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Determining initial ocular comfort differences between 0.7% olopatadine and 0.035% ketotifen fumarate

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ABSTRACT

Purpose: To compare the ocular comfort at application of topical, over-the-counter, 0.7% olopatadine and 0.035% ketotifen fumarate anti-allergy eye drops.
Methods: This study recruited participants who were minimally symptomatic based upon Standard Patient Evaluation of Eye Dryness (SPEED) questionnaire scores (≤3 units) and who had minimal between-eye inter-ocular comfort differences as judged by visual analog scale scores (VAS; ≤7 units). Baseline comfort was evaluated by eye with a VAS. One drop of 0.7% olopatadine or 0.035% ketotifen fumarate was then applied to the right eye with the alternative drop being immediately applied to the left eye. Participants were next evaluated with the same comfort VAS by eye at drop application, and then at 30 s, 1 min, and 2 min post-application. LogMAR visual acuities and bulbar conjunctival redness were evaluated pre- and post-drop application to judge initial changes.
Results: This study enrolled 159 participants who had a mean ± SD age of 26.3 ± 7.7 years, and 78.6% of the participants were female. The VAS found that the 0.7% olopatadine drop was more comfortable than the 0.035% ketotifen fumarate drop at all time-points. There were no between-eye differences in LogMAR visual acuities, yet bulbar redness was significantly less in 0.7% olopatadine treated eyes compared 0.035% ketotifen fumarate treated eyes.
Conclusion: This study found that topically applied 0.7% olopatadine drops were initially more comfortable than 0.035% ketotifen fumarate drops.

1. Introduction

Allergic conjunctivitis is estimated to affect between 6% and 30% of the general population, and up to 40% of the people in the United States have had at least one ocular allergic event in their lifetime [1,2]. Allergic conjunctivitis is only occasionally observed in isolation with 52% of allergic rhinitis patients reporting concomitant ocular allergy symptoms [3]. Allergic rhinoconjunctivitis has been associated with other atopic disorders such as asthma, eczema, eosinophilic esophagitis, and food allergies, which suggests that eye care practitioners should be completing a full systems review when investigating allergic conjunctivitis [4].

Allergic conjunctivitis is an inflammatory disease of the conjunctiva that is classified as a Type I hypersensitivity reaction [5]. Once an allergen is introduced to a sensitized individual, mast cells, which are found in high quantities in the conjunctival epithelium, become activated by cross-linking of immunoglobulin E (IgE) on their surface, which in turn releases histamine and inflammatory mediators from the cell (e.g., leukotrienes, cytokines, prostaglandins) [6]. Histamine, an early-phase mediator, causes the clinical signs and symptoms of vasodilation, vasopermeability, and itching. The late phase of this inflammatory cascade occurs with the invasion of neutrophils, eosinophils, and basophils six to ten hours after the allergen introduction, which is subsequently followed by lymphocytes and monocytes infiltration [7]. The community thankfully has a few effective topical medications for treating and even preventing the negative sequalae associated with allergic conjunctivitis [8].

Topical therapy categories include mast cell stabilizers, antihistamines, dual-acting agents containing antihistamine and mast-cell stabilizing properties, or vasoconstrictor / antihistamine combination

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drugs [9]. A commonly-prescribed class of allergic conjunctivitis drugs are dual-acting agents containing antihistamine and mast-cell stabilizing properties due to their ability to target both the early and late-phase mediators [10]. These medications typically start to take effect nearly instantly; however, it takes about two weeks to see full efficacy. For patients with chronic allergic conjunctivitis, it is recommended that they use their topical medications consistently. Given that it is crucial for patients to have high compliance with these medications, it is paramount that they are well-tolerated. Initial comfort of a newly prescribed topical medication is one factor that may impact patient compliance.

