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ORIGINAL ARTICLE

Topical Olopatadine in the Treatment of Allergic Conjunctivitis: A Systematic Review and Meta-analysis

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ABSTRACT

Purpose: To assess the safety and efficacy of topical olopatadine versus placebo and other topical anti-allergic medications in treating allergic conjunctivitis.

Methods: We systematically searched the literature for randomized-controlled trials that included patients with allergic conjunctivitis, compared olopatadine versus placebo or alternative anti-allergic medications, and examined itch, conjunctival hyperemia, composite symptom or sign scores, and/or occurrence of adverse events. We assessed the safety and efficacy of topical olopatadine when compared with placebo or alternative anti-allergic medications using meta-analysis.

Results: When compared with placebo, topical olopatadine is associated with a pooled-mean difference (MD) in ocular itch of -1.33 ($p < 0.00001$) and ocular hyperemia of -0.92 ($p < 0.00001$). When compared with other agents, olopatadine was inferior to alcaftadine on ocular itch (pooled-MD = 0.39 ; $p < 0.00001$) but comparable with epinastine and ketotifen.

Conclusions: Topical olopatadine is a safe and effective treatment modality for allergic conjunctivitis, whereas alcaftadine appears to be superior to olopatadine in reducing ocular itch.

Keywords: Allergic conjunctivitis, antihistamine, cornea and external eye, mast cell stabilizer, meta-analysis, olopatadine

Allergic conjunctivitis is a common ocular morbidity worldwide. The prevalence of ocular allergy ranged from 5% to 22% with geographical variations, depending on the age distribution of the populations and the subtypes of ocular allergy.¹ Allergic conjunctivitis mostly affects the younger age groups and can be subcategorized into different forms with individual clinical presentation, severity, and immunopathology. However, itching remains the hallmark in all forms of ocular allergy. Currently, topical medications for allergic conjunctivitis include topical antihistamines, mast cell stabilizers,

eosinophil deactivators, lubricants, and cyclosporine ophthalmic solution.² For severe disease, topical corticosteroids and non-steroidal anti-inflammatory drugs (NSAIDs) are usually required. Oral antihistamines are occasionally used for symptomatic relief, especially in patients with concurrent rhinitis or sinusitis.³

Olopatadine is a dual-action, selective H₁-receptor antagonist and a mast cell stabilizer. It prevents immunologically stimulated pro-inflammatory mediator release from human conjunctival mast cells.^{4–8} Since its discovery in the late 1990s, several randomized-controlled trials

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(RCTs), mostly based on conjunctival allergen challenge (CAC) models, have provided evidence of its efficacy versus placebo or other alternatives. However, many of these studies differed in designs and evaluated allergic conjunctivitis with various scales. This systematic review and meta-analysis seeks to confirm the efficacy and safety of topical olopatadine by summarizing the findings across all reported RCTs.

MATERIALS AND METHODS

Search Strategy

We searched in EMBASE and MEDLINE via the OVID platform, the Cochrane Central Register of Controlled Trials, ClinicalTrials.gov (www.clinicaltrials.gov) and the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP), for randomized-controlled trials that evaluated topical olopatadine versus placebo or alternative anti-allergic medications for allergic conjunctivitis. We employed the Cochrane highly sensitive search strategy, using the search terms described in Appendix 1. We did not apply any language restrictions in our search but only included articles in English for analysis. We performed the final search in all databases on January 4, 2015.

Inclusion and Exclusion Criteria

Two reviewers (KWK and NW) independently assessed the titles and abstracts to identify articles that fulfilled the inclusion criteria of: (1) randomized-controlled trials; (2) studies that included patients with any forms of allergic conjunctivitis, including those with provocation or conjunctival allergen challenge models; (3) compared olopatadine versus placebo or alternative anti-allergic medications; and (4) examined at least one of the following outcomes: itch, hyperemia, composite symptom, or sign scores and occurrence of adverse events. We excluded studies that did not provide quantification data or sufficient statistical parameters for analysis, and studies that compared topical olopatadine with oral or nasal medications separately, or in combination.

Data Extraction

Two reviewers (NW and KWK) independently performed data extraction. We used a customized form to record the authors of the study, year of publication, sample size, duration of follow-up, intervention arms, and outcome measures. We extracted the outcomes at a follow-up, where a maximum treatment effect was attained. In studies where only median values were reported, the arithmetic means were estimated using the median values and ranges.⁹

In studies where only figures or graphs were presented, the images were analyzed with the WebPlotDigitizer program (<http://arohatgi.info/WebPlotDigitizer/>, accessed November 29, 2015) to obtain numerical values. We obtained standard deviations and standard errors from the *p* values following the instructions in the *Cochrane Handbook for Systematic Reviews of Interventions*.¹⁰

Assessment of Risk of Bias

We assessed the risk of bias of the included studies using the Cochrane Risk of Bias tool.¹¹ We evaluated random sequence generation and allocation concealment (selection bias), masking of participants and personnel (performance bias), masking of outcome assessment (detection bias), incomplete outcome data (attrition bias), and selection reporting (reporting bias). We graded each domain as low, unclear and high risk of bias, as outlined in the *Cochrane Handbook for Systematic Reviews of Interventions*.¹⁰

Primary Outcomes

Itch is the universal symptom for ocular allergies, irrespective of the hypersensitivity subtypes, and it is often the most striking symptom that patients reported to clinicians.¹² The maximal differences in itch scores were measured either numerically as reported, or extrapolated from graphs or charts using the WebPlotDigitizer. Hyperemia is another primary outcome measure. It is the most common and quantifiable sign in allergic conjunctivitis.¹² As with ocular itch, maximal differences in hyperemia scores were extracted for analyses.

Reduction from baseline score is not chosen for analysis, as this meta-analysis included a large number of studies and that the scores used across different studies are not the same. We used the maximal difference in symptom scores between the two medications being compared taken at any time point following administration. This is because different study designs might have differed in the length of assessment and application of the study drugs, hence using any fixed time point would bias their effects.

Secondary Outcomes

Composite symptom or sign scores serve as an averaged summary for a range of predefined symptoms or signs associated with allergic conjunctivitis. We planned to record any documented composite symptom or sign scores and perform a subgroup analysis to assess and compare the differences between scores from an individual symptom (itch) or sign (hyperemia)

and those with composite symptoms or signs. We also assessed the adverse effects of the studied drugs as a secondary outcome measure. The odds of adverse effects in the olopatadine group were compared with the control groups. Any reported adverse effects would be analyzed.

Statistical Analysis

We used the Review Manager software (version 5.2; The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) for the meta-analyses. We analyzed itch and hyperemia as ordered categorical variables. In studies where conjunctival hyperemia was further classified by the site of involvement, bulbar conjunctival hyperemia was adopted for analyses. The main analysis was conducted using the mean difference (MD), which is more relevant in clinical interpretations. In studies where only medians and sample sizes or ranges were provided, we estimated the means by online statistical software.⁹ Since different scales were used in measuring the outcomes across the studies, we also analyzed the standardized mean difference (SMD) to give a more uniform summary estimate. The 95% confidence intervals (CIs) and *p* values were reported.² Statistical heterogeneities among the included studies were analyzed using the Cochrane Q-statistics χ^2 -test and I^2 statistics. If significant heterogeneity was observed (i.e., $I^2 > 50\%$), the random effects model was used for the pooled estimates; otherwise the fixed effects model was used.

