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Oral H1 antihistamines as 'add-on' therapy to topical treatment for eczema (Review)

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TABLE OF CONTENTS

[Intervention Review]

Oral H1 antihistamines as ‘add-on’ therapy to topical treatment for eczema

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ABSTRACT

Background

The symptoms of eczema can lead to sleeplessness and fatigue and may have a substantial impact on quality of life. Use of oral H1 antihistamines (H1 AH) as adjuvant therapy alongside topical agents is based on the idea that combining the anti-inflammatory effects of topical treatments with the blocking action of histamine on its receptors in the skin by H1 AH (to reduce the principal symptom of itch) might magnify or intensify the effect of treatment. Also, it would be unethical to compare oral H1 AH alone versus no treatment, as topical treatment is the standard management for this condition.

Objectives

To assess the effects of oral H1 antihistamines as 'add-on' therapy to topical treatment in adults and children with eczema.

Search methods

We searched the following databases up to May 2018: the Cochrane Skin Group Specialised Register, CENTRAL, MEDLINE, Embase, and the GREAT database (Global Resource of EczemA Trials; from inception). We searched five trials registers and checked the reference lists of included and excluded studies for further references to relevant randomised controlled trials (RCTs). We also searched the abstracts of four conference proceedings held between 2000 and 2018.

Selection criteria

We sought RCTs assessing oral H1 AH as 'add-on' therapy to topical treatment for people with eczema compared with topical treatment plus placebo or no additional treatment as add-on therapy.

Data collection and analysis

We used standard Cochrane methodological procedures. Primary outcome measures were 'Mean change in patient-assessed symptoms of eczema' and 'Proportion of participants reporting adverse effects and serious adverse events'. Secondary outcomes were 'Mean change in physician-assessed clinical signs', 'Mean change in quality of life', and 'Number of eczema flares'.

Main results

We included 25 studies (3285 randomised participants). Seventeen studies included 1344 adults, and eight studies included 1941 children. Most studies failed to report eczema severity at baseline, but they were conducted in secondary care settings, so it is likely that they

recruited patients with more severe cases of eczema. Trial duration was between three days and 18 months. Researchers studied 13 different H1 AH treatments. We could not undertake pooling because of the high level of diversity across studies in terms of duration and dose of intervention, concomitant topical therapy, and outcome assessment. Risk of bias was generally unclear, but five studies had high risk of bias in one domain (attrition, selection, or reporting bias). Only one study measured quality of life, but these results were insufficient for statistical analysis.

Although this review assessed 17 comparisons, we summarise here the results of three key comparisons in this review.

Cetirizine versus placebo

One study compared cetirizine 0.5 mg/kg/d against placebo over 18 months in 795 children. Study authors did not report patient-assessed symptoms of eczema separately for pruritus. Cetirizine is probably associated with fewer adverse events (mainly mild) (risk ratio (RR) 0.68, 95% confidence interval (CI) 0.46 to 1.01) and the need for slightly less additional H1 AH use as an indication of eczema flare rate (P = 0.035; no further numerical data given). Physician-assessed clinical signs (SCORing Atopic Dermatitis index (SCORAD)) were reduced in both groups, but the difference between groups was reported as non-significant (no P value given). Evidence for this comparison was of moderate quality.

One study assessed cetirizine 10 mg/d against placebo over four weeks in 84 adults. Results show no evidence of differences between groups in patient-assessed symptoms of eczema (pruritus measured as part of SCORAD; no numerical data given), numbers of adverse events (RR 1.11, 95% CI 0.50 to 2.45; mainly sedation, other skin-related problems, respiratory symptoms, or headache), or physician-assessed changes in clinical signs, amount of local rescue therapy required, or number of applications as an indicator of eczema flares (no numerical data reported). Evidence for this comparison was of low quality.

Fexofenadine versus placebo

Compared with placebo, fexofenadine 120 mg/d taken in adults over one week (one study) probably leads to a small reduction in patient-assessed symptoms of pruritus on a scale of 0 to 8 (mean difference (MD) -0.25, 95% CI -0.43 to -0.07; n = 400) and a greater reduction in the ratio of physician-assessed pruritus area to whole body surface area (P = 0.007; no further numerical data given); however, these reductions may not be clinically meaningful. Results suggest probably little or no difference in adverse events (mostly somnolence and headache) (RR 1.05, 95% CI 0.74 to 1.50; n = 411) nor in the amount of 0.1% hydrocortisone butyrate used (co-intervention in both groups) as an indicator of eczema flare, but no numerical data were given. Evidence for this comparison was of moderate quality.

Loratadine versus placebo

A study of 28 adults compared loratadine 10 mg/d taken over 4 weeks versus placebo. Researchers found no evidence of differences between groups in patient-assessed pruritus, measured by a 100-point visual analogue scale (MD -2.30, 95% CI -20.27 to 15.67); reduction in physician-assessed clinical signs (SCORAD) (MD -4.10, 95% CI -13.22 to 5.02); or adverse events. Study authors reported only one side effect (folliculitis with placebo) (RR 0.25, 95% CI 0.01 to 5.76). Evidence for this comparison was of low quality. Number of eczema flares was not measured for this comparison.

Authors' conclusions

Based on the main comparisons, we did not find consistent evidence that H1 AH treatments are effective as 'add-on' therapy for eczema when compared to placebo; evidence for this comparison was of low and moderate quality. However, fexofenadine probably leads to a small improvement in patient-assessed pruritus, with probably no significant difference in the amount of treatment used to prevent eczema flares. Cetirizine was no better than placebo in terms of physician-assessed clinical signs nor patient-assessed symptoms, and we found no evidence that loratadine was more beneficial than placebo, although all interventions seem safe.

The quality of evidence was limited because of poor study design and imprecise results. Future researchers should clearly define the condition (course and severity) and clearly report their methods, especially participant selection and randomisation; baseline characteristics; and outcomes (based on the Harmonising Outcome Measures in Eczema initiative).

PLAIN LANGUAGE SUMMARY

Do H1 antihistamine tablets or liquids help improve eczema symptoms in people who are already using creams or ointments for their eczema?

Review question

Are H1 antihistamines (which inhibit the action of chemicals released as part of an allergic reaction; known as 'histamines'), taken as tablets or liquid, effective and safe in people of any age with diagnosed eczema, if given in addition to creams and ointments, compared to treatment with an inactive substance (placebo) or nothing added to creams and ointments?

Background

Eczema (also known as 'atopic eczema/dermatitis') is a skin disorder frequently affecting both children and adults. In developed countries, 10% to 20% of all people are affected by eczema during their lifetime. The main symptom is itch, which results in scratching and, together with skin inflammation, frequently produces reddening of the skin. The symptoms of eczema can lead to sleeplessness and fatigue, lowering quality of life. Antihistamines are frequently given for itch (specifically H1 antihistamines taken by mouth), and they may alleviate the symptoms of eczema when given in addition to conventional treatments directly applied to the skin (e.g. emollients, moisturisers, steroid creams), although they are not thought to cure it. Many antihistamines are available without prescription, for instance, cetirizine or loratadine. Although H1 antihistamines are frequently prescribed for treating eczema, we do not know whether they are effective and safe.

Study characteristics

We searched for relevant studies up to May 2018. We included 25 randomised controlled trials with 3285 participants of all ages with diagnosed eczema. Eight studies included children or adolescents, and 17 included adults. The gender of participants and the severity of symptoms often were not reported. All studies were conducted in secondary care settings, including hospital clinics, research clinics, dermatology centres, and surgery centres, meaning that participants were likely to have more severe eczema than if recruitment occurred from first point of contact settings (i.e. primary care). All but one study compared H1 antihistamine versus placebo. Researchers studied 13 different H1 antihistamines, most of which were less sedating H1 antihistamines (known as 'second-generation antihistamines'). Studies lasted between three days and 18 months. Seven trials received funding from pharmaceutical companies; they are the largest trials included in this review.

Key results

We found no convincing evidence that H1 antihistamines help patients with eczema.

One study compared cetirizine 0.5 mg/kg/d versus placebo (in children over a period of 18 months). No data were provided on patient-assessed itch symptoms of eczema. Cetirizine is probably associated with fewer (mainly mild) adverse events and the need for slightly less additional H1 antihistamine to prevent flares. Even though physician-assessed clinical signs were reduced in both groups, results show no differences between groups (all moderate-quality evidence).

When compared with placebo, we found no evidence that an increased dose of cetirizine 10 mg/d over four weeks makes a difference in terms of patient-assessed itch, number of side effects, physician-assessed signs, or number of eczema flares as measured by the amount of treatment used (all low-quality evidence). Side effects reported in both groups included drowsiness, skin-related problems, breathing issues, and headaches.

Compared with placebo, fexofenadine 120 mg/d given to adults for one week probably slightly improves patient-assessed itch, as well as producing a greater reduction in the area of itch, as assessed by a physician, and it probably makes little or no difference in the number of participants experiencing side effects (mostly drowsiness and headaches) or in the extent of treatment required as an indicator of the number of eczema flares (all moderate-quality evidence).

We found no evidence of a difference between placebo and loratadine 10 mg/d given to adults for four weeks in patient-assessed itch, occurrence of side effects, or physician-assessed signs of eczema (all low-quality evidence). This study did not measure the number of eczema flares. Study authors reported only one side effect (folliculitis), which occurred with placebo.

Only one study measured quality of life, but results could not be analysed.

Quality of the evidence

For all outcomes across key comparisons, evidence was of low to moderate certainty. Reasons for lowering the quality of evidence include concerns over how studies were carried out and inclusion of too few participants, leading to less accurate results.

Summary of findings for the main comparison. Cetirizine 0.5 mg/kg/d versus placebo (18-month intervention)

Cetirizine 0.5 mg/kg/d compared with placebo for eczema

Patient or population: children with eczema

Settings: secondary

Intervention: cetirizine 0.5 mg/kg/d

Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Cetirizine 0.5 mg/kg/d				
Primary outcome 1. **Mean change in patient-assessed symptoms** Pruritus was assessed once as part of SCORAD Follow-up: 18 months	See comment	See comment	-	-	-	This outcome was assessed as part of the SCORAD assessment, but the data were not presented separately for pruritus. Thus, no data for analysis of this outcome were available from this study.
Primary outcome 2. **Proportion of participants reporting adverse effects and serious adverse events throughout the study period** Follow-up: 18 months	Study population		**RR 0.68** (0.46 to 1.01)	795 (1 study)	⊕⊕⊕⊖ **moderate**[a]	The difference was non-significant and most reported symptoms and events were mild and were attributed to intercurrent respiratory or gastrointestinal infection or exacerbations of allergic disorders.
	136 per 1000	**93 per 1000** (63 to 138)				
Secondary outcome 1. **Mean change in physi-**	See comment	See comment	-	795 (1 study)	⊕⊕⊕⊖ **moderate**[a]	No evidence for a treatment-related reduction in SCORAD scores between baseline and the final visit was observed by study authors, as the

cian-assessed clinical signs Measured by SCORAD Follow-up: 18 months						difference between groups was reported to be non-significant (from 24.9 to 15.2 in the cetirizine group and from 25.1 to 15.7 in the placebo group). Data could not be analysed because standard deviations were missing.
***Secondary outcome 2.* Mean change in quality of life**	See comment	See comment	-	-	-	No study addressed this outcome.
***Secondary outcome 3.* Number of eczema flares, measured by, for example, 'escalation of treatment' or 'use of topical anti-inflammatory medications'** Follow-up: 18 months	See comment	See comment	-	795 (1 study)	⊕⊕⊕⊖ **moderate**[a]	This outcome assessed the use of a variety of topical and systemic medications including oral use of H1 antihistamines. No significant difference between groups was observed, with 1 exception: participants in the placebo group were more likely to have used H1 antihistamines (P = 0.035). No data for analysis were available from the study. In other words, the intervention probably makes little or no difference in the use of additional H1 antihistamines to prevent flares.

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; RR: risk ratio; SCORAD: SCORing Atopic Dermatitis index.

GRADE Working Group grades of evidence.
High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.

[a]Downgraded by one level for limitations in design due to unclear judgement for most domains.