One potentially well-tolerated, new, over-the-counter, antihistamine/mast-cell stabilizer dual-acting agent is 0.7% olopatadine (Pataday Once Daily Relief Extra Strength; Alcon, Fort Worth, TX). While the literature has found that lower concentrations of olopatadine provide good comfort upon application [11–13], there is currently a dearth of information related to the comfort of 0.7% olopatadine at application. There is likewise little information related to how 0.7% olopatadine might compare to other commonly used over-the-counter allergic conjunctivitis medications such as 0.035% ketotifen fumarate. Thus, the purpose of this study was to compare the comfort of 0.7% olopatadine to 0.035% ketotifen fumarate, which is also a dual-acting agent, at initial application. This information would be beneficial clinically to help guide patient education and expectations of initial comfort of these drops.

2. Methods

2.1. Participants

Participants were recruited via clinical records, email, or fliers at the University of Alabama at Birmingham School of Optometry and Southern College of Optometry. Participants were prescreened for study eligibility with a scripted telephone call and if all criteria were met, a study visit was scheduled (Table 1). During the first portion of the study visit, eligibility was further determined by screening the potential participants with a Standardized Patient Evaluation of Eye Dryness (SPEED) questionnaire and a visual analog scale (VAS) designed to numerically evaluate inter-ocular comfort. With the VAS, participants rated their ocular comfort unilaterally based on a scale of “very uncomfortable” on the far-left side of the line to “very comfortable” on the far-right side of the line. All scores were converted to a 0 to 100 scale with scores of 100 being maximum comfort. Participants were required to have inter-ocular VAS comfort score differences of ≤7 units [14]. Participants were likewise eligible for the study only if they had minimally symptomatic binocular SPEED questionnaire (≤3 units) scores. All eligible participants provided written informed consent. All participants enrolled in this study were healthy and free of ocular disease that could influence initial comfort as determined by the questions in Table 1. This study received IRB approval from each study site, and this study conformed to the Declaration of Helsinki.

Table 1
Questionnaire Used for Eligibility Criteria.

Question	Accepted Answer
How old are you?	18 years or older
Do you have a comfort difference between your eyes?	No
Have you ever worn hard contact lenses?	No
Are you currently using any topical eye medication?	No
Do you have any known systemic health conditions that affect your eyes?	No
Do you have a history of viral eye disease?	No
Do you have a history of diabetes?	No
Do you have a history of eye surgery?	No
Do you have a history of severe eye trauma?	No
Do you currently have an active eye infection or inflammation?	No
Are you currently using isotretinoin-derivatives?	No
If you are a current contact lens wearer, are you willing to wear glasses on the day of the study visit?	Yes
For females, are you pregnant or nursing?	No

2.2. Clinical exam

The clinical examination commenced by having the participants complete the aforementioned ocular comfort VAS by eye. Monocular Logarithm of the Minimum Angle of Resolution (LogMAR) visual acuity was next completed while wearing habitual correction on a Bailey-Lovie chart. Bulbar redness and limbal redness were next determined with a Keratograph 5M (Oculus, Arlington, WA) with its internal software by taking a single image of both the right and left eyes to determine nasal and temporal redness for both the bulbar and limbal regions.

Research Electronic Data Capture (REDCap) [15,16] was next accessed by the study examiner to randomize the participant to either 0.7% olopatadine or 0.035% ketotifen fumarate (Alaway; Bausch + Lomb, Bridgewater, NJ) to be applied into the right eye while the other drop was immediately applied into the left eye. After the pre-determined drops were applied as dictated by the randomization schedule, the participant was asked to rate the comfort of each eye separately on the above-described ocular comfort VAS. The participant completed the VAS by eye at 0 min (application), 30 s, 1 min, and 2 min post-application. After the VAS testing was completed, the participant completed five Likert questions that compared the two drops at application (Table 2). Since participants were masked to the drops, they were simply asked to rate their preference for drop one (right eye) or drop two (left eye). Data were sorted by drop after the study, and the data were reported accordingly. Post-drop changes in LogMAR visual acuities and bulbar and limbal redness were then re-measured as described above. These data were likewise sorted by drop after the study. Each visit took approximately twenty minutes to complete, and the sequence of testing was kept consistent for each examination.