We performed subgroup analyses to evaluate the effects of olopatadine versus placebo and alternative medications in different age groups and types of hypersensitivity reactions (type I: Seasonal Allergic Conjunctivitis and Perennial Allergic Conjunctivitis; type IV: Atopic Keratoconjunctivitis and Vernal Keratoconjunctivitis). We also divided the studies into those adopting subject-based or eye-based approaches. In the former, the same medication was applied in either one or both eyes of an individual; whereas for the latter, two different medications were applied to the two eyes of the same individual. We also divided the studies into those that were based on CAC models, where symptoms were induced experimentally in a standard controlled fashion, and environmental studies. In CAC studies, short-term outcome measures were often measured from 0 to 20 min after application and hence, were more homogenous in nature. By stratification by study design, we would address the issue of heterogeneity and variation in study designs across the included trials. We investigated publication bias by examining the funnel plots. We also performed sensitivity analyses, where applicable, to assess the robustness of our results by excluding studies of lower methodologic quality or any of the included studies one at a time.

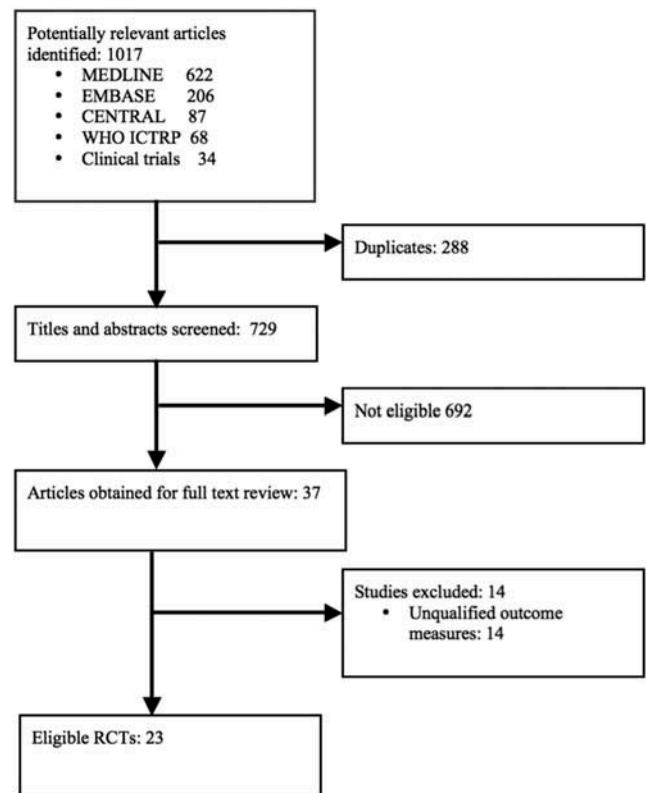


FIGURE 1. PRISMA Flow of study inclusion.

RESULTS

Figure 1 shows the study inclusion process. We identified a total of 1017 studies from our literature search in the five databases. After removing 288 duplicates, we assessed 729 titles and abstracts and excluded 692 records that were not eligible according to our inclusion criteria. We then retrieved 37 articles for full text review but excluded 14 studies, in which there were no qualified outcome measures. Finally, we included 23 RCTs in the meta-analysis.

Characteristics of the Included Studies

Table 1 shows the characteristics of the included trials. There were 23 studies, involving a total of 3388 eyes. A total of 17 of the 23 studies compared topical olopatadine with placebo, of which 11 included only adults and six included both adults and children. For the studies comparing topical olopatadine with placebo, participants from 10 of the 17 studies were randomly assigned to receive one drop of topical olopatadine in one eye and one drop of placebo in the fellow eye (eye-based design). For these studies, the outcomes were evaluated as eye-based. For the remaining seven studies, participants were randomly assigned to receive topical olopatadine in both eyes, or placebo eye drops in both eyes only. The outcomes in these studies were

TABLE 1. The characteristics of the included trials.

Study (year)	Country	Olopatadine concentration (%)	Age group ^a	Subject-based vs eye-based	Olopatadine			Placebo			Ketotifen			Epinastine			Alcaftadine			Eye-based mean age ^c
					<i>n</i> ^b	Age ^c	<i>n</i> ^b	<i>n</i> ^b	Age ^c	<i>n</i> ^b	<i>n</i> ^b	Age ^c	<i>n</i> ^b	<i>n</i> ^b	Age ^c	<i>n</i> ^b	Age ^c	<i>n</i> ^b	Age ^c	
Abelson, et al. (2004) ³⁰	USA	0.20	Mixed	Subject	258	36.8 ± 14.8	262	36.0 ± 13.2	–	–	–	–	–	–	–	–	–	–	–	–
Abelson, et al. (2007) ²⁵	USA	0.20	Adult	Eye	92	N/A	92	N/A	–	–	–	–	–	–	–	–	–	–	–	–
Abelson and Spitalny (1998) ³⁴	USA	0.05, 0.10	Adult	Eye	168	38 ± 16.2	168	38 ± 16.2	–	–	–	–	–	–	–	–	–	–	–	–
Abelson and Turner (2003) ³⁹	USA	0.10	Adult	Subject	128	38.5 ± 11.6	134	38.2 ± 11.3	–	–	–	–	–	–	–	–	–	–	–	–
Ackerman, et al. (2013) ^{23,d}	USA	0.20	Mixed	Subject	86	37.0 ± 14.8	82	39.3 ± 12.3	–	–	–	–	–	–	–	–	86	39.3 ± 12.4	–	–
Avunduk, et al. (2005) ^{14,d}	Turkey	0.10	Adult	Subject	26	N/A	28	N/A	24	N/A	–	–	–	–	–	–	–	–	–	–
Berdy, et al. (2000) ¹⁷	USA	0.10	N/A	Eye	32	N/A	–	–	32	N/A	–	–	–	–	–	–	–	–	–	–
Borazan, et al. (2009) ^{13,d}	Turkey	0.10	Mixed	Eye	20	26.9 ± 10.6	20	27.4 ± 10.4	20	26.1 ± 7.9	20	29.3 ± 12.8	–	–	–	–	–	–	–	–
Butrus, et al. (2000) ⁴⁰	USA	0.10	Adult	Eye	40	44.2	22	47.5	–	–	–	–	–	–	–	–	–	–	–	–
Deschenes, et al. (1999) ²⁶	USA	0.10	Adult	Eye	36	–	36	–	–	–	–	–	–	–	–	–	–	–	36 ± 14.2	–
Fujishima, et al. (2014) ^{19,d}	Japan	0.10	Adult	Eye	43	39.4 ± 10.7	86	39.5 ± 10.9	–	–	–	43	39.7 ± 11.1	–	–	–	–	–	–	–
Fukushima, et al. (2014) ¹⁹	Japan	0.10	Adult	Eye	50	–	–	–	–	–	50	–	–	–	–	–	–	–	33.3 ± 9.2	–
Ganz, et al. (2003) ¹⁵	USA	0.10	Mixed	Subject	68	35.2 ± 14.4	–	–	64	37.5 ± 16.8	–	–	–	–	–	–	–	–	–	–
Greiner, et al. (2011) ^{24,d}	USA	0.10	Adult	Subject	66	38.5 ± 11.2	66	38.9 ± 9.9	–	–	–	–	–	–	–	–	68	41.0 ± 14.1	–	–

