TITLE: Olopatadine for the Treatment of Allergic Conjunctivitis: A Review of the Clinical Efficacy, Safety, and Cost-Effectiveness

DATE: 17 March 2016

CONTEXT AND POLICY ISSUES

Allergic conjunctivitis, which mainly comprises seasonal allergic conjunctivitis (SAC) and perennial allergic conjunctivitis (PAC), is an IgE-mast cell-mediated hypersensitivity to allergens, manifests as varying degrees of eyes itching, tearing, eyelid edema and conjunctival hyperemia,\(^1\) and is recently estimated to have a prevalence as high as 40% of the population of the United States.\(^2\)

The mainstay in the treatment options for allergic conjunctivitis includes the use of topical agents with mast cell stabilizing and/or antihistaminic properties.\(^3-5\) Common topical solutions for allergic conjunctivitis include olopatadine ophthalmic solution (Patanol, Pataday) and ketotifen, which have a dual mechanism of action as mast cell stabilizers and antihistaminics, and cromolyn which is a mast cell stabilizer.\(^3,4,6,7\) Olopatadine and ketotifen ophthalmic solutions can carry, in addition to the medicinal ingredient, a preservative agent such as benzalkonium chloride.\(^6,8\)

A previous CADTH Rapid Response review completed in 2012 compared olopatadine to cromolyn and ketotifen\(^9\) and found that “Treatment of allergic conjunctivitis with olopatadine, ketotifen or cromolyn showed reductions in signs and symptom scores compared to baseline. Both olopatadine and ketotifen were well tolerated. The efficacy results of olopatadine compared to ketotifen were inconsistent. One study of limited quality showed that olopatadine and ketotifen have greater efficacy than cromolyn. There is limited amount of evidence on the cost-effectiveness of olopatadine compared with ketotifen or cromolyn”(p. 2)

This Rapid Response report aims to review the clinical- and cost-effectiveness of olopatadine for the treatment of allergic conjunctivitis. This is an update to the previous CADTH Rapid Response review.
RESEARCH QUESTIONS

1. What is the clinical efficacy and safety of olopatadine for the treatment of allergic conjunctivitis?

2. What is the cost-effectiveness of olopatadine for the treatment of allergic conjunctivitis?

KEY FINDINGS

Pooled estimates from four studies included in a systematic review showed that there was some evidence that olopatadine may be more effective than ketotifen in improving ocular itching, but not tearing, after 14 days of treatment. Data from one recent RCT showed that there was a similar reduction in the composite score (itching, tearing, and conjunctival hyperemia) with olopatadine or ketotifen after 28 days of treatment. Both drugs were found safe in the systematic review and the RCT. There were no studies identified comparing olopatadine to cromolyn, and no cost-effectiveness analyses of olopatadine for the treatment of allergic conjunctivitis were found.

METHODS

Literature Search Strategy

This report makes use of a literature search strategy developed for a previous CADTH report. For the current report, a limited literature search was conducted on key resources including PubMed, OVID, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit retrieval by study type. Where possible, retrieval was limited to the human population. The search was limited to English-language documents published between February 23, 2012 and February 18, 2016 to capture any articles published since the previous report.

Selection Criteria and Methods

One reviewer screened the titles and abstracts of the retrieved publications and examined the full-text publications for the final article selection. Selection criteria are outlined in Table 1.

<table>
<thead>
<tr>
<th>Table 1: Selection Criteria</th>
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</thead>
<tbody>
<tr>
<td><strong>Population</strong></td>
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<tr>
<td>Individuals with allergic conjunctivitis</td>
</tr>
<tr>
<td><strong>Intervention</strong></td>
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<tr>
<td>Olopatadine ophthalmic solution (Patanol, Pataday)</td>
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<tr>
<td><strong>Comparator</strong></td>
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<tr>
<td>Placebo, cromolyn (cromoglicic acid, cromoglycate), or ketotifen fumarate (ketotifen, zatidor)</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
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<tr>
<td>Clinical benefits, clinical harms, cost-effectiveness</td>
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<tr>
<td><strong>Study Designs</strong></td>
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<tr>
<td>Health technology assessments (HTA), systematic reviews (SR), meta-analyses (MA), randomized controlled trials (RCTs), and economic evaluations</td>
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</tbody>
</table>
Exclusion Criteria

Articles were excluded if they did not meet the selection criteria in Table 1, if they were published prior to February 2012, if they were duplicate publications of the same study, or if they were referenced in a selected systematic review.

