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REVIEW ARTICLE

Antihistamines for treating rhinosinusitis: systematic review and meta-analysis of randomised controlled studies

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Abstract

Background: Without the release of histamines, patients with rhinosinusitis may not benefit from antihistamines. Additionally, anticholinergic effects may do more harm than good. This study aimed to investigate the effectiveness of antihistamines in treating rhinosinusitis.

Methods: An electronic search was performed. Randomised controlled trials comparing antihistamines with either placebo or other treatments for patients with rhinosinusitis were selected.

Results: Two studies (184 patients) met the inclusion criteria. Loratadine decreased nasal obstruction in allergic rhinitis patients with acute rhinosinusitis (mean difference = −0.58; confidence interval = −0.85 to −0.31, $p < 0.01$), but had no benefit on total symptom score (mean difference = −1.25; confidence interval = −2.77 to 0.27, $p = 0.11$), or rhinorrhoea symptoms (mean difference = −0.06; confidence interval = −0.37 to 0.25, $p = 0.71$).

Conclusion: There is limited evidence to support the use of antihistamines in treating rhinosinusitis. The number of included studies in this systematic review is limited. Antihistamines may relieve nasal obstruction in allergic rhinitis patients with acute rhinosinusitis.

Key words: Histamine Antagonists; Sinusitis; Rhinitis, Allergic; Nasal Obstruction

Introduction

Rhinosinusitis is defined as inflammation of the nose and paranasal sinuses. Hence, anti-inflammatory agents, such as corticosteroids,[1] macrolides with anti-neutrophilic function,[2] and doxycycline with anti-matrix metalloproteinase 9 activity,[3] are part of the comprehensive medical treatment. Although commonly used in treating rhinosinusitis, antihistamines may not be beneficial.

Antihistamines are histamine H_1 receptor reverse agonists; they should be efficacious in treating rhinitis, not rhinosinusitis. The anticholinergic property of first-generation antihistamines increases the viscosity of discharge. It inhibits ciliary beat, as cilia do not work effectively in dry nasal mucosa. These effects potentially cause more harm than benefit in treating rhinosinusitis. Second-generation antihistamines do not have an anticholinergic property, and thus do not cause the aforementioned adverse effects. However, they are still not efficacious in treating rhinosinusitis, as they are highly specific to histamine receptors, and the pathophysiology of rhinosinusitis is not related to the release of histamine from mast cells.[4]

Nevertheless, antihistamines are commonly used in treating rhinosinusitis. Wang and colleagues conducted a survey on the treatment of acute rhinosinusitis, which revealed that antihistamine was the most commonly prescribed medication by Asian paediatricians, and in the top three medicines prescribed by Asian physicians.[5] Antihistamines were the most commonly prescribed medicine for treating mild acute rhinosinusitis.

This study aimed to investigate the effectiveness and adverse events of antihistamines in treating both acute rhinosinusitis and chronic rhinosinusitis, when compared to placebo and other treatments.

Materials and methods

Eligibility criteria

Randomised controlled trials (RCTs) that compared antihistamines with either placebo or no treatment in treating all subtypes of rhinosinusitis (acute

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rhinosinusitis, and chronic rhinosinusitis with and without polyps) were included. The outcomes measured included patient cure rate (for acute rhinosinusitis), patient-reported outcome, endoscopy, radiography and adverse events. Trials using any co-interventions were included if the co-interventions were equally applied in both groups.

Information sources and search strategy

Electronic literature searches for RCTs were conducted systematically, using Medline and Embase. The last date of the search was 10 September 2015. Combinations of the following Medical Subject Headings terms and keywords were used: antihistamines; histamines H1 antagonist; chlorpheniramine; diphenhydramine; promethazine; triprolidine; hydroxyzine; cetirizine; loratadine; desloratadine; fexofenadine; levocetirizine; and rhinosinusitis. References of included studies and additional sources were searched to identify any missing published or unpublished trials.