Kamis, et al. (2006) ⁴¹	Turkey	0.10	Mixed	Eye	51	-	51	-	-	-	-	-	-	-	-	-	24.8 ± 10.2
Lanier, et al. (2004) ²¹	USA	0.10	Adult	Eye	53	-	-	-	-	-	53	-	-	-	-	-	44.4
Leonardi, et al. (2003) ²⁷	USA	N/A	Adult	Eye	10	31.5 ± 11.3	10	31.5 ± 11.3	-	-	-	-	-	-	-	-	-
Mah, et al. (2007) ²⁰	USA	0.20	Adult	Eye	54	39.9 ± 12.6	-	-	-	-	55	39.7 ± 12.8	-	-	-	-	-
McLaurin, et al. (2014) ^{22,d}	USA	0.20	Mixed	Subject	190	37.9 ± 14.9	186	36.7 ± 12.6	-	-	-	-	192	38.7 ± 13.1	-	-	-
Rosenwasser, et al. (2008) ⁴²	USA	0.20	Adult	Subject	40	45.8 ± 11.6	20	43.6 ± 11.3	-	-	-	-	-	-	-	-	-
Sarker, et al. (2011) ¹⁶	Bangladesh	0.10	Mixed	Subject	80	28 ± 11	-	-	86	28 ± 12	-	-	-	-	-	-	-
Spangler, et al. (2001) ²⁸	USA	0.10	Adult	Eye	73	37.35	74	39.3	-	-	-	-	-	-	-	-	-
Yaylali, et al. (2003) ⁴³	Turkey	0.10	Mixed	Eye	20	-	20	-	-	-	-	-	-	-	-	-	19 ± 3.0

^aMixed refers to both pediatric and adult populations were included.

^bNumber of eyes.

^cAge in years (mean ± SD).

^dStudy included in more than one meta-analyses.

evaluated as subject-based. Five studies compared the efficacy of topical olopatadine versus topical ketotifen;^{13–17} five compared topical olopatadine with epinastine;^{13,18–21} and three compared topical olopatadine with alcaftadine.^{22–24} The concentrations of topical medications were 0.1% and 0.2% olopatadine; 0.05% epinastine; 0.1% ketotifen; and 0.25% alcaftadine. In studies where other concentrations of epinastine, ketotifen, or alcaftadine were reported, only outcomes from aforementioned concentrations were selected for analyses. In studies where both 0.1% and 0.2% olopatadine were reported, two subgroups were averaged as instructed by the Cochrane Handbook.

Risk of Bias Assessment

Figure 2 summarizes the risk of bias assessment for the included studies. Most studies mentioned that the subjects were randomly assigned using random numbers. Masking was mentioned explicitly in 14 studies but not the other 10.^{17,22–30} The risk of attrition bias was low as the numbers of participants who exited the studies were reported clearly. We could not comment on the risk of selective reporting because we did not have access to the study protocols.

Outcome Measures

Olopatadine Versus Placebo

Figure 3A summarized the effects of topical olopatadine versus placebo on ocular itch. A total of 1345 eyes were treated with topical olopatadine and 1355 with placebo. Topical placebos were mostly artificial tears or normal saline.^{24,31–33} Four studies used the same vehicles that were used to carry the active drugs.^{26,29,30,34} One study gave a detailed description of the placebo content, which included dibasic sodium phosphate, sodium chloride, disodium EDTA, povidone and benzalkonium chloride.³⁰ In the meta-analysis, topical olopatadine use was associated with a significantly lower post-treatment ocular itch, with a pooled-MD of -1.33 (95% CI = -1.43 to -1.23 ; $p < 0.00001$; $I^2 = 85\%$).

Subgroup analyses by patient-based or eye-based studies showed similar results, with subject-based studies showing a pooled-MD of -1.08 (95% CI = -1.37 to -0.79 ; $p < 0.0001$; $I^2 = 76\%$) and eye-based studies a pooled-MD of -1.49 (95% CI = -1.54 to -1.45 , $p < 0.00001$; $I^2 = 38\%$; Figure 4). Test for heterogeneity between the subgroup strata generated a p value of 0.006. In subgroup analyses by age, the pooled-MD was -1.38 (95% CI = -1.49 to -1.28 ; $p < 0.00001$; $I^2 = 88\%$; Figure 5) in

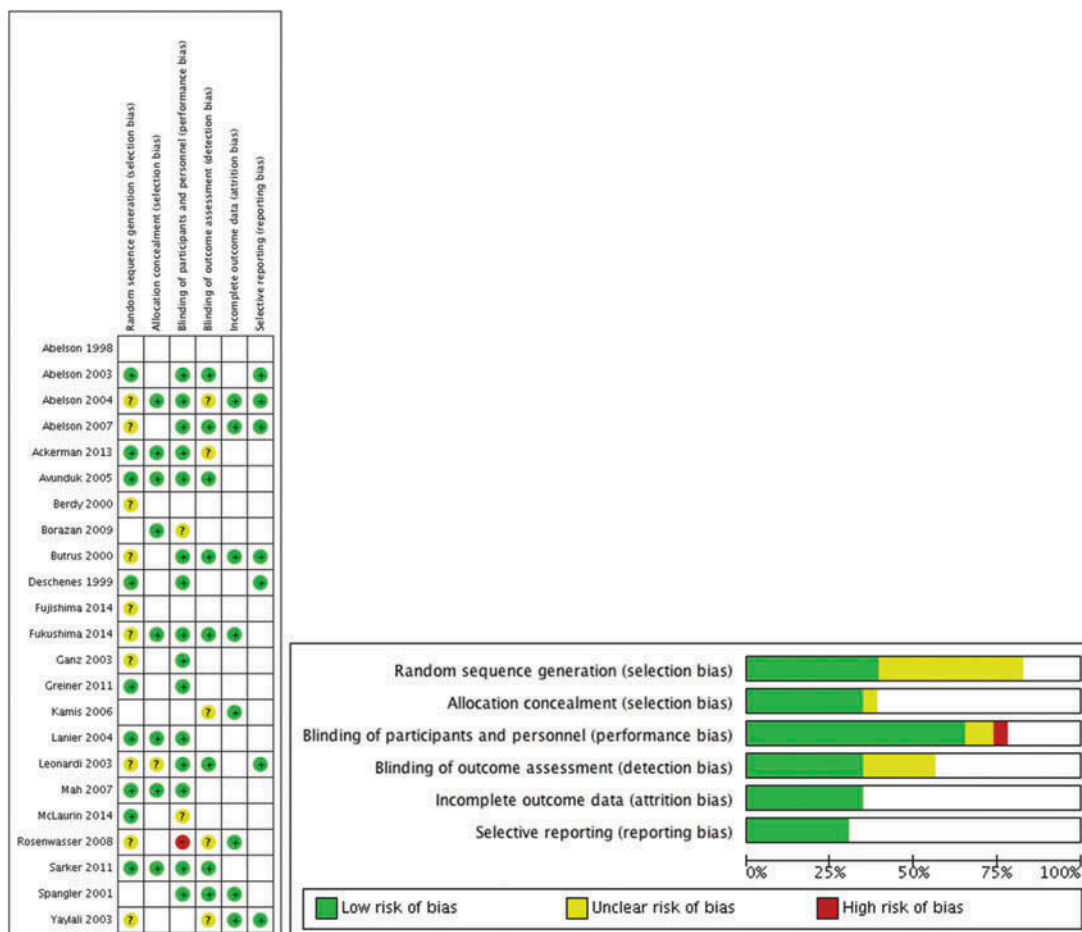


FIGURE 2. Risk of bias assessment.

