Therapeutic Class Overview
Ophthalmic Antihistamines

Therapeutic Class

- **Overview/Summary:** All of the ophthalmic antihistamines are Food and Drug Administration (FDA)-approved for the management of signs and symptoms associated with allergic conjunctivitis. Moreover, ketotifen is also approved for the temporary relief of itchy eyes due to pollen, ragweed, grass, animal hair and dander. Allergic conjunctivitis is the most common form of ocular allergy.[1-10] Itching manifests as the main symptom but other common signs and symptoms include ocular burning, chemosis, conjunctival and eyelid edema, hyperemia, photophobia, and tearing.[11,12] Symptoms usually occur in both eyes; however, one eye may be affected more than the other.[12] Vernal conjunctivitis is a severe form of allergic conjunctivitis that may involve the cornea.[13] None of the ophthalmic antihistamines are FDA-approved for the treatment of vernal conjunctivitis. Following topical administration to the conjunctiva, ophthalmic antihistamines competitively bind with histamine receptor sites to reduce itching and vasodilation.[1] The ocular antihistamines included in this review are relatively selective for the histamine H_1 receptor but may also inhibit the degranulation of mast cells, thus limiting the release of inflammatory mediators, such as histamine, eosinophil and neutrophil chemotactic factors, and platelet-activating factor.[2-4,6-9] Emedastine (Emadine®) has only H_1-antihistamine activity.[5] The topical antihistamines have been shown to have a faster onset of action compared to oral antihistamines and ophthalmic mast-cell stabilizers.[14] All of the ophthalmic antihistamines and/or mast-cell stabilizers have been approved for use in children.[1-9] The most common side effects of the ophthalmic antihistamine preparations include ocular burning and stinging and headache.[1-9] In general, drug interactions are limited due to low systemic bioavailability by the ocular route. The administration schedule for these products ranges from once daily to four times daily, with only ophthalmic alcaftadine (Lastacaft®) and olopatadine 0.2% (Pataday®) available for once-daily use.[2,8] Ophthalmic formulations of azelastine (Optivar®) and epinastine (Elestat®) are available generically, and ketotifen (Alaway®, Zaditor®) is also available over-the-counter.[15]

Table 1. Current Medications Available in Therapeutic Class[1-9]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Alcaftadine (Lastacaft®)	Allergic conjunctivitis†	Ophthalmic solution: 0.25% (5 mL)	-
Azelastine (Optivar®)	Allergic conjunctivitis†	Ophthalmic solution: 0.05% (10 mL)	✔
Bepotastine (Bepreve®)	Allergic conjunctivitis†	Ophthalmic solution: 1.5% (10 mL)	-
Emedastine (Emadine®)	Allergic conjunctivitis‡	Ophthalmic solution: 0.05% (5 mL)	-
Epinastine (Elestat®)	Allergic conjunctivitis§	Ophthalmic solution: 0.05% (8, 15 mL)	✔
Ketotifen (Alaway®, Zaditor®)	Allergic conjunctivitis§, ocular itching‖	Ophthalmic solution: 0.025% (OTC, RX) (1, 5, 10 mL)	✔ *
Olopatadine (Pataday®, Patanol®)	Allergic conjunctivitis†‡	Ophthalmic solution: 0.1% (5 mL) 0.2% (2.5 mL)	-

* Product is also available over-the-counter in at least one dosage form or strength.
† For the treatment of ocular itching associated with allergic conjunctivitis.
‡ For the treatment of signs and symptoms of allergic conjunctivitis.
§ For the prevention of ocular itching associated with allergic conjunctivitis.
‖ For the temporary relief of itchy eyes due to pollen, ragweed, grass, animal hair and dander.

Evidence-based Medicine

- In general, the ophthalmic antihistamines/mast-cell stabilizers have been shown to be significantly more effective than placebo for reducing the symptoms of allergic conjunctivitis including ocular itching, conjunctival redness at all time periods post-administration.[16-20]
- Limited head-to-head trials comparing olopatadine, azelastine and ketotifen formulations have failed to routinely show the "superiority" of one ophthalmic antihistamine over another for the management of allergic conjunctivitis.[21-26]
- A meta-analysis of four trials found that patients were 1.3 times more likely to perceive their treatment response as "good" with ophthalmic antihistamines and antihistamines/mast-cell stabilizers compared to patients receiving pure ophthalmic mast-cell stabilizers; however, this difference in response failed to reach statistical significance.[27]
- The ophthalmic antihistamines have consistently shown a greater improvement in allergy symptoms and/or patient comfort scores compared to ophthalmic mast-cell stabilizers and ocular vasoconstrictors; however, many of these trials were conducted using single doses of study medication (conjunctival allergen challenge model) in a small number of patients.[28-38]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
  - Ophthalmic formulations of agents from the following classes are useful in treating allergic conjunctivitis: corticosteroids, vasoconstrictor/antihistamine combinations, antihistamines, nonsteroidal anti-inflammatories (NSAIDs), mast-cell stabilizers, antihistamine/mast-cell stabilizers and immunosuppressants.[13]
  - Treat mild allergic conjunctivitis with an over-the-counter (OTC) antihistamine/vasoconstrictor or second-generation topical histamine H_1-receptor antagonist. No preference is given to any one OTC antihistamine/vasoconstrictor or antihistamine.[39]
  - If the condition is frequently recurrent or persistent, use mast-cell stabilizers. No single mast-cell stabilizer is preferred over another.[39]
  - Medications with antihistamine and mast-cell stabilizing properties may be utilized for either acute or chronic disease. No one antihistamine/mast-cell stabilizer is preferred over another.[39]
  - If the symptoms are not adequately controlled, a brief course (one to two weeks) of low-potency topical corticosteroid may be added to the regimen. The lowest potency and frequency of corticosteroid administration that relieves the patient's symptoms should be used because of the potential for adverse side effects with their protracted use (e.g., cataract formation and elevated intraocular pressure).[13,39]
  - Ketorolac, a NSAID, is also Food and Drug Administration (FDA) approved for the treatment of allergic conjunctivitis.[13,39]
- Other Key Facts:
  - Ophthalmic formulations of alcaftadine and emedastine are classified as pregnancy category B while all of the other agents in this class have a pregnancy category C rating.
  - Ophthalmic alcaftadine (Lastacaft®) and olopatadine 0.2% (Pataday®) are the only agents within the class that are approved for once-daily use.
  - Ophthalmic formulations of azelastine, epinastine and ketotifen are available generically.
  - Ketotifen is also available over-the-counter.[15]

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Therapeutic Class Review
Ophthalmic Antihistamines

Overview/Summary

The ophthalmic antihistamines are Food and Drug Administration (FDA)-approved for the management of signs and symptoms associated with allergic conjunctivitis and include alcaftadine (Lastacaft®), azelastine (Optivar®), bepotastine (Bepreve®), emedastine (Emadine®), epinastine (Elestat®), ketotifen (Alaway®) and olopatadine (Patanol®).[1-11] Ketotifen is also approved for the temporary relief of itchy eyes due to pollen, ragweed, grass, animal hair, and dander. Alcaftadine was approved by the FDA in July 2010, and represents the newest agent in the class.[12]