Summary of findings 2. Cetirizine 10 mg/d versus placebo (4-week intervention)

Cetirizine 10 mg/d compared with placebo for eczema

Patient or population: adults with eczema

Settings: secondary

Intervention: cetirizine 10 mg/d

Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Cetirizine 10 mg/d				
Primary outcome 1. **Mean change in patient-assessed symptoms** Pruritus was assessed once as part of SCORAD and once by patient case report form (CRF) Follow-up: 4 weeks	See comment	See comment	-	84 (1 study)	⊕⊕⊖⊖ **low**[a]	Pruritus as part of SCORAD: no significant differences were observed between the intervention group and the placebo group Pruritus by patient CRF: according to study authors, no significant difference was observed between groups. It is of note that values reported in Table 2 of the publication actually increased from baseline to last visit, although the legend states that "lower values indicate less pruritus". We tried to contact the study authors to inquire about this but did not succeed in doing so.
Primary outcome 2. **Proportion of participants reporting adverse effects and serious adverse events throughout the study period** Follow-up: 4 weeks	Study population		**RR 1.11** (0.50 to 2.45)	84 (1 study)	⊕⊕⊖⊖ **low**[b]	Non-significant difference between groups in the occurrence of at least 1 adverse event. Most side effects pertained to sedation, others to skin-related problems, respiratory symptoms or headache.
	214 per 1000	**238 per 1000** (107 to 524)				
Secondary outcome 1. **Mean change in physician-assessed clinical signs** Total sum of 4 symptoms (signs) scores, each measured on 4-point Likert scale (0 = absent; 3 = severe) Follow-up: 4 weeks	See comment	See comment	-	84 (1 study)	⊕⊕⊖⊖ **low**[c]	It was reported that the total symptom/signs score decreased in both groups but there was no significant difference between groups.

***Secondary outcome 2.* Mean change in quality of life**	See comment	See comment	-	-	-	No study addressed this outcome.
***Secondary outcome 3.* Number of eczema flares, measured by, for example, 'escalation of treatment' or 'use of topical anti-inflammatory medications'** Follow-up: 4 weeks	See comment	See comment	-	84 (1 study)	⊕⊕⊖⊖ **low**[c]	No difference in amount of local rescue therapy (emollient or 1% hydrocortisone) nor in the number of applications was observed among groups.

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; CRF: case report form; RR: risk ratio.

GRADE Working Group grades of evidence.
High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.

[a]Downgraded by two levels: one level due to limitations in study design (all domains judged as having unclear or high risk of bias) and irreproducible reporting of outcomes (legend states that lower values indicate less pruritus but pruritus increased in all groups from baseline to last visit; study author was contacted to clarify this issue but did not respond); and one level due to imprecision (small sample size).
[b]Downgraded by two levels: one level due to limitations in study design (all domains judged as having unclear or high risk of bias); and one level due to serious imprecision (wide CI due to small sample size).
[c]Downgraded by two levels: one for limitations in design (all domains judged as having unclear or high risk of bias), and one level due to serious imprecision (wide CI due to small sample size).

Summary of findings 3. Fexofenadine 120 mg/d versus placebo (1-week intervention)

Fexofenadine 120 mg/d compared with placebo for eczema

Patient or population: adults with eczema

Settings: secondary

Intervention: fexofenadine 120 mg/d

Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Fexofenadine 120 mg/d				
Primary outcome 1. **Mean change in patient-assessed symptoms** This outcome was measured as the mean change in patient-assessed pruritus (range 0 to 8) between baseline and the night of day 6 Follow-up: 1 week	Mean change was -0.5	**Mean change was 0.25 lower** (0.43 lower to 0.07 lower)	-	400 (1 study)	⊕⊕⊕⊖ **moderate**[a]	A significantly larger reduction was observed in the fexofenadine group compared to the placebo group. However, the effect observed appeared to be small.
Primary outcome 2. **Proportion of participants reporting adverse effects and serious adverse events throughout the study period** Follow-up: 1 week	Study population		**RR 1.05** (0.74 to 1.50)	411 (1 study)	⊕⊕⊕⊖ **moderate**[a]	No significant difference between groups. The most frequent adverse events referred to somnolence and headache.
	221 per 1000	**232 per 1000** (164 to 332)				
Secondary outcome 1. **Mean change in physician-assessed clinical signs** This outcome was assessed as investigator-assessed change in the ratio of pruritus area to body surface area Follow-up: 1 week	See comment	See comment	-	Number of participants not reported (1 study)	⊕⊕⊕⊖ **moderate**[a]	It was stated that in terms of investigator-assessed change in the ratio of pruritus area to body surface area, significantly more patients in the fexofenadine group than in the placebo group experienced a reduction in pruritus (P = 0.007). No further numerical data were provided.
Secondary outcome 2. **Mean change in quality of life**	See comment	See comment	-	-	-	No study addressed this outcome.
Secondary outcome 3. **Number of eczema flares, measured by, for example, 'escalation of treatment' or 'use of topical anti-inflammatory medications'**	See comment	See comment	-	Number of participants not reported (1 study)	⊕⊕⊕⊖ **moderate**[a]	Study authors reported no significant difference between the 2 groups in the amount of 0.1% hydrocortisone butyrate cream used during the study. No data for analysis could be extracted from this study.

Amount of 0.1% hydrocortisone butyrate cream used during the study Follow-up: 1 week						

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; RR: risk ratio.

GRADE Working Group grades of evidence.
High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.

[a]Downgraded by one level for limitations in design due to insufficient follow-up period (1 week) (indirectness).

Summary of findings 4. Loratadine 10 mg/d versus placebo (4-week intervention)

Loratadine 10 mg/d compared with placebo for eczema

Patient or population: male and female adults aged 15 years and older with eczema

Settings: secondary

Intervention: loratadine 10 mg/d

Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	No additional treatment	Loratadine 10 mg/d				
Primary outcome 1. **Mean change in patient-assessed symptoms** Reduction in pruritus on 100-mm VAS from baseline	Mean reduction was **29.4**	Mean reduction was **2.30 lower** (20.27 lower to 15.67 higher)	-	28 (1 study)	⊕⊕⊙⊙ **low**[a]	The difference was non-significant. However, baseline differences were not adjusted for.

Follow-up: 4 weeks						
Primary outcome 2. **Proportion of participants reporting adverse effects and serious adverse events throughout the study period** Follow-up: 4 weeks	Study population 83 per 1000	**21 per 1000** (1 to 480)	**RR 0.25** (0.01 to 5.76)	28 (1 study)	⊕⊕⊖⊖ **low**[a]	There was only 1 event (folliculitis) in the placebo group and 0 events in the intervention group.
Secondary outcome 1. **Mean change in physician-assessed clinical signs** SCORAD Follow-up: 4 weeks	Mean reduction was **16.9**	Mean reduction was **4.1 lower** (13.22 lower to 5.02 higher)	-	28 (1 study)	⊕⊕⊖⊖ **low**[a]	The difference was non-significant.
Secondary outcome 2. **Mean change in quality of life**	See comment	See comment	-	-	-	No study addressed this outcome.
Secondary outcome 3. **Number of eczema flares, measured by, for example, 'escalation of treatment' or 'use of topical anti-inflammatory medications'** Follow-up: 4 weeks	See comment	See comment	-	-	-	No study addressed this outcome.

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; RR: risk ratio; SCORAD: SCORing Atopic Dermatitis index; VAS: visual analogue scale.

GRADE Working Group grades of evidence.
High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.

[a]Downgraded by two levels: one level for limitations of design due to unclear judgement of all but one domain, which was judged as low (selection bias), and one level due to imprecision (small sample size).

Summary of findings 5. Loratadine 10 mg/d versus placebo (2-week intervention)

Loratadine 10 mg/d compared with placebo for eczema
Patient or population: male and female adults with eczema

Settings: secondary

Intervention: loratadine 10 mg/d

Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Loratadine 10 mg/d				
Primary outcome 1. Mean change in patient-assessed symptoms VAS pruritus 10 cm Follow-up: 2 weeks	Mean reduction was **1.32**	Mean reduction was **0.96 higher** (2.01 higher to 0.09 lower)	-	71 (1 study)	⊕⊕⊝⊝ **low**[a]	The difference in the pruritus sum between day 0 and day 13 did not significantly differ between the 10 mg/d group and the placebo group. However, baseline scores were not equally distributed between groups, and this analysis does not account for baseline differences.
Primary outcome 2. Proportion of participants reporting adverse effects and serious adverse events throughout the study period Follow-up: 2 weeks	See comment	See comment	-	73 (1 study)	-	Study authors reported the occurrence of 16 adverse events in all 4 groups but failed to report them for each group separately.
Secondary outcome 1. Physician-assessed clinical signs Number for whom treatment success was judged as good or very good Follow-up: 2 weeks	**211 per 1000**	**219 more per 1000** (from 2 fewer to 674 more)	**RR 2.04** (0.99 to 4.20)	73 (1 study)	⊕⊕⊝⊝ **low**[a]	Participants in the 10 mg/d group were about twice as likely to be judged to have good or very good treatment success but the difference was not significant.
Secondary outcome 2. Mean change in quality of life	See comment	See comment	-	-	-	No study addressed this outcome.
Secondary outcome 3. Number of eczema flares, measured by, for example, 'escalation of	See comment	See comment	-	-	-	Not assessed

treatment' or 'use of topical anti-inflammatory medications'	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; RR: risk ratio; VAS: visual analogue scale.

GRADE Working Group grades of evidence.
High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.

[a]Downgraded by two levels from high to low due to unclear judgement in most domains and serious imprecision (wide CI due to small sample size).

BACKGROUND

Description of the condition

For unfamiliar terms, see the Glossary of Terms provided in Table 1.

Definition

Eczema is a chronic, inflammatory, non-infectious skin disease. It is among the most common skin diseases, which, although predominantly affecting children, may also persist into adulthood (Thomas 2008). The main sites of eczema migrate from infancy to childhood. The final typical location is in the folds of the elbows, in the hollows of the knees, and frequently also in the neck during adolescence and adulthood (Archer 2000; Thomas 2008).

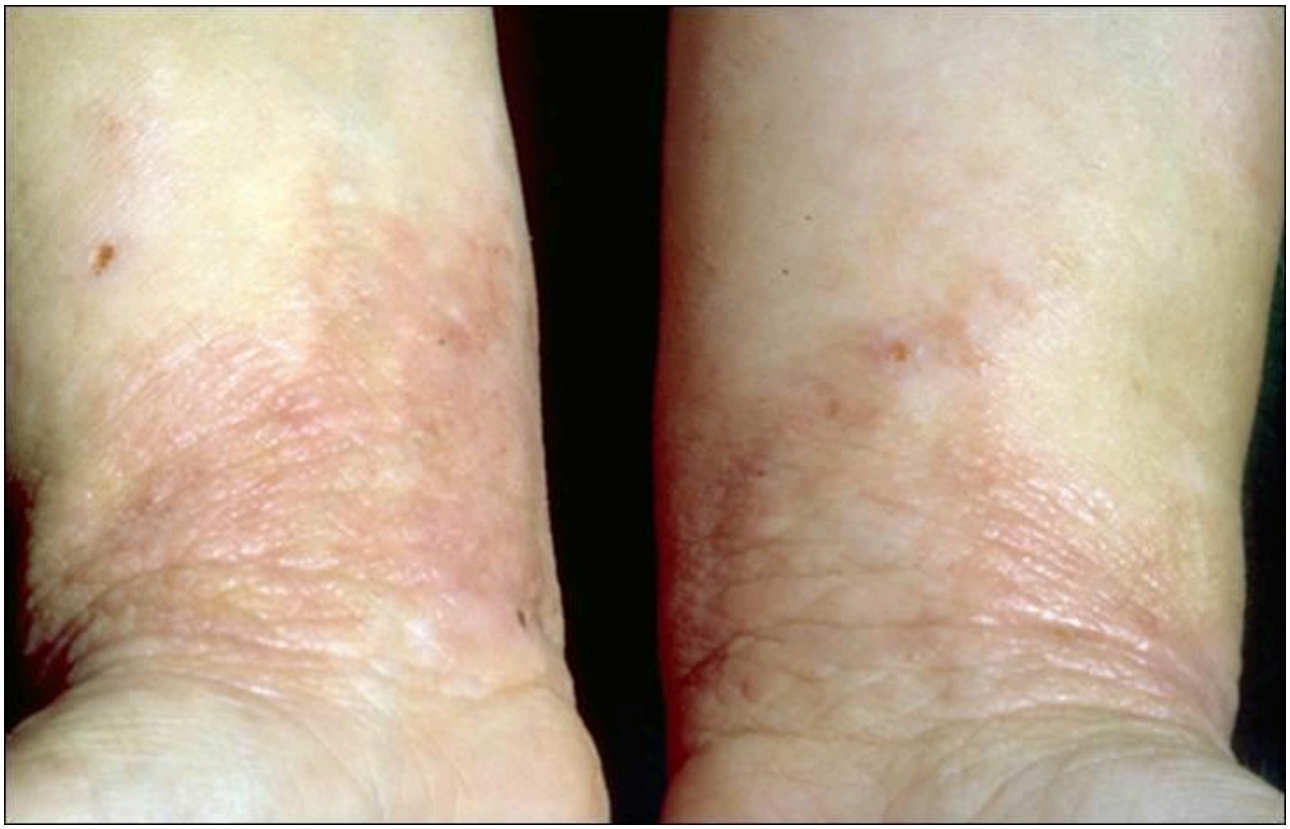
Eczema often occurs in families with atopic diseases including asthma, allergic rhinitis/hay fever (and food allergy), and atopic eczema. These diseases share a common pathogenesis and are frequently present together in the same individual and family. The word 'atopy' refers to the genetic tendency to produce immunoglobulin E (IgE) antibodies in response to small quantities of common environmental proteins such as pollen, house dust mites, and food allergens (Stone 2002; Thomsen 2015). Around 30% of people with eczema develop asthma, and 35% develop allergic rhinitis (Luoma 1983). However, it is known that atopy does not concurrently occur in all patients with atopic eczema. In view of this, it has been proposed recently that the term 'eczema' should be used to define patients both with and without atopy. In keeping with the 'Revised nomenclature for allergy for global use' (Johansson 2004), and similar to other Cochrane Reviews evaluating eczema therapies (van Zuuren 2017), we will therefore use the term 'eczema' throughout this review.