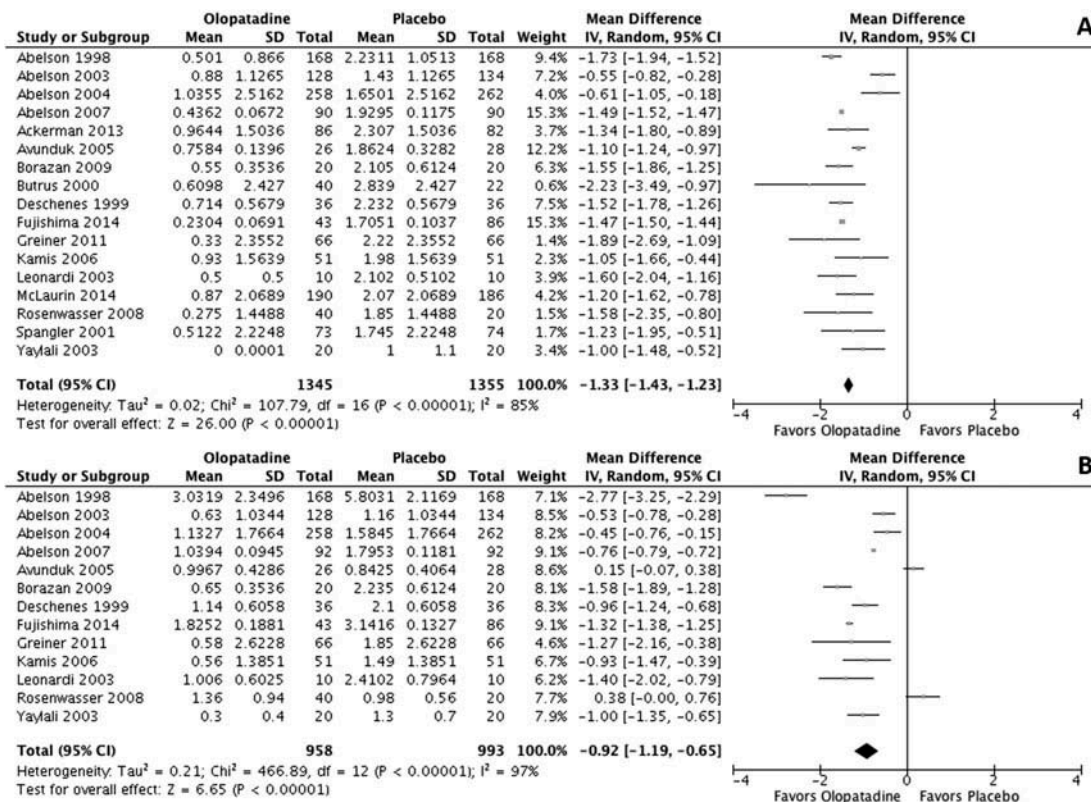


FIGURE 3. Forest plot showing the mean differences in itch (3A) and hyperemia (3B) scores comparing topical olopatadine versus placebo.

studies where only adults were included, whereas in studies with both adults and children, the pooled-MD was -1.15 (95% CI = -1.44 to -0.86 ; $p < 0.00001$; $I^2 = 63\%$; Figure 5). Heterogeneity test between subgroup generated a p value of 0.14. None of the included studies involved only children.

Figure 3B shows the summary effects of topical olopatadine versus placebos on ocular hyperemia. A total of 958 eyes treated with topical olopatadine and 993 treated with placebo were analyzed. The pooled-MD was -0.92 (95% CI = -1.19 to -0.65 ; $p < 0.00001$; $I^2 = 97\%$). In the subgroup analyses by patient- or eye-based designs,

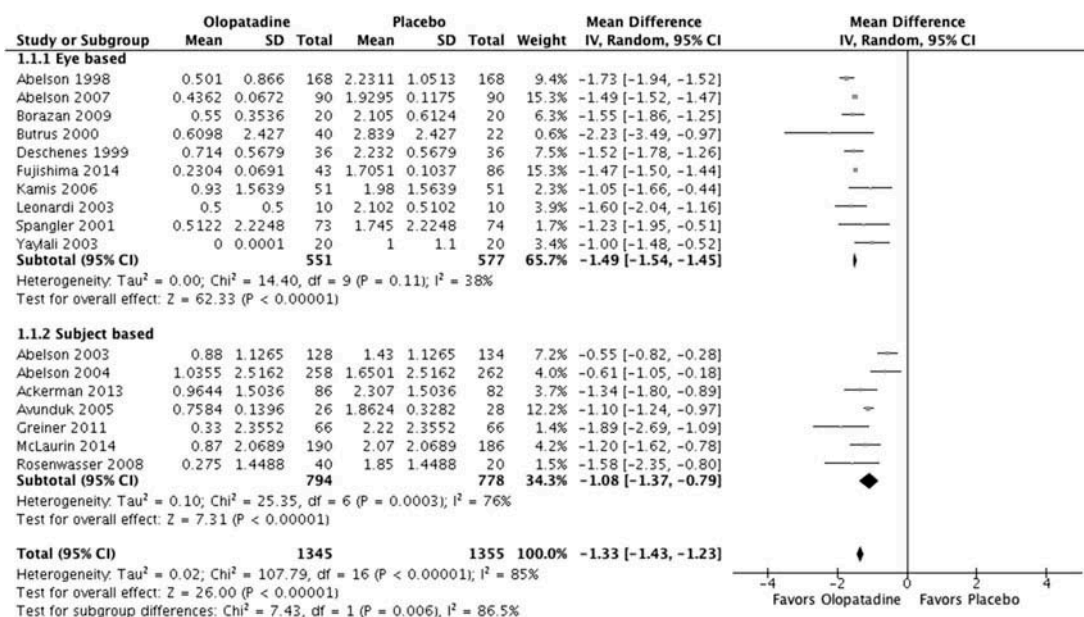


FIGURE 4. Mean differences in itch score stratified by study approach comparing topical olopatadine versus placebo.

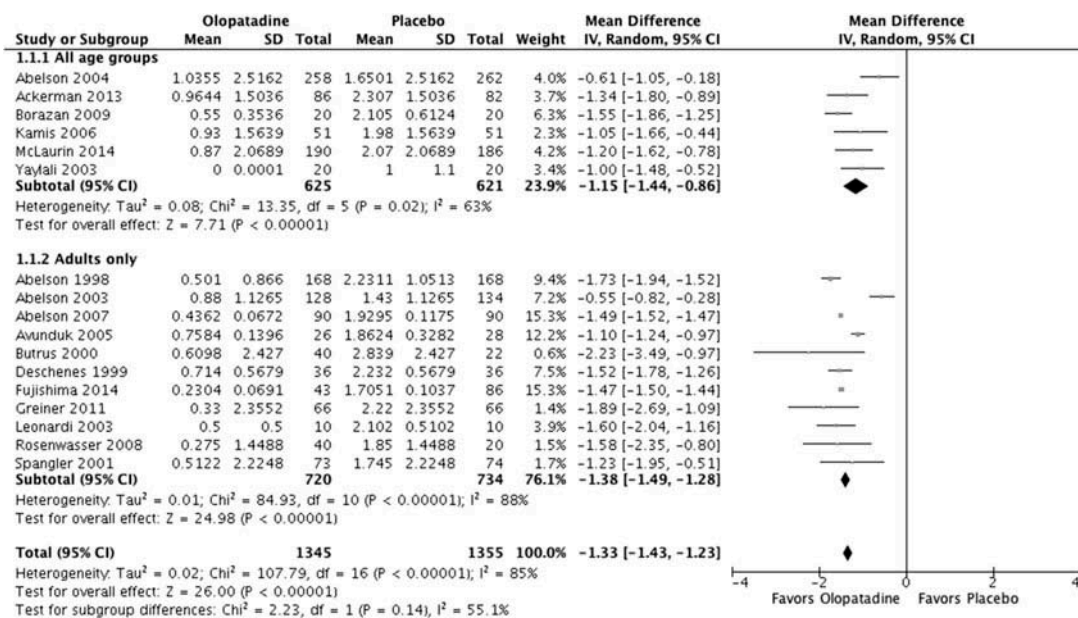


FIGURE 5. Mean differences in itch score stratified by age group comparing topical olopatadine versus placebo.