Ophthalmic antihistamine preparations provide symptomatic relief of allergic conjunctivitis through various mechanisms. Ophthalmic formulations of alcaftadine, azelastine, bepotastine, epinastine, ketotifen, and olopatadine have both histamine type 1 (H_1-antihistamine) and mast cell stabilizing properties, while emedastine has only H_1-antihistamine activity.[13] Following topical administration to the conjunctiva, ophthalmic antihistamines competitively bind with histamine receptor sites and reduce itching and vasodilation.[14] The ocular antihistamines included in this review are relatively selective for the histamine H_1 receptor but may also inhibit the degranulation of mast cells, thus limiting the release of inflammatory mediators, such as histamine, eosinophil and neutrophil chemotactic factors, and platelet-activating factor.[14] Compared to oral antihistamines and ophthalmic mast cell stabilizers, the topical antihistamines have been shown to have a faster onset of action.[12] All of the ophthalmic antihistamines and/or mast cell stabilizers have been approved for use in children.[1-11] Ophthalmic formulations of alcaftadine and emedastine are classified as pregnancy category B while all of the other agents in this class have a pregnancy category C rating. The most common side effects of the ophthalmic antihistamine preparations are ocular burning and stinging, and headache.[1-11] In general, drug interactions are limited due to low systemic bioavailability by the ocular route. The administration schedule for these products ranges from once-daily to four times daily, with only ophthalmic alcaftadine and olopatadine 0.2% (Pataday®) available for once-daily use.[4,8] Ophthalmic formulations of azelastine and epinastine are available generically, and ketotifen is also available in over-the-counter (OTC) formulations.[15]

The most common form of ocular allergy is allergic conjunctivitis.[13] The major categories of allergic conjunctivitis are atopic conjunctivitis (associated with atopic dermatitis), giant papillary conjunctivitis (most often associated with soft contact lens wear), seasonal conjunctivitis, simple allergic conjunctivitis, and vernal conjunctivitis.[14,16] Based on clinical features, allergic conjunctivitis may also be subdivided into acute, seasonal, and perennial allergic conjunctivitis.[17] While itching is the main symptom, other common signs and symptoms of allergic conjunctivitis include ocular burning, chemosis, conjunctival and eyelid edema, hyperemia, photophobia, and tearing.[13,17] Symptoms usually occur in both eyes; however, one eye may be affected more than the other.[17] Vernal conjunctivitis is a severe form of allergic conjunctivitis that may involve the cornea.[14] None of the ophthalmic antihistamines are FDA-approved for the treatment of vernal conjunctivitis.

Allergic conjunctivitis results from classic Type I IgE-mediated hypersensitivity, where the immediate response to allergens is mediated predominantly by mast cells.[17] The mast cells are present in the conjunctiva in high concentrations and release chemical mediators when activated by allergen-IgE cross-linkage. During the early response, histamine is the main mediator and it causes itching, vasodilation, and vasopermeability. During the late phase of the allergic reaction, mast cells release chemokines and cytokines, which results in the influx of other inflammatory cells and continued inflammation.

According to the American Academy of Ophthalmology, mild allergic conjunctivitis may be treated with an OTC antihistamine/vasoconstrictor or topical antihistamine.[16] Because ophthalmic vasoconstrictors have a short duration of action and may cause rebound hyperemia and conjunctivitis medicamentosa, they should only be used short term.[13] Ophthalmic mast cell stabilizers may be used if the condition is recurrent or persistent since they have a slower onset of action than topical antihistamines.[13,16]

Ophthalmic allergy preparations with dual antihistamine and mast cell stabilizing properties may be used for either acute or chronic disease, and no preference is given to one specific ophthalmic antihistamine versus another.[16] There are limited head-to-head trials comparing the agents in this review to each other.[18-33] While a few studies have reported some differences between agents, the overall clinical significance of these differences is not known since many of these trials were conducted using single doses of study medication (conjunctival allergen challenge model), in a small number of patients, and/or with comparisons to products that are no longer commercially available.

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade Name)	Medication Class	Generic Availability
Alcaftadine (Lastacaft®)	Antihistamine/ Mast cell stabilizer	-
Azelastine (Optivar®)	Antihistamine/ Mast cell stabilizer	✔
Bepotastine (Bepreve®)	Antihistamine/ Mast cell stabilizer	-
Emedastine (Emadine®)	Antihistamine	-
Epinastine (Elestat®)	Antihistamine/ Mast cell stabilizer	✔
Ketotifen (Alaway®, Zaditor®)	Antihistamine/ Mast cell stabilizer	✔ *
Olopatadine (Pataday®, Patanol®)	Antihistamine/ Mast cell stabilizer	-

*Product is also available over-the-counter in at least one dosage form or strength.

Indications

Table 2. Food and Drug Administration-Approved Indications[1-11]

Generic Name	Allergic Conjunctivitis	Ocular Itching
Alcaftadine	✔ *	
Azelastine	✔ *	
Bepotastine	✔ *	
Emedastine	✔ †	
Epinastine	✔ ‡	
Ketotifen	✔ ‡ (RX)	✔ § (OTC)
Olopatadine	✔ *†	

OTC=over-the-counter, RX=prescription
*For the treatment of ocular itching associated with allergic conjunctivitis.
†For the treatment of signs and symptoms of allergic conjunctivitis.
‡For the prevention of ocular itching associated with allergic conjunctivitis.
§For the temporary relief of itchy eyes due to pollen, ragweed, grass, animal hair, and dander.

Pharmacokinetics

Table 3. Pharmacokinetics[1,3-17]

Generic Name	Onset (minutes)	Duration (hours)	Renal Excretion (%)	Active Metabolites	Serum Half-Life (hours)
Alcaftadine	Not reported	Not reported	Not reported	Carboxylic acid metabolite	2*
Azelastine	3 minutes	8	Feces (75)	Hepatic (N-desmethyl-azelastine)	22
Bepotastine	<15 minutes (1 to 2 hours peak)	8	Urine (75 to 90)	Minimal (not reported)	Not reported
Emedastine	Not reported	Not reported	Urine (44)	Hepatic (none)	3 to 4
Epinastine	3 to 5 minutes	8	Feces (30); urine (55)	Minimal (not reported)	12
Ketotifen	Minutes	8 to 12	Feces (30 to 40); urine (60 to 70)	Hepatic (ketotifen N-glucuronide, nor-ketotifen)	9 to 21
Olopatadine	<30 minutes	8	Urine (60 to 70)	Hepatic (none)	3

*Half-life reported for the active metabolite

Clinical Trials

Clinical studies evaluating the safety and effectiveness of the ophthalmic antihistamines for their Food and Drug Administration (FDA)-approved indications are summarized in Table 4.[18-45]

Ophthalmic Antihistamines and Antihistamines/Mast cell stabilizers (Dual Mechanism)

There have been a number of studies evaluating the efficacy of topical antihistamines and antihistamines/mast cell stabilizers in the treatment of allergic conjunctivitis. Because of the rapid onset of action of antihistamines, most studies used the conjunctival allergen challenge model to establish the relative efficacy of these ocular formulations versus placebo. Most studies showed improvement in symptoms, especially for itching, in those treated with ophthalmic formulations of antihistamines and antihistamines/mast cell stabilizers compared to placebo.

Alcaftadine, the ophthalmic histamine H_1-receptor antagonist most recently approved by the FDA, was shown to significantly reduce conjunctival redness and almost all other allergic signs and symptoms at both 15 minutes and 16 hours after drug administration compared to its vehicle alone (P<0.05 for both comparisons).[18] In a second study of patients with a history of ocular allergens (N=170), all treatment groups (alcaftadine 0.05%, 0.10% and 0.25% and olopatadine 0.1%) were associated with lower ocular itching scores compared to placebo (P<0.05 for all comparisons). Compared to placebo, all treatments were associated with a significant improvement in conjunctival redness scores at both 15 minutes and 16 hours post-administration (P<0.05 for all comparisons), clinical significance (≥1 unit difference from placebo) was only reported for the alcaftadine 0.25% treatment group. At 16 hours, patients treated with alcaftadine 0.25% reported lower ocular itching scores compared to patients receiving olopatadine (P =0.017), although this strength is not currently approved by the FDA.[19]

Using the conjunctival allergen challenge model for allergic conjunctivitis, bepotastine ophthalmic solution was shown to be more effective than placebo in relieving ocular itching after 15 minutes and eight hours in adults and children.[20,21] There are no published studies comparing ophthalmic bepotastine to other ophthalmic allergy preparations for the treatment of allergic conjunctivitis.