Clinical features and symptoms

Eczema is characterised by an itchy, red rash, but it may also present with a wide spectrum of clinical signs such as erythema, papules, vesicles, prurigo nodules, crusts, scales, dry skin, and lichenification (Hanifin 1980). Burning, pain, and itch are the most frequent and distressing symptoms. It has been stated that "the diagnosis of eczema cannot be made if there is no history of itch" (Hanifin 1980). People with eczema often feel a strong urge to scratch as a consequence of itching (Darsow 2012). Scratching, together with skin inflammation, frequently produces reddening of the skin. The symptoms of eczema can lead to sleeplessness and fatigue and may have a substantial impact on the quality of life of those affected (Carroll 2005).

Various sets of diagnostic criteria for eczema have been developed and validated, but no consensus about their use has been reached (Brenninkmeijer 2008). The most extensively validated and widely used set of diagnostic criteria has been proposed by a United Kingdom (UK) Working Party (Williams 1994). According to these criteria, an individual must have an itchy skin condition in the last 12 months and must meet three or more of the following criteria: onset in the first two years of life, a history of flexural involvement, a history of generalised dry skin, a history of other atopic disease, or visible flexural dermatitis. An image of the typical lesions found in eczema is shown in Figure 1.

Figure 1. Typical eczema lesions on wrist insides and forearms.



Epidemiology and causes

In many countries, eczema is the most frequently encountered chronic condition during infancy, but there is wide variation in the prevalence of eczema at a global level (Mallol 2013; Odhiambo 2009). Recent data from the International Study of Asthma and Allergies in Childhood (ISAAC Phase 1) have shown that the prevalence of eczema (itchy flexural rash in the past 12 months) ranges from 0.9% to 22.5% in six- and seven-year-old children, and from 0.2% to 24.6% in those aged 13 to 14 years (Odhiambo 2009). The global total prevalence in children aged six to seven years was 7.9%, and in the 13- to 14-year-old age group, 7.3% (ISAAC Phase 3) (Mallol 2013). For adults, recent studies have estimated 12-month prevalence (i.e. the percentage of people who had the condition within the last 12 months) at 14.3% in Vinding 2014, and at 10.2% in Silverberg 2013a, in Denmark and the United States (USA), respectively.

The onset of eczema usually occurs in early childhood, with most manifestations arising before the age of six (Bieber 2008; Nutten 2015; Weidinger 2016). Eczema can persist over long periods of time. However, its course can show a relapsing-remitting pattern including repeated flares (Garmhausen 2013; Illi 2004). Eczema used to be considered mainly a childhood disease (Weidinger 2016), but recent evidence suggests that a considerable proportion of individuals do not encounter remittance (Weidinger 2016). A recent cohort study found persistent eczema in 50% of those given the diagnosis at school age (Mortz 2015), and another large-scale study reported a lifetime prevalence of eczema of 40.7% among adults (Rönmark 2012).

Eczema is a complex disease that is most likely to be caused by gene and environmental interactions (Bieber 2008). In addition to allergic sensitisation and gene polymorphisms, a large number of environmental and lifestyle factors are potentially involved in the aetiology (Weidinger 2016). These include pet exposure, breastfeeding and tobacco smoke (Apfelbacher 2011), climate factors (Silverberg 2013b), and microbial exposure (Flohr 2014).

Biology

It has been thought that an immunological defect in Th2 helper cells may give rise to increased IgE production (Bieber 2008). However, although increased IgE levels are often found in patients with eczema, wide variation has been noted in the presence of allergies to aeroallergens (Flohr 2014).

Moreover, as a result of abnormal lipid metabolism or epidermal protein formation (e.g. caused by filaggrin mutation; Baurecht 2007), the skin barrier in eczema functions poorly, giving rise to dry skin, which is prone to epidermal barrier disruption. Skin inflammation and epidermal barrier disruptions are phenomena that reinforce each other (Weidinger 2016). Furthermore, damage to the epithelial barrier increases immune exposure to environmental allergens, stimulating the formation of IgE (Bieber 2008).

The rate of microbial colonisation of the skin is caused by a number of defects in innate cutaneous immunology, for example, with *Staphylococcus aureus* colonisation in eczema (Ring 2012a). This can lead to disease exacerbations and may require additional antimicrobial treatment (Ring 2012a). The cutaneous innate immune system is a key determinant of the physical, chemical, microbial, and immunological barrier functions of the epidermis (Kuo 2013). The innate cutaneous immunology (as well as the adaptive immunology of the skin) in patients with eczema is thought to be malfunctional (Biedermann 2015), leading to an inadequate host response to a pathogen or a persistent inflammatory state (Kuo 2013).

Psychological factors such as stress can influence the clinical course of eczema and the itch-scratch cycle (Ring 2012b). Other co-factors can have an effect, such as abnormal microbial colonisation leading to skin infection and psychosomatic factors influencing the autonomic nervous system and production of mediators like, for example, neuropeptides and eosinophils (Bieber 2009; Buddenkotte 2010; Ring 2012a; Ring 2012b).

Description of the intervention

The standard approach to treating eczema revolves around the restoration of epidermal barrier function with the use of emollients and moisturisers (Weidinger 2016). Topical corticosteroids are still the favoured therapy for acute flares, but they are also used proactively along with topical calcineurin inhibitors to maintain remission. Non-specific immunosuppressive drugs, such as cyclosporine or azathioprine, are used in severe refractory cases (Weidinger 2016; Werfel 2016). Use of emollients, moisturisers, and topical corticosteroids is often supplemented by add-on therapies such as ultraviolet (UV) therapy or antihistamines, but immunomodulatory systemic drugs such as cyclosporine may be prescribed in severe cases (Werfel 2016; Ring 2012b; Sidbury 2014). Add-on therapy in general is an approach that is used to enhance a therapeutic effect through use of an additional drug.

Oral H1 antihistamines (H1 receptor antagonists) are widely used as a systemic 'add-on' therapy to topical treatments, which include glucocorticosteroids, immunomodulators such as pimecrolimus or tacrolimus, tar preparations, anti-infective topicals, and doxepin (Ring 2012a). Although four distinct types of histamine receptors are recognised (H1 involved in allergic responses, H2 in gastric acid secretion, H3 in neurotransmission, and H4 in immune responses), in human skin, only H1 and H2 receptors have been demonstrated (Greaves 2005). H1 antihistamines (H1 AH) are prescribed especially with the intention of alleviating the itch that accompanies eczema (Greaves 2005; He 2018).

Antihistamines in general are used to counteract the release of histamines. When histamines are released, they bind to specific receptors, and typical reactions (allergic reactions or allergy symptoms) occur (Mann 1989). Histamine induces pruritus, sneezing, increased vascular permeability, and smooth muscle contraction of the respiratory and gastrointestinal tracts (Takahashi 2004). H1 AH, which are not structurally related to histamine, do not antagonise the binding of histamine but bind to different sites on the receptor to produce an effect opposite to the effect that histamines would produce (Church 2013; Simons 2011). Thus, H1 AH are not receptor antagonists but are inverse agonists, in that they produce the opposite effect on the receptor to histamine (Leurs 2002; Simons 2008). As a consequence, the preferred term used to define these drugs is 'H1 antihistamines' rather than 'histamine antagonists' (Church 2013).

According to their chemical structure and properties, H1 AH are usually classified as first- or second-generation H1 AH. First-generation antihistamines may cause sedation and consequently can be useful for treating sleep disturbances due to itching. Second-

generation antihistamines are less sedating, as the molecule is less likely to cross the blood-brain barrier; however, they are not given without the possibility of sedative effects, and some (particularly terfenadine and astemizole, which are no longer in use) may cause irregularities in heart rhythm (cardiac arrhythmia). A category of third-generation antihistamines has been used to describe some of the later antihistamines. This term is not generally agreed upon, as it has been noted that such agents do not differ sufficiently from earlier compounds in terms of desirable and undesirable effects (Greaves 2005; Handley 1998; Holgate 2003; Simons 2004; Yanai 2012).

Agitation, confusion, somnolence, tachycardia, constipation, urinary retention, and adverse cardiac reactions have been reported as adverse effects of antihistamines, particularly of first-generation antihistamines such as chlorpheniramine (Yanai 2012). Because of side effects such as sedation and drowsiness, use of these drugs in the daytime has been limited (Greaves 2005).

The aim of developing second-generation antihistamines, such as astemizole or terfenadine, which are no longer in use, or loratadine, which does not penetrate the blood-brain barrier, was to produce more tolerable agents without sedative side effects but with the same effectiveness as first-generation antihistamines (Kay 2000). Motor and cognitive functions are substantially less impaired with the use of second-generation antihistamines (Herman 2003). However, astemizole and terfenadine have been found to cause ventricular tachycardia, although this occurs rarely (Woosley 1996). Hence, they are no longer in use.

The goal of developing third-generation antihistamines was to use therapeutically active metabolites of established parent drugs to produce agents that are not cardiotoxic (Handley 1998). Fexofenadine, for instance, is the active metabolite of terfenadine.

However, it has been argued that the sedative effects of H1 AH may be beneficial. The Sidbury 2014 review noted that short-term, intermittent use of sedating antihistamines (not stated which class) may help those with disturbed sleep due to itch. Another review concluded that a non-sedating H1 AH (cetirizine) was effective in reducing itch when given at a high sedating dose (Klein 1999). Again, itch reduction was linked to induction of drowsiness.

Current guidelines for the treatment of eczema do not provide recommendations in terms of a dose range for H1 AH nor a minimum duration of treatment (Werfel 2016). However, dosage and scheduling should be based on the drug profile of each individual medication (Sidbury 2014).

How the intervention might work

The pathophysiology of itch (pruritus) in eczema is complex and still is not fully understood (Ständer 2002; Tominaga 2016). Although histamines have been implicated as a mediator of pruritus, many other pruritogens have also been identified (Akiyama 2013). Of these, interleukin-31 (IL-31), thymic stromal lymphopoietin (TSLP), and lysophosphatidic acid (LPA) may underlie pruritus in patients with eczema (Tominaga 2016). Histamine-independent mechanisms triggered by, for example, neuropeptides, proteinases, cytokines, and opioids, are thought to play a role in the pathophysiology of itch in atopic dermatitis (Ständer 2002; Tominaga 2016). Interleukin-31, a cytokine produced by T cells, is currently suggested as the most important pruritogen identified in human and animal models (Tominaga 2016). Neuropeptides, proteinases, and opioids are also thought to play a role in the release of histamine (Tominaga 2016). In summary, pruritus in eczema is most likely a result of peripheral and central mechanisms including pruritogenic mediators and modulators, sensory nerve fibres, and nerve fibre density in skin and spine, and central itch transmission (Tominaga 2016).

Although it is not exactly clear how itch in eczema is mediated, clinical use of H1 AH remains frequent (Herman 2003). Antihistamines used in eczema are histamine 1 (H1) blockers. H1 AH are thought to suppress actions of histamine such as itch, increased vascular permeability of the skin, and local vasodilation (Greaves 2005). All of these responses are features of the acute allergic reaction of the skin (Takahashi 2004), which is characterised by visible wheals and flares. Wheals and flares may itch; thus, it is thought that H1 AH may be able to suppress the cardinal symptom itch, as well as other symptoms in eczema, by blocking H1 AH receptors.

Evidence from animal models suggests that H1 AH may be able to reduce scratch behaviour in mice (Murota 2010). Whether this can be applied to humans needs to be shown. However, evidence is available for psychomotor impairment after oral H1 AH intake (Takahashi 2004). Scratching exacerbates itch, as is commonly expressed by the itch-scratch cycle. It may be hypothesised that H1 AH influence this cycle, but evidence for this remains to be put forward.