Critical Appraisal of Individual Studies

The quality of the included systematic reviews and clinical effectiveness studies was assessed using the AMSTAR,$^{10}$ and Downs and Black checklists,$^{11}$ respectively. Numeric scores were not calculated. Instead, the strengths and limitations of the study are summarized and presented narratively.

SUMMARY OF EVIDENCE

Quantity of Research Available

The literature search yielded 113 citations. No potentially relevant reports were identified in the grey literature. After screening of abstracts from the literature search and from other sources, six potentially relevant studies were selected for full-text review. Two studies were included in the review. The PRISMA flowchart in Appendix 1 details the process of the study selection.

Summary of Study Characteristics

A detailed summary of the included SRs and studies is provided in Appendix 2 and 3, respectively.

The Cochrane systematic review,$^{12}$ published in 2015, included 30 RCTs with a total of 4344 participants with SAC or PAC, with 17 different drugs or treatment comparisons. One comparison, olopatadine versus ketotifen, was relevant to this Rapid Response review. Data from four studies (drug concentration was olopatadine 0.1% in all four studies, and ketotifen 0.025% in three studies, and 0.05% in one study) was pooled in a meta-analysis. Among these four studies, duration of treatment was from 2 to 4 weeks, and the sample size ranged from 32 to 92 patients. Primary outcomes were itching and tearing at 14 days, and secondary outcomes were serious adverse events.

The controlled trial,$^{13}$ published in 2014, randomized patients presenting with ocular itching and hyperemia to preserved olopatadine 0.1% solution (37 patients) or preservative-free ketotifen 0.025% solution (38 patients). Primary outcomes were reduction in the composite score (itching, tearing, and conjunctival hyperemia) at 28 days, and secondary outcomes were ocular adverse events.

Summary of Critical Appraisal

The included systematic review$^{12}$ provided a priori design, had a duplicate study selection and data extraction procedure in place, performed a comprehensive literature search, provided a list of included studies and study characteristics, and conducted a quality assessment of included studies which was used in formulating conclusions. A list of excluded studies was not provided,

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there was no assessment of publication bias, and there was considerable heterogeneity in reporting among the included studies. Conflict of interest was not stated.

The included trial\(^\text{13}\) had a clearly described hypothesis, patients were randomized, the method of selection from the source population was described, the selected patients were representative of the population from which they were recruited, main outcomes, interventions, patient characteristics, and main findings were clearly described, estimates of random variability and actual probability values were provided, and losses to follow-up were described. The patients were not blinded to the treatment strategies, and it is not clear whether the study had sufficient power to detect a clinically important effect.

Details of the strengths and limitations of the included studies are summarized in Appendix 4.

**Summary of Findings**

Main findings of included studies are summarized in detail in Appendix 5.

1. What is the clinical efficacy and safety of olopatadine for the treatment of allergic conjunctivitis?

The literature search identified one systematic review/meta-analysis,\(^\text{12}\) and one RCT\(^\text{13}\) that compared the clinical efficacy and safety of olopatadine and ketotifen for the treatment of allergic conjunctivitis.

The systematic review included 30 trials with a total of 4344 participants randomised, with 17 different drugs or treatment comparisons.\(^\text{12}\) Meta-analysis conducted for one comparison that is relevant to this Rapid Response review, olopatadine 0.1\% versus ketotifen 0.025\% or 0.05\%, with data from four studies. Duration of treatment was from 4 weeks in three studies and two weeks in one study, and the sample size was relatively small, from 32 to 92 patients. Primary outcomes were itching and tearing at 14 days, and secondary outcomes were serious adverse events.

