

WYOMING PDLAC
THERAPEUTIC CLASS REVIEW
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**OPHTHALMICS FOR ALLERGIC
CONJUNCTIVITIS**

This publication is a result of the collaboration of the Goold Health Systems, Inc. Clinical Workgroup and represents the opinion of these authors based on a review of the literature available at the time it was written. It is intended for the sole purpose of providing information to committee members in order to compare medications within a specified subset of clinical parameters. It is not intended to provide specific clinical advice for any condition, or to be an exhaustive review of all potential aspects of pharmacotherapies for any given condition. Medical evidence is rapidly changing, and no representation is made regarding the use of this material beyond the stated purpose.

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SYNOPSIS

Allergic conjunctivitis affects up to 40% of the general population²² and is a common clinical problem for both ophthalmic and allergic practices. Although many cases are seasonal, a large number of patients have year-round or perennial symptoms. Nevertheless, seasonal allergic conjunctivitis is the most common. This form is usually associated with being exposed to airborne allergens, for instance grass, tree pollen, and mold. Perennial allergic conjunctivitis typically continues through the year. This form, in general, is activated by dust mites and animal dander.²⁸

Allergic conjunctivitis is an inflammation of the conjunctiva, a membrane covering the white part of the eye, caused by an allergy. Symptoms of allergic conjunctivitis include ocular itching and redness, edema of the conjunctiva, increased lacrimation (production of tears) and ocular dryness. These symptoms are caused by a release of histamine, as well as other substances, from mast cells.²⁷

It is well established that allergic conjunctivitis has a significant influence on quality of life. Impaired emotional wellbeing and social functioning have been documented. Total costs related to allergic conjunctivitis amount to at least \$6 billion/year⁷. Although most cost studies pertaining to allergic conjunctivitis have evaluated direct costs due to physician consultation and medical treatment, it is now clear that indirect costs are a major aspect. This includes absenteeism from work or school because of illness and decreased productivity when at work. Proper treatment of allergic conjunctivitis patients should not only greatly improve their quality of life, but also reduce health care costs associated with this condition.

Specific therapy reduces symptoms but does nothing to alter the clinical course of the condition. Non pharmacologic measures to help improve symptoms of allergic conjunctivitis include applying a cold compress to the affected eye(s), doing eyewashes with tear substitutes, and avoiding the specific allergen that is causing the inflammation. Pharmacologic measures can be used as topical treatment. The therapeutic categories include: histamine H-1 antagonists, mast cell stabilizers, corticosteroids, or NSAIDs. There are some medications available that have a dual mechanism of targeting H-1 receptors as well as being mast cell stabilizers.²⁷

The agents used in treatment of allergic conjunctivitis include: *histamine H-1 antagonists*- azelastine (Optivar®), emedastine (Emadine®), epinastine (Elestat®), ketotifen (Alaway® and Zaditor OTC®), and olopatadine (Patanol® and Pataday®); *mast cell stabilizers*- cromolyn (Opticrom® and Crolom®), lodoxamide (Alomide®), nedocromil (Alocril®), and pemirolast (Alamast®); *corticosteroids*- loteprednol (Alrex®, Lotemax®); and *nonsteroidal anti-inflammatory drugs (NSAIDs)*- ketorolac (Acular®).

FDA APPROVED INDICATIONS^{1-6, 8-18}

The ophthalmic products in this review are indicated for the temporary relief of the signs and symptoms of allergic conjunctivitis.

DOSAGE FORMS, DOSE, AND MANUFACTURER^{1-6, 8-18}

Unless otherwise specified, the ophthalmic medications should be instilled into the affected eye(s).