Due to sedating properties of at least first-generation H1 AH, as well as the sedating quality of high doses of newer-generation H1 AH (Klein 1999), it is also possible that patients with eczema who have sleep problems as a result of itch may benefit from the induced drowsiness and consequently better sleep quality.

Use of systemic antihistamines as adjuvant therapy together with topical agents such as, for example, topical corticosteroids or topical immune modulators in eczema (Kawashima 2003), is based on the idea that combining the anti-inflammatory effects of topical treatments with blocking action of histamine on its receptors in the skin by H1 AH might magnify or intensify the effect of treatment (Greaves 2005; Kawashima 2003). In other words, it is expected that effects resulting from topical anti-inflammatory treatments are augmented.

Why it is important to do this review

As part of a comprehensive health technology assessment (HTA) of treatments available for eczema, randomised controlled trials (RCTs) investigating the effects of antihistamines in eczema were summarised in a HTA report (Hoare 2000). Authors of this report identified 21 RCTs of any oral antihistamines for treatment of eczema. Of these, studies investigating sedating antihistamines and studies investigating H2 antihistamines (alone or combined with H1 AH) were unable to demonstrate clear benefit of the intervention. Studies investigating less-sedating antihistamines show conflicting results. For instance, one RCT investigated the effects of various doses of cetirizine, demonstrating a possible effect of a very high dose (Hannuksela 1993). Generally, authors of the HTA report stated that study reporting was poor, rendering it difficult to draw firm conclusions. We believe it is important to update the evidence base.

We conducted a systematic search of the literature to inform the guideline of care for management of eczema put forth by the American Academy of Dermatology (AAD) (Sidbury 2014). This guideline concluded that short-term, intermittent use of sedating antihistamines (not stated which class) may bring some benefit for sleeping problems that arise as a consequence of itch. No recommendation was made for non-sedating antihistamines as routine treatment for eczema. Another review concluded that a non-sedating H1 AH (cetirizine) was effective in reducing itch when given at a high sedating dose (Klein 1999). Again itch reduction was linked to induction of drowsiness.

A recent systematic review did not identify any RCT investigating single use of oral H1 AH versus placebo for eczema, so currently no evidence is available to support or refute the effectiveness of H1 AH used alone (Apfelbacher 2013). It appears as though physicians and researchers alike are reluctant to withhold anti-inflammatory topical treatment from patients for ethical reasons on the grounds of established effectiveness. However, in clinical practice, antihistamines are often used as 'add-on' therapy to topical treatment in the management of eczema. It is therefore important to systematically review studies investigating whether adding H1 AH to topical treatment improves eczema over and above the improvement due to topical treatment alone.

As outlined above in the How the intervention might work section, no unanimity has been reached regarding the possible pathways H1 AH may travel in the treatment of eczema. However, irrespective of whether it is known how they work, their frequent use in clinical practice is of paramount importance to at least enable judgement of whether or not patients with eczema benefit from their use (Herman 2003). This is why it is important to systematically review existing studies to ascertain whether or not use of oral H1 AH as add-on therapy is justified.

The proposed outline for this review was published as a protocol 'Oral H1 antihistamines as ‘add-on’ therapy to topical treatment for eczema' (Apfelbacher 2016).

OBJECTIVES

To assess the effects of oral H1 AH as 'add-on' therapy to topical treatment in adults and children with eczema.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs), including cross-over trials, that used oral H1 AH as add-on therapy to topical treatments for eczema.

Types of participants

We included people of all ages with a clinical diagnosis of eczema, identified as 'atopic eczema' or 'eczema', made by a dermatologist or a physician. If the diagnosis was confirmed by a general medical practitioner, this must have involved the use of standardised diagnostic criteria such as the Hanifin and Rajka definitions - Hanifin 1980 - or the UK modification - Williams 1994.

We excluded other forms of eczema, such as those caused by contact allergens or skin irritants, along with mixed forms of eczema.

We also excluded studies that included people with other diagnoses, if investigators did not report separately results for those with a diagnosis of eczema.

Types of interventions

Interventions included oral antihistamines (H1 antagonists) of all classes (sedating, non-sedating) given as add-on therapy to topical treatments for eczema (e.g. topical corticosteroids, topical immunomodulators, other topical eczema therapies, either alone or combined).

Comparators included placebo as add-on therapy to topical treatment, or no additional treatment as add-on therapy to topical treatment.

Types of outcome measures

We did not consider these prespecified outcomes as criteria for study inclusion eligibility (see Section 5.1.2, of the *Cochrane Handbook for Systematic Reviews of Interventions,* version 5.1 (Higgins 2011)). Outcomes included the core outcome set as suggested by the Harmonising Outcome Measures in Eczema (HOME) initiative (Schmitt 2012; Schmitt 2014): clinical signs, symptoms, quality of life, and long-term control of eczema flares.

We considered separately outcomes measured up to one week (short term), at more than one week to six weeks (medium term), and at more than six weeks (long term).

Primary outcomes

- Mean change in patient-assessed symptoms of eczema, as measured by a standardised or validated eczema symptoms score (e.g. visual analogue scale for itching, patient-oriented eczema measure (Charman 2004))
- Proportion of participants reporting adverse effects and serious adverse events throughout the study period

Secondary outcomes

- Mean change in physician-assessed clinical signs, as measured by a standardised or validated eczema signs score (e.g. Eczema Area and Severity Index (Hanifin 2001), SCORing Atopic Dermatitis index (SCORAD) (ETFAD 1993))
- Mean change in quality of life, as measured by a standardised or validated quality of life measure (e.g. Dermatology Life Quality Index - DLQI (Finlay 1994))
- Number of eczema flares, measured by, for example, ‘escalation of treatment’ or ‘use of topical anti-inflammatory medications’ (Thomas 2015)

Search methods for identification of studies

We aimed to identify all relevant RCTs regardless of language or publication status (published, unpublished, in press, or in progress).

Electronic searches

The Cochrane Skin Information Specialist searched the following databases up to 9 May 2018.

- Cochrane Skin Group Specialised Register via the search strategy presented in Appendix 1.
- Cochrane Central Register of Controlled Trials (CENTRAL; 2018, Issue 4), in the Cochrane Library, via the strategy presented in Appendix 2.
- MEDLINE via Ovid (from 1946) via the strategy presented in Appendix 3.
- Embase via Ovid (from 1974) via the strategy provided in Appendix 4.
- The Global Resource of EczemA Trials - Centre of Evidence Based Dermatology (accessed at http://www.greatdatabase.org.uk, on 9 May 2018, browsed to results for 'antihistamines and mast cell stabilisers').

Trials registers

Two review authors (UM, CA) searched the following databases using the terms 'eczema, atopic eczema, atopic dermatitis' on 10 May 2018.

- International Standard Randomized Controlled Trials Number (ISRCTN) registry (www.isrctn.com).
- ClinicalTrials.gov (www.clinicaltrials.gov).
- Australian New Zealand Clinical Trials Registry (www.anzctr.org.au).
- World Health Organization International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch/AdvSearch.aspx).
- EU Clinical Trials Register (www.clinicaltrialsregister.eu/).

Searching other resources

Reference lists

Two review authors (UM, CA) examined the bibliographies of included and excluded studies for further references to potentially eligible RCTs.

Adverse effects

We did not perform a separate search for adverse effects of the target intervention. However, we examined data on adverse effects from the included studies that we identified.

Conference proceedings

One review author (UM) scanned abstracts from the International Research Workshops on Eczema (George Rajka International Symposia on Atopic Dermatitis (ISAD)) from 2000 to 2018, and conference proceedings of the European Academy of Dermatology and Venereology (EADV) from 2000 to 2017, the European Academy of Allergy and Clinical Immunology (EAACI) from 2000 to 2017, and the American Academy of Dermatology (AAD) from 2012 to 2017, to identify further potentially relevant RCTs. We conducted this search on 30 May 2018.

Correspondence

We contacted trial investigators and requested that they provide missing data or clarify study details.

Data collection and analysis

Some portions of the Methods section of this review use text that was originally published in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), as well as text that was originally published in other Cochrane protocols co-authored by review authors BC and Esther J van Zuuren and Zbys Fedorowicz (predominantly van Zuuren 2013).

Selection of studies

Two review authors (UM, CA) determined trial eligibility and resolved disagreements by discussion.

Two review authors (UM, CA) independently assessed titles and abstracts of trials identified during literature searches. We obtained full-text copies of studies appearing to meet the inclusion criteria, and of studies with insufficient detail to allow a clear decision based on title and abstract review. Three review authors (UM, CA, MB) independently reviewed the full-text papers and resolved disagreements over eligibility through discussion, consensus, or consultation with a third review author (UM, CA, MB). Hsin-Wen Wu, Toshiya Ebata, Masaki Futamura, Anneke Steens, Michal Gina, Ángela Merchán, and Stanislav Iakhno assessed studies that were published in a language that was not English or German.

We have presented details of studies excluded after assessment of full-text copies along with reasons for their exclusion in the Characteristics of excluded studies table.

Data extraction and management

Three review authors (UM, CA, MB) extracted data using a previously developed and piloted data extraction form. We resolved disagreements on data extraction by consensus. Toshiya Ebata, Masaki Futamura, and Ángela Merchán extracted data from studies that were published in a language that was not English or German. Two review authors (UM, CA) checked and entered the data into RevMan 5.3 (Review Manager (RevMan), including into the Characteristics of included studies tables. We contacted trial investigators and asked them to provide missing data or to clarify study details when necessary.

Assessment of risk of bias in included studies

We assessed the risk of bias of included studies according to the guidelines provided in Chapter 8, of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Two review authors (UM, CA) independently assessed included studies using a simple contingency form and in accordance with the domain-based evaluation method (Higgins 2011). In a further step, we compared the results of these evaluations. When we detected inconsistencies, we discussed and resolved these within the whole review author group.

We assessed the following domains as having low, unclear, or high risk of bias.

- (Random) sequence generation (selection bias).
- Allocation concealment (selection bias).
- Blinding of participants and personnel (performance bias).
- Blinding of outcome assessment (detection bias).
- Incomplete outcome data (attrition bias). We considered dropouts/withdrawals < 20% for short- and medium-term studies, and < 30% for long-term studies, as adequate. We also took into account reasons for dropouts and withdrawals.
- Selective outcome reporting (reporting bias).
- Other bias (including potential conflicts of interest and pharmaceutical funding).

We have reported assessments for each trial in the Characteristics of included studies tables and in associated 'Risk of bias' tables.

Two review authors (UM, CA) also categorised and reported the overall risk of bias of each of the included studies according to the following criteria.

- Low risk of bias (plausible bias unlikely to seriously alter the results) if all criteria were met.
- Unclear risk of bias (plausible bias that raises some doubts about the results) if one or more criteria were assessed as unclear.
- High risk of bias (plausible bias that seriously weakens confidence in the results) if risk of bias was rated as high for any one of the six domains.

We reported these assessments in the risk of bias tables in the Characteristics of included studies section of this review.

Measures of treatment effect

We have presented dichotomous outcomes data as risk ratios (RRs) with associated 95% confidence intervals (CIs). We used any outcomes that were statistically significant ($P < 0.05$) to calculate the number needed to treat for an additional beneficial outcome (NNTB) or the number needed to treat for an additional harmful outcome (NNTH).

We presented continuous outcomes as mean differences (MDs) with 95% CIs. If different instruments were used to measure an outcome, we calculated standardised mean differences (SMDs).

Unit of analysis issues

Cross-over trials

Unit of analysis issues can arise in studies that have randomised participants to multiple treatments in multiple periods, or in studies that reported an inadequate washout period between interventions. We planned to analyse these data based on advice provided in Section 16.4.4, of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We also assessed carry-over and period effects descriptively. However, all cross-over trials included in this review did not adequately report data to allow such analyses; therefore, we reported these results narratively.

Studies with multiple treatment groups

For studies with multiple treatment groups, which may have provided participant data that contributed to multiple comparisons, we assessed which comparisons were clinically meaningful. If multiple pair-wise comparisons were identified, we followed Section 16.5.4, of the *Cochrane Handbook for Systematic Reviews of Interventions,* and created a 'shared' group (Higgins 2011).

Dealing with missing data

For studies less than 10 years old, we contacted study investigators or sponsors when we encountered missing data. We inspected missing data for evidence against the assumption that data are missing completely at random (Higgins 2011). If we made this assumption, we planned to re-analyse the data when possible using an intention-to-treat (ITT) principle (Section 16.1, of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011)).

When analysing dichotomous outcomes, we examined the imbalance in dropout rates between study arms to identify attrition bias (Section 16.1, of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011)), and we used per-protocol data.