Study selection and data synthesis

Two authors (K Seresirikachorn and W Chitsuthipakorn) independently performed trial selection, and two authors (K Seresirikachorn and L Khattiyawittayakun) independently extracted details of the included studies. The quality of included studies was assessed by evaluating the risk of bias, as guided by the *Cochrane Handbook for Systematic Reviews of Interventions*.[6] Data were pooled for meta-analysis. Risk ratios and 95 per cent confidence intervals (CIs) were used for dichotomous data. Mean differences and 95 per cent CIs were used for continuous data. A fixed-effect method was used. Statistical assessments were performed using Review Manager ('RevMan') software, version 5.1.6.[7]

Results

Study selection

A total of 305 references were identified and retrieved from electronic searches. One more record was identified from the references of these studies. Of those, 297 were excluded in first-level screening (of the title and abstract) as they were irrelevant. Seven studies were removed after full-text screening. In the end, two studies were included.[8,9] Characteristics of the included studies are shown in Table I. A flow chart of study retrieval and selection is presented in Figure 1. Standard deviations were not reported and could not be imputed in one study.[9] The corresponding author was contacted for raw data, but these data were not obtained.

Participants

There were a total of 184 participants, of which 52.2 per cent were men. The mean age of patients was 36.9 years. No literature on paediatric patients or patients with chronic rhinosinusitis without polyps

TABLE I
CHARACTERISTICS OF INCLUDED STUDIES

Study (year)	Study design	Subject	Age range (years)	All patients (*n*)	Allergic rhinitis patients (*n* (%))	Antihistamine	Co-intervention	Comparator	Study duration (months)	Outcome measure
Braun *et al.*[8] (1997)	RCT	Acute rhinosinusitis	15–65	139	139 (100)	Loratadine 10 mg once daily	None	Placebo	1	Symptom score
Haye *et al.*[9] (1998)	RCT	Chronic rhinosinusitis with polyps	18–68	45	16 (35.6)	Cetirizine 20 mg once daily	None	Placebo	3	Number of days with fewer symptoms; polyp size

RCT = randomised controlled trial

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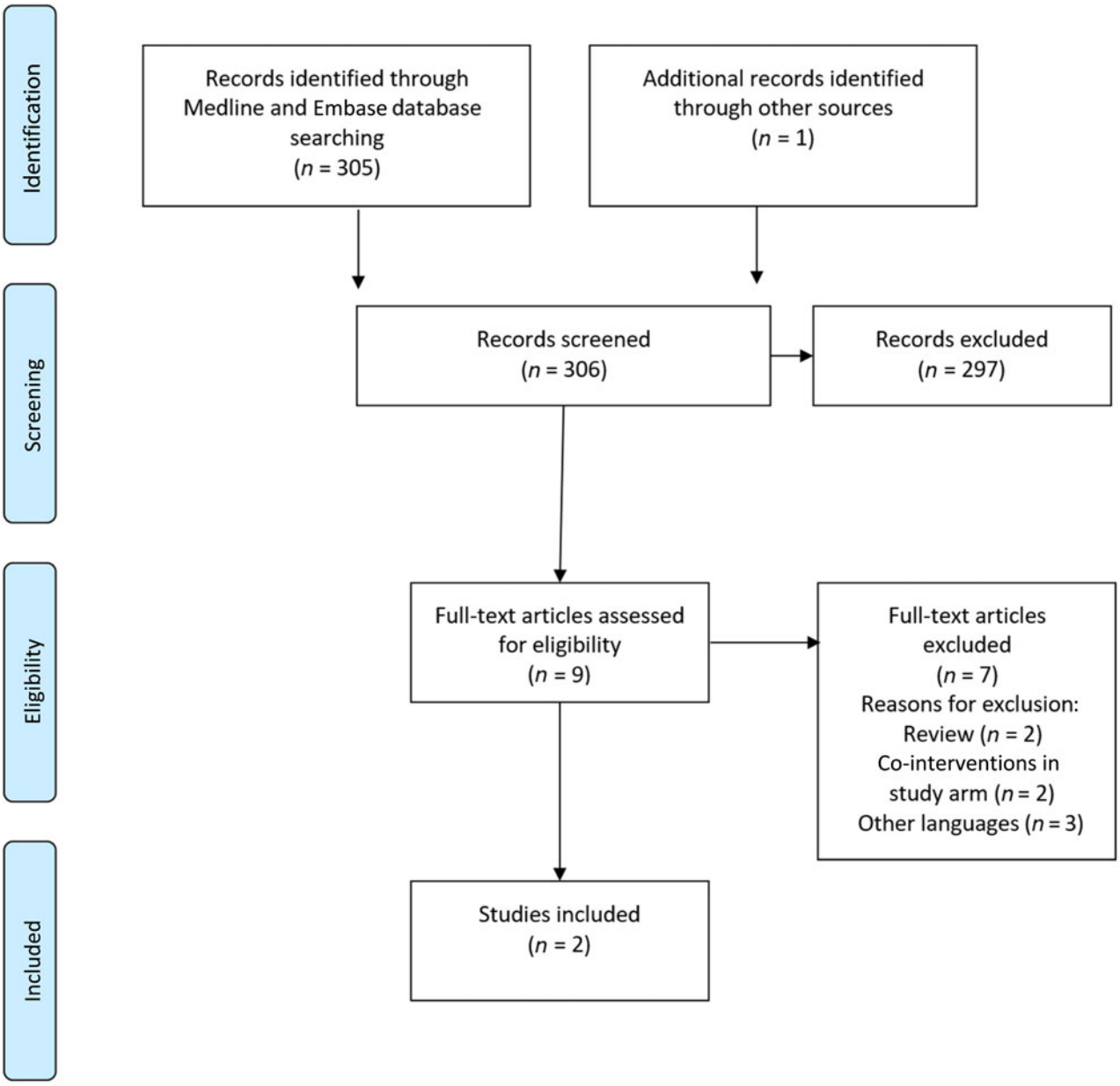