Ophthalmic olopatadine is available by prescription in twice-daily (0.1%) and once-daily (0.2%) formulations. Using the conjunctival allergen challenge model, one dose of ophthalmic olopatadine 0.2% was comparable to two doses of ophthalmic olopatadine 0.1%, and both regimens were more effective than placebo in terms of mean itching scores.[22] Both active agents were found to be safe and well-tolerated. Using the conjunctival allergen challenge model, ophthalmic olopatadine (0.1%) was reported to be significantly more effective than ophthalmic azelastine in the management of itching associated with allergic conjunctivitis, and both agents were more effective than placebo.[23] Clinical studies comparing ophthalmic olopatadine to ophthalmic ketotifen have produced mixed results. Using the conjunctival allergen challenge model, ophthalmic olopatadine 0.1% was reported to be more effective than ophthalmic ketotifen in reducing the itching associated with allergic conjunctivitis (N=32).[28] In this study, ophthalmic olopatadine 0.1% caused less ocular discomfort than ophthalmic ketotifen and was preferred by 73% of patients compared to 27% with ophthalmic ketotifen. In an environmental study of patient preference, a significantly higher percentage of patients with active symptoms of seasonal or perennial allergic conjunctivitis selected ophthalmic olopatadine 0.1% over ophthalmic ketotifen primarily on the basis of efficacy and comfort (N=100).[29] In a three-week parallel-group study in patients with seasonal allergic conjunctivitis (N=66), ophthalmic ketotifen was associated with higher global efficacy ratings compared to ophthalmic olopatadine 0.1% at day 21 (91 vs 55% and 94 vs 42% for patient and investigator assessment, respectively). Comfort ratings were comparable between the two agents.[30] In a similar 30-day study in patients with seasonal allergic conjunctivitis, ketotifen and olopatadine (0.1%) were found to be comparable in scores for tearing, itchiness, redness, chemosis and eyelid swelling reduction (*P* values not reported).[31]

Using the conjunctival allergen challenge model, ophthalmic formulations of emedastine and ketotifen significantly reduced mean itching scores at all time points compared with placebo ($P<0.05$), but no statistically significant differences were reported between emedastine and ketotifen in mean itching scores at any time points (*P* values not reported).[24] In a randomized controlled trial of patients with seasonal allergic conjunctivitis (N=100), no differences in efficacy were reported between ophthalmic formulations of emedastine, epinastine, ketotifen, and olopatadine (*P* values not reported). Moreover, all agents were more efficacious than ophthalmic fluorometholone in preventing itching and redness ($P<0.001$ for all comparisons).[33]

In a small study (N=40) measuring ocular comfort, ophthalmic epinastine was rated as more comfortable than ophthalmic azelastine or ophthalmic ketotifen after administration of a single drop; and ophthalmic ketotifen was reported to be more comfortable than ophthalmic azelastine.[25] Using the conjunctival allergen challenge model, ophthalmic olopatadine 0.1% was significantly more effective than ophthalmic epinastine in controlling itching, redness, and chemosis.[26] Ophthalmic olopatadine 0.2% was also shown to be more effective than ophthalmic epinastine in preventing ocular itching and redness using the conjunctival allergen challenge model.[27] All of the ocular allergy preparations gave similar results in terms of reducing chemosis, eyelid swelling, and tearing.

Medication Class Comparisons

Using the conjunctival allergen challenge model, ophthalmic naphazoline/pheniramine and ophthalmic olopatadine were associated with significantly lower ocular allergy index scores (erythema, eyelid swelling, chemosis, and itching) than placebo. Ophthalmic naphazoline/pheniramine was more effective than ophthalmic olopatadine in relieving redness and chemosis, while ophthalmic olopatadine was more effective than ophthalmic naphazoline/pheniramine in relieving itching.[34]

A meta-analysis of four trials found that patients were 1.3 times more likely to perceive their treatment response as “good” with ophthalmic antihistamines and antihistamines/mast cell stabilizers compared to patients receiving pure ophthalmic mast cell stabilizers.[35] However, this difference in response failed to reach statistical significance. Topical antihistamines have a faster onset of action than the ophthalmic mast cell stabilizers.[13]

The efficacy of ophthalmic cromolyn (strength not reported), ophthalmic azelastine, and placebo were evaluated in patients with seasonal allergic conjunctivitis or rhinoconjunctivitis (N=144).[36] Both active treatments showed a marked effect on itching, tearing, and conjunctival redness on day three with a sustained improvement on days seven and 14. Global assessment of efficacy was at least 'satisfactory' for 90%, 81%, and 66% of patients receiving ophthalmic azelastine, ophthalmic cromolyn, and placebo. The most frequent side effects were transient application site reactions which tended to disappear with increasing duration of treatment, and, less frequently, taste perversion.

Using the conjunctival allergen challenge model, a single dose of ophthalmic ketotifen was shown to be more effective than a two-week regimen of ophthalmic cromolyn 4% in alleviating symptoms of allergic conjunctivitis (N=56).[37] In another conjunctival allergen challenge study, ophthalmic ketotifen was reported to be significantly more effective than ophthalmic nedocromil in reducing ocular itching after both the five-minute and 12-hour post treatment allergen challenges (N=59).[41] Ophthalmic ketotifen-treated eyes were significantly more comfortable than ophthalmic nedocromil-treated eyes at 1 to 10 minutes after medication instillation. While ophthalmic emedastine and ophthalmic nedocromil were both more effective than placebo in controlling ocular itching and redness after an allergen challenge, ophthalmic emedastine was more effective than ophthalmic nedocromil in alleviating redness and itching at three and 10 minutes after an allergen challenge (N=30).[40]

In a small study, a single dose of ophthalmic olopatadine was reported to be more comfortable and efficacious in reducing the itching caused by an allergen challenge than a two-week course of ophthalmic nedocromil (N=52).[42] However, in a two-week crossover study, physicians and patients judged ophthalmic nedocromil and ophthalmic olopatadine to be similarly effective in preventing signs and symptoms of perennial allergic conjunctivitis.[43] Comparative studies have shown ophthalmic olopatadine and ophthalmic emedastine were more effective in reducing ocular itching than ophthalmic ketorolac, a nonsteroidal anti-inflammatory drug.[13,39,44]

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Antihistamines and Antihistamines/Mast cell stabilizers (Dual Mechanism)				
Torkildsen et al[18] Alcaftadine 0.25% ophthalmic solution, one drop administered bilaterally vs. placebo	DB, MC, PC, RCT Patients >10 years of age with a history of allergic conjunctivitis and a reproducible, positive reaction to a conjunctival allergen challenge (CAC)	N=58 4 visits (study duration not reported)	Primary: Ocular itching (assessed by subject at 3, 5 and 7 minutes following CAC) and conjunctival redness (assessed by investigator at 7, 15 and 20 minutes following CAC) Secondary: Other signs and symptoms of allergic conjunctivitis (assessed by investigator at 7, 15 and 20 minutes following CAC)	Primary: Alcaftadine was associated with a statistically significant reduction in conjunctival redness at 16 hours (duration of action) and 15 minutes (onset of action) after drug administration compared to vehicle. The differences in mean ocular itching scores at duration of action were -1.731, -1.687 and -1.576 at three, five and seven minutes post CAC, respectively (*P*<0.001 for all time points). The differences in mean ocular itching scores at onset of action were -1.500, -1.491 and -1.474 at three, five and seven minutes post CAC, respectively (*P*<0.001 for all time points). Mean conjunctival redness scores were statistically significantly lower for the alcaftadine group compared to the vehicle group at seven, 15 and 20 minutes post CAC at both 15 minutes and 16 hours following study medication instillation (*P*<0.05 for all time points and both duration of action and onset of action visits). Of note, this change does not reach the level of clinical significance (>1 point difference in absolute mean scores between vehicle and alcaftadine groups as defined by the FDA). Secondary: Alcaftadine was associated with a statistically significant reduction in most secondary endpoints at 16 hours (duration of action) and 15 minutes (onset of action) after drug administration compared to vehicle. Adverse events occurred at a higher incidence in the vehicle