There was a statistically significant difference in the reduction of itching at 14 days in favour of olopatadine compared to ketotifen. The mean difference was -0.32 (95\% confidence interval [CI] -0.59 to -0.06). There was high level statistical heterogeneity ($I^2 = 83\%$). There was no statistically significant difference in the reduction of tearing at 14 days between olopatadine and ketotifen (Mean difference -0.06; 95\%CI -0.35 to 0.22). There was high level statistical heterogeneity ($I^2 = 90\%$). No serious adverse events were reported in the four included studies.

The authors concluded that there was some evidence that olopatadine may be more effective than ketotifen in improving some ocular symptoms such as itching, and that both drugs are safe.

The controlled trial randomized 75 patients presenting with ocular itching and hyperemia to olopatadine 0.1\% (preserved) or ketotifen 0.025\% (preservative-free).\(^\text{13}\) Primary outcomes were reduction in the composite score (itching, tearing, and conjunctival hyperemia) at 28 days, and secondary outcomes were ocular adverse events.
There was no statistically significant difference between olopatadine and ketotifen in the reduction in the composite score (itching, tearing, and conjunctival hyperemia) at 28 days: (P = 0.67). Conjunctival inflammation was reported in 1 patient with ketotifen. Viral conjunctivitis and new confirmed allergic conjunctivitis was reported in 2 patients with olopatadine.

The authors concluded that there was a rapid and comparable improvement in SAC after 28 days of treatment with both preservative-free ketotifen and preserved olopatadine ophthalmic solutions, with a slightly better ocular tolerance with unpreserved ketotifen eye drops.

2. What is the cost-effectiveness of olopatadine for the treatment of allergic conjunctivitis?

There was no evidence found on the cost-effectiveness of olopatadine for the treatment of allergic conjunctivitis.

Limitations

The meta-analysis pooled comparative data on olopatadine and ketotifen treatments from four RCTs which have relatively small sample size and high heterogeneity. It is unclear whether the included RCT has sufficient power to detect a clinically important effect, and the patients were not blinded to the treatment strategies. There was no study found comparing olopatadine to cromolyn. There were no cost studies found on the use of olopatadine, limiting the knowledge on its cost-effectiveness in the treatment of allergic conjunctivitis, and the generalizability of the findings to the Canadian context.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

A previous CADTH Rapid Response review completed in 2012 found that both olopatadine and ketotifen were well tolerated though the efficacy results of olopatadine compared to ketotifen were inconsistent.

Evidence from a systematic review/meta-analysis, published after the 2012 CADTH review, showed that there was some evidence that olopatadine 0.1% may be more effective than ketotifen 0.025% or 0.05% in improving ocular itching, but not tearing, after 14 days of treatment. However heterogeneity was high, reflecting variability in individual study results. Data from one recent RCT showed that there was a similar reduction in the composite score (itching, tearing, and conjunctival hyperemia) with olopatadine 0.1% or ketotifen 0.025% after 28 days of treatment. Both drugs were found to be safe.

A recent RCT used direct conjunctival allergen instillation into the eyes of subjects with allergic conjunctivitis to cause acute ocular allergic reactions, and compared the efficacy and safety of different concentrations of olopatadine ophthalmic solutions (0.77%, 0.2% and 0.1%) and with its vehicle solution (benzalkonium chloride). Olopatadine 0.77% was found statistically significantly superior to all comparators in reducing ocular itching and redness, with a comparable safety profile between treatment groups (the vehicle provided the least effectiveness and caused the least adverse events). This finding suggests that olopatadine included in this Rapid Response report may have been even more at a higher dose.
REFERENCES