When analysing continuous outcomes, we conducted a per-protocol analysis instead of using the ITT population.

Assessment of heterogeneity

We planned to consider the clinical diversity of studies, as well as their statistical heterogeneity, by examining the I^2 summary statistic. We would pool studies if the I^2 statistic was less than 60%, but we would not pool them if I^2 was greater than 80%. When I^2 was between 60% and 80% and could be explained by a clinical and coherent argument, we may have pooled studies into a meta-analysis. However, due to clinical diversity in terms of duration of the intervention, H1 AH used, varying doses applied in the trial, variation in concomitant topical treatments allowed, and outcome assessment, studies were not comparable, and we could not pool any of the studies identified for inclusion in this review.

Assessment of reporting biases

We planned to assess reporting bias by following the recommendations for funnel plot asymmetry (Egger 1997), as described in Section 10.4.3.1, of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We planned to create these plots for outcomes if we had pooled at least 10 studies. If we noted asymmetry, we planned to explore possible sources by performing sensitivity analyses. However, because we had undertaken no pooling, we could not generate plots.

Data synthesis

Three review authors (CA, MB, BC) analysed the data in RevMan and reported results in accordance with advice provided in Chapter 9, of the *Cochrane Handbook for Systematic Reviews of Interventions* (Review Manager (RevMan); Higgins 2011). If we found an adequate number of studies ($n > 2$) that were clinically homogeneous, we would enter them into a meta-analysis (Treadwell 2006). For dichotomous data, we planned to apply a Mantel-Haenszel analysis method using a random-effects model to calculate the effect estimate. For continuous data, we used an inverse variance analysis method with a random-effects model. However, due to the aforementioned clinical diversity, studies included in this review were not comparable, and we were not able to pool any of the studies identified.

When results for individual studies were estimated with low numbers of outcomes (< 10 in total), or when the total sample size was less than 30 participants and a risk ratio was used, we also reported the proportion of outcomes in each group together with a P value from Fisher's exact test.

Subgroup analysis and investigation of heterogeneity

We planned to carry out the following subgroup analyses if we identified moderate to substantial heterogeneity (as defined above).

- Atopic versus non-atopic participants (i.e. sensitised showing elevated levels of IgE antibodies to inhalant allergens).
- Concomitant hay fever versus no concomitant hay fever.
- Children versus adults.
- Sedating versus non-sedating antihistamines.

However, as no pooling was undertaken, we could not carry out any subgroup analyses.

Sensitivity analysis

We planned to conduct sensitivity analyses to assess the robustness of review results by examining the following.

- If we found enough studies with low risk of bias (n > 2), we would enter these into an additional meta-analysis.
- We would look separately at studies that were prospectively registered in clinical trials registers.

However, as no pooling occurred, we conducted no sensitivity analyses.

'Summary of findings' table

We included five 'Summary of findings' (SoF) tables in this review to summarise the most important comparisons.

- Cetirizine 0.5 mg/kg/d versus placebo.
- Cetirizine 10 mg/d versus placebo.
- Fexofenadine 120 mg/d versus placebo.
- Loratadine 10 mg/d versus placebo.
- Loratadine 10 mg/d versus placebo.

We included the following outcomes in the SoF tables.

- Mean change in eczema symptoms score (reported for "pruritus", as this was the only patient-oriented measure assessed in these studies).
- Proportion of participants reporting adverse events and proportion reporting serious adverse events.
- Mean change in eczema clinical signs score.
- Mean change in quality of life.
- Number of eczema flares.

The rationale for selection of studies reported in the SoF tables (main comparisons) was based first on clinical relevance/opinion, then on the standard dose of treatment, then on the duration of follow-up (favouring longer-term follow-up over short-term follow-up) and the number of participants included, and then finally, on overall risk of bias and quality of evidence. Altogether, the decision was based on a combination of the aforementioned items, and trade-offs had to be made.

We assessed the quality of the body of evidence using the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias), according to Section 12.2.1, of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), and we reported the quality of evidence for each outcome in the SoF tables and descriptively in the Effects of interventions section for non-key comparisons. The quality of evidence could be rated as high, moderate, low, or very low.

RESULTS

Description of studies

See Characteristics of included studies and Characteristics of excluded studies.

Results of the search

Electronic searches up to 10 May 2018 retrieved 658 records in total, and 656 after removal of duplicates. Screening of abstracts (up to 2018) from the International Research Workshops on Eczema (George Rajka International Symposia on Atopic Dermatitis (ISAD)) and of conference proceedings of the European Academy of Dermatology and Venereology (EADV) from 2000 to 2017, the European Academy of Allergy and Clinical Immunology (EAACI) from 2010 to 2017, and the American Academy of Dermatology (AAD) from 2012 to 2017 revealed no additional eligible studies.

Searches of trials registers revealed eight ongoing trials that matched our inclusion criteria. We have described ongoing trials identified through this search in the Characteristics of ongoing studies section. We will include these in future updates if study results become available. Among these eight, we found two completed studies from this search that met the inclusion criteria (Cambazard 2001; Jung 1989), but they had not been published. However, we were able to obtain the unpublished study reports, and we have included them. We found one study in a trials register - NCT00160563 - but the register stated that it had been terminated. We contacted study authors but have not heard from them yet. We placed this study in the studies awaiting classification section (Characteristics of studies awaiting classification).

Two review authors (UM, CA) examined the bibliographies of included and excluded (other than in protocol) studies for further references to potentially eligible RCTs. This search yielded two additional trials for further assessment (Schmoeckel 1992; Simons 2003).

After removal of duplicates, we found that we had obtained a total of 666 records via searches of all our sources.

We excluded 577 records based on review of titles and abstracts. We obtained full texts of the remaining 89 records. Two native speakers with a scientific background independently assessed references that had not been published in English or German. They documented study findings in English on the standardised eligibility form that we had used throughout the eligibility screening process. Those studies were reported as Chinese (e.g. Liu 2008), Dutch (e.g. DeBeule 1974a), Japanese (e.g. Ohtani 2004), Polish (e.g. Bogdaszewska 1968), Russian (e.g. Balabolkin 1983), and Spanish publications (e.g. Leon 1989). At least two members of the review author group (CA, UM) assessed all studies published in English or German for eligibility.

Based on assessment of full texts, we excluded 42 studies (see Characteristics of excluded studies), moved five to the ongoing trials section (see Characteristics of ongoing studies), and moved six to studies awaiting classification (see Characteristics of studies awaiting classification), leaving 36 references reporting on 25 included studies (see Characteristics of included studies).

For further details of our screening process, see the study flow diagram provided in Figure 2.

Figure 2. Study flow diagram.

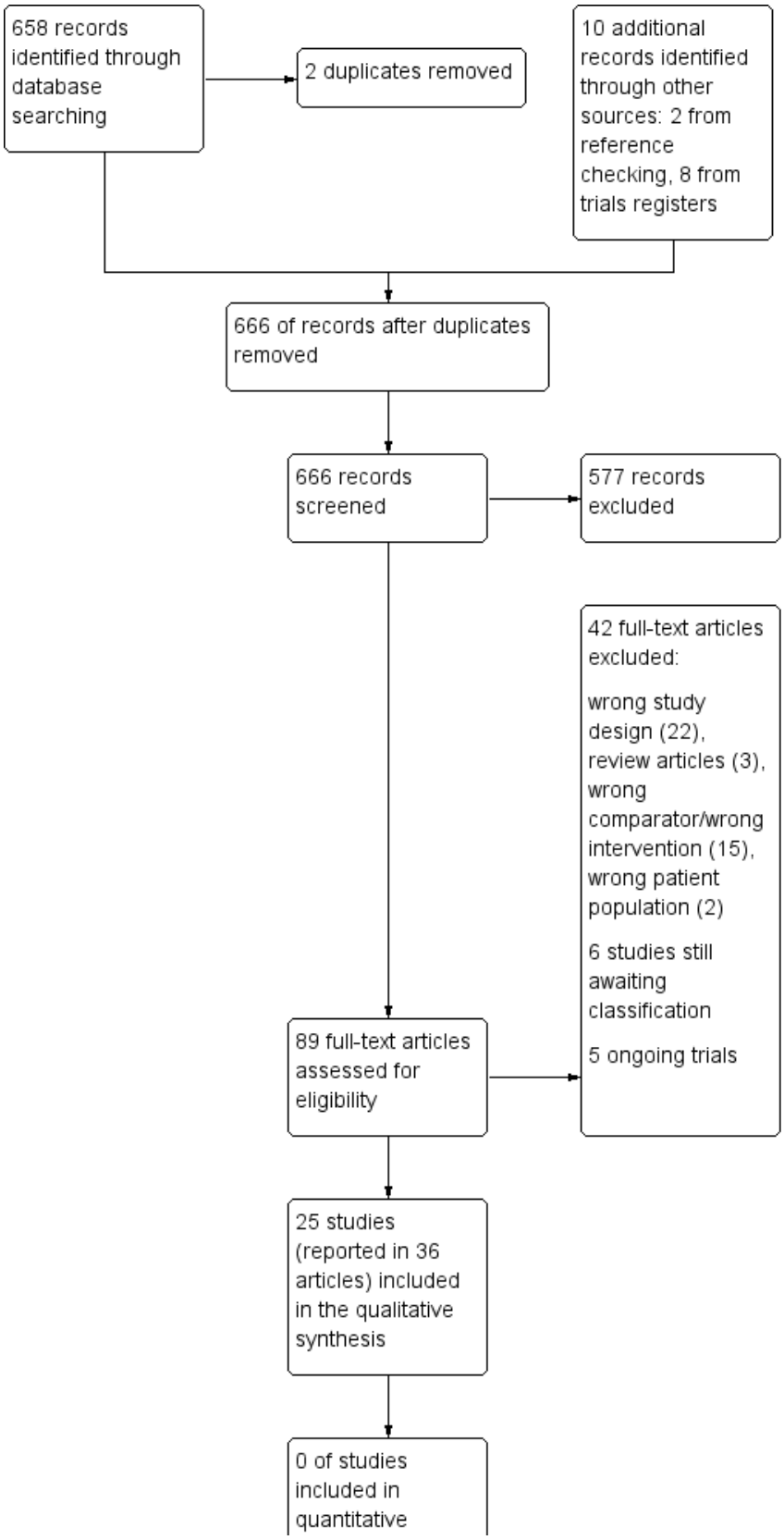
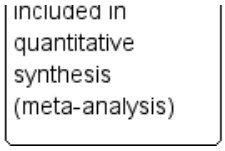


Figure 2. (Continued)



Included studies

Thirty-six references referred to a total of 25 studies, which met the criteria for inclusion of studies in this review.

We have presented in Table 2 a summary of the specific H1 AH investigated in the included studies.

Design

All included studies were randomised controlled trials (RCTs). None used a quasi-randomised design. Of the 25 included studies, 19 used a parallel design (Cambazard 2001; Diepgen 2002; Doherty 1989; Falk 1993; Hannuksela 1993; Henz 1998; Iikura 1992; Jung 1989; Kawashima 2003; Kimura 2009; Kircik 2013; Kuniyuki 2009; LaRosa 1994; Leon 1989; Monroe 1992; Munday 2002; Ruzicka 1998; Simons 2007; Tharp 1998). Five were cross-over studies (Berth Jones 1989; Frosch 1984; Hjorth 1988; Langeland 1994; Savin 1986), and one was a single-patient RCT using a cross-over design (Nuovo 1992). All studies apart from three provided one comparison of an H1 AH versus placebo. Doherty 1989 compared terfenadine and acrivastine each with placebo. Henz 1998 compared cetirizine and azelastine each with placebo. Monroe 1992 compared loratadine with placebo and hydroxyzine with placebo.

Twelve of the included studies were conducted as a part of multi-centre trials (Cambazard 2001; Diepgen 2002; Hannuksela 1993; Henz 1998; Iikura 1992; Jung 1989; Kawashima 2003; Kuniyuki 2009; Munday 2002; Ruzicka 1998; Simons 2007; Tharp 1998). The remainder (n = 13) were single-centre trials (Berth Jones 1989; Doherty 1989; Falk 1993; Frosch 1984; Hjorth 1988; Kimura 2009: Kircik 2013; Langeland 1994; LaRosa 1994; Leon 1989; Monroe 1992; Nuovo 1992; Savin 1986).

Participants and sample sizes

We included 25 studies with a total of 3285 randomly assigned participants. We have provided a detailed summary of all included studies in the Characteristics of included studies tables. The number of participants ranged from one to 795. Studied samples were usually small. Only four studies investigated the effects of H1 AH in a sizable sample (n ≥ 200) (Cambazard 2001; Diepgen 2002; Kawashima 2003; Simons 2007). Ten trials investigated participants in samples ranging from 50 to 199 (Falk 1993; Hannuksela 1993; Henz 1998; Iikura 1992; Jung 1989; Kuniyuki 2009; Monroe 1992; Munday 2002; Ruzicka 1998; Tharp 1998), and 10 studies included fewer than 50 participants (Berth Jones 1989; Doherty 1989; Frosch 1984; Hjorth 1988; Kimura 2009; Kircik 2013; Langeland 1994; LaRosa 1994; Leon 1989; Savin 1986). As mentioned, only Nuovo 1992 was a single-patient RCT.

Eight studies (participants = 1941) investigated samples of children (aged 0 to 12 years) or adolescents (aged 12 to 18 years), or both (Cambazard 2001; Diepgen 2002; Iikura 1992; Jung 1989; LaRosa 1994; Leon 1989; Munday 2002; Simons 2007). Seventeen studies (participants = 1325) were conducted with adults (Berth Jones 1989; Doherty 1989; Falk 1993; Frosch 1984; Hannuksela 1993; Henz 1998; Hjorth 1988; Kawashima 2003; Kimura 2009; Kircik 2013; Kuniyuki 2009; Langeland 1994; Monroe 1992; Nuovo 1992; Ruzicka 1998; Savin 1986; Tharp 1998).

Most studies failed to report on the severity of eczema (Berth Jones 1989; Cambazard 2001; Doherty 1989; Falk 1993; Frosch 1984; Henz 1998; Hjorth 1988; Jung 1989; Kawashima 2003; Kimura 2009; Kircik 2013; Kuniyuki 2009; LaRosa 1994; Leon 1989; Munday 2002; Nuovo 1992; Ruzicka 1998; Simons 2007; Tharp 1998). Two studies included individuals with at least moderate eczema (Monroe 1992; Savin 1986), two with moderate to severe eczema (Hannuksela 1993; Langeland 1994), one with moderate eczema (Iikura 1992), and one with mild to moderate eczema (Diepgen 2002).

Setting

All included studies were conducted in secondary care settings, including hospital clinics, research clinics, dermatology centres, and surgery centres. None were carried out in primary care settings. A vast majority of studies were carried out in Europe and North America (Berth Jones 1989; Cambazard 2001; Diepgen 2002; Doherty 1989; Falk 1993; Frosch 1984; Hannuksela 1993; Henz 1998; Hjorth 1988; Jung 1989; Kircik 2013; Langeland 1994; LaRosa 1994; Monroe 1992; Munday 2002; Nuovo 1992; Ruzicka 1998; Savin 1986; Tharp 1998); three were conducted in Japan (Kawashima 2003; Kimura 2009; Kuniyuki 2009), one in Japan and Brazil (Iikura 1992), and one in Mexico (Leon 1989). Simons 2007 was conducted in 10 European countries, Australia, and South Africa.

Seven studies were published up until 1990 (Berth Jones 1989; Doherty 1989; Frosch 1984; Hjorth 1988; Jung 1989; Leon 1989; Savin 1986), 10 between 1991 and 2000 (Falk 1993; Hannuksela 1993; Henz 1998; Iikura 1992; Langeland 1994; LaRosa 1994; Monroe 1992; Nuovo 1992; Ruzicka 1998; Tharp 1998), and eight between 2001 and 2017 (Cambazard 2001; Diepgen 2002; Kawashima 2003; Kimura 2009; Kircik 2013; Kuniyuki 2009; Munday 2002; Simons 2007).

Interventions

In our analyses (trials yielding outcome data for analysis or for a narrative description), we included the following H1 AH.

- First-generation H1 AH.
  - Chlorpheniramine (Frosch 1984; Nuovo 1992).
  - Chlorpheniramine maleate (Munday 2002).
  - Hydroxyzine (Monroe 1992).
  - Ketotifen (Falk 1993; Iikura 1992; Leon 1989).

- Second-generation or newer H1 AH, or both.
  * Acrivastine (Doherty 1989).
  * Azelastine (no longer in use) (Henz 1998).
  * Cetirizine (Cambazard 2001; Diepgen 2002; Hannuksela 1993; Henz 1998; Jung 1989; LaRosa 1994; Tharp 1998).
  * Levocetirizine (Kircik 2013; Simons 2007).
  * Fexofenadine (Kawashima 2003).
  * Loratadine (Kimura 2009; Langeland 1994; Monroe 1992; Ruzicka 1998).
  * Olapatadine (Kuniyuki 2009).
  * Tazifylline LN2974 (Savin 1986).
  * Terfenadine (no longer in use) (Berth Jones 1989; Doherty 1989; Hjorth 1988; Nuovo 1992).

The duration of the intervention and the respective dosages are shown in Table 2. An oral H1 AH had to be used as an add-on therapy to topical treatment with, for example, topical corticosteroids, topical immunomodulators or other topical eczema therapy, or both. Use of emollients or moisturisers was also considered a topical treatment. Table 2 provides the topical treatments used in each included study.

Twenty-four of the 25 included studies compared the respective H1 AH versus placebo, and in one study, no additional treatment was the comparator (Kuniyuki 2009).

Duration of the interventions

Table 2 shows the duration of treatment for each included study. The minimum duration was three days (Savin 1986); the maximum duration was 18 months (Diepgen 2002).

Trials were categorised according to how long participants received the intervention.

The duration of the oral application of H1 AH was short term (up to one week) in five studies (Berth Jones 1989; Jung 1989; Kawashima 2003; Monroe 1992; Savin 1986), medium term (from one to six weeks) in 11 studies (Doherty 1989; Frosch 1984; Hannuksela 1993; Henz 1998; Hjorth 1988; Kimura 2009; Kircik 2013; Langeland 1994; Munday 2002; Nuovo 1992; Ruzicka 1998), and long term (over more than six weeks) in nine studies (Cambazard 2001; Diepgen 2002; Falk 1993; Iikura 1992; Kuniyuki 2009; LaRosa 1994; Leon 1989; Simons 2007; Tharp 1998).

Outcomes

We had stated that we would consider separately outcomes measured up to one week (short term), from one to six weeks (medium term), and over more than six weeks (long term). As no pooling was conducted, all reported outcomes were described individually for each intervention. Table 3 summarises the outcomes from included studies considered in this review.

Primary outcome 1. Mean change in patient-assessed symptoms of eczema, as measured by a standardised or validated eczema symptoms score (e.g. visual analogue scale for itching, patient-oriented eczema measure (Charman 2004))

With regard to our prespecified primary outcome, 23 studies reported a measure of pruritus (Berth Jones 1989; Cambazard 2001; Diepgen 2002; Doherty 1989; Falk 1993; Frosch 1984; Hannuksela 1993; Henz 1998; Hjorth 1988; Jung 1989; Kawashima 2003; Kimura 2009; Kircik 2013; Kuniyuki 2009; Langeland 1994; LaRosa 1994; Leon 1989; Monroe 1992; Munday 2002; Nuovo 1992; Ruzicka 1998; Savin 1986; Tharp 1998). Nine studies assessed pruritus by VAS (Berth Jones 1989; Doherty 1989; Frosch 1984; Kimura 2009; Kircik 2013; Kuniyuki 2009; Langeland 1994; Ruzicka 1998; Savin 1986). Three studies assessed pruritus as part of the SCORAD assessment (Cambazard 2001; Diepgen 2002; Hannuksela 1993). Four studies used a 4-point Likert scale for assessment of pruritus (Jung 1989; Henz 1998; Leon 1989; Munday 2002). A 7-point Likert scale was used by Nuovo 1992. Kawashima 2003 assessed pruritus on a scale from 0 to 8. Falk 1993 used a Likert scale but the scaling was unclear. A percentage score of pruritus was used by Monroe 1992. Three further studies assessed pruritus but failed to provide details on its assessment (Hjorth 1988; LaRosa 1994; Tharp 1998). Two of the included studies did not assess pruritus (Iikura 1992; Simons 2007).

Primary outcome 2. Proportion of participants reporting adverse effects and serious adverse events throughout the study period

Eighteen of the included studies assessed the occurrence of adverse events (Berth Jones 1989; Cambazard 2001; Diepgen 2002; Frosch 1984; Hannuksela 1993; Iikura 1992; Jung 1989; Kawashima 2003; Kimura 2009; Kircik 2013; Kuniyuki 2009; Langeland 1994; LaRosa 1994; Munday 2002; Nuovo 1992; Ruzicka 1998; Simons 2007; Tharp 1998). Five studies did not assess this outcome (Doherty 1989; Falk 1993; Hjorth 1988; Leon 1989; Savin 1986). Two studies assessed adverse events but failed to report them separately for patients with eczema (Henz 1998; Monroe 1992).

Secondary outcome 1. Mean change in physician-assessed clinical signs, as measured by a standardised or validated eczema signs score (e.g. Eczema Area and Severity Index (Hanifin 2001), SCORing Atopic Dermatitis index (SCORAD) (ETFAD 1993))

Four studies assessed this outcome by SCORAD (Cambazard 2001; Diepgen 2002; Kimura 2009; Kuniyuki 2009). Thirteen studies assessed this outcome by various assessments (Berth Jones 1989; Doherty 1989; Falk 1993; Frosch 1984; Hannuksela 1993; Henz 1998; Iikura 1992; Jung 1989; Kawashima 2003; LaRosa 1994; Munday 2002; Ruzicka 1998; Tharp 1998) (see Table 3 for details).

Eight studies did not employ a measure of physician-assessed clinical signs (Hjorth 1988; Kircik 2013; Langeland 1994; Leon 1989; Monroe 1992; Nuovo 1992; Savin 1986; Simons 2007).

Secondary outcome 2. Mean change in quality of life, as measured by a standardised or validated quality of life measure (e.g. Dermatology Life Quality Index - DLQI (Finlay 1994))

The protocol for this review stated that we would assess this outcome; however, only one study provided quality of life outcomes of any kind (Kircik 2013), and these were insufficient for statistical analysis.

Secondary outcome 3. Number of eczema flares, measured by, for example, 'escalation of treatment' or 'use of topical anti-inflammatory medications' (Thomas 2015)

Eleven studies assessed this outcome (Cambazard 2001; Diepgen 2002; Frosch 1984; Hannuksela 1993; Kawashima 2003; Kuniyuki 2009; Langeland 1994; LaRosa 1994; Munday 2002; Nuovo 1992; Tharp 1998) (see Table 3 for details).

Declaration of interest and funding

Only one study stated that study authors were free from potential conflicts of interest (Kawashima 2003). None of the other trials provided any information on potential conflicts of

interest. Seven studies declared that they had received funding from a pharmaceutical company (Cambazard 2001; Diepgen 2002; Hannuksela 1993; Jung 1989; Kawashima 2003; Kircik 2013; Simons 2007). One study did not declare its source of funding (Tharp 1998), but because the last author of the publication was an employee of Pfizer Inc., this pharmaceutical company is likely to be the funding body for this study. One study report declared receipt of funding from the National Center for Health Services Research - Office of the Assistant Secretary for Health (OASH) (Nuovo 1992). As many of the reviewed studies were published before reporting of declarations of interests and/or funding became more common, it is difficult to infer whether reviewed studies that did not provide this information were truly free from potential conflicts of interest.

Excluded studies

Eighty-nine studies were still potential candidates for inclusion after screening of titles or abstracts, or both. We excluded 42 studies after assessment of the full text and documented the reasons for their exclusion in the Characteristics of excluded studies table.

We excluded most of these studies on grounds of having the wrong study design (e.g. lack of randomisation). We excluded the remainder for having the wrong comparator (e.g. one H1 AH vs one or several other H1 AH but not vs placebo or no treatment as an 'add-on' therapy) or the wrong patient population (e.g. participants not having received a diagnosis of eczema), or because they were review articles (e.g. articles not reporting a single trial but discussing several trials).

Studies awaiting classification

Several studies are still awaiting classification because they provided limited information and review authors could not discern whether they should be included in or excluded from this review. Whether two studies were randomised remains unclear (Borelli 1969; Chunharas 2002). Three studies were conducted in samples of patients with various diagnoses (eczema was one of them) (DeBeule 1974; Laugier 1978; Simons 2003), and study authors presented results only for the whole sample - not separately by diagnostic group. One trial was registered in 2005 and then was terminated (NCT00160563). However, we do not know whether it was terminated before the study commenced, or whether it was started and then terminated for reasons we would like to establish. We tried to contact the study authors in all cases, requesting additional information, but we have received no responses.

Ongoing studies

We classified five studies as ongoing (CRT EU 23679; CTR EU 23697; CTR EU 29342; CTR EU 39698; UMIN000010519); we will assess them again, once their results have been published.

Risk of bias in included studies

In this review, we assessed each of the included studies for risk of bias (RoB), and we report the judgements for each individual domain in the risk of bias table associated with each study (see Characteristics of included studies). Domains of interest are allocation, blinding, incomplete outcome data, selective outcome reporting, and other sources of bias. Please refer to Figure 3, which shows our judgements about each RoB item expressed as percentages of included studies in each category of risk, and Figure 4, which shows the judgement for each domain by study.

Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

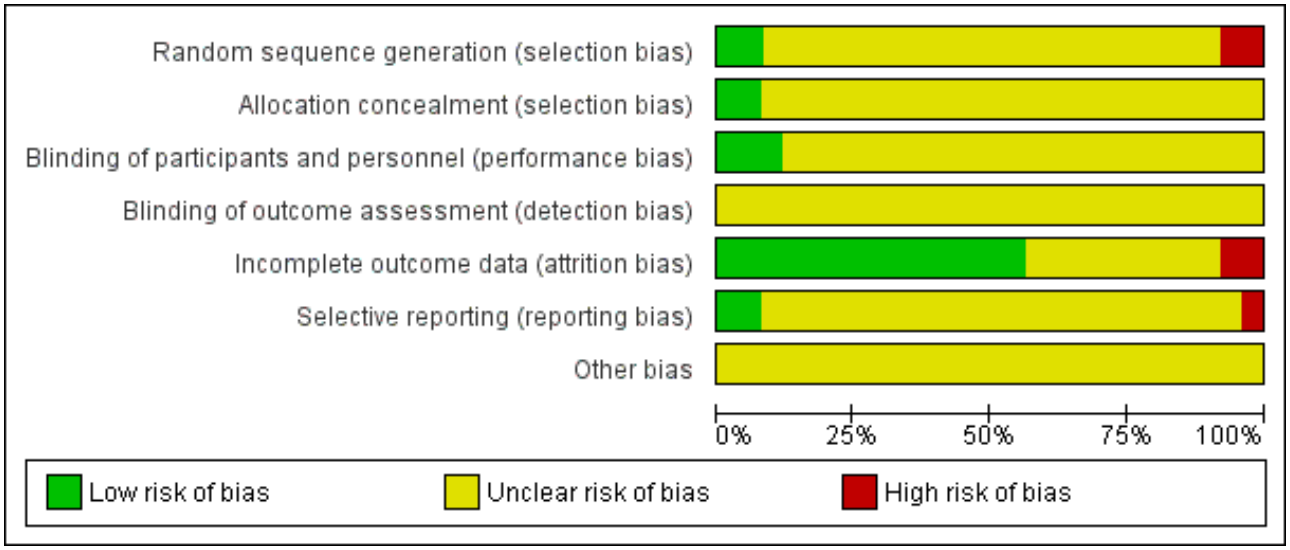


Figure 4. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

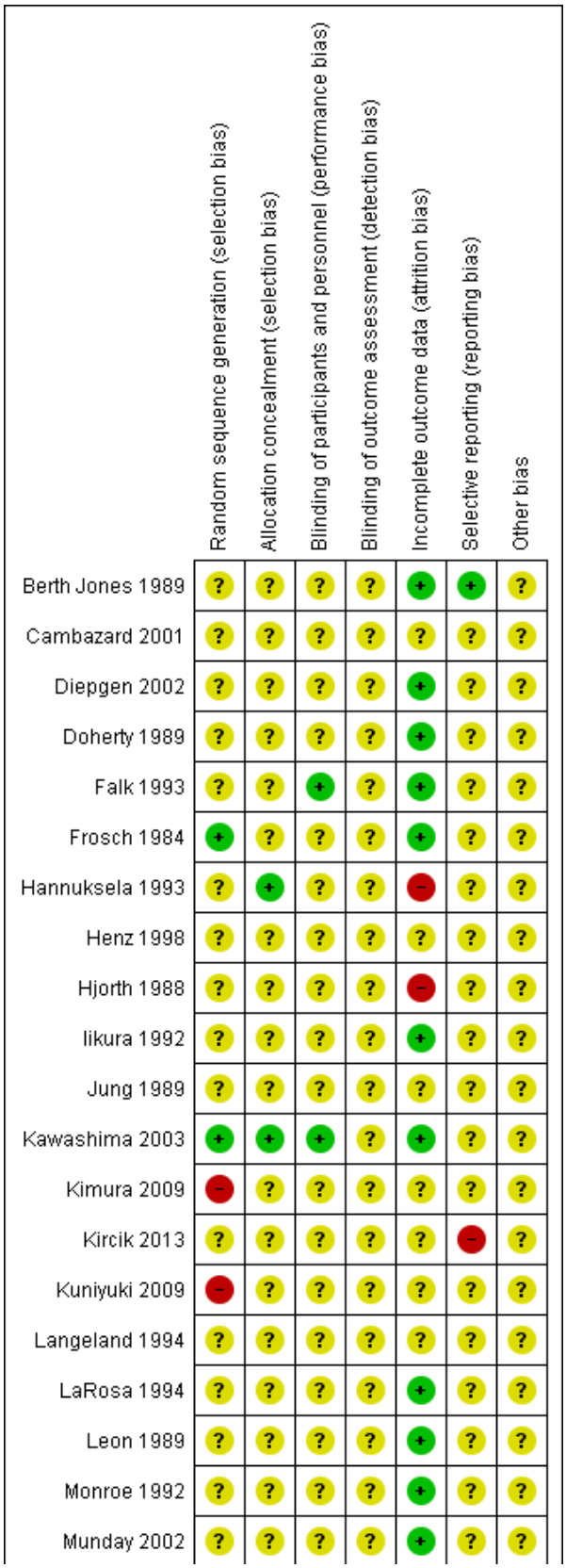
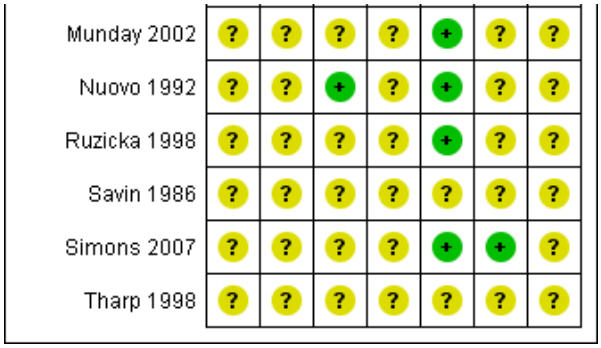


Figure 4. (Continued)



Most studies lacked sufficient information to judge whether the methods used were capable of eliminating threats to their validity. No study provided complete clarity on every item in our 'RoB' assessment, suggesting widespread inadequate reporting of methods or results. One trial at least provided sufficient information on four of the seven domains considered in this review (Kawashima 2003). However, we could not assess three domains due to insufficient reporting.

Of the 25 studies for which we assessed RoB, six were associated with unclear RoB in all domains (Cambazard 2001; Henz 1998; Jung 1989; Langeland 1994; Savin 1986; Tharp 1998). We judged eight as unclear in all domains but one, which we judged as low risk (Diepgen 2002; Doherty 1989; Iikura 1992; LaRosa 1994; Leon 1989; Monroe 1992; Munday 2002; Ruzicka 1998). Four studies were associated with unclear RoB in all domains but one, which we judged as high risk (Hjorth 1988; Kimura 2009; Kircik 2013; Kuniyuki 2009). We judged five studies as having unclear RoB in five domains but low risk in two domains (Berth Jones 1989; Falk 1993; Frosch 1984; Nuovo 1992; Simons 2007). One study was associated with unclear RoB in most domains, and one each with low and high risk (Hannuksela 1993). We judged only one study as having low RoB in four domains (Kawashima 2003).

Summarising RoB within the 25 studies for which RoB was assessed revealed that five (25%) had at least one domain that was rated as having high RoB. In two instances, this referred to incomplete outcome data (attrition bias), in another two, to selection bias, and once, to reporting bias. For all other studies, we judged at least one domain to be at unclear RoB. Across the 25 studies included in this review, we considered five as having an overall high risk of bias (n = 5; 20%) and 20 as having an overall unclear risk of bias (n = 20; 80%).

Allocation

Random sequence generation

In most of the 25 trials in this review, study authors did not describe the method of sequence generation at all or at best provided unclear information. Two studies described the method used to generate the allocation sequence in sufficient detail (Frosch 1984; Kawashima 2003); therefore, we judged this domain as having low risk of bias for these studies. For two studies, we judged the method to be at high RoB (Kimura 2009; Kuniyuki 2009).

Allocation concealment

Most studies did not provide sufficient information regarding how the allocation sequence was concealed; hence we judged them as having unclear risk in this domain. Two studies assured that allocation concealment was ensured. Both Kawashima 2003 and Hannuksela 1993 reported that sealed envelopes had been used to disguise group membership.

Blinding

Blinding of participants and personnel (performance bias)

Most of the included studies insufficiently described the procedures utilised to blind study participants and personnel from knowing which intervention a participant received, and consequently we judged them to be at unclear risk in this domain. Falk 1993, Kawashima 2003, and Nuovo 1992 achieved blinding by ensuring that the study medication had an identical appearance, and thus we judged them to have low risk of bias in this domain.

Blinding of outcome assessment (detection bias)

None of the included trials demonstrated adequate blinding of outcome assessment. Due to lack of information, we consequently rated risk of bias due to lack of blinding of outcome assessment as unclear in all trials.

Incomplete outcome data

We rated one parallel RCT as being at high risk with regard to attrition bias (Hannuksela 1993). The attrition rate was 28.7%. We also rated one cross-over trial as high risk due to a large number of dropouts (14/30) (Hjorth 1988). None of these studies could sufficiently show that dropouts or losses to follow-up did not systematically differ from participants remaining in the trial. We judged 14 studies to be at low risk (Berth Jones 1989; Diepgen 2002; Doherty 1989; Falk 1993; Frosch 1984; Iikura 1992; Kawashima 2003; LaRosa 1994; Leon 1989; Monroe 1992; Munday 2002; Nuovo 1992; Ruzicka 1998; Simons 2007). Nuovo 1992 was a single-patient trial reporting all data points from this cross-over trial; thus we judged that it had low RoB. Remaining studies (9/25) did not provide sufficient information to allow judgement of low or high risk (Cambazard 2001; Henz 1998; Jung 1989; Kimura 2009; Kircik 2013; Kuniyuki 2009; Langeland 1994; Savin 1986; Tharp 1998); consequently we rated them as having unclear risk.

Selective reporting

According to the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), most studies are likely to fall into the category of unclear for this domain because the difficulty involved in establishing what outcomes may have been collected and not reported. Publication of study protocols before

study commencement or at least before study completion has contributed significantly to our improved ability to detect selective outcome reporting; however, dissemination of study protocols was fairly uncommon until a few years ago.

For most studies, it is unlikely that a protocol would have been published. We attempted to obtain protocols for larger trials (n > 200) (Diepgen 2002; Kawashima 2003), but we did not succeed in doing so. As a consequence, we judged 22 studies as having unclear risk of reporting bias. We tried to resort to information from trial registrations when possible (see Table 4). We considered two studies to be at low risk of reporting bias (Berth Jones 1989; Simons 2007). We judged one study as having high risk of reporting bias because reporting of data was extremely rudimentary in the report and did not allow us to run necessary analyses (Kircik 2013). We contacted the study authors, but they failed to respond. Although some data were available (medians and interquartile ranges for primary outcome 1 (patient-assessed symptoms) and secondary outcome 2 (quality of life)), researchers presented no group comparisons and provided insufficient data for us to run the statistical analyses ourselves.

Other potential sources of bias

We assessed all included studies for additional potential sources of bias. We checked each study for inclusion of a conflict of interest statement, whether information about the source of funding could be obtained, and whether the study was initiated by a pharmacological company (Bero 2013). However, all trials failed to provide this information adequately, and consequently we judged them as having unclear risk of bias. Thus, further risk of bias may be present but information provided is insufficient for judgement of whether additional bias exists.

Effects of interventions

See: **Summary of findings for the main comparison** Cetirizine 0.5 mg/kg/d versus placebo (18-month intervention); **Summary of findings 2** Cetirizine 10 mg/d versus placebo (4-week intervention); **Summary of findings 3** Fexofenadine 120 mg/d versus placebo (1-week intervention); **Summary of findings 4** Loratadine 10 mg/d versus placebo (4-week intervention); **Summary of findings 5** Loratadine 10 mg/d versus placebo (2-week intervention)

Due to clinical diversity among studies in terms of duration of the intervention, the H1 AH used, and doses provided, as well as variation in the concomitant topical treatment allowed (see Table 2) and in outcome assessment (see Table 3), we were unable to pool any of the studies that we identified for inclusion in this review. Consequently, we have reported the effects of interventions for each trial individually. For the main comparisons, see Summary of findings for the main comparison Summary of findings 2 Summary of findings 3 and Summary of findings 4.

Comparison 1

Acrivastine 24 mg/d versus placebo

We identified one parallel study that compared this intervention in adults (Doherty 1989). Researchers reported an intermediate-term intervention (10 days) but assessed the first primary outcome seven days after baseline (short-term).

Primary outcome 1. Patient-assessed symptoms: VAS pruritus seven days after baseline

Visual analogue scale (VAS) pruritus score (seven days after baseline and adjusted for baseline scores as a covariate; range 0 to 100) increased more in the placebo group; however, the 95% confidence interval (CI) associated with the mean difference (MD) was wide and included zero, meaning that the result was non-significant (MD -11.40, 95% CI -29.44 to 6.64; P = 0.22; participants = 23; studies = 1; Analysis 1.1). We downgraded the outcome from high to low quality of evidence because of unclear risk of bias for most domains and because of imprecision (wide CI due to small sample size or high variability in outcome measurement).

Secondary outcome 1. Mean change in physician-assessed clinical signs

This study provided data not for mean change but for the number of participants for whom treatment helped to relieve itching (physician-assessed). The comparison favoured acrivastine over placebo (risk ratio (RR) 2.69, 95% CI 1.12 to 6.49; P = 0.03; participants = 27; studies = 1; Analysis 1.2). Fisher's exact test confirmed this analysis (P = 0.021). The number needed to treat for an additional beneficial outcome (NNTB) was 2. The 95% CI for the NNTB ranged from 1 to 7. We downgraded the outcome from high to low quality of evidence because of unclear risk of bias for most domains and imprecision (wide CI due to small sample size).

Comparison 2

Azelastine 4 mg/d versus placebo

We identified one parallel study that compared this intervention in adults (Henz 1998). Investigators reported an intermediate-term intervention (two weeks). The study yielded retrievable/extractable data only in part, as study authors combined the data presented to include a variety of dermatological conditions including eczema. Attempts to contact the main study author were not successful.

Primary outcome 1. Mean change in patient-assessed symptoms of eczema

This study measured reduction in pruritus (assessed at baseline, week 1, week 2) marked at night on diary cards (itching recorded every night on a 4-point scale: 0 = none, 1 = mild, 2 = moderate, 3 = severe). Study authors presented results in a graph separately for patients with eczema and showed no statistically significant differences between azelastine and placebo. They did not report exact P values nor mean changes. Hence, no study data were available for analysis. We downgraded the quality of evidence from high to low due to unclear risk of bias in all domains and serious imprecision (small sample size).

Secondary outcome 1. Physician-assessed clinical signs: mean overall response rate (number of participants who responded to treatment) two weeks after baseline

Although this study assessed a measure of 'physician-assessed clinical signs', researchers presented not a mean change measure but the mean overall response rate (number of participants who responded to treatment). They presented data separately for participants with eczema. Response rates were higher in the azelastine group, but researchers observed no significant differences between intervention and placebo groups (RR 1.75, 95% CI 0.64 to 4.82; P = 0.28; participants = 55; studies = 1; Analysis 2.1). We downgraded the quality of evidence from high to low due to

unclear risk of bias in all domains and serious imprecision (wide CI due to small sample size).

Comparison 3

Cetirizine versus placebo

We identified seven parallel studies that compared this intervention (Cambazard 2001; Diepgen 2002; Hannuksela 1993; Henz 1998; Jung 1989; LaRosa 1994; Tharp 1998).

One study provided a short-term intervention (up to one week) (Jung 1989), two an intermediate-term intervention (one to six weeks) (Hannuksela 1993; Henz 1998), and four long-term (more than six weeks) interventions (Cambazard 2001; Diepgen 2002; LaRosa 1994; Tharp 1998).

The dosage given ranged from 5 mg/d to 40 mg/d, or from 0.25 mg/kg bodyweight per day to 0.75 mg/kg bodyweight per day.

Short-term interventions

Jung 1989 reported a short-term intervention (one week; n = 98) conducted in children three to six years of age. One group received 5 mg/d (n = 33), another 10 mg/d (n = 36), and a third placebo (n = 29).

Primary outcome 1. Mean change in patient-assessed symptoms

Study results show that pruritus was reduced by 39% in the 5 mg/d group, by 44% in the 10 mg/d group, and by 39% in the placebo group (no significant difference). No data from the study were available for analysis. We downgraded the quality of evidence from high to low due to serious risk of bias (all domains judged as having unclear risk of bias) and insufficient reporting of findings.

Primary outcome 2. Proportion of participants reporting adverse effects and serious adverse events throughout the study period

The number of adverse events did not differ significantly between the 5 mg/d group and the placebo group (RR 0.59, 95% CI 0.11 to 3.27; P = 0.54; participants = 62; studies = 1; Analysis 3.1), or between the 10 mg/d group and the placebo group (RR 0.81, 95% CI 0.18 to 3.70; P = 0.78; participants = 65; studies = 1; Analysis 3.1). We downgraded the quality of evidence from high to low due to serious risk of bias (all domains judged as having unclear risk of bias) and serious imprecision (wide CI due to small sample size).

Secondary outcome 1. Mean change in physician-assessed clinical signs

We assessed global evaluation of treatment efficacy as the percentage of improvement as "good or excellent". Study authors determined that 46% in the 5 mg/d group had improved, along with 40% in the 10 mg/d group and 20% in the placebo group, and that no significant differences had emerged. No data were available from this study for analysis. We downgraded the quality of evidence from high to moderate due to serious risk of bias (all domains judged as having unclear risk of bias).

Intermediate-term interventions

Henz 1998 reported an intermediate-term intervention (two weeks) comparing 10 mg/d of cetirizine (n = 16) versus placebo (n = 11) in adults. This study yielded retrievable/extractable data only in part, as researchers combined data presented to include a variety of dermatological conditions, including eczema. Attempts to contact the main author were not successful.

Primary outcome 1. Mean change in patient-assessed symptoms of eczema

This study measured reduction in pruritus (assessed at baseline, week 1, week 2) marked at night on diary cards (itching recorded every night on a 4-point scale: 0 = none, 1 = mild, 2 = moderate, 3 = severe). Investigators presented results in a graph separately for patients with eczema and showed no statistically significant differences between cetirizine and placebo. No data from the study were available for analysis. We downgraded the quality of evidence from high to low due to serious risk of bias (all domains judged as having unclear risk of bias) and serious imprecision (small sample size).

Secondary outcome 1. Physician-assessed clinical signs: mean overall response rate (number of participants who responded to treatment) two weeks after baseline

Although this study employed a measure of 'physician-assessed clinical signs', researchers presented not a mean change measure but the mean overall response rate (number of participants who responded to treatment). They presented data separately for patients with eczema and showed no significant differences between intervention and placebo groups (RR 0.69, 95% CI 0.17 to 2.80; P = 0.60; participants = 27; studies = 1; Analysis 4.1). Fisher's exact test yielded a P value of 0.662. We downgraded the quality of evidence from high to low because of serious risk of bias (all domains judged as having unclear risk of bias) and serious imprecision (small sample size).

Hannuksela 1993 reported an intermediate-term intervention (four weeks; n = 178) and compared 10 mg/d (n = 42), 20 mg/d (n = 45), or 40 mg/d of cetirizine (n = 47) versus placebo (n = 42) in adults. We judged this study as having high risk regarding attrition bias.

Primary outcome 1. Mean change in patient-assessed symptoms

Investigators assessed pruritus once as part of SCORAD and once by patient case report form (CRF). No data from the study were available for analysis.

- Pruritus as part of SCORAD: all groups showed significant improvement between baseline and the last visit. Researchers observed no significant differences between any of the active treatments and placebo.
- Pruritus by patient CRF (case report form): again, all groups were significantly improved at the last visit compared to baseline. Study authors reported that the 20 mg/d (P = 0.04) and 40 mg/d (P = 0.05) groups were significantly better than the placebo group.

The values reported in Table 2 of the study publication show an increase from baseline to the last visit, although the legend states that "lower values indicate less pruritus". We contacted the study authors but were not able to resolve this inconsistency. No data from the study were available for analysis. Caution is needed in interpreting these study findings.

We downgraded the quality of evidence by two levels from high to low due to serious risk of bias (high for the domain incomplete outcome data and for several domains judged as having unclear risk of bias) and due to reporting of outcomes that could not be reproduced (i.e. the legend states lower values indicate less pruritus, but pruritus increased in all groups from baseline to last

visit). We contacted study authors to clarify this issue but received no response (Summary of findings 2).

Primary outcome 2. Proportion of participants reporting adverse effects and serious adverse events throughout the study period

In all, 10 of 42 participants in the 10 mg/d group and 9 of 42 in the placebo group reported the occurrence of at least one adverse event (RR 1.11, 95% CI 0.50 to 2.45; P = 0.79; participants = 84; studies = 1; Analysis 5.1; Summary of findings 2). A total of 14 of 45 participants in the 20 mg/d group reported at least one adverse event (RR 1.45, 95% CI 0.70 to 3.00; P = 0.31; participants = 87; studies = 2; Analysis 5.1). We downgraded the quality of evidence by two levels from high to low due to serious risk of bias (high for the domain incomplete outcome data and for several domains judged as having unclear risk of bias) and serious imprecision (wide CI due to low sample size).

However, results show a significant difference in occurrence of adverse events between 40 mg/d and placebo, in favour of the placebo group. In total, 24 of 47 in the 40 mg group and 9 of 42 in the placebo group reported at least one adverse event (RR 2.38, 95% CI 1.25 to 4.53; P = 0.008; participants = 89; studies = 1; Analysis 5.1). The number needed to treat for an additional harmful outcome (NNTH) was 3 (95% CI 2 to 9). We downgraded the quality of evidence from high to low due to serious risk of bias (several domains judged as having unclear risk of bias) and serious imprecision (wide CI due to small sample size). Most side effects pertained to sedation, others to skin-related problems, respiratory symptoms, or headache.

Secondary outcome 1. Mean change in physician-assessed clinical signs

The total symptom score significantly decreased in all groups between baseline and the last visit according to study authors, who also reported that the decrease was significantly more marked for the 40 mg/d group than for the placebo group, thus favouring the 40 mg intervention group. No data from the study were available for analysis. We downgraded the quality of evidence by two levels from high to low due to serious risk of bias (high for the domain incomplete outcome data and for several domains judged as having unclear risk of bias) and serious imprecision (due to small sample size).

Secondary outcome 3. Number of eczema flares, measured by, for example, 'escalation of treatment' or 'use of topical anti-inflammatory medications'

Study authors observed no differences among groups in the amount of local rescue therapy (emollient or 1% hydrocortisone) nor in the number of applications. No data from the study were available for analysis. We downgraded the quality of evidence by two levels from high to low due to serious risk of bias (high for the domain incomplete outcome data and for several domains judged as having unclear risk of bias) and serious imprecision (due to small sample size).

Long-term interventions

Cambazard 2001 reported the results of a long-term intervention (eight weeks; n = 223) of 0.5 mg/d per kg bodyweight versus placebo conducted in children between 11 and 71 months of age.

Primary outcome 1. Mean change in patient-assessed symptoms

Investigators assessed pruritus as part of the SCORAD. However, they did not report this outcome separately but provided only the total SCORAD score. No data from the study were available for analysis.

Primary outcome 2. Proportion of participants reporting adverse effects and serious adverse events throughout the study period

Study authors observed very few adverse events. Comparison of the four treatment groups on the basis of frequency of adverse events did not reveal a statistically significant difference. No data from this study were available for analysis. We downgraded the quality of the evidence by two levels to low: one level for limitations in design due to serious risk of bias (all domains judged as having unclear risk of bias), and one level for reporting bias due to non-publication of results.

Secondary outcome 1. Physician-assessed clinical signs

Investigators assessed this outcome by using a modified SCORAD. Scores decreased by 7.9 units in the placebo group and by 9.4, 9.1, and 9.1 units in the 0.25, 0.50, and 0.75 mg/kg body weight each day (bw/d) cetirizine dosage groups, respectively. The difference observed between placebo and the reference dosage of 0.50 mg/kg bw/d cetirizine was not significant. No significant dose-effect relationship between change in modified SCORAD index and dosage of study medication was evident. No data from the study were available for analysis. We downgraded the quality of evidence by two levels to low: one level for limitations in design due to serious risk of bias (all domains judged as having unclear risk of bias), and one level for reporting bias due to non-publication of results.

Secondary outcome 3. Number of eczema flares, measured by, for example, 'escalation of treatment' or 'use of topical anti-inflammatory medications'

On average, participants in the placebo group used 7.2 g 1% hydrocortisone cream and