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				group compared to alcaftadine group (13.3% and 6.7% respectively, *P* value not reported).
Greiner et al[19] Alcaftadine 0.05% vs alcaftadine 0.01% vs alcaftadine 0.25% vs olopatadine 0.1% vs placebo	DM, PRO, PC, AC, RCT Patients ≥18 years of age with a history of ocular allergies and/or a positive skin test reaction to specified allergens within the last 24 months, and with a best-corrected visual acuity of 0.6 log MAR or better in each eye	N=170 5 weeks	Primary: Ocular itching (at visit 4, 5 minutes after an allergen challenge), conjunctival redness (at visit 4, 15 minutes after an allergen challenge) Secondary: Ciliary and episcleral redness, chemosis, lid swelling, tearing, ocular mucus discharge, nasal symptoms, adverse events	Primary: At 15 minutes after the administration of the study drug (onset of action), all active treatment groups exhibited greater clinically (≥1 unit difference) and statistically significant (P<0.001) reductions compared to placebo in itching scores at all time points. Mean differences from placebo for alcaftadine 0.25% were -1.95, -1.92, and -1.77 units at three, five, and seven minutes post CAC time points, respectively. In contrast, mean differences from placebo for olopatadine were -1.89, -1.84, and -1.66, respectively. At seven minutes, the difference in the prevention of itching was statistically significant for alcaftadine 0.25% compared to olopatadine (*P*=0.017). At 15 minutes after the administration of the study drug, the mean conjunctival redness scores for all active treatment groups were lower than those observed in the placebo group at every post-challenge time point (*P*<0.05). At 15 minutes after the administration of the study drug, the difference in mean scores for olopatadine and alcaftadine 0.25% achieved clinical significance compared with placebo at seven minutes post-challenge, with -1.27 and -1.35 unit differences, respectively (*P* value not reported). At 16 hours after the administration of the study drug (duration of action), alcaftadine was associated with lower mean ocular itching scores than both placebo and olopatadine (*P* value not reported). At seven minutes post-challenge, the difference in the prevention of itching was statistically significant for alcaftadine 0.25% versus olopatadine (*P*=0.017). At 16 hours after the administration of the study drug, alcaftadine 0.25% and olopatadine groups exhibited statistically

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				significant reductions in mean conjunctival redness compared to placebo (*P*<0.05). Secondary: At the 15-minute and 16-hour post-challenge time points, all treatment groups exhibited statistically significantly lower mean scores compared to placebo in all secondary endpoints (*P*<0.05). The incidence of adverse events observed in the alcaftadine groups was not dose-related. All ocular adverse events were self-limited and mild in severity. The most common non-ocular adverse event was nasopharyngitis. There were no ocular adverse events reported in the olopatadine treatment group.
Abelson et al[20] Bepotastine 1% 1 drop each eye OTO vs bepotastine 1.5% 1 drop each eye OTO vs placebo 1 drop each eye OTO	DB, PC, PRO, RCT Patients ≥10 years (range 11-73 years) with a history of allergic conjunctivitis, study used CAC model	N=107 7 weeks (5 visits)	Primary: Ocular itching at 3, 5 and 7 minutes post challenge; redness at 7, 15 and 20 minutes post challenge; safety Secondary: Not reported	Primary: Bepotastine 1% and 1.5% were associated with clinically and statistically significant reductions in mean ocular itching scores compared with placebo in the 15-minute onset of action and eight-hour duration of action CAC tests (all *P*<0.001). Statistically significant reductions in conjunctival hyperemia were achieved with both bepotastine concentrations; however, these reductions were not considered clinical significant. Overall, 13 patients experienced a treatment-emergent adverse event considered related to the study drug (six=bepotastine 1%, four=bepotastine 1.5%, and three=placebo; *P* values not reported). Secondary: Not reported
Macejko et al[21] Bepotastine 1.5% one drop in each eye prior to CAC test	DB, MC, PC, Phase III, PRO, RCT,	N=130 7 weeks	Primary: Mean score changes (Scale=0 to 3;	Primary: Within three minutes post CAC challenge and at each other time point thereafter (performed 15 minutes or eight hours after test agent instillation), bepotastine 1.0% and 1.5%

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs bepotastine 1.5% one drop in each eye prior to CAC test vs placebo one drop in each eye prior to CAC test	Patients ≥10 years of age with a history of allergic conjunctivitis, a positive allergen skin test within the previous 24 months and conjunctival allergen challenge (CAC) response on 2 separate occasions		0=comfortable and 3=extremely uncomfortable or intolerable) for ocular itching and conjunctival hyperemia	demonstrated at least a 1.2-unit reduction for ocular itching when compared with placebo (*P*<0.0001). Ocular itching improvements for bepotastine 1.0% and 1.5% were substantially less at the 16-hour CAC test than at 15 minutes and eight hours post-challenge. Conjunctival redness improved by 0.4 to 0.6 units at most time points at the onset of action CAC test for both bepotastine the 1.0% and 1.5% concentrations of bepotastine compared to placebo (*P*≤0.0125). There was, however, less conjunctival redness improvement seen at the eight- and 16-hour CAC test assessments. The most commonly reported adverse events included: nasopharyngitis (8.5% of all subjects), eye irritation (3.8%), and mild taste on instillation (3.1%). There were no reports of drowsiness or dry mouth. Dry eye was reported for a single subject in each of the placebo and bepotastine 1.0% treatment groups. Most events were reported as mild and transient, with no patients discontinuing therapy due to an event.
Abelson et al[22] Olopatadine 0.1% 1 drop one eye every 8 hours for 2 doses vs olopatadine 0.2% 1 drop one eye OTO vs placebo 1 drop one eye every 8 hours for 2 doses or OTO	DB, PC, RCT Patients who responded to the ocular allergen challenge, mean age 41 years, study used CAC model	N=23 3 weeks (3 visits)	Primary: Ocular itching at 3, 5 and 7 minutes post challenge (allergen administered 24 hours after study drug instilled); safety Secondary: Not reported	Primary: At the 24-hour time point, two doses of olopatadine 0.1% and one dose of olopatadine 0.2% significantly reduced itching scores in comparison to placebo (*P*=0.002 and *P*=0.0007, respectively); however, there were no statistically significant differences between olopatadine 0.1% and olopatadine 0.2% (*P*=0.081). Olopatadine 0.1% and 0.2% were both found to be safe and well tolerated as used in this study. No adverse events occurred while on drug therapy. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Study medications were administered contralaterally.				
Spangler et al[23] Azelastine 0.05% 1 drop OTO vs olopatadine 0.1% 1 drop OTO vs placebo (artificial tears) 1 drop OTO Study medications were administered contralaterally.	DB, MC, PRO, RCT Patients with a history of allergic conjunctivitis, mean age ~40 years, study used CAC model	N=111 21 days (3 visits)	Primary: Ocular itching assessments every 30 seconds for a total period of 20 minutes post challenge, mean itching scores Secondary: Not reported	Primary: At visit three (evaluation visit), azelastine and olopatadine were both significantly more effective than placebo at reducing itching post challenge (both *P*<0.05). Olopatadine was significantly more effective than azelastine in preventing itching at 3.5 minutes through 20 minutes post challenge (*P*<0.05). No adverse events were reported Secondary: Not reported
D'Arienzo et al[24] Emedastine 0.05% OTO vs ketotifen 0.025% OTO vs placebo OTO Study medications were administered contralaterally.	DB, PC, RCT, SC Patients with a history of allergic conjunctivitis, mean age 41 years, study used CAC model	N=45 3 weeks (3 visits)	Primary: Ocular itching at 3, 5 and 10 minutes post challenge; safety Secondary: Not reported	Primary: Both emedastine and ketotifen significantly reduced mean itching scores at all time points compared with placebo (all *P*<0.05). There were no statistically significant differences between emedastine and ketotifen in mean itching scores at any time points (*P* values not reported). No adverse events were reported in this study. Secondary: Not reported
Torkildsen et al[25] Epinastine 0.05% 1 drop in one eye	DB, RCT, SC, XO Patients with allergic	N=40 4 weeks (4 visits)	Primary: Ocular comfort (11 point scale with 0=very	Primary: The mean ocular comfort score was significantly lower (indicating more comfort) with epinastine than azelastine at 30 seconds, one, two, and five minutes; and ketotifen at zero