subject-based studies showed a pooled-MD of -0.25 (95% CI = -0.68 to 0.17 ; $p = 0.24$; $I^2 = 88\%$) and eye-based studies -1.31 (95% CI = -1.63 to -0.99 ; $p < 0.00001$; $I^2 = 98\%$; Figure 6). Test for heterogeneity between subgroups generated a p value of <0.00001 . Subgroup analysis by age showed that the pooled-MD in studies with adults only was -0.89 (95% CI = -1.22 to -0.56 ; $p < 0.00001$; $I^2 = 98\%$), whereas in studies including all age groups -0.99 (95% CI = -1.53 to -0.46 ; $p < 0.00001$; $I^2 = 89\%$; Figure 7). Heterogeneity test between subgroups yielded a p value of 0.74 . Subgroup analyses based on CAC-based and environmental studies yielded similar stratum-specific mean differences. In terms of ocular itch, CAC-based studies showed a pooled-MD of -1.49 (95% CI = -1.52 to

-1.46 ; $p < 0.00001$; $I^2 = 13\%$), while environmental studies showed a pooled-MD of -0.98 (95% CI = -1.29 to -0.68 ; $p < 0.00001$; $I^2 = 82\%$; Figure 8). In terms of ocular hyperemia, CAC studies showed a pooled-MD of -2.85 (95% CI = -4.43 to -1.27 ; $p < 0.00001$; $I^2 = 99\%$), while environmental studies showed -0.83 (95% CI = -2.67 to -1.17 ; $p < 0.00001$; $I^2 = 98\%$; Figure 9).

We also analyzed for standardized mean differences. For ocular itch, topical olopatadine use was associated with a pooled-SMD of -2.62 (95% CI = -3.25 to -1.99 ; $p < 0.00001$; $I^2 = 98\%$) when compared with placebo. For ocular hyperemia, topical olopatadine was associated with a pooled-SMD of -1.92 (95% CI = -2.66 to -1.17 ; $p < 0.00001$; $I^2 = 98\%$; Figures 10 and 11) when

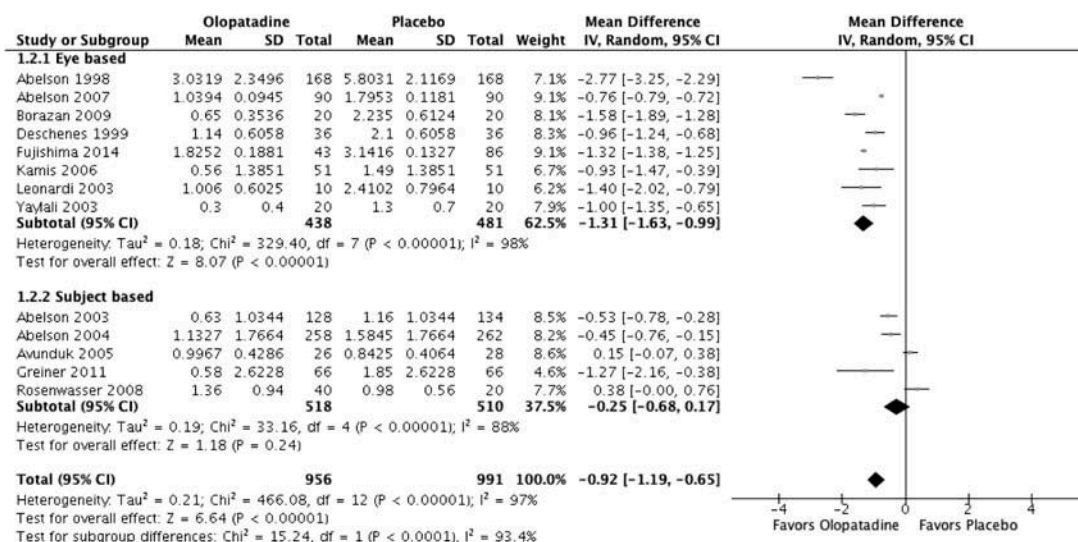


FIGURE 6. Mean differences in hyperemia score stratified by study approach comparing topical olopatadine versus placebo.

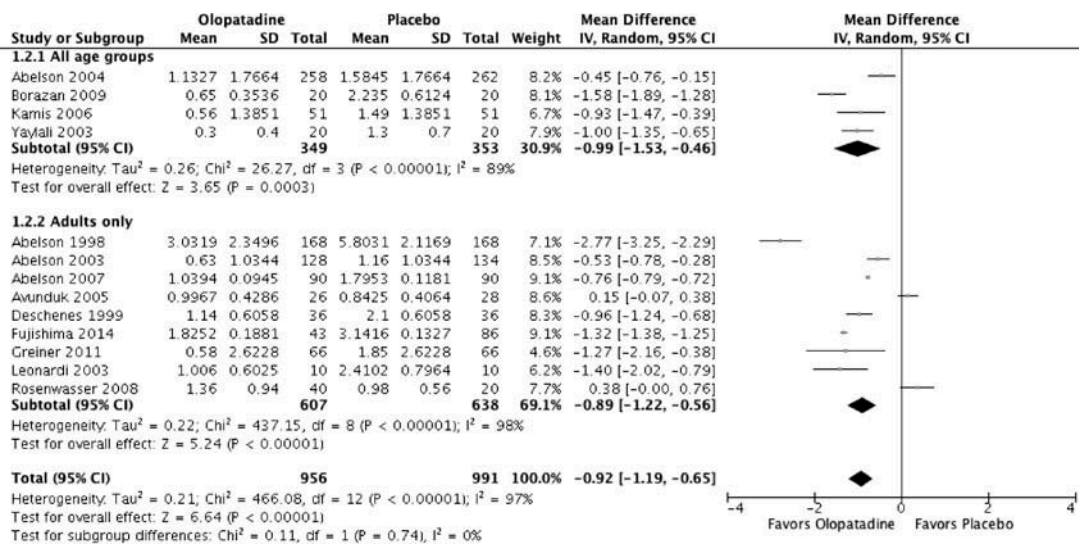


FIGURE 7. Mean differences in hyperemia score stratified by age group comparing topical olopatadine versus placebo.

compared with placebo. These results suggested that there was a statistically significant effect of olopatadine in reducing ocular itch and hyperemia.

Olopatadine Versus Alternative Medications

Overall, 220 olopatadine-treated and 221 epinastine-treated eyes were analyzed for ocular itch. The pooled-MD was -0.23 (95% CI = -0.50 to 0.03 , $p = 0.08$; $I^2 = 91\%$; Figure 12). As for conjunctival hyperemia, 220 eyes treated with olopatadine were compared with 221 treated with epinastine. The pooled-MD was -0.23 (95% CI = -0.85 to 0.39 ; $p = 0.48$; $I^2 = 98\%$; Figure 13).