FIG. 1
Flow diagram of study selection.

was found. One study included patients with acute rhinosinusitis,[8] while the other investigated patients with chronic rhinosinusitis with polyps.[9] Concomitant allergic rhinitis was part of the inclusion criteria in one study, as confirmed by patient history, a positive skin prick test result and serum-specific immunoglobulin E antibodies,[8] while allergic rhinitis patients (35.6 per cent) were a minor population in the other study.[9]

Antihistamines for acute rhinosinusitis

In one of the included studies, by Braun and colleagues, 139 allergic rhinitis patients with acute rhinosinusitis were randomised to receive either 10 mg of loratadine or placebo for 28 days.[8] Both groups were given the following co-interventions: 14 days of antibiotics and 10 days of oral corticosteroids. At day 28, antihistamines, as an adjunct treatment, significantly decreased nasal obstruction (mean difference = −0.58; 95 per cent CI = −0.85 to −0.31, $p < 0.01$), but did not reduce total symptom scores (mean difference = −1.25; 95 per cent CI = −2.77 to 0.27, $p = 0.11$), or rhinorrhoea symptoms (mean difference = −0.06; 95 per cent CI = −0.37 to 0.25, $p = 0.71$). Cure rate was not assessed.

Sensitivity analysis was performed by analysing data at day 14 in order to confirm these findings. Similar results were revealed. At day 14, antihistamines, as an adjunct treatment, significantly decreased nasal obstruction (mean difference = −0.34; 95 per cent CI = −0.64 to −0.04, $p = 0.02$), but did not reduce total symptom scores (mean difference = −0.26; 95 per cent CI = −3.11 to 0.59, $p = 0.18$) or rhinorrhoea

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symptoms (mean difference = −0.12; 95 per cent CI = −0.39 to 0.15, $p = 0.39$).

Antihistamines for chronic rhinosinusitis with polyps

In the other included study, by Haye and colleagues,[9] 45 patients with chronic rhinosinusitis with polyps were randomised to receive either 20 mg of cetirizine or placebo for 3 months. The primary outcome was the number of days with fewer than one symptom, which did not align with the aim of this review. The authors reported that cetirizine effectively reduced nasal obstruction, nasal sneezing and rhinorrhoea;[9] however, total and individual symptom scores were not given. Nasal endoscopy findings were also assessed. There were no improvements in terms of the number and size of polyps in either the antihistamine group or placebo group, and there was no difference between the groups.[9] As no standard deviations were reported, the data could not be analysed.