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs ketotifen 0.025% or azelastine 0.05% 1 drop in the other eye	conjunctivitis, mean age 40 years		comfortable) at 0, 0.5, 1, 2 and 5 minutes after instillation (visit 1); patient description of ocular sensation 3 minutes after medication instilled; ocular drying (visits 2 to 4), safety Secondary: Not reported	minutes (immediately) after instillation (all *P*<0.05). The mean ocular comfort score was significantly lower with ketotifen than azelastine at 30 seconds, one, and two minutes (all *P*<0.05). The percentage of patients who reported positive descriptors (e.g., refreshing, soothing) with epinastine, ketotifen, and azelastine was 85, 55, and 41% (*P* values not reported). There were no significant differences between the treatments with regards to ocular drying (*P* values not reported). All of the 26 reported adverse events were not serious (six for epinastine, seven for ketotifen and 12 for azelastine; *P* values not reported). Secondary: Not reported
Lanier et al[26] Epinastine 0.05% 1 drop OTO vs olopatadine 0.1% 1 drop OTO vs placebo 1 drop OTO	DB, PC, PRO, RCT, SC Patients (age not reported) with a history of allergic conjunctivitis, study used CAC model	N=66 Duration not reported (3 visits)	Primary: Ocular itching at 3, 5 and 7 minutes post challenge; redness and chemosis at 10, 15, and 20 minutes post challenge Secondary: Not reported	Primary: Olopatadine-treated eyes exhibited significantly lower mean itching and conjunctival redness scores than the contralateral epinastine-treated eyes (N=53, *P*=0.003 and *P*<0.001, respectively). Olopatadine-treated eyes also exhibited significantly less chemosis, ciliary redness, and epscleral redness than epinastine-treated eyes (all *P*≤0.001). Comparisons to placebo were not reported. Secondary: Not reported
Mah et al[27] Epinastine 0.05% 1 drop OTO vs	DB, PC, RCT Patients (age not reported) who responded to the	N=92 7 weeks (4 visits)	Primary: Ocular itching at 3, 5 and 7 minutes post challenge; redness at 7, 15,	Primary: Olopatadine-treated eyes exhibited significantly lower mean ocular itching scores vs epinastine-treated eyes at five (*P*=0.024) and seven minutes (*P*=0.003) post challenge.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
olopatadine 0.2% 1 drop OTO vs placebo 1 drop OTO Study medications were administered contralaterally.	ocular allergen challenge, study used CAC model		and 20 minutes post challenge; drop comfort at 0.5, 1, 2 and 5 minutes post challenge; safety Secondary: Not reported	Olopatadine-treated eyes exhibited significantly lower mean redness scores vs epinastine-treated eyes at all time points post challenge (P<0.05). Olopatadine was rated as significantly more comfortable than epinastine at one minute post-drop instillation (P=0.003). All adverse events were not serious and unrelated to study medication. Secondary: Not reported
Berdy et al[28] Ketotifen 0.025% 1 drop OTO vs olopatadine 0.1% 1 drop OTO Study medications were administered contralaterally.	DB, PRO, RCT Patients (age not reported) who responded to the CAC, study used CAC model	N=32 Duration not reported (3 visits)	Primary: Ocular itching at 3, 5, and 10 minutes post challenge (allergen administered 12 hours after study drug instilled); ocular comfort; patient satisfaction Secondary: Not reported	Primary: Twelve hours after medication administration, efficacy scores for olopatadine were significantly higher than those for ketotifen at three and five minutes post challenge (1.84 and 1.75 vs 1.25 and 1.34, respectively; P<0.05). Olopatadine-treated eyes were rated significantly more comfortable than those treated with ketotifen immediately after drug instillation (1.25 vs 2.09; P<0.05) and 12 hours later, as measured by patient ratings of ocular comfort. Of the 22 patients who had a preference, 16 (73%) were more satisfied with olopatadine than with ketotifen. Secondary: Not reported
Leonardi et al[29] Ketotifen 0.025% vs olopatadine 0.1%	DB (2 centers) Patients (age not reported) with current symptoms of SAC or PAC	N=100 4 weeks (2 visits)	Primary: Patient rating of comfort, efficacy, and preference Secondary: Not reported	Primary: A significantly greater percentage of patients (81%) selected olopatadine when asked which medication they preferred; which they found more comfortable; which they found more efficacious in reducing symptoms of allergy; and which they would select if visiting the doctor's office (P<0.0001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Patients were instructed to use both medications as needed over four weeks, but not to exceed two drops of medication per eye per day.				Seventy-six percent of patients considered both efficacy and comfort when making their preference decisions (*P*<0.0001). No adverse events were reported. Secondary: Not reported
Ganz et al[30] Ketotifen 0.025% both eyes BID vs olopatadine 0.1% both eyes BID	DB, PG, PRO, RCT Patients with SAC (age not reported)	N=66 3 weeks	Primary: Responder rate (patients with excellent or good global efficacy) on day 5 and 21, patient and investigator ratings of global efficacy, comfort, safety Secondary: Not reported	Primary: The responder rate was higher with ketotifen than with olopatadine on day five (72 vs 54% for patient assessment and 88 vs 55% for investigator assessment, respectively) and day 21 (91 vs 55% and 94 vs 42%, respectively) (*P* values not reported). Global efficacy ratings were higher with ketotifen, and severity scores for hyperemia and itching were significantly lower (*P* values not reported). Both drugs elicited comparable comfort ratings (*P* values not reported). The most common adverse events were burning/stinging and headache. Secondary: Not reported
Avunduk et al[31] Ketotifen 0.025% 2 drops both eyes BID vs olopatadine 0.1% 2 drops both eyes BID vs	DB, PRO, RCT Patients with SAC, age range 18-61 years	N=39 30 days	Primary: Itching, tearing, redness, chemosis, eyelid swelling, safety Secondary: Not reported	Primary: The mean itching scores were significantly lower on days 15 and 30 in patients receiving ketotifen and olopatadine compared to placebo (all *P*<0.05). There were no significant differences in mean itching scores in patients receiving ketotifen or olopatadine at any examination time. The mean tearing scores were significantly lower on days 15 and 30 in patients receiving ketotifen compared to placebo (all *P*<0.05). The mean tearing scores were significantly lower on day 15 (*P*<0.05) but not day 30 (*P* value not reported) in patients receiving olopatadine compared to placebo. There