2.3. Sample size & statistical considerations

VAS scoring at drop application was the primary outcome. Comfort data from Pucker et al indicate that the mean VAS score for a participant who has just applied an artificial tear to their eye is 75.4 ± 21.6 units (higher scores = more comfortable) [17]. When considering a variance of 21.6 units and Papas et al’s data related to a clinically important difference for comfort being 6.8 units on a similar scale (effect size), it was determined by using an unpaired *t*-test that 159 participants were needed to detect a significant between-treatment difference in the primary outcome if one were present (power = 80%; alpha = 0.05) [14]. An unpaired *t*-test was used because it was assumed that the two eyes could have independent responses; thus, the calculated sample size was adequately powered for detecting paired or unpaired between-eye responses. All data were analyzed with SAS Version 9.4 (SAS; Cary, NC, USA). Descriptive statistics were used to describe data trends. All data were evaluated to ensure that they met the requirements of the statistical tests performed. The VAS comfort data were analyzed with a mixed model analysis to determine if there was a significant interaction between time and treatment, and given that each study participant served as their own comparison, paired t-tests were used to evaluate both inter- and intra-drop statistical comparisons. Likert question data were summarized as percentages, and these data were statistically analyzed with chi-square tests by comparing the following groupings: strong preference for 0.7% olopatadine + preference for 0.7% olopatadine, no drop preference, and strong preference for 0.035% ketotifen fumarate + preference for 0.035% ketotifen fumarate.

3. Results

This study enrolled 159 participants, and all participants completed

Table 2
Likert Scale Questionnaire.

Which drop do you think provided better overall eye comfort at instillation?	1. Strong Preference for Drop One 2. Preference for Drop One 3. No Drop Preference 4. Preference for Drop Two 5. Strong Preference for Drop Two
Which drop do you think made your eye sting the least at instillation?	1. Strong Preference for Drop One 2. Preference for Drop One 3. No Drop Preference 4. Preference for Drop Two 5. Strong Preference for Drop Two
Which drop do you think made your eye burn the least at instillation?	1. Strong Preference for Drop One 2. Preference for Drop One 3. No Drop Preference 4. Preference for Drop Two 5. Strong Preference for Drop Two
Which drop do you think made your vision fluctuate / blur the least at instillation?	1. Strong Preference for Drop One 2. Preference for Drop One 3. No Drop Preference 4. Preference for Drop Two 5. Strong Preference for Drop Two
Which drop do you think made your eye have the least foreign body sensation at instillation?	1. Strong Preference for Drop One 2. Preference for Drop One 3. No Drop Preference 4. Preference for Drop Two 5. Strong Preference for Drop Two

the study. The mean ± SD age of the participants was 26.3 ± 7.7 years with 79% of the participants being female. A total of 59.8% of the participants were current contact lens wearers outside of the study. This study found that there was no significant difference in between-eye comfort at the baseline timepoint ($p = 0.59$); however, participants favored 0.7 % olopatadine over 0.035% ketotifen fumarate at all time points after drop application (All $p < 0.002$; Table 3). The mixed model analysis indicated that there was a significant interaction between treatment and time suggesting that eyes treated with 0.7% olopatadine approached baseline comfort faster than eyes treated with 0.035% ketotifen fumarate ($p < 0.0001$). When analyzing the Likert questionnaire data, participants were statistically more likely to report that they either strongly preferred or preferred 0.7% olopatadine compared to 0.035% ketotifen fumarate with regard to overall comfort (46.54% vs 38.36%), stinging (46.54% vs 37.11%), burning (44.03% vs 36.48%), or vision fluctuation/blur (23.90% vs 20.13%) at application (all $p < 0.01$; Fig. 1). There was no significant difference in drop preference regarding foreign body sensation at application (35.85% vs 27.04%; $p = 0.44$).

The mean pre-drop and post-drop application LogMAR visual acuity and bulbar and limbal conjunctival redness values are summarized in Tables 4, 5, and 6. No significant between-eye differences were noted for visual acuity or redness pre-drop application. Visual acuity was stable over time for each drop, and no between-drop differences in visual acuity were noted post-drop application (All $p \geq 0.05$; Table 4). Eyes treated with 0.7% olopatadine had a significant reduction in bulbar and limbal conjunctival redness compared to 0.035% ketotifen fumarate post-drop application (Table 5); however, treatment with both drops resulted in significantly less redness post-drop application compared to pre-drop application (Table 6). No adverse events occurred during this study.