A total of 226 olopatadine-treated and 226 ketotifen-treated eyes were analyzed for ocular itch. The pooled-

MD was -0.22 (95% CI = -0.64 to 0.20 ; $p = 0.31$; $I^2 = 96\%$; Figure 14). As for conjunctival hyperemia, 194 eyes treated with olopatadine were compared with 194 treated with ketotifen. The pooled-MD was -0.25 (95% CI = -0.64 to 0.15 ; $p = 0.22$; $I^2 = 93\%$; Figure 15), Insert Figure 15 near here, suggesting no significant difference in efficacy between olopatadine and ketotifen.

A totally of 344 olopatadine-treated and 346 alcaftadine 0.25%-treated eyes were analyzed for ocular itch. The pooled-MD was 0.39 (95% CI = 0.28 to 0.50 ; $p < 0.00001$; $I^2 = 0\%$; Figure 16). Only one study assessed conjunctival hyperemia,²⁴ thus a meta-analysis was not feasible.

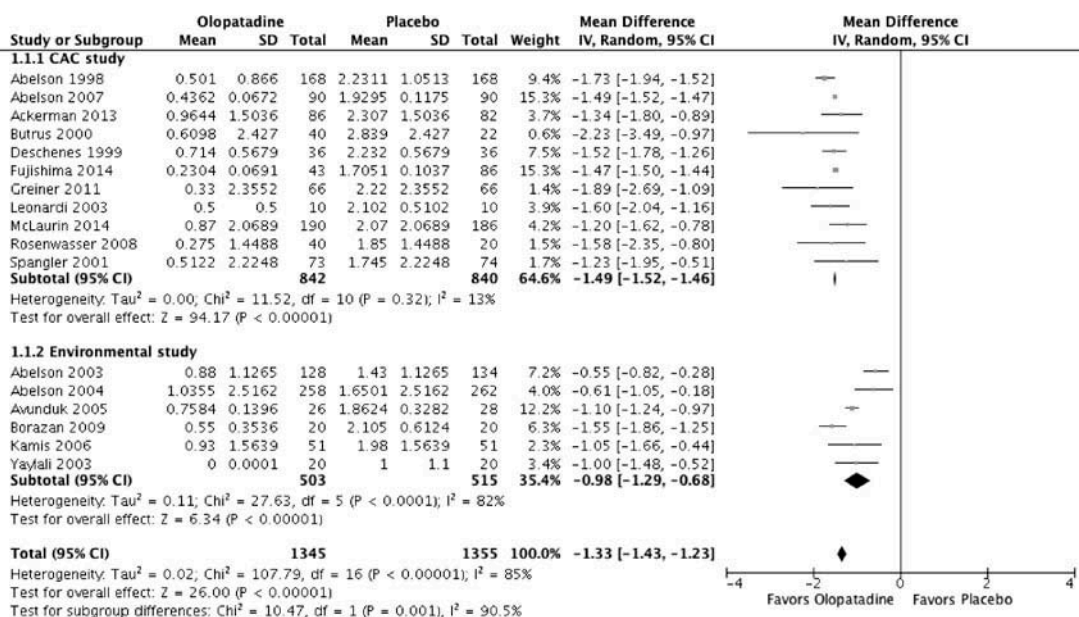


FIGURE 8. Mean differences in itch score in CAC-based versus environmental studies comparing topical olopatadine versus placebo.

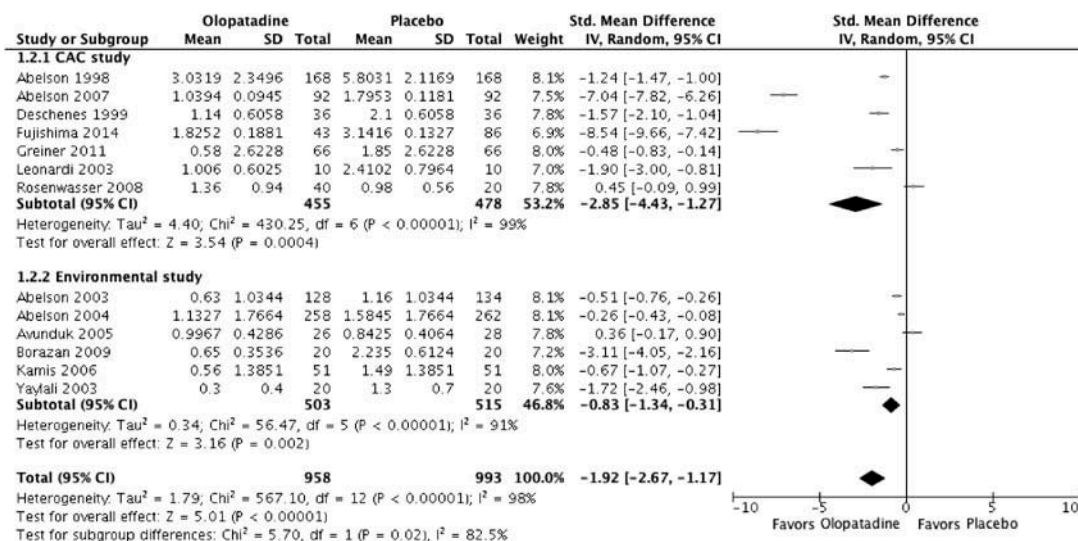


FIGURE 9. Mean differences in hyperemia score in CAC-based versus environmental studies comparing topical olopatadine versus placebo.

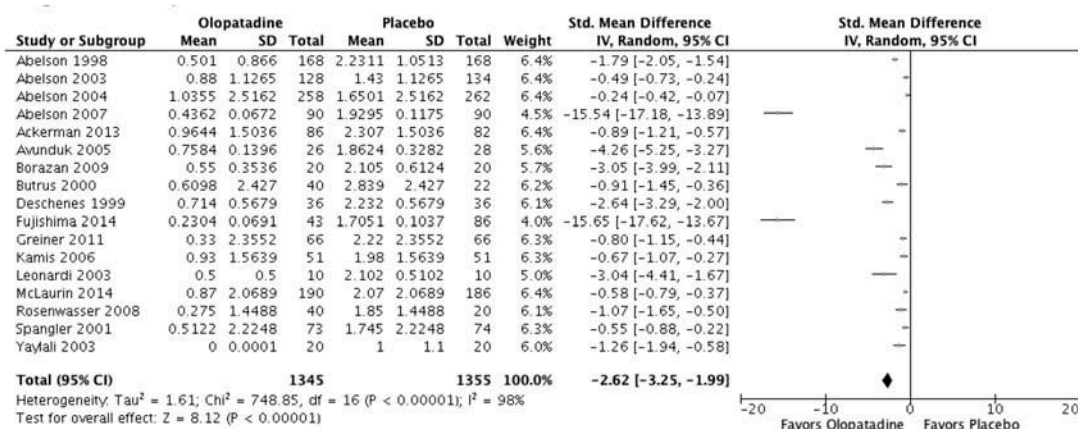


FIGURE 10. Standardized mean differences in itch score comparing topical olopatadine versus placebo.