Antihistamines for chronic rhinosinusitis without polyps

There was no study.

First-generation antihistamines for rhinosinusitis

There was no study.

Antihistamines for rhinosinusitis with and without allergy

Although beneficial effects of loratadine were shown in allergic rhinitis patients with acute rhinosinusitis in one study, by Braun and colleagues,[8] the beneficial effects of antihistamines for patients without allergy were not investigated. The study by Haye and colleagues had a mixed population, and 35.6 per cent of the participants had allergic rhinitis.[9] However, data for patients with allergies and those without were not reported separately, and thus these data could not be used for statistical analysis.

Antihistamines for paediatric rhinosinusitis

There was no study.

Intranasal antihistamines for rhinosinusitis

There was no study.

Adverse events

When data were pooled to assess somnolence, there was no difference between patients given antihistamines versus placebo (risk ratio = 0.68; 95 per cent CI = 0.14 to 3.29, $p = 0.64$). There was no difference between antihistamines and placebo in terms of any adverse event (risk ratio = 0.96; 95 per cent CI = 0.61 to 1.51, $p = 0.85$). The adverse events of using first-generation antihistamines in treating rhinosinusitis were not investigated.

Risk of bias

One of the two included studies had a low risk of bias in terms of random sequence generation.[9] Both studies had an unclear risk of bias regarding allocation concealment. One included study had a low risk of bias in terms of the blinding of outcome assessment.[9] Both studies had a low risk of bias regarding incomplete outcome data and selective reporting (Figure 2). In general, the two included studies had selection and detection biases, but had a low risk of attrition and reporting biases (Figure 3).

Discussion

The antihistamines in this study improved nasal obstruction for allergic rhinitis patients with acute rhinosinusitis. Beneficial effects of antihistamines on nasal obstruction have been reported in a meta-analysis of patients with persistent allergic rhinitis.[10] When interleukin (IL)-4 and IL-8 were measured by immunoassay on fluids recovered from nasal lavage, anti-inflammatory effects of second-generation antihistamines were shown, decreasing cytokine levels and reducing leucocyte infiltration.[11] Jang and colleagues investigated the effects of levocetirizine on human

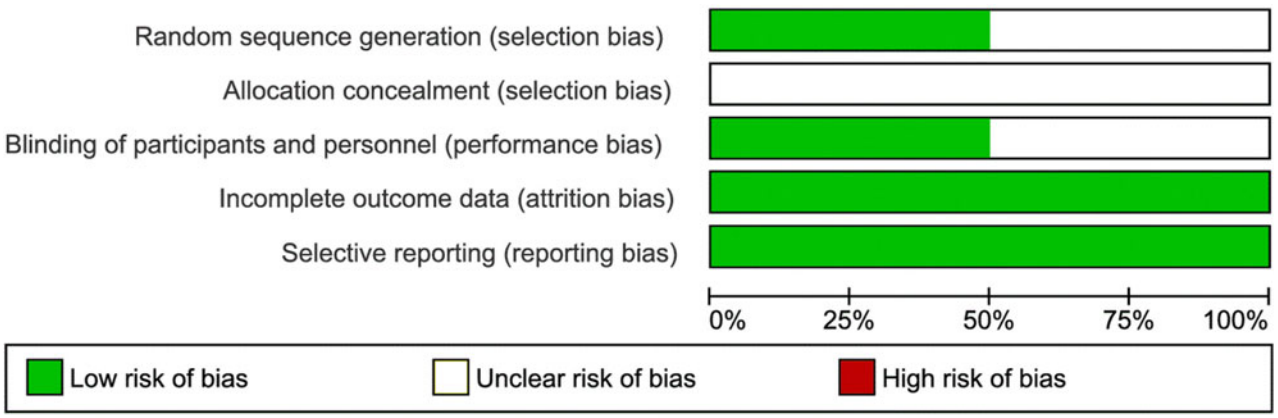

FIG. 2

Risk of bias graph: each risk of bias item presented as percentages across all included studies.