4. Discussion

This investigation was conducted to determine initial comfort differences between topical 0.7% olopatadine and topical 0.035% ketotifen fumarate, which are two commonly prescribed over-the-counter anti-allergy eye drops. This study determined that 0.7% olopatadine was significantly more comfortable compared to 0.035% ketotifen fumarate at application and at least 2 min after application. This study likewise found that neither drop posed any negative changes to vision or ocular redness during this same timeframe. The literature suggests that between 25% and 50% of patients are not compliant with their medication regimens, and one reason that patients are more likely to adhere to their regimen is if there is a reduction of medication-induced side effects, such as improved comfort upon application [11,18]. While there are multiple factors that contribute to good patient medication compliance (e.g., effectiveness, cost, ease of use, comfort), the data from the current study suggest that 0.7% olopatadine drops provide superior initial comfort compared to 0.035% ketotifen fumarate drops, which in turn may increase compliance in some patients.

The two allergy eye medications included in this study have been previously compared at lesser concentrations [11–13]. In one of the first studies on this topic, Artal et al found that a subset ($n = 35$) of their 80 participants preferred 0.1% olopatadine over 0.05% ketotifen fumarate when asked a forced choice question that compared the comfort of the two drops at application [11]. This double-masked study also found that 49% of participants reported moderate burning and another 49% of participants reported mild burning upon application of 0.05% ketotifen fumarate while no participants reported discomfort upon application of 0.1% olopatadine. The study did not comment on if included participants had active allergic conjunctivitis or not [11]. In a separate, double-masked study, Leonardi and Zafirakis recruited participants ($n = 100$) who had a previous history and signs and symptoms of seasonal or perennial allergic conjunctivitis who were asked to use 0.1% olopatadine and 0.025% ketotifen fumarate over a four-week period [12]. Either drop could be used at any time during the study. The investigators evaluated treatment efficacy with regards to itching, redness, and eyelid swelling. They also administered a comfort questionnaire, which asked about participant's preferred drop and which drop was more

Table 3
Comfort Visual Analog Scale Results after Drop Application.

Timing	0.7% olopatadine (Mean ± SD)	0.035% ketotifen (Mean ± SD)	Mean Difference (Mean ± SD)	Drop Comparison (P-Value)
Baseline	93.95 ± 6.51	93.88 ± 6.57	−0.07 ± 1.66	0.59
Application	82.37 ± 18.80	65.92 ± 25.32	−16.46 ± 23.69	<0.0001
30 s	86.72 ± 14.47	75.58 ± 20.73	−11.14 ± 20.01	<0.0001
1 min	90.42 ± 12.19	83.34 ± 17.09	−7.08 ± 15.71	<0.0001
2 min	92.82 ± 9.74	89.45 ± 13.17	−3.38 ± 13.28	0.002