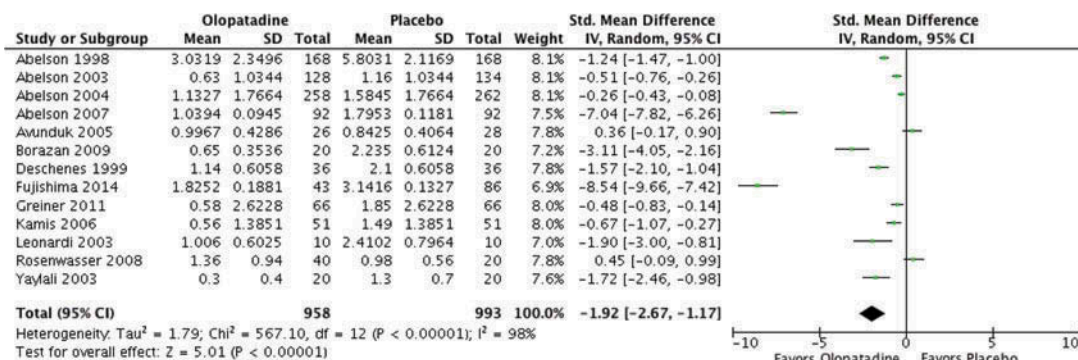


FIGURE 11. Standardized mean differences in hyperemia score comparing topical olopatadine versus placebo.

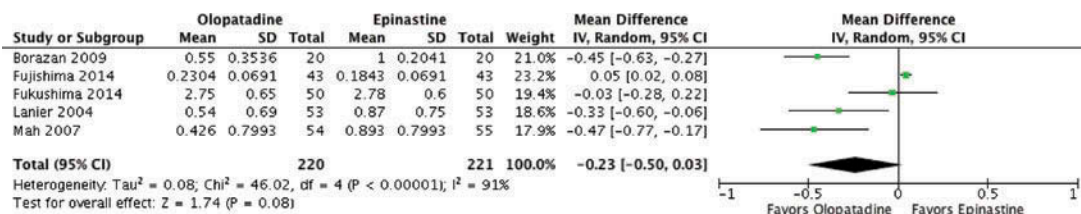


FIGURE 12. Mean differences in itch score comparing topical olopatadine versus epinastine.

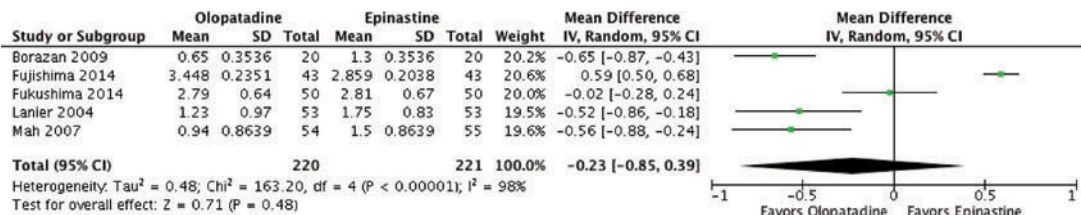
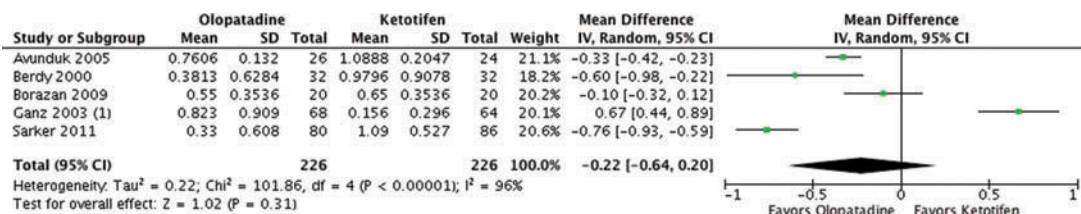


FIGURE 13. Mean differences in hyperemia score comparing topical olopatadine versus epinastine.

**Footnotes**

(1) using right eye data

FIGURE 14. Mean differences in itch score comparing topical olopatadine versus ketotifen.

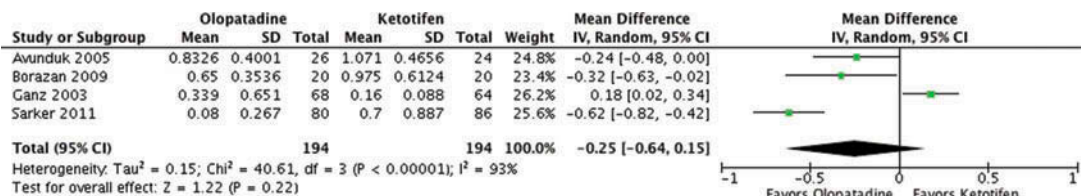


FIGURE 15. Mean differences in hyperemia score comparing topical olopatadine versus ketotifen.

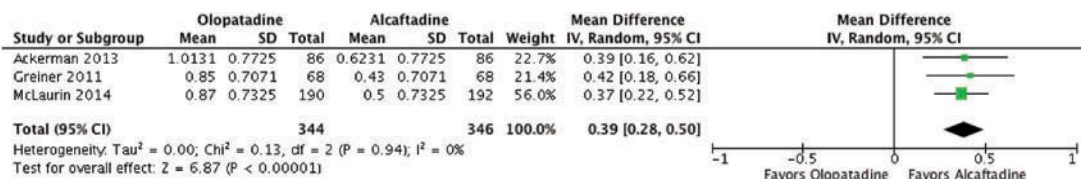


FIGURE 16. Mean differences in itch score comparing topical olopatadine versus alcaftadine.

Secondary Outcomes

We performed sensitivity analysis by excluding any individual study one at a time and found there was no significant change in the results. There was no significant publication bias detected from the funnel plots (data not shown).

Composite scores were not reported in any of the included studies and therefore a meta-analysis could not be performed. In the assessment of safety, no serious adverse outcome was reported following the use of topical olopatadine in any of the included studies.

DISCUSSION

Results of the current systematic review and meta-analysis revealed that topical olopatadine was statistically more efficacious in reducing both ocular itch and hyperemia in allergic conjunctivitis when compared with placebo. Despite a wide variation in terms of the study designs, dosing schedules of medicine and timing in outcome assessment, we hoped to include all the relevant trials in the first step and perform subgroup analyses in groups of studies that share similar nature in order to minimize the heterogeneity of studies. The effects of olopatadine versus placebo remained statistically significant prior to and after stratification by potential confounders, i.e., study design and age of participants. Since none of the trials specifically recruited patients with VKC or AKC, our meta-analysis was only able to show the effect of olopatadine in type I hypersensitivity reaction, in either environmental or experimental setting.

In our meta-analyses, topical olopatadine was significantly associated with a reduction in ocular itch and hyperemia by a pooled-MD of -1.33 and -0.92 , respectively. The reduction in pooled-SMD in ocular itch and hyperemia were -2.62 and -1.92 , respectively. The p values indicated a statistically significant reduction in ocular itch and hyperemia. We also reviewed the impact of topical olopatadine on the quality-of-life of patients with allergic conjunctivitis but only found a few papers relevant.^{35–37} Most of the studies used a rhinoconjunctivitis quality-of-life questionnaire. The largest study compared subjects' experience with 0.2% olopatadine solution to their previous experience with 0.1% olopatadine instead of directly comparing olopatadine to a placebo.³⁵ In the study, more than 70% of participants responded that topical olopatadine had successfully treated their eye allergies in 1 week. Changes from baseline in subcategories and the overall quality-of-life improved with statistical significance. The maximum change from baseline was seen in eye symptoms, correlating to the statistical effect found in our meta-analysis. More studies would be needed to evaluate the impact of topical olopatadine in the

treatment of allergic conjunctivitis using a questionnaire specifically designed for the disease.