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo (artificial tears) 2 drops both eyes BID				were no significant differences in mean tearing scores in patients receiving ketotifen or olopatadine at any examination time. No significant differences in mean scores for redness, chemosis, or eyelid swelling were found in patients receiving ketotifen, olopatadine, or placebo. No adverse events were observed during the study. Secondary: Not reported
Hida et al[32] Ketotifen 0.025% vs olopatadine 0.1%	PG, SC Patients with VKC (age not reported)	N=not reported 21 days	Primary: Itching, burning, tearing, conjunctival hyperemia, mucous discharge, photophobia, safety Secondary: Not reported	Primary: On evaluating ocular itching, burning, tearing, conjunctival hyperemia, mucous discharge, and photophobia, the ketotifen group showed a significant improvement of total signs and symptoms (P<0.05). Between the baseline and day seven, treatment with olopatadine resulted in decreased burning, but after day 21, ketotifen was slightly better (P values not reported). Sand sensation, papillae and Horner-Trantas dots were not significantly different in both groups (P values not reported). The authors concluded that both drugs were efficient and safe in relieving the main symptoms and signs of VKC. Between the same time points, there was a significant difference in favor of ketotifen-treated patients (P<0.05), showing improvement of itching, tearing, conjunctival hyperemia, mucous discharge, and photophobia Secondary: Not reported
Borazan et al[33] Ketotifen 0.025% one eye BID	DB, PC, PRO, RCT	N=100 2 weeks	Primary: Itching, redness, tearing, chemosis,	Primary: After one and two weeks of treatment, all agents were significantly more effective than placebo in alleviating itching,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs olopatadine 0.1% one eye BID vs emedastine 0.05% one eye BID vs epinastine 0.05% one eye BID vs fluorometholone 0.1% one eye BID vs placebo one eye BID One eye of each patient was treated with the study drug and the other eye was treated with placebo.	Patients with SAC, mean age 26 years		and eyelid swelling assessed after 1 and 2 weeks of treatment; conjunctival impression cytology at baseline and after treatment Secondary: Not reported	redness, tearing, chemosis, and eyelid swelling (all *P*<0.001). Fluorometholone was significantly less effective than the other agents in reducing itching and redness at all control visits (*P* values not reported). Although scores for tearing, chemosis, and eyelid swelling showed a clinical improvement in all groups, there were no statistically significant between-group differences (*P* values not reported). At the end of treatment conjunctival impression cytology scores were significantly lower for drug-treated eyes than for placebo-treated eyes (*P*<0.01). There were no significant differences between treatment groups (*P* values not reported). Secondary: Not reported
Medication Class Comparisons				
Greiner et al[34] Naphazoline/pheniramine 0.025%/ 0.3% (Visine A®, Naphcon-A®) 40 µL one eye OTO vs	DB, PC, PRO, RCT Patients with allergic conjunctivitis, mean age 42.5 years, study used	N=83 Duration not reported (3 visits)	Primary: Ocular allergy index including erythema in 3 vessel beds, chemosis, eyelid swelling, and itching at 7, 12	Primary: At visit three (evaluation visit), both naphazoline/pheniramine and olopatadine were associated with significantly lower ocular allergy index scores than placebo at all times (*P*<0.001). Ocular allergy index scores were significantly lower with naphazoline/pheniramine than with olopatadine at 12 minutes and 20 minutes (*P*=0.005 and *P*=0.001, respectively).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
olopatadine 0.1% 40 µL one eye OTO vs placebo 40 µL one eye OTO	CAC model		and 20 minutes post challenge Secondary: Not reported	Olopatadine was associated with significantly lower itching compared with naphazoline/pheniramine at seven minutes (*P*=0.029). Secondary: Not reported
Owen et al[35] Ophthalmic mast cell stabilizers (cromolyn 17 trials, lodoxamide 1 trial, and nedocromil 5 trials) vs placebo Ophthalmic antihistamines (antazoline* 1 trial, azelastine 1 trial, emedastine 1 trial, levocabastine* 6 trials) vs placebo Ophthalmic mast cell stabilizers (cromolyn 5 trials, lodoxamide 1 trial, and nedocromil 2 trials) vs antihistamines (levocabastine* 8 trials)	MA of 40 DB, RCT Patients with SAC (age not reported)	N=not reported Duration varied	Primary: Subjective symptoms (e.g., ocular itching, burning, soreness, lacrimation), patient's perception of improvement in subjective symptoms Secondary: Not reported	Primary: Eight studies recorded subjective symptoms while comparing cromolyn to placebo interventions. An improvement in subjective symptoms was reported in five studies with no difference between treatments reported in three trials. A meta-analysis of six trials showed that patients using cromolyn were 17 times (95% CI, 4 to 78) more likely to perceive benefit than those using placebo, although this estimate may be partially influenced by publication bias. (The authors noted that the trials that reported marked and statistically significant benefits of cromolyn over placebo were mostly small.) No important side effects were reported with the cromolyn treatment. In a small RCT of four weeks duration, patients using lodoxamide reported significantly fewer symptoms of burning and itching, eyelid swelling, lacrimation, and photophobia compared with those using placebo (*P* values not reported). Subjective symptoms were less pronounced in patients using nedocromil compared with patients using placebo with the differences reported as statistically significant in three studies and borderline significant in two studies (*P* values not reported). Patients using nedocromil were 1.8 times (95% CI, 1.3 to 2.6) more likely to report that their symptoms were moderately or totally controlled than those using a placebo. Apart from an unpleasant taste immediately after instillation of nedocromil, no other important side effects were reported.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Pooled data showed that patients using mast cell stabilizers were 4.9 times (95% CI, 2.5 to 9.6; *P* value not reported) more likely to perceive benefit than those using placebo. No trials were identified directly comparing the use of one mast cell stabilizer with another. Because of the rapid mode of action of antihistamines, most studies used short-term conjunctival provocation tests to establish the relative efficacy of topical antihistamines and placebo. Most studies showed improvement in symptoms, especially for itching, in those treated with antihistamines compared to placebo. No evidence from these trials to support the use of one topical antihistamine over another. Limited evidence suggests that antihistamines have a faster therapeutic effect than mast cell stabilizers; however, there was little difference in treatment efficacy after two weeks. Two short-term provocation studies reported statistically significant less itching and redness in patients treated with antihistamines compared to mast cell stabilizers (*P*<0.05), whereas no significant differences in subjective symptoms were noted in six longer studies. Four trials showed that patients using antihistamines were 1.3 times (95% CI, 0.8 to 2.2) more likely to perceive a "good" treatment effect than patients using mast cell stabilizers, although this beneficial effect was not statistically significant (*P* value not reported). Secondary: Not reported
James et al[36] Azelastine (strength not reported) both eyes BID vs	DB (azelastine vs placebo), MC, PG, OL (azelastine vs cromolyn) Patients with SAC	N=144 2 weeks	Primary: Ocular signs and symptoms, global assessment of efficacy, safety	Primary: Both active treatments showed a marked effect on itching, tearing, and conjunctival redness on day three with a sustained improvement on days seven and 14. A clear response to treatment occurred in 85.4% of azelastine patients, 83.0% of cromolyn patients, and 56.3% of placebo patients (compared to