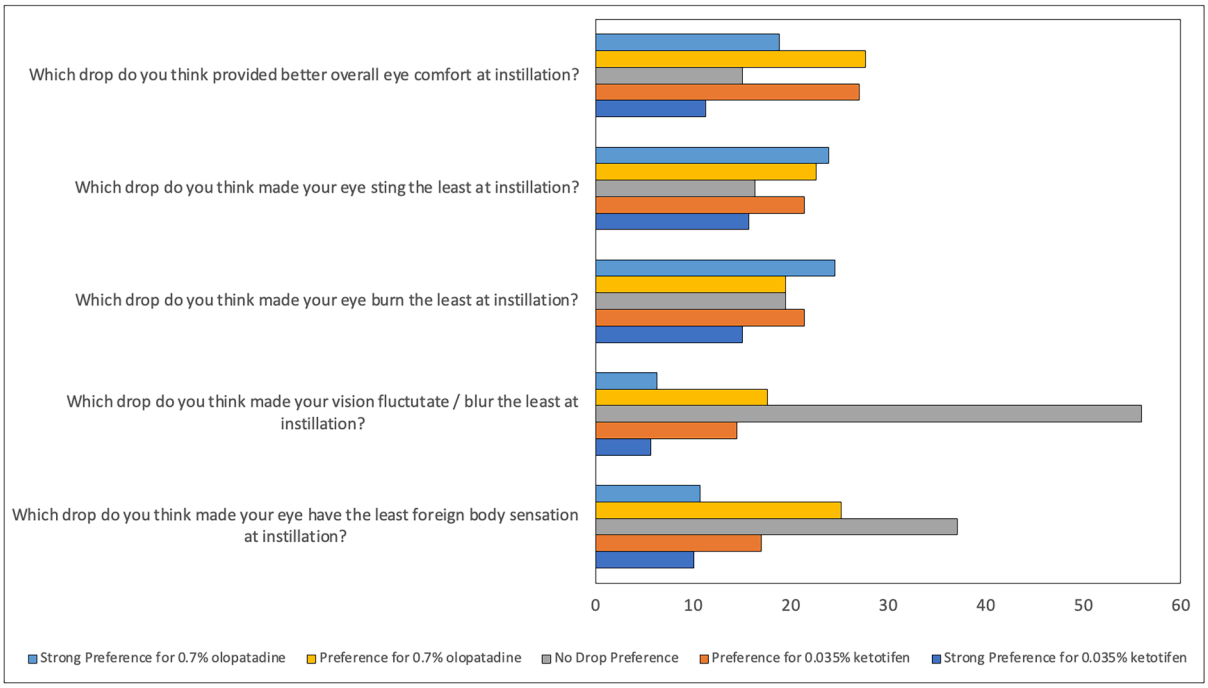

Fig. 1. Likert Scale Results by Percent of Participants.

Table 4
Pre-Drop and Post-Drop LogMAR Visual Acuity.

	0.7% olopatadine (Mean ± SD)	0.035% ketotifen (Mean ± SD)	Drop Comparison (P-Value)
Visual Acuity			
Baseline	−0.06 ± 0.13	−0.06 ± 0.12	1.0
Post-Drop Application	−0.05 ± 0.13	−0.06 ± 0.13	0.39
Drop Comparison (P-Value)	0.05	0.56	N/A

comfortable overall. This study found that 81% of participants reported that 0.1% olopatadine was more comfortable than 0.025% ketotifen fumarate, and 81% of participants also reported that they preferred to use 0.1% olopatadine more often than 0.025% ketotifen fumarate [12]. Lastly, in a prospective, randomized, double-masked, contralaterally controlled antigen study, Berdy et al evaluated the efficacy and comfort upon application of 0.1% olopatadine and 0.025% ketotifen fumarate and found that the participants rated 0.1% olopatadine as significantly more comfortable at application compared to 0.025% ketotifen fumarate (average ocular comfort of 1.25 vs 2.09; 0–8 scale with 0 being most comfortable; $p < 0.05$) [13]. Results from these previous studies align with the current study, with the current study finding that participants self-reported via the Likert questions that they preferred the comfort of 0.7% olopatadine at application over 0.035% ketotifen fumarate. Also, this same Likert questionnaire found that participants had a preference or strong preference for 0.7% olopatadine over 0.035% ketotifen fumarate when asked about overall comfort, burning, stinging, and vision fluctuation/blur at drop application. This suggests that the participants noticed multiple between-drop differences that likely affected their drop perceptions.

In the current study, 0.7% olopatadine had superior comfort compared to 0.035% ketotifen fumarate at drop application up to 2 min post-application based upon an investigator-designed VAS questionnaire. The VAS analyzed the comfort of the masked drops applied in real-time with the VAS showing that 0.7% olopatadine had a statistically significant and clinically meaningful difference in comfort compared to 0.035% ketotifen fumarate at application through 1-minute post-application (≥6.8 units). The mixed model analysis likewise suggests

Table 5
0.7% Olopatadine versus 0.035% Ketotifen Fumarate Comparison of Bulbar and Limbal Conjunctival Redness.