6. Pr Pataday®: olopatadine hydrochloride ophthalmic solution 0.2% w/v olopatadine (as olopatadine hydrochloride) [product monograph] [Internet]. Mississauga (ON): Alcon Canada Inc.; 2012 Aug 29. [cited 2016 Feb 18]. Available from: http://www.alcon.ca/pdf/Product_pharma/Product_pharma_pataday_eng.pdf


Appendix 1: Selection of Included Studies

113 citations identified from electronic literature search and screened

107 citations excluded

6 potentially relevant articles retrieved for scrutiny (full text, if available)

6 potentially relevant reports

4 reports excluded (irrelevant population, interventions or outcomes)

2 reports included in review
### Appendix 2: Characteristics of the Included Systematic Review

#### Table A1: Characteristics of Included Systematic Reviews

<table>
<thead>
<tr>
<th>First Author, Year, Country,</th>
<th>Literature Search Strategy</th>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
<th>Studies included Main outcomes</th>
</tr>
</thead>
</table>
| Castillo, 2015, UK            | Systematic review and meta-analysis
  "We searched CENTRAL (which contains the Cochrane Eyes and Vision Trials Register) (2014, Issue 7), Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid MEDLINE Daily, Ovid OLDMEDLINE (January 1946 to July 2014), EMBASE (January 1980 to July 2014), the metaRegister of Controlled Trials (mRCT) (www.controlled-trials.com), ClinicalTrials.gov (www.clinicaltrials.gov) and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/search/en). We did not use any date or language restrictions in the electronic searches for trials. We last searched the electronic databases on 17 July 2014." (p 1) | "We included randomised controlled trials (RCTs) comparing topical antihistamine and mast cell stabilisers, alone or in combination, with placebo, no treatment or to any other antihistamine or mast cell stabiliser, or both, that examined people with seasonal or perennial allergic conjunctivitis, or both. We considered any follow-up time between one week and one year" (p 2) | "This review did not cover other allergic conjunctivitis entities such as vernal keratoconjunctiviti, atopic keratoconjunctiviti, and giant papillary conjunctivitis." (p 2) | Primary outcome: severity of 4 main ocular symptoms: itching, irritation, watering eye, and photophobia (dislike of light)" (by questionnaire) Secondary outcomes • Adverse events. • Signs of hyperaemia and redness, chemosis, tarsal papillae (little bumps on inner surface of eyelid). • Duration of symptoms (days) of acute episodes. • Incidence of acute episodes (per year). (by investigator’s assessment) |
## Appendix 3: Characteristics of the Included Primary Study

<table>
<thead>
<tr>
<th>First Author, Year, Country</th>
<th>Design</th>
<th>Study Objectives</th>
<th>Interventions/Comparators</th>
<th>Patients</th>
<th>Main outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortemousque, 2014, France, Tunisia</td>
<td>RCT</td>
<td>“To compare preservative-free ketotifen 0.025% ophthalmic solution to olopatadine 0.1% ophthalmic solution in the treatment of seasonal allergic conjunctivitis (SAC) in clinical practice.” (p 2)</td>
<td>Preservative-free ketotifen 0.025% ophthalmic solution Olopatadine 0.1% ophthalmic solution</td>
<td>75 patients ≥ 18 years old, presenting with moderate to severe itching and conjunctival hyperemia</td>
<td>Composite score of primary criteria (itching, tearing, and conjunctival hyperemia) Tolerance (adverse events)</td>
</tr>
</tbody>
</table>
# Appendix 4: Summary of Critical Appraisal of Included Studies