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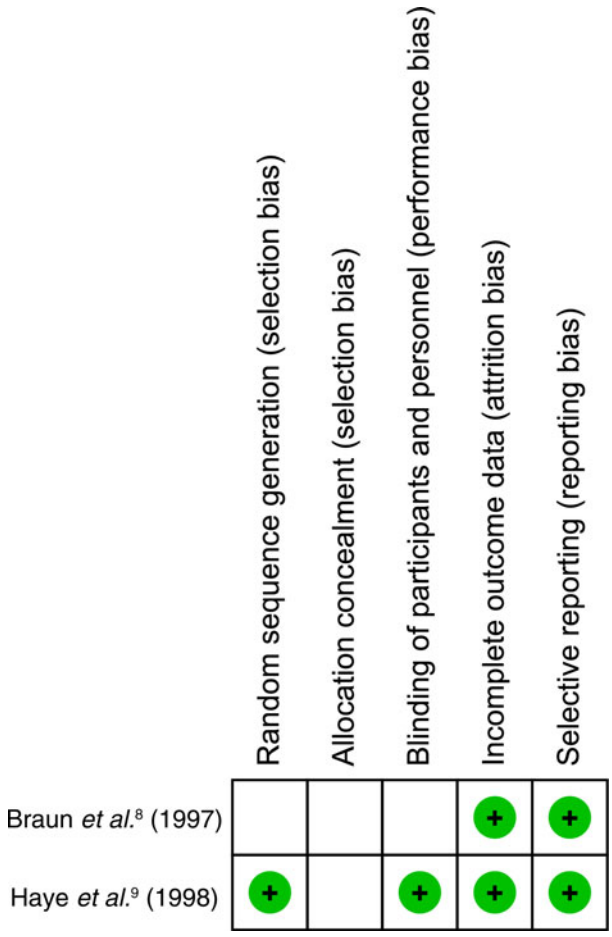

FIG. 3
Risk of bias summary: each risk of bias item for each included study.

rhinovirus infection in primary human nasal epithelial cells.[12] In that study, the inhibitory effects of levocetirizine on human rhinovirus replication, and on human rhinovirus induced upregulation of intercellular adhesion molecule 1, IL-6, and IL-8, toll-like receptor 3 expression and nuclear factor kappa B activation were revealed.

First-generation antihistamines may not be effective in treating rhinosinusitis. McCormick and colleagues studied the effectiveness of the combination of antihistamines and nasal decongestants in treating acute rhinosinusitis in children, and reported similar responses to treatment when compared to placebo.[13] The antihistamine used was brompheniramine. This study was excluded because the co-intervention of nasal decongestant was only given to the study arm. Although nasal decongestant was added to brompheniramine, the response did not differ from that of placebo. Thus, first-generation antihistamines are considered not effective in the treatment of rhinosinusitis.[13]

To date, this is the only systematic review assessing the effectiveness of antihistamines for treating adult rhinosinusitis. Although this present review aimed to include all trials studying both adult and paediatric populations, no trial investigating paediatric rhinosinusitis was included. One previously published systematic review, by Shaikh and Wald, aimed to assess the effectiveness of antihistamines, decongestants and nasal irrigation for treating paediatric rhinosinusitis.[14] They reported that no trial met the inclusion criteria. Shaikh and Wald excluded the study by McCormick and colleagues[13] because their diagnostic criteria of positive radiographs with a minimum symptom duration of 7 days was inadequate, as radiographs may be positive in children with common cold.

Another systematic review, by De Sutter and colleagues, assessed the effectiveness of antihistamines for treating common cold.[15] They reported a short-term clinical improvement during the first 2 days of treatment. Overall, symptoms had not improved after 3 days. These findings are similar to those of the present systematic review, which found no overall symptom improvement associated with the use of antihistamines for treating rhinosinusitis.

Clinically, the findings of this systematic review suggest that antihistamines may be beneficial to allergic rhinitis patients with acute rhinosinusitis. Although antihistamines do not improve total nasal symptoms, they may relieve nasal obstruction. This meta-analysis is limited by the fact that only two studies were included. More randomised controlled trials are required to evaluate the effectiveness of antihistamines in the treatment of rhinosinusitis.