| Drug | Dosage Forms | Dose | Manufacturer |
|---|---|---|--|
| azelastine (Optivar®) | <u>Solution, 0.05%:</u> 6ml | 1 drop BID for up to 8 weeks | Med Pointe Pharmaceuticals |
| cromolyn (Opticrom®) (Crolom®) | <u>Solution, 4%:</u> 10ml | 1-2 drops OU 4-6x daily | Various generic manufacturers (Allergan inc) (Bausch & Lomb) |
| emedastine (Emadine®) | <u>Solution, 0.05%:</u> 5ml | 1 drop up to QID | Alcon Laboratories |
| epinastine (Elestat®) | <u>Solution, 0.05%:</u> 5ml, 10ml | 1 drop OU BID | Allergan |
| ketorolac (Acular®) | <u>Solution, 0.5%:</u> 5ml | 1 drop QID | Allergan |
| ketotifen (Alaway®) (Zaditor OTC)® | <u>Solution, 0.025%:</u> 5ml | 1 drop BID | Various generic manufacturers (Bausch & Lomb) (Novartis) |
| loxamide (Alomide®) | <u>Solution, 0.1%:</u> 10ml | 1-2 drops QID | Alcon Laboratories |
| loteprednol (Alrex®) (Lotemax®) | <u>Suspension, 0.2%:</u> 5ml, 10ml <u>Suspension, 0.5%:</u> 2.5ml, 5ml, 10ml, 15ml | <i>0.2%:</i> 1 drop QID <i>0.5%:</i> 1-2 drops QID | Bausch & Lomb |
| nedocromil (Alocril®) | <u>Solution, 2%:</u> 5ml | 1 to 2 drops OU BID | Allergan |
| olopatadine (Patanol®) (Pataday®) | <u>Solution, 0.1%:</u> 5ml <u>Solution, 0.2%:</u> 2.5mL in a 4mL fill oval bottle | <i>0.1%:</i> 1 drop BID every 6-8 hrs <i>0.2%:</i> 1 drop QD | Alcon |
| pemirolast (Alamast®) | <u>Solution, 0.1%:</u> 10ml | 1-2 drops QID | Vistakon Pharmaceuticals |

PHARMACOLOGY 1-6, 8-18

The table below shows the mechanism of action for the medications in this therapeutic category.

| Drug | Antagonizes H1 receptors | Mast cell stabilizer | Anti-inflammatory |
|--|--------------------------|----------------------|-------------------|
| azelastine (Optivar®) | X | X | |
| cromolyn (Opticrom®) (Crolom®) | | X | |
| emedastine (Emadine®) | X | | |
| epinastine (Elestat®) | X | X | |
| ketorolac (Acular®) | | | X |
| ketotifen (Alaway®) (Zaditor® OTC) | X | X | |
| lodoxamide (Alomide®) (Lotemax®) | | X | |
| loteprednol (Alrex®) | | | X |
| nedocromil (Alocril®) | | X | |
| olopatadine (Patanol®) (Pataday®) | X | X | |
| pemirolast (Alamast®) | | X | |

PHARMACOKINETICS 1-6, 8-18

As systemic absorption is minimal, the pharmacokinetic properties of these agents are not considered to be clinically significant or relevant for the purpose of this review.

CLINICAL TRIALS

Efficacy Trials

Clinical trials performed to obtain FDA approval confirmed all the medications in this therapeutic class to be superior in efficacy, as well as showing safety of the drug, when compared to placebo. ⁸⁻¹⁸

Newer/Comparator Trials

A systematic review and meta-analysis by Owen CG et al in 2004 attempted to compare the effectiveness of several topical treatments in the controlling of ocular allergy relief in association with seasonal allergic conjunctivitis. The search for data was done using Cochrane Library, Medline, and EMBASE, searching for double-masked randomized controlled trials. The search looked for mast cell stabilizers (including sodium cromoglycate (or cromolyn), nedocromil, and lodoxamide), topical antihistamines, and topical mast cell stabilizers with topical antihistamines, all compared with placebo. Six trials were found that reported sodium cromoglycate (or cromolyn) was 17 times more probable to notice benefit than with placebo. There were five different trials that found nedocromil was almost two times more probable to be of benefit with their allergy either totally or moderately controlled compared to those using placebo. Both of these results had a 95% confidence interval.³⁹

The review also reported that four trials that used topical antihistamines showed they were 1.3 times more probable than mast cell stabilizers to notice a “good” treatment effect, although this was not statistically significant. The study concluded that overall, although there was evidence that both mast cell stabilizers and topical antihistamines had a benefit over using placebo, there was not enough evidence to support or recommend using one type of medication over another for the treatment of seasonal allergic conjunctivitis.³⁹

A meta-analysis by Swamy et al, examining 8 studies totaling 712 patients treated with ophthalmic NSAIDS (products not specified in abstract), confirmed superiority of NSAIDS vs. placebo for treatment of conjunctival itching.²⁰

The following table represents data from head to head comparative trials.