Our meta-analysis also revealed similar effects between topical olopatadine, epinastine, and ketotifen in relieving ocular itch and hyperemia. Similar to olopatadine, epinastine is a second-generation H₁-selective antihistamine and mast cell stabilizer. Ketotifen is also a second-generation antihistamine and mast cell stabilizer, with a longer mean elimination half-life. Both epinastine and ketotifen fumarate are dual-action medications composed of an antihistamine/mast cell stabilizer. Thus, it is reasonable to expect that they have similar efficacies. Alcaftadine is an antagonist of H₁, H₂, and H₄ receptors, and the only medication in this analysis that is not a mast cell stabilizer but performed significantly better in treating ocular itch. In our meta-analysis, it is noteworthy that alcaftadine, being solely an antihistamine agent, achieved a superior effect to olopatadine. Hence, it is likely that histamine receptors other than H₁, such as H₄, could play a role in the treatment response. Furthermore, however, the lack of significance may be related to the relatively small number of studies that are available for comparing topical olopatadine with ketotifen and epinastine. More studies would therefore be warranted.

A recent Cochrane review specifically looked at the efficacy of antihistamine and mast cell stabilizer in type I hypersensitivity patients who were recruited in RCTs that did not use a within-person approach.³⁸ This approach was effective in lowering the clustering effect introduced by the eye-based method. However, the review on olopatadine only identified four eligible studies. In our present study, we maximized the eligible studies by extending the inclusion criteria to all types of ocular hypersensitivities and study designs, by including both types of studies. Our results from subgroup analyses revealed that in either subject-based studies or eye-based trials, topical olopatadine was superior to placebo in reducing ocular itch score. This is consistent with the earlier review. However, among subject-based studies that analyzed effects on hyperemia between topical olopatadine and placebo, the pooled MD did not achieve statistical significance from our analysis. This is in contrast to the earlier review, and studies adopting an eye-based approach.

There are several limitations in the current study. First, our study may be affected by reporting or publication bias, which would be difficult to control for. Second, the inclusion of CAC-model based studies could enhance the quality of data as a standardized washout protocol was followed before any assessment of these participants. However, in some other clinical studies not using the CAC-model, such washout protocol was lacking and may result in a non-uniform baseline in the comparison of medications. Third, the wide variation in study designs, inclusion criteria, baseline symptoms and signs, would render our overall meta-analysis difficult to interpret. These inherent problems

of heterogeneities across studies have been addressed using subgroup analyses that pooled studies with similar nature. Finally, it was apparent in the subgroup analysis that the effect of topical olopatadine was consistent among all subgroups. However, all the studies included only patients with type I hypersensitivity and therefore the treatment effect of olopatadine in type IV hypersensitivity allergic conjunctivitis remains to be elucidated.

In conclusion, this systemic review and meta-analysis confirmed topical olopatadine ophthalmic solution to be a safe and effective medication for allergic conjunctivitis in reducing both ocular itch and hyperemia, and it has a favorable safety and efficacy profile similar to other commonly prescribed medications such as ketotifen and epinastine. Alcaftadine appears to have a superior effect in reducing ocular itch than topical olopatadine.

DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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SEARCH STRATEGIES

Search Strategy on OVID MEDLINE

1. randomized controlled trial.pt. (405714)
2. (randomized or randomised).ab,ti. (415609)
3. placebo.ab,ti. (170338)
4. dt.fs. (1802201)
5. randomly.ab,ti. (232864)
6. trial.ab,ti. (400620)
7. groups.ab,ti. (1480734)
8. 1 or 2 or 3 or 4 or 5 or 6 or 7 (3594126)
9. exp animals/ (18325646)
10. exp humans/ (14207181)
11. 9 not (9 and 10) (4118465)
12. 8 not 11 (3088481)
13. keratoconjunctivitis/ (2828)
14. conjunctivitis, Allergic/ (2801)
15. conjunctiv\$.tw. (30781)
16. keratoconjunctiv\$.tw. (3839)
17. allergic conjunctiv\$.tw. (1424)
18. vernal conjunctiv\$.tw. (184)
19. atopic conjunctiv\$.tw. (27)
20. giant papillary conjunctiv\$.tw. (233)
21. 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 (35342)
22. Histamine H1 Antagonists, Non-Sedating/ or Anti-Allergic Agents/ or Histamine H1 Antagonists/ or olopatadine.mp. or Mast Cells/ (43387)
23. pataday.mp. (8)
24. patanol.mp. (23)
25. opatanol.mp. (6)
26. 22 or 23 or 24 or 25 (43388)
27. 21 and 26 (941)
28. 12 and 27 (622)

Search Strategy on EMBASE

1. exp randomized controlled trial/ (360314)
2. exp randomization/ (64436)
3. exp double blind procedure/ (123883)
4. exp single blind procedure/ (19241)
5. random\$.tw. (957021)
6. 1 or 2 or 3 or 4 or 5 (1089216)
7. (animal or animal experiment).sh. (3510040)
8. human.sh. (15383860)
9. 7 and 8 (539029)

10. 7 not 9 (2971011)
11. 6 not 10 (994670)
12. exp clinical trial/ (1008310)
13. (clin\$ adj3 trial\$.tw. (321703)
14. ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj3 (blind\$ or mask\$)).tw. (181353)
15. exp placebo/ (279042)
16. placebo\$.tw. (220909)
17. random\$.tw. (957021)
18. exp experimental design/ (10931)
19. exp crossover procedure/ (41224)
20. exp control group/ (81863)
21. exp latin square design/ (340)
22. 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 (1967725)
23. 22 not 10 (1860505)
24. 23 not 11 (875729)
25. exp comparative study/ (1092876)
26. exp evaluation/ (10612)
27. exp prospective study/ (270968)
28. (control\$ or prospectiv\$ or volunteer\$.tw. (4185038)
29. 25 or 26 or 27 or 28 (5109969)
30. 29 not 10 (4399140)
31. 30 not (11 or 23) (3526481)
32. 11 or 24 or 31 (5396880)
33. keratoconjunctivitis/ (4683)
34. atopic keratoconjunctivitis/ (238)
35. allergic conjunctivitis/ (3502)
36. vernal conjunctivitis/ (1068)
37. giant papillary conjunctivitis/ (133)
38. conjunctiv\$.tw. (46106)
39. keratoconjunctiv\$.tw. (5262)
40. 33 or 34 or 35 or 36 or 37 or 38 or 39 (52470)

41. exp olopatadine/ (877)
42. exp patanol/ (877)
43. exp pataday/ (877)
44. exp opatanol/ (877)
45. 41 or 42 or 43 or 44 (877)
46. 40 and 45 (377)
47. 32 and 46 (206)

Search Strategy on Clinicaltrials.gov

Search terms: "Olopatadine" AND "allergic conjunctivitis"

Search Strategy on WHO ICTRP

Search terms: "Olopatadine" AND "allergic conjunctivitis"

Search Strategy on Cochrane Central Register of Controlled Trials

1. (olopatadine or patanol or pataday or opatanol).mp. and *conjunctivitis/ [mp=title, original title, abstract, mesh headings, heading words, keyword] (0)
2. (olopatadine and conjunctivitis).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (85)
3. ((olopatadine or patanol) and conjunctivitis).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (87)
4. ((olopatadine or patanol or pataday or opatanol) and conjunctivitis).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (87)