	0.7% olopatadine (Mean ± SD)	0.035% ketotifen (Mean ± SD)	Inter-Drop Comparison (P-Value)
Pre-Drop Redness			
Nasal Bulbar	0.70 ± 0.34	0.68 ± 0.31	0.32
Temporal Bulbar	0.65 ± 0.26	0.66 ± 0.28	0.62
Nasal Limbal	0.38 ± 0.25	0.37 ± 0.26	0.56
Temporal Limbal	0.35 ± 0.22	0.36 ± 0.23	0.25
Post-Drop Redness			
Nasal Bulbar	0.59 ± 0.28	0.65 ± 0.28	<0.0001
Temporal Bulbar	0.59 ± 0.24	0.62 ± 0.27	0.04
Nasal Limbal	0.32 ± 0.22	0.35 ± 0.24	0.06
Temporal Limbal	0.31 ± 0.21	0.34 ± 0.24	0.007

Table 6
Baseline versus Outcome Intra-Drop Comparison of Bulbar Conjunctival Redness.

	Pre-Drop Redness (Mean ± SD)	Post-Drop Redness (Mean ± SD)	Intra-Drop Comparison (P-Value)
0.7% olopatadine			
Nasal Bulbar	0.70 ± 0.34	0.59 ± 0.28	<0.0001
Temporal Bulbar	0.65 ± 0.26	0.59 ± 0.24	<0.0001
Nasal Limbal	0.38 ± 0.25	0.32 ± 0.22	<0.0001
Temporal Limbal	0.35 ± 0.22	0.31 ± 0.21	<0.0001
0.035% ketotifen			
Nasal Bulbar	0.68 ± 0.31	0.65 ± 0.28	0.006
Temporal Bulbar	0.66 ± 0.28	0.62 ± 0.27	<0.0001
Nasal Limbal	0.37 ± 0.26	0.35 ± 0.24	0.001
Temporal Limbal	0.36 ± 0.23	0.34 ± 0.24	0.006

that 0.7% olopatadine treated eyes approached baseline comfort significantly faster than 0.035% ketotifen fumarate treated eyes. These data suggest that while there were significant comfort differences across the first two minutes post-drop application, these between-drop differences may not be noticeable by patients after 1 min. The difference between initial comfort found in this study is likely attributed to the pH difference between 0.7% olopatadine (pH of 7.2) and 0.035% ketotifen fumarate (pH between 4.4 and 6.0). The formulation of 0.7% olopatadine allows the medication to be in solution at a pH much closer to that of human tears than 0.035% ketotifen fumarate, which is the likely reason why the 0.7% olopatadine-containing drops provides better initial comfort than the 0.035% ketotifen fumarate-containing drops.

While the current study found that ocular redness was significantly less with 0.7% olopatadine compared to 0.035% ketotifen fumarate, it is unlikely that this difference is clinically meaningful in the asymptomatic participants who were recruited for this study. This claim is based upon the fact that most clinical grading cards utilize whole integer differences between grades with it being unlikely that practitioners are able to consistently notice differences between grades of much less than a 0.5 grade difference [19]. These grades were all likewise within the normal range of redness. A similar result was found with visual acuity with the participants on average having stable, normal visual acuities when corrected. Thus, this study did not find any safety concerns with regards to redness or visual acuity with the initial application of either drop in the normal participants who were recruited for this study.

Although this study provided new knowledge related to the initial comfort of over-the-counter allergy eye drops, it is not without limitation. One study limitation is that while this study was testing ocular allergy eye drops, it recruited participants who were asymptomatic. Asymptomatic participants were chosen for this study because this study aimed to evaluate drop comfort and not efficacy. This study design characteristic directly allowed for a more uniform baseline comfort, which would allow the study to determine subtle comfort differences if they were present. Nevertheless, diseased eyes may have heightened sensitivity, and a future follow-up study should be performed with the same design that includes participants with active allergic conjunctivitis to determine how the results of the current study may translate to a group of participants with the disease of interest.