Conclusion

There were limited numbers of included studies in this systematic review, and it involved studies with risks of bias. Limited evidence supports the use of antihistamines for treating patients with acute rhinosinusitis. Second-generation antihistamines may be chosen as they have anti-inflammatory effects, thus relieving nasal obstruction. Allergic rhinitis patients may be the target group, as opposed to a non-allergic subgroup or chronic rhinosinusitis patients with and without polyps. There is no evidence that antihistamines improve cure rate, total nasal symptom scores or rhinorrhoea symptoms. Second-generation antihistamines are safe, with no significant adverse events.

References

1 Fokkens WJ, Lund VJ, Mullol J, Bachert C, Alobid I, Baroody F *et al*. EPOS 2012: European position paper on rhinosinusitis and nasal polyps 2012. A summary for otorhinolaryngologists. *Rhinology* 2012;**50**:1–12
2 Wallwork B, Coman W, Mackay-Sim A, Greiff L, Cervin A. A double-blind, randomized, placebo-controlled trial of macrolide in the treatment of chronic rhinosinusitis. *Laryngoscope* 2006; **116**:189–93
3 Van Zele T, Gevaert P, Holtappels G, Beule A, Wormald PJ, Mayr S *et al*. Oral steroids and doxycycline: two different approaches to treat nasal polyps. *J Allergy Clin Immunol* 2010;**125**:1069–76
4 Naclerio RM, Proud D, Kagey-Sobotka A, Lichtenstein LM, Hendley JO, Gwaltney JM Jr. Is histamine responsible for the symptoms of rhinovirus colds? A look at the inflammatory mediators following infection. *Pediatr Infect Dis J* 1988;**7**:218–22

https://doi.org/10.1017/S002221511700192X Published online by Cambridge University Press

5 Wang DY, Wardani RS, Singh K, Thanaviratananich S, Vicente G, Xu G *et al*. A survey on the management of acute rhinosinusitis among Asian physicians. *Rhinology* 2011;**49**:264–71
6 Higgins JP, Green S, eds. *Cochrane Handbook for Systematic Reviews of Interventions*, Version 5.1.0 (updated March 2011). Copenhagen: Cochrane Collaboration, 2011
7 Review Manager (RevMan) [computer program]. Version 5.1.6. Copenhagen: Nordic Cochrane Centre, Cochrane Collaboration, 2011
8 Braun JJ, Alabert JP, Michel FB, Quiniou M, Rat C, Cougnard J *et al*. Adjunct effect of loratadine in the treatment of acute sinusitis in patients with allergic rhinitis. *Allergy* 1997;**52**: 650–5
9 Haye R, Aanesen JP, Burtin B, Donnelly F, Duby C. The effect of cetirizine on symptoms and signs of nasal polyposis. *J Laryngol Otol* 1998;**112**:1042–6
10 Hore I, Georgalas C, Scadding G. Oral antihistamines for the symptom of nasal obstruction in persistent allergic rhinitis--a systematic review of randomized controlled trials. *Clin Exp Allergy* 2005;**35**:207–12
11 Ciprandi G, Cirillo I, Vizzaccaro A, Tosca MA. Levocetirizine improves nasal obstruction and modulates cytokine pattern in patients with seasonal allergic rhinitis: a pilot study. *Clin Exp Allergy* 2004;**34**:958–64
12 Jang YJ, Wang JH, Kim JS, Kwon HJ, Yeo NK, Lee BJ. Levocetirizine inhibits rhinovirus-induced ICAM-1 and cytokine expression and viral replication in airway epithelial cells. *Antivir Res* 2009;**81**:226–33
13 McCormick DP, John SD, Swischuk LE, Uchida T. A double-blind, placebo-controlled trial of decongestant-antihistamine for the treatment of sinusitis in children. *Clin Pediatr (Phila)* 1996;**35**:457–60
14 Shaikh N, Wald ER. Decongestants, antihistamines and nasal irrigation for acute sinusitis in children. *Cochrane Database Syst Rev* 2014;(10):CD007909
15 De Sutter AI, Saraswat A, van Driel ML. Antihistamines for the common cold. *Cochrane Database Syst Rev* 2015;(11): CD009345

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