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
cromolyn (strength not reported) both eyes QID vs placebo both eyes BID	or rhinoconjunctivitis and symptomatic at time of inclusion, age range 16 to 65 years		Secondary: Not reported	placebo *P*=0.005 and *P*=0.007, respectively). Global assessment of efficacy was at least satisfactory for 90.0% of azelastine patients, 81.3% of cromolyn patients, and 66.3% of placebo-treated patients (*P* values not reported). The most frequent adverse effects were transient application site reactions, which tended to disappear with increasing duration of treatment, and, less frequently, taste perversion. Secondary: Not reported
Greiner et al[37] Cromolyn 4% one eye QID for 2 weeks then 1 drop OTO vs placebo other eye QID for 2 weeks then ketotifen 0.025% 1 drop OTO	AC, SB Patients who responded to the conjunctival provocation test (age not reported), study used CAC model	N=56 2 weeks	Primary: Ocular itching, tearing, and redness post challenge; comfort and safety Secondary: Not reported	Primary: At the 15-minute and four-hour challenges, ketotifen was more effective than cromolyn in preventing itching at all assessments (*P*<0.001) and redness (*P*≤0.001) at most assessments. Tearing scores were higher in cromolyn-treated eyes than in ketotifen-treated eyes. Patients reported greater comfort in the ketotifen-treated than in the cromolyn-treated eye (*P*=0.066). The most common adverse event associated with cromolyn was burning/stinging. A single dose of ketotifen was more effective than a two-week regimen of cromolyn in alleviating symptoms of allergic conjunctivitis in the CAC model. Secondary: Not reported
Katelaris et al[38] Cromolyn 2%* 1 drop both eyes QID vs	DB, MC, PG, RCT Patients ≥4 years of age with SAC, mean age 35 years (range 4-77	N=185 6 weeks	Primary: Ocular itching, conjunctival redness Secondary:	Primary: After the first instillation of cromolyn and olopatadine on day zero, self-rated ocular itching and redness decreased rapidly and were statistically significant (*P*<0.05). At 30 minutes after the first instillation, self-rated ocular itching and redness decreased by ~30% and ~20% in both groups, respectively. By

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
olopatadine 0.1% 1 drop both eyes BID and placebo 1 drop both eyes BID	years)		Physicians' impression of overall improvement, safety	four hours, itching had decreased by ~38% in both groups, and redness had decreased by ~26% with cromolyn and ~38% with olopatadine. Differences between treatments were not statistically significant. By day three, both treatments had produced significant reductions from baseline in ocular signs and symptoms. The reductions in itching were significantly greater with olopatadine than cromolyn from days 14 to 42 (*P*<0.05). The reductions in redness were significantly greater with olopatadine than cromolyn at day 42 (*P*<0.05). Secondary: The difference in physicians' impression of overall improvement on days 30 and 42 significantly favored olopatadine over cromolyn (both days; *P*<0.05). Both treatments were well tolerated by patients in all age groups; however, olopatadine appeared to have better local tolerability in children <11 years of age.
Discepola et al[39] Emedastine 0.05% 1 eye and placebo in other eye OTO vs ketorolac 0.5% in 1 eye and placebo in the other eye OTO About 14 days later, patients received the alternate treatment in one eye and placebo in the contralateral eye.	DB, PC, RCT, SC, XO Patients (age not reported) with a history of allergic conjunctivitis, study used CAC model	N=36 4 weeks	Primary: Ocular itching and redness at 3, 10 and 20 minutes post challenge; discomfort Secondary: Not reported	Primary: Emedastine significantly inhibited ocular itching and redness in vascular beds following ocular administration (*P*<0.05). In contrast, ketorolac failed to significantly inhibit ocular itching or redness in this study (*P* value not reported). Patient assessment of comfort indicated emedastine was significantly more comfortable than ketorolac upon topical ocular administration (*P*<0.05). Secondary: Not reported
Orfeo et al[40]	DB, PC, RCT	N=30	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Emedastine 0.05% one eye OTO and placebo other eye OTO vs nedocromil 2% one eye OTO and placebo other eye OTO Each patient received both study drugs on two different visits.	Patients with a history of allergic conjunctivitis (age not reported), study used CAC model	Duration not reported (3 visits)	Ocular itching and redness at 3, 10, and 20 minutes post challenge Secondary: Not reported	Emedastine and nedocromil were more effective than placebo in controlling ocular itching and redness after the allergen challenge (P<0.01). Additional information was not reported. Emedastine was more effective than nedocromil in alleviating redness and itching three and 10 minutes after the allergen challenge (P<0.01). Secondary: Not reported
Greiner et al[41] Ketotifen 0.025% 1 drop one eye OTO vs nedocromil 2% 1 drop one eye OTO vs placebo (artificial tears) 1 drop one eye OTO Study medications were administered contralaterally.	AC, DB, PC, RCT, SC Patients >10 years with a history of allergic hypersensitivity to animal dander or grass, tree, or ragweed pollens (not currently in season); mean age 39 years; study used CAC model	N=59 35 days (4 visits)	Primary: Ocular itching every 30 seconds for 20 minutes post challenge (allergen administered 5 minutes and 12 hours after medication instilled); medication comfort at 0, 0.5, 1, 2, 5 and 10 minutes after instillation; terms used to describe comfort; patient preference based on comfort and perceived efficacy; safety	Primary: Ketotifen-treated eyes experienced significantly less ocular itching than nedocromil- or placebo-treated eyes after both the five-minute and 12-hour post treatment allergen challenges (P<0.05). Nedocromil-treated eyes showed no statistical or clinical differences from placebo at any time point (P>0.05). Ketotifen-treated eyes showed no differences in comfort from those that received placebo but were significantly more comfortable than nedocromil-treated eyes at one, two, five and 10 minutes after instillation (all P<0.05). Five minutes after the medication was instilled, “comfortable” was the most common descriptive term for ketotifen and placebo (72% and 49%, respectively, compared with 27% for nedocromil). “Stinging” was the most common descriptive term for nedocromil (31%). The proportion of unfavorable descriptive terms (burning, stinging, or irritation) was 6% for ketotifen, 12% for placebo and 55% for nedocromil (P values were not reported). On the basis of comfort and subjective efficacy, 60% of