In summary, this study found that 0.7% olopatadine and 0.035% ketotifen fumarate were both safe at application; however, 0.7% olopatadine was found to provide superior comfort compared to 0.035% ketotifen fumarate at drop application and for at least 2 min post-drop application. These data are important for eye care practitioners who recommend over-the-counter anti-allergy eye drops because recommending more comfortable drops may result in better patient compliance; however, further studies are needed to confirm that increased comfort truly increases patient drop compliance. This medication trait may subsequently result in better disease control and overall better patient outcomes. These data are likewise important for patient education because it provides credence to the idea that not all over-the-counter medications are the same in comfort upon application.

Declaration of Competing Interest

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References

[1] Leonardi A, et al. Epidemiology of allergic conjunctivitis: clinical appearance and treatment patterns in a population-based study. Curr Opin Allergy Clin Immunol 2015;15(5):482–8.
[2] Singh K, Axelrod S, Bielory L. The epidemiology of ocular and nasal allergy in the United States, 1988–1994. J Allergy Clin Immunol 2010;126(4):778–83.
[3] Rosario N, Bielory L. Epidemiology of allergic conjunctivitis. Curr Opin Allergy Clin Immunol 2011;11(5):471–6.
[4] Dupuis P, Prokopich C, Hynes A, et al. A contemporary look at allergic conjunctivitis. Allergy Asthma Clin Immunol 2020;16(5).
[5] Baab S, Le PH, Kinzer EE. Allergic Conjunctivitis. Florida: StatPearls Publishing LLC; 2021.
[6] Abbas M, Moussa M, Akel H. Type I Hypersensitivity Reaction. Florida: StatPearls Publishing LLC; 2021.
[7] Bonini SBS, Berruto A, Tomassini M, Carlesimo S, Bucci MG, Balsano F. Conjunctival provocation test as a model for the study of allergy and inflammation in humans. Int Arch Allergy Appl Immunol 1989;88(1–2):144–8.
[8] Fauquert JL. Diagnosing and managing allergic conjunctivitis in childhood: The allergist's perspective. Pediatr Allergy Immunol 2019;30(4):405–14.
[9] Ben-Eli H, Solomon A. Topical antihistamines, mast cell stabilizers, and dual-action agents in ocular allergy: current trends. Curr Opin Allergy Clin Immunol 2018;18(5):411–6.

[10] Kimchi NB. Leonard, The allergic eye: recommendations about pharmacotherapy and recent therapeutic agents. Curr Opin Allergy Clin Immunol August 2020;20(4):414–20.
[11] Artal MN, Luna JD, Discepola M. A forced choice comfort study of olopatadine hydrochloride 0.1% versus ketotifen fumarate 0.05%. Acta Ophthalmol Scand Suppl 2000;230:64–5.
[12] Leonardi A, Zafirakis P. Efficacy and comfort of olopatadine versus ketotifen ophthalmic solutions: a double-masked, environmental study of patient preference. Curr Med Res Opin 2004;20(8):1167–73.
[13] Berdy GJ, et al. A comparison of the relative efficacy and clinical performance of olopatadine hydrochloride 0.1% ophthalmic solution and ketotifen fumarate 0.025% ophthalmic solution in the conjunctival antigen challenge model. Clin Ther 2000;22(7):826–33.
[14] Papas EB, Keay L, Golebiowski B. Estimating a just-noticeable difference for ocular comfort in contact lens wearers. Invest Ophthalmol Vis Sci 2011;52(7):4390–4.
[15] Harris PA, et al. The REDCap consortium: Building an international community of software platform partners. J Biomed Inform 2019;95:103208.
[16] Harris PA, et al. Research electronic data capture (REDCap)–a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 2009;42(2):377–81.
[17] Pucker AD, et al. Application of systane complete for the treatment of contact lens discomfort. Cont Lens Anterior Eye 2021;44(4):101399.
[18] Ashburn Jr FS, Goldberg I, Kass MA. Compliance with ocular therapy. Surv Ophthalmol 1980;24(4):237–48.
[19] Pult H, et al. Limbal and bulbar hyperaemia in normal eyes. Ophthalmic Physiol Opt 2008;28(1):13–20.