket cost, against current/no medication. The findings can be used to predict the acceptability of new DED medications. For a medicine with time to effectiveness of

one month that needs to be administered three times a day and cost $100 per month, the predicted uptake was 15% if the burning/stinging sensation lasted 2 h after medication administration. However, the predicted uptake increased to 32% if the burning/stinging sensation lasted only a few minutes.

5 Conclusion

In conclusion, though effective medications for DED are available, achieving optimal symptom alleviation remains a challenge as side effects could impact medication adherence. Our study has several important clinical implications. Our findings show that burning/stinging sensation after medication use was a major concern to patients. This suggests that companies should develop medications or formulate concentrations that reduce burning/stinging sensation, and physicians should discuss the potential side effects of medications, especially burning/stinging sensation after medication use with their patients. The predicted uptake could potentially be enhanced if the duration of burning/stinging sensation is reduced. Meanwhile physicians could recommend or prescribe remedies to alleviate burning/stinging sensation. Future efforts should also target patients who cannot effectively control their symptoms with current medications, as they are more likely to be open to trying new medications. Incorporating patient preferences in treatment decisions could potentially improve patient acceptance of and adherence to a treatment regimen.

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Declarations

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Ethics approval The study was approved by the SingHealth Centralised Institutional Review Board (CIRB Ref. No.: 2018/2022).

Consent to participate Informed consent was obtained from all participants prior to commencing interviews.

Consent for publication All authors provide this consent.

Availability of data and material Data are available upon reasonable request.

Code availability Data are available upon reasonable request.

Author contributions Semra Ozdemir, Sharon Wan Jie Yeo, Jia Jia Lee, Eric Finkelstein, and Louis Tong contributed to the study conception and design. Semra Ozdemir and Jia Jia Lee developed the study materials. Sharon Wan Jie Yeo performed the interviews. Semra Ozdemir and Adithya Bhaskar conducted the analysis. All authors contributed to the interpretation of the results, writing, and critical review of the final manuscript.

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