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			Secondary: Not reported	patients preferred ketotifen, 21% preferred nedocromil, and 19% preferred placebo. No serious adverse events were reported during the study. Mild burning was reported by two patients for nedocromil-treated eyes. Secondary: Not reported
Butrus et al[42] Nedocromil 2% 1 drop one eye BID for 2 weeks then 1 drop OTO vs placebo 1 drop one eye BID for 2 weeks then olopatadine 0.1% 1 drop OTO vs placebo 1 drop one eye BID for 2 weeks then 1 drop OTO Study medications were administered contralaterally.	DB, PC, RCT, SC Patients with allergic conjunctivitis, mean ages 42-48 years in the treatment arms, study used CAC model	N=52 21 days (3 visits)	Primary: Ocular itching at 3, 5 and 10 minutes post challenge; patient preference based on comfort and efficacy Secondary: Not reported	Primary: Olopatadine was clinically and statistically more efficacious than nedocromil at reducing itching in the CAC model at all time points (P<0.001). Olopatadine-treated eyes were rated as being significantly more comfortable than nedocromil-treated eyes (P= 0.034). Of the 14 patients treated with olopatadine and nedocromil, 10 patients (71%) were more satisfied with olopatadine than with nedocromil, and 4 patients (29%) had no preference. Secondary: Not reported
Alexander et al[43] Nedocromil 2% BID vs olopatadine 0.1% BID	RCT, XO Patients with PAC and previous olopatadine experience	N=28 2 weeks	Primary: Patient satisfaction, severity of ocular symptoms (daily diary scores), physician's	Primary: Both medications were well accepted. Of the 28 patients, 16 (57.1%) would request a nedocromil prescription, 10 (35.7%) an olopatadine prescription (P=0.157); 22 patients (78.6%) would recommend nedocromil to other allergy sufferers, while 18 (64.3%) would recommend olopatadine (P=0.480).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
After 1 week, patients were XO to the other treatment for 1 additional week.			assessment of clinical signs, global assessments of effectiveness Secondary: Not reported	Both drugs significantly (*P*<0.01) and comparably decreased erythema, conjunctival injection, and overall conjunctival signs from baseline. Light sensitivity scores were significantly lower with nedocromil (*P*=0.0125); other symptom scores were comparable between medications. Both physicians and patients judged nedocromil and olopatadine to be similarly effective in preventing signs and symptoms of allergic conjunctivitis. Secondary: Not reported
Yaylali et al[44] Olopatadine 0.1% one eye BID and placebo other eye BID vs ketorolac 0.5% one eye QID and placebo other eye QID	PC, PG, RCT, SC Patients with SAC, average age 19 years	N=40 15 days	Primary: Hyperemia and itching at 30 minutes then at 2, 7 and 15 days Secondary: Not reported	Primary: Hyperemia and itching were improved significantly in eyes treated with olopatadine and ketorolac compared to placebo at all control examinations (all *P*<0.05). The mean score of hyperemia was found to be lower in the olopatadine group compared to the ketorolac group, but the difference was not statistically significant (*P*>0.05). However, the itching score was significantly lower in the olopatadine group compared to the ketorolac group from the second day through to the end of the study (*P*<0.05). Secondary: Not reported
Berdy et al[45] Loteprednol 0.2% 1 drop in both eyes QID bilaterally for 14 days, then 1 drop in both eyes at evaluation visit vs	DB, PG, RCT, SC Patients >18 years of age (mean age of 43 years) with a history of SAC or PAC with no severe atopic, vernal or giant	N=50 21 days	Primary: Itching, redness and IOP Secondary: Not reported	Primary: There was greater itching relief in the olopatadine group compared to the loteprednol group at three, five, and 10 minutes (*P*=0.001, *P*<0.001 and *P*<0.001, respectively). Loteprednol showed a statistically significant decrease in itching scores compared to placebo at minutes three and five (*P*<0.05). No statistical significant difference between these two groups were seen at minute 10 (*P* value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
olopatadine 0.1% 1 drop in both eyes QID bilaterally for 14 days, then 1 drop in both eyes at evaluation visit vs vehicle 1 drop in both eyes QID bilaterally for 14 days, then 1 drop in both eyes at evaluation visit One drop of conjunctival allergen challenge 15 minutes after the study drug was administered at increasing concentrations in 10 minute intervals.	papillary conjunctivitis			There was a significant difference in itching relief between olopatadine and placebo (P<0.001 at three, five and 10 minutes). Olopatadine showed statistical significance for the prevention of redness vs loteprednol at minutes 10, 15 and 20 (P=0.003, P=0.011 and P=0.034, respectively). No statistically significant difference at minutes 10, 15 and 20 was seen between the loteprednol group vs the placebo group in the prevention of redness (P value not reported). There was a statistically significant difference between the prevention of redness between the olopatadine group vs the placebo group at minutes 10, 15 and 20 (P<0.001, P=0.012 and P=0.027, respectively). There was a statistically significant increase in IOP during the third visit with loteprednol compared to olopatadine and placebo (P<0.001). There were no adverse events reported during the course of study. Secondary: Not reported

The conjunctival allergen challenge model usually consisted of 3 visits. At visit 1, the allergen concentration that elicited the desired ocular allergic response was determined, and this concentration was confirmed at visit 2. At visit 3, the study drugs were administered prior to the allergen challenge.
Drug regimen abbreviations: BID=twice daily, OTC=over-the-counter, OTO=one time only, QID=four times daily
Study abbreviations: AC=active-controlled, CI=confidence interval, DB=double-blind, DD=double-dummy, MA=meta-analysis, MC=multi-center, OL=open-labeled, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, SB=single-blind, SC=single center, XO=cross over
Miscellaneous abbreviations: CAC=conjunctival allergen challenge, SAC=seasonal allergic conjunctivitis, PAC=perennial allergic conjunctivitis, VKC=vernal keratoconjunctivitis

Special Populations

Table 5. Special Populations[2-11]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Alcaftadine	No dosage adjustment is required in the elderly. Safety and effectiveness in children <2 years of age have not been established.	Not reported	Not reported	B	Unknown
Azelastine	No dosage adjustment is required in the elderly. Safety and effectiveness in children <3 years of age have not been established.	No dosage adjustment is required.	No dosage adjustment is required.	C	Unknown
Bepotastine	No dosage adjustment is required in the elderly. Safety and effectiveness in children <2 years of age have not been established.	No dosage adjustment is required.	No dosage adjustment is required.	C	Unknown
Emedastine	No dosage adjustment is required in the elderly. Safety and effectiveness in children <3 years of age have not been established.	No dosage adjustment is required.	No dosage adjustment is required.	B	Unknown
Epinastine	No dosage adjustment is required in the elderly. Safety and effectiveness in children <3 years of age have not been established.	No dosage adjustment is required.	No dosage adjustment is required.	C	Unknown
Ketotifen	No dosage adjustment is required in the elderly. Safety and effectiveness in children <3 years of age have not been established.	No dosage adjustment is required.	No dosage adjustment is required.	C	Unknown
Olopatadine	No dosage adjustment is required in the elderly. Safety and effectiveness in children <3 years of	No dosage adjustment is required.	No dosage adjustment is required.	C	Unknown

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
	age have not been established.				

Adverse Drug Events

The most frequently reported adverse effects for the ophthalmic antihistamine preparations are summarized in Table 6. The most common side effects with these agents are ocular burning and stinging, and headache. Refrigeration of the ophthalmic solution may reduce the incidence of burning and stinging.[13]

Table 6. Adverse Drug Events[2-11]

Adverse Event(s)	Alcaftadine	Azelastine	Bepotastine	Emedastine	Epinastine	Ketotifen	Olopatadine
Central Nervous System							
Abnormal dreams	-	-	-	<5	-	-	-
Asthenia	-	-	-	<5	-	-	<5
Fatigue	-	1 to 10	-	-	-	-	-
Headache	<3	15	2 to 5	11	1 to 3	10 to 25	<5
Dermatological							
Dermatitis	-	-	-	<5	-	-	-
Pruritus	<4	1 to 10	-	<5	-	-	-
Rash	-	-	-	-	-	<5	-
Gastrointestinal							
Nausea	-	-	-	-	-	-	<5
Taste perversion	-	10	25	<5	-	-	<5
Ocular							
Blurred vision	-	1 to 10	-	<5	-	-	<5
Burning	<4	30	-	<5	1 to 10	<5	<5
Conjunctival injection	-	-	-	-	-	10 to 25	-
Conjunctivitis	-	1 to 10	-	-	-	<5	<5
Corneal infiltrates	-	-	-	<5	-		-
Corneal staining	-	-	-	<5	-	-	-
Discharge	-	-	-	-	-	<5	-
Discomfort	-	-	-	<5	-	-	-
Dry eye	-	-	-	<5	-	<5	<5
Eyelid disorder/edema	-	-	-	-	-	<5	<5
Folliculosis	-	-	-	-	1 to 10	-	-
Foreign body sensation	-	-	-	<5	-	-	<5
Hyperemia	-	-	-	<5	1 to 10	-	<5
Irritation	<4	-	2 to 5	-	-	-	-
Itching	-	-	-	-	1 to 10	<5	<5