Ophthalmics for Allergic Conjunctivitis-6

| Study | Design & Comparators | Sample Size & Duration | Patient characteristics | Assessed Outcomes | Results | Conclusions |
|----------------------------------|---|-----------------------------|--|--|--|---|
| Borazan et al ²⁹ 2008 | <p>Prospective, randomized, double-blinded, placebo-controlled study</p> <p>Olopatadine vs ketotifen vs epinastine vs emedastine vs fluorometholone</p> | <p>N=100</p> <p>2 weeks</p> | <p>Diagnosis of seasonal allergic conjunctivitis</p> | <p>-Signs and symptoms of allergic conjunctivitis, including itching, redness, tearing, chemosis, and eyelid swelling.</p> <p>-Scored on a 4-point scale</p> <p>-Ocular surface variables were assessed by conjunctival impression cytology.</p> | <p>-One eye was treated with placebo and the other was treated with study drug, while symptoms were assessed at baseline and then after 1 and 2 weeks of treatment.</p> <p>-Results of week 1 and 2 reported that all medications were significantly more effective than placebo for improving</p> <p>-Fluorometholone was significantly less effective than the other agents in reducing itching and redness.</p> <p>-Ocular surface findings by impression cytology improved significantly after all treatments compared with placebo.</p> | <p>- All the medications in this study gave similar results in terms of reducing tearing, chemosis, and eyelid swelling.</p> <p>- Olopatadine, ketotifen, epinastine, and emedastine were more efficacious than fluorometholone in the prevention of itching and redness.</p> |
| Shulman 2003 ³⁰ | <p>Randomized, double-masked, active-control, parallel-group</p> <p>Pemirolast 0.1% vs Nedocromil 2%</p> | <p>N= 80</p> <p>8 weeks</p> | <p>Diagnosis of seasonal allergic conjunctivitis</p> | <p>-Signs and symptoms of allergic conjunctivitis, with itching as primary efficacy variable.</p> <p>-Completed questionnaires to assess comfort.</p> | <p>-No significant differences were found between pemirolast 0.1% and nedocromil 2% on any signs and symptoms (including itching, redness, chemosis, and eyelid swelling).</p> <p>-Pemirolast was rated significantly more comfortable than</p> | <p>- Pemirolast was as efficacious as nedocromil.</p> <p>- Pemirolast was superior to nedocromil in comfort, which may lead to increased patient satisfaction and thus increased compliance with therapy.</p> |

Ophthalmics for Allergic Conjunctivitis-7

| Study | Design & Comparators | Sample Size & Duration | Patient characteristics | Assessed Outcomes | Results | Conclusions |
|--|--|----------------------------|--|--|---|---|
| | | | | | <p>nedocromil.</p> <p>-A significantly higher rate of subjects experienced no signs or symptoms at work or school in the pemirolast group vs the nedocromil group (58% vs 28%; p=0.005).</p> <p>-Adverse events did not differ significantly between groups.</p> | |
| <p>Yaylai et al³¹ 2003.</p> | <p>Placebo-controlled, randomized, parallel group, single center study</p> <p>Olopatadine 0.1% in one eye and placebo in one eye Vs Ketorolac 0.5% in one eye and placebo in one eye</p> | <p>N=40</p> <p>15 days</p> | <p>Diagnosis of seasonal allergic conjunctivitis</p> | <p>Hyperaemia and itching were evaluated at 30 minutes and at 2, 7, and 15 days.</p> | <p>-Both factors significantly improved in eyes treated with olopatadine compared with those receiving placebo at all exams (all p< 0.05).</p> <p>- Both factors significantly improved in eyes treated with ketorolac compared with those receiving placebo at all exams (all p< 0.05).</p> <p>-When olopatadine was compared with ketorolac, it was reported that the mean score of hyperaemia was lower in the olopatadine group vs the ketorolac group, but it was not statistically different (p>0.05).</p> | <p>-Olopatadine and ketorolac were more effective than placebo in treating signs and symptoms of seasonal allergic conjunctivitis.</p> <p>-Olopatadine reduced itching significantly more than ketorolac.</p> |

Ophthalmics for Allergic Conjunctivitis-8

| Study | Design & Comparators | Sample Size & Duration | Patient characteristics | Assessed Outcomes | Results | Conclusions |
|------------------------------------|--|------------------------------------|--|--|---|---|
| | | | | | <p>-The itching score was significantly lower in the olopatadine group vs the ketorolac group at the day 2 exam and throughout the end of the study (p<0.05).</p> | |
| <p>Mah et al¹⁹ 2007</p> | <p>Double-masked, randomized, placebo-controlled, conjunctival allergen challenge(CAC)</p> <p>Olopatadine 0.2% Vs Epinastine 0.05%</p> | <p>N= 92</p> <p>7 week-4 visit</p> | <p>-Diagnosis of allergic conjunctivitis</p> <p>-Visit 1 screened subjects for positive ocular allergic responses and visit 2 confirmed these responses.</p> | <p>-at visit 4, after 5 minutes subjects were challenged to evaluate onset of action, as well as drop comfort</p> <p>Primary: ocular itching assessed at 3, 5, and 7 min and redness was assessed at 7, 15, and 20 minute post challenge.</p> <p>Drop comfort assessed at upon instillation, and at 30 sec, and 1, 2 and 5 minute post drop instillation</p> | <p>-4 treatment groups: olopatadine/placebo, epinastine/placebo, olopatadine/epinastine, and placebo/placebo.</p> <p>-Olopatadine treated eyes showed significantly lower mean ocular itching scores vs epinastine treated eyes at 3, 5 (p=0.024), and 7 min (p=0.003) post challenge.</p> <p>-Olopatadine eyes showed significantly lower mean redness scores vs epinastine at all times post challenge (ciliary: p≤0.013), conjunctival: p≤0.015), episcleral: p≤0.006).</p> <p>-Olopatadine rated as significantly more comfortable than epinastine at 1 min post-drop instillation.</p> | <p>-Olopatadine was superior to epinastine in prevention of ocular itching and redness at onset. This was shown with the CAC model.</p> |

| Study | Design & Comparators | Sample Size & Duration | Patient characteristics | Assessed Outcomes | Results | Conclusions |
|----------------------------------|--|---|---|--|---|--|
| | | | | | -Adverse events were all non-serious. | |
| Greiner et al ³² 2003 | <p>Single-center, double-masked, contralateral, randomized, placebo- and active-controlled clinical trial.</p> <p>Ketotifen Vs Nedocromil Vs Placebo</p> | <p>N=59</p> <p>35 days and 4 visits</p> | <p>Subjects > 10 years of age with a history of allergic hypersensitivity who responded to the conjunctival allergen challenge at screening visits 1 and 2 qualified for randomization at visit 3.</p> | <p>-Conjunctival allergen challenge (CAC) at 5 minutes post dose on visit 3 and 12 hours post dose on visit 4.</p> <p>-Ocular itching was evaluated every 30 seconds for 20 minutes at each visit.</p> <p>-Comfort of the medication was evaluated at visit 4 at 30 seconds at instillation, and at 1, 2, 5, and 10 minutes post dose.</p> <p>-Overall eye comfort was queried by subjects choosing from descriptive terms and overall eye preference based on comfort and perceived efficacy.</p> | <p>-Ketotifen-treated eyes showed significantly less ocular itching induced by CAC than the nedocromil group, as well as the placebo group at both the 5 minute and 12 hour post treatment allergen challenges ($p < 0.05$).</p> <p>-Nedocromil treated eyes did not show statistical or clinical differences from placebo at any point.</p> <p>-Ketotifen treated eyes did not show differences in comfort from those treated with placebo but were significantly more comfortable than nedocromil treated eyes at 1, 2, 5, and 10 minutes after instillation. (All $p < 0.05$).</p> <p>-60% of subjects preferred ketotifen on the basis of comfort and subject efficacy vs 21% nedocromil and 19% placebo.</p> | <p>-Ketotifen showed to be significantly more effective than nedocromil at both 5 minutes and 12 hours post treatment in the CAC model.</p> <p>-Ketotifen showed to be significantly more comfortable than nedocromil.</p> |

Ophthalmics for Allergic Conjunctivitis-10

| Study | Design & Comparators | Sample Size & Duration | Patient characteristics | Assessed Outcomes | Results | Conclusions |
|------------------------------------|--|------------------------|---|--|---|--|
| Lanier et al ³³ 2004 | Prospective, randomized, double-masked, contralateral-controlled, single center allergen challenge study Olopatadine 0.1% vs Epinastine 0.05% | N=66 4 visits | History of allergic conjunctivitis Visit 1 and 2 a positive conjunctival allergic response was elicited. | -Itching and conjunctival redness in the conjunctival allergen challenge (CAC) -Bilaterally challenged 5 minutes after study drop instillation. -Subjective itching was assessed at 3, 5, and 7 min post challenge -Objective redness and chemosis assessed at 10, 15, and 20 min post challenge. | -3 treatment groups: olopatadine/epinastine, olopatadine/placebo, and epinastine/placebo -Olopatadine treated eyes showed significantly lower mean itching and conjunctival redness scores than contralateral epinastine treated eyes [-0.19 (p=0.003) and -0.54 (p<0.001) respectively]. -Olopatadine treated eyes showed significantly less chemosis -0.24 (p<0.001), ciliary redness -0.55 (p<0.001), and episcleral redness -0.58 (p<0.001) than epinastine treated eyes. | -It was shown that olopatadine was significantly more effective than epinastine in controlling itching, redness, and chemosis in the CAC model when associated with allergic conjunctivitis. |
| Torkildsen et al ²¹ | Single-center, randomized, double-masked, crossover study Epinastine Vs Azelastine OR Ketotifen | N=40 4 visits | Adults with a history of allergic conjunctivitis, confirmed on skin testing conducted within the previous 2 years | Short term ocular comfort and drying effects -Ocular comfort assessed by subjects on an 11-point scale (0=very comfortable to 10=very | -Two treatment groups: epinastine/azelastine or epinastine/ketotifen. -Mean comfort score was significantly lower with epinastine (meaning more comfort) vs azelastine at 0.5, 1, 2, and 5 minutes (between-treatment | -Epinastine was rated as more comfortable than azelastine and ketotifen after administration of a single drop. -None of the three medications were associated with significant acute ocular drying effects. |

| Study | Design & Comparators | Sample Size & Duration | Patient characteristics | Assessed Outcomes | Results | Conclusions |
|--------------------------------|--|------------------------|------------------------------------|---|--|---|
| | | | | <p>uncomfortable) and assessed at 0.5, 1, 2, and 5 minutes after instillation.</p> <p>-At visit 2 through 4, subjects assessed for ocular drying and tear-film stability using fluorescein staining and ocular protection index (OPI) evaluation, respectively.</p> | <p>differences, 2.9, 1.85, 1.35, and 0.63 respectively; $p < 0.001$, $p < 0.001$, $p = 0.001$, and $p = 0.019$) and compared with ketotifen immediately after instillation (between-treatment difference, 1.2; $p = 0.014$).</p> <p>-Mean ocular comfort score was significantly lower with ketotifen compared with azelastine at 0.5, 1 and 2 minutes (between-treatment differences, 2.35, 1.35, and 1.10 respectively; $p = 0.001$, $p = 0.023$, and $p = 0.028$).</p> <p>-85% of patients chose positive comfort descriptors to describe epinastine vs azelastine.</p> <p>-No significant differences in fluorescein staining or OPI observed.</p> | |
| Berdy et al ³⁴ 2000 | Prospective, randomized, double-masked, contralateral controlled, single-center, antigen challenge study | N=32 | History of allergic conjunctivitis | <p>-Primary efficacy variables included ocular itching and subject satisfaction</p> <p>-Subjects graded itching on a 5 point scale at 3, 5, and 10</p> | <p>-2 treatment groups: olopatadine in rt eye/ketotifen in left eye, and olopatadine in left eye/ketotifen in rt eye</p> <p>-12 hours after administration, olopatadine showed significantly higher efficacy scores than</p> | <p>-Olopatadine reported to be more effective than ketotifen in reducing itching that is associated with allergic conjunctivitis in the antigen challenge model.</p> <p>-Olopatadine caused less ocular</p> |

Ophthalmics for Allergic Conjunctivitis-12

| Study | Design & Comparators | Sample Size & Duration | Patient characteristics | Assessed Outcomes | Results | Conclusions |
|------------------------------------|---|------------------------|------------------------------------|---|---|--|
| | Olopatadine 0.1% Vs Ketotifen 0.025% | 3 visits | | minute post-challenge. -Tolerability variables were slit-lamp findings and visual acuity (on all visits), ocular comfort after drug instillation (visit 3), and adverse events (visit 2 and 3) | ketotifen at 3 and 5 minute post challenge (1.84 and 1.75 vs 1.25 and 1.34; p<0.05). -Olopatadine treated eyes were rated significantly more comfortable than those treated with ketotifen immediately following drug instillation (1.25 vs 2.09; p<0.05) and 12 hours later, as measured by subject ratings of ocular comfort. -73% (16 subjects) were more satisfied with olopatadine than ketotifen. | discomfort than ketotifen. It was preferred by 3 times as many subjects than ketotifen. |
| Butrus et al ³⁵ 2000 | Single-center, randomized, double-masked, contralateral controlled study Olopatadine 0.1% vs nedocromil 2% vs placebo (a "natural tears" lubricant eye drop) | N=52 3 visits | History of allergic conjunctivitis | -Itching and comfort -Nedocromil may require a 2-week loading period for maximal efficacy, subjects in this group received for 14 days (between visits 2 and 3 while all other received placebo during this period). | -Olopatadine reported to be clinically and statistically superior to nedocromil at reducing itching (mean unit difference: -1.60 at 3 minutes, -1.68 at 5 minutes, -1.19 at 10 minutes; p<0.001). -One drop of olopatadine was more efficacious than 29 drops of nedocromil. -Olopatadine treated eyes were rated as significantly more comfortable than nedocromil treated eyes (0.73 vs 1.55; | -Olopatadine was reported to be more efficacious in reducing itching and more comfortable than nedocromil in the CAC model when associated with allergic conjunctivitis. |

| Study | Design & Comparators | Sample Size & Duration | Patient characteristics | Assessed Outcomes | Results | Conclusions |
|------------------------------------|---|--------------------------------------|---|--|--|---|
| | | | | <p>-Visit 3, subjects rated the comfort of each drop using a scale from 0 to 8.</p> <p>-Itching was scored using a scale from 0 to 4 at 3, 5, and 10 minutes after challenge. Paired t tests were performed on the mean itching and ocular comfort scores at each time point.</p> <p>-Subjects rated treatment according to preference based on terms of comfort and efficacy.</p> | <p>p=0.034).</p> <p>-71% (10 subjects) stated they were more satisfied with olopatadine than nedocromil.</p> | |
| D'Arienzo et al ³⁶ 2002 | <p>Single-center, randomized, double-masked, placebo-controlled study.</p> <p>Emedastine Vs Ketotifen</p> | <p>N=45</p> <p>14 days, 3 visits</p> | <p>Diagnosis of acute allergic conjunctivitis</p> | <p>-Itching was scored based on a standardized 5-point scale. (0=none and 4=severe itching) at 3, 5, and 10 minutes post-challenge.</p> | <p>-3 treatment groups: emedastine/placebo, ketotifen/placebo, and emedastine/ketotifen</p> <p>-Both emedastine and ketotifen significantly inhibited itching (p<0.05) compared with placebo at all time points after the</p> | <p>-Reports of this study suggest that emedastine and ketotifen were not statistically different with respect to decreasing itching in the CAC model.</p> |

Ophthalmics for Allergic Conjunctivitis-14

| Study | Design & Comparators | Sample Size & Duration | Patient characteristics | Assessed Outcomes | Results | Conclusions |
|-----------------------------------|--|------------------------|---|--|--|--|
| | Vs Placebo (an artificial tears product) | | | -Differences in efficacy scores between treatments and vs placebo were compared using 2-sample t tests of equal variance. | conjunctival allergen challenge (CAC). Mean raw scores were not statistically different. -Mean itching efficacy scores were not statistically different between active treatments. -No adverse events were reported in this study. | |
| Berdy et al ³⁷ 2002 | Single-center, randomized, double-masked, parallel-controlled conjunctival allergen challenge study Olopatadine 0.1% vs Loteprednol 0.2% vs Placebo | N=50 3 visits | Subjects with a history of allergic conjunctivitis and seasonal allergic conjunctivitis (SAC) | -Loteprednol may require a 2-week loading period for maximal efficacy, subjects in this group received for 14 days (between visits 2 and 3 while all other received placebo during this period -Subjects evaluated itching 3, 5, and 10 minutes post challenge with allergen using a standardized 5-point scale. -Investigator evaluated redness | -The difference in inhibition of itching and redness was clinically significant (≥ 1 unit difference) and statistically significant ($p < 0.05$) in favor of olopatadine compared with loteprednol at all 3 time points. -Loteprednol group had a statistically significant increase in IOP after 2 weeks of treatment ($p < 0.001$). | -This study reported that olopatadine was more efficacious than loteprednol for reducing acute signs and symptoms of SAC during early phase of ocular reaction. -Olopatadine appeared to be better tolerated. |

| Study | Design & Comparators | Sample Size & Duration | Patient characteristics | Assessed Outcomes | Results | Conclusions |
|-----------------------------------|--|------------------------------|---|--|---|---|
| | | | | <p>at 10, 15, and 20 minutes after challenge.</p> <p>-Intraocular pressure (IOP) was measured at baseline and after the 4-day loading period.</p> | | |
| Spangler et al ²³ 2001 | <p>Prospective, randomized, double-masked, contralateral controlled, multicenter, allergen-challenge study.</p> <p>Olopatadine 0.1% vs Azelastine 0.05% vs placebo</p> | <p>N=111</p> <p>3 visits</p> | Subjects with a history of allergic conjunctivitis | <p>-Primary variable was itching.</p> <p>-Immediately after challenge, subjects assessed itching on a scale of 0 to 4 (0=no itching and 4=severe itching) every 30 seconds for 20 minutes.</p> | <p>-3 treatment groups: olopatadine/placebo, olopatadine/azelastine, and azelastine/placebo</p> <p>-Both treatments were significantly more effective than placebo at reducing itching post-challenge.</p> <p>-Olopatadine was significantly more effective than azelastine in reducing itching at 3.5 minutes through 20 minutes post-challenge (av mean unit difference of -0.31; p<0.05).</p> | -For management of itching associated with allergic conjunctivitis, this study reported that olopatadine was significantly more effective than azelastine in the conjunctival allergen challenge model. |
| Shulman et al ³⁸ 2003 | <u>Study 1</u> : Single-center, prospective, double-blind, single-dose, crossover, | <u>Study 1</u> : N=45 | Study 1 included adults with symptomatic eyes of ocular allergies | -Primary variable was overall ocular discomfort, measured on a 4-point scale original to these studies | <p>-Combined results of two separate clinical trials reported.</p> <p>-<u>Study 1</u>: Overall discomfort was significantly lower with</p> | -Pemirolast was found to be significantly more comfortable than cromolyn, ketorolac, and nedocromil. |

| Study | Design & Comparators | Sample Size & Duration | Patient characteristics | Assessed Outcomes | Results | Conclusions |
|-------|--|--|-------------------------|---|--|-------------|
| | <p>parallel-group study</p> <p>Pemirolast vs cromolyn vs ketorolac</p> <p><i>Study 2:</i> Single-center, prospective, randomized, double-blind, single-dose, contralateral, active-control study</p> <p>Pemirolast vs Nedocromil</p> | <p>7 days</p> <p><i>Study 2:</i> N=48</p> <p>1 day</p> | | <p>(0=absent, 3=severe).</p> <p>-Secondary variables included burning/stinging, foreign-body sensation, tearing, and photophobia.</p> | <p>pemirolast than with cromolyn (p=0.001) or ketorolac (p<0.001)</p> <p>-In terms of overall discomfort, number of subjects with a clinically significant increase (≥ 1 unit) in score was significantly lower with pemirolast compared to ketorolac (p=0.021).</p> <p>-Burning/stinging were significantly lower with pemirolast than cromolyn (p<0.001 and p=0.014 respectively).</p> <p>-Mean change in score compared with pre-instillation were consistently lower with pemirolast than with cromolyn for both burning/stinging (p<0.001) and tearing (p=0.014).</p> <p><i>Study 2:</i> Overall discomfort was significantly lower with pemirolast vs nedocromil (p=0.001).</p> <p>-The number of subjects with a clinically significant increase in overall discomfort score was</p> | |

Ophthalmics for Allergic Conjunctivitis-17

| Study | Design & Comparators | Sample Size & Duration | Patient characteristics | Assessed Outcomes | Results | Conclusions |
|-------|----------------------|------------------------|-------------------------|-------------------|--|-------------|
| | | | | | <p>significantly lower with pemirolast than nedocromil (p=0.007).</p> <p>-Ocular tolerability parameters were reported in both studies as no change.</p> | |

CONTRAINDICATIONS ^{1-6, 8-18}

All medications in this therapeutic class carry a contraindication of hypersensitivity to their active ingredient or to any component of the compound. There are two drugs in particular that carry their own contraindications unique to the class. These contraindications are listed in the table below.

| Drug | Contraindication |
|----------------------------------|---|
| azelastine (Optivar®) | concurrent use of alcohol or other central nervous system depressants |
| loteprednol (Alrex®) | hypersensitivity to corticosteroids, ocular viral, mycobacterial or fungal infections |

SPECIAL POPULATIONS ^{1-6, 8-18}

The only formulation that has not established safety and efficacy in the pediatric population is Alrex®. For renal/hepatic insufficiency, there was no information provided.

| Drug | Pediatrics | Pregnancy Category |
|---|------------|--------------------|
| azelastine (Optivar®) | ≥ 3 yrs | C |
| cromolyn (Opticrom®) (Crolom®) | ≥ 4 yrs | B |
| emedastine (Emadine®) | ≥ 3 yrs | B |
| epinastine (Elestat®) | ≥ 3 yrs | C |
| ketorolac (Acular®) | ≥ 3 yrs | C |
| ketotifen (Alaway®) (Zaditor® OTC) | ≥ 3 yrs | C |

| Drug | Pediatrics | Pregnancy Category |
|--|------------|--------------------|
| Iodoxamide (Alomide®) | ≥ 2 yrs | B |
| loteprednol (Alrex®) | No | C |
| nedocromil (Alocril®) | ≥ 3 yrs | B |
| olopatadine (Patanol®) (Pataday®) | ≥ 3 yrs | C |
| pemirolast (Alamast®) | ≥ 3 yrs | C |

ADVERSE REACTIONS^{1-6, 8-18}

All drugs in this class have burning, stinging or eye irritation as reported adverse effects. Other adverse drug reactions are noted in the table below. In addition, adverse effects associated with Lodoxamide (Alomide®) include blurred vision and dry eyes; however, there was no incidence reported. Loteprednol (Alrex®) was associated with blurred vision, as well as photophobia; but, once again, the incidence was not reported. Emadine®, Alocril®, ketotifen, and olopatadine appear to have the greatest occurrence of adverse events. In addition, Alocril® showed a 1-10% incidence of asthma.

| Drug | azelastine (Optivar®) | emedastine (Emadine®) | epinastine (Elestat®) | ketotifen (Alaway®) (Zaditor®) | nedocromil (Alocril®) | olopatadine (Patanol®) (Pataday®) | pemirolast (Alamast®) |
|---|--------------------------|--------------------------|--------------------------|--------------------------------------|--------------------------|---|--------------------------|
| asthenia | - | <5% | - | - | - | <5% | - |
| blurred vision | - | <5% | - | - | - | <5% | - |
| cold/flu symptoms | - | - | - | √ | - | <5% | 10-25% |
| conjunctivitis | - | - | - | √ | 1-10% | - | - |
| corneal infiltrates/staining | <5% | - | - | - | - | - | - |

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| Drug | azelastine (Optivar®) | emedastine (Emadine®) | epinastine (Elestat®) | ketotifen (Alaway®) (Zaditor®) | nedocromil (Alocril®) | olopatadine (Patanol®) (Pataday®) | pemirolast (Alamast®) |
|------------------------|--------------------------|--------------------------|--------------------------|--------------------------------------|--------------------------|---|--------------------------|
| dream disturbance | - | <5% | - | - | - | - | - |
| dry eyes | - | <5% | - | √ | - | <5% | - |
| foreign body sensation | - | <5% | - | - | - | <5% | 10-25% |
| folliculosis | - | √ | - | - | - | - | - |
| hyperemia | - | - | √ | - | - | <5% | - |
| infection | - | - | √ | - | - | - | - |
| keratitis | - | <5% | - | √ | - | <5% | - |
| lid edema | - | - | - | - | - | <5% | - |
| mydriasis | - | - | - | √ | - | - | - |
| nasal congestion | - | - | - | - | 1-10% | - | - |
| nausea | - | - | - | - | - | <5% | - |
| ocular pain | - | <5% | - | √ | - | - | - |
| pharyngitis | - | - | √ | √ | - | <5% | - |
| photophobia | - | - | - | √ | 1-10% | - | - |
| pruritus | - | <5% | - | - | - | <5% | - |
| rash/allergy symptoms | - | - | - | √ | - | <5% | - |
| rhinitis | - | - | √ | √ | 1-10% | <5% | 10-25% |

| Drug | azelastine (Optivar®) | emedastine (Emadine®) | epinastine (Elestat®) | ketotifen (Alaway®) (Zaditor®) | nedocromil (Alocril®) | olopatadine (Patanol®) (Pataday®) | pemirolast (Alamast®) |
|-------------------|--------------------------|--------------------------|--------------------------|--------------------------------------|--------------------------|---|--------------------------|
| sinusitis | - | - | √ | - | - | <5% | - |
| taste disturbance | 10% | <5% | - | - | 10-30% | <5% | - |

DRUG-DRUG INTERACTIONS ^{1-6, 8-18}

As the systemic absorption is minimal, there are no reported drug interactions with these agents.

SUMMARY

Allergic conjunctivitis is a common medical problem that can occur at any point in time, dependent upon a specific allergen causing the ocular allergy effects. There are currently several treatment options available to help ameliorate symptoms associated with allergic conjunctivitis; however, avoidance of the allergen remains the best treatment. Efficacy trials have established the safety and efficacy of mast cell stabilizers, topical antihistamines, topical corticosteroids, and topical NSAIDs. Head to head trials of the drugs in this class exist, with some reporting statistically significant differences in specific symptom measures with the use of olopatadine when compared to other medications in this review. However, there is insufficient data to support the clinical superiority of one agent over another. None of them have any serious safety issues.

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