## Table A3: Summary of Critical Appraisal of Included Study

<table>
<thead>
<tr>
<th>First Author, Publication Year</th>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Critical appraisal of included systematic reviews (AMSTAR™)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Castillo, “2015”</td>
<td>• a priori design provided</td>
<td>• list of excluded studies not provided,</td>
</tr>
<tr>
<td></td>
<td>• duplicate study selection and data extraction procedure in place</td>
<td>• no assessment of publication bias performed</td>
</tr>
<tr>
<td></td>
<td>• comprehensive literature search performed</td>
<td>• considerable heterogeneity in the reporting among the included trials</td>
</tr>
<tr>
<td></td>
<td>• list of included studies, study characteristics provided</td>
<td>• conflict of interest not stated</td>
</tr>
<tr>
<td></td>
<td>• quality assessment of included studies provided and used in formulating conclusions</td>
<td></td>
</tr>
<tr>
<td><strong>Critical appraisal of included study (Downs &amp; Black™)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortemousse, “2014”</td>
<td>• hypothesis clearly described</td>
<td>• patients not blinded</td>
</tr>
<tr>
<td></td>
<td>• patients randomized</td>
<td>• not sure if study had sufficient power to detect a clinically important effect</td>
</tr>
<tr>
<td></td>
<td>• method of selection from source population and representation described</td>
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<tr>
<td></td>
<td>• main outcomes, interventions, patient characteristics, and main findings clearly described</td>
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<td></td>
<td>• estimates of random variability and actual probability values provided</td>
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<td></td>
<td>• losses to follow-up described</td>
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</table>
### Appendix 5: Main Study Findings and Authors’ Conclusions

#### Table A4: Main Study Findings and Authors’ Conclusions

<table>
<thead>
<tr>
<th>First Author, Publication Year</th>
<th>Main Study Findings</th>
<th>Authors’ Conclusions</th>
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</thead>
<tbody>
<tr>
<td><strong>Research question 1</strong> (clinical efficacy and safety of olopatadine for the treatment of allergic conjunctivitis)</td>
<td></td>
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</tbody>
</table>
| Castillo, 2015                  | 30 trials were identified with a total of 4344 participants randomised, with 17 different drugs or treatment comparisons. Meta-analysis was only possible in one comparison, olopatadine versus ketotifen, with data from 4 studies. Duration of treatment is from 2 to 4 weeks, and sample size was relatively small, from 32 to 92 patients. **Primary outcomes:**  
*Itching at 14 days:* there is a statistically significant difference in the reduction of itching at 14 days in favour of olopatadine, compared to ketotifen. Mean difference: -0.32 (95% confidence interval CI -0.59 to -0.06). There was high level statistical heterogeneity (I² = 83%)  
*Tearing at 14 days:* there is no statistically significant difference in the reduction of tearing at 14 days between olopatadine and ketotifen. Mean difference: -0.06 (95%CI -0.35 to 0.22). There was high level statistical heterogeneity (I² = 90%)  
**Secondary outcomes:**  
No serious adverse events reported in the 4 included studies. | "There was some evidence from individual trials that olopatadine may be more effective than ketotifen in improving some ocular symptoms such as itching. Both drugs are safe." (p 21) |
| Mortemousquie, 2014             | **Primary outcomes:**  
Reduction in the composite score (itching, tearing, and conjunctival hyperemia) at 28 days: there is no statistically significant difference between olopatadine and ketotifen (P = 0.67)  
Olopatadine:  
Day 1: 7.0 ± 1.4  
Day 28: 1.0 ± 1.2  
Reduction: -6.0 ± 1.6  
Ketotifen  
Day 1: 6.8 ± 1.2  
Day 28: 0.9 ± 1.0  
Reduction: -5.9 ± 1.6  
**Secondary outcomes:**  
Conjunctival inflammation reported in 1 patient with ketotifen  
Viral conjunctivitis and new confirmed allergic conjunctivitis reported in 2 patients with olopatadine | "A rapid and comparable improvement in SAC was achieved after 28 days of treatment with both preservative-free ketotifen and preserved olopatadine ophthalmic solutions, with a slightly better ocular tolerance with unpreserved ketotifen 0.025% eye drops." (p 2) |
| **Research question 2** (cost-effectiveness of olopatadine for the treatment of allergic conjunctivitis) |                                                                                       |                                                                                       |
|                                                                                  | There was no evidence found on the cost-effectiveness of olopatadine for the treatment of allergic conjunctivitis |                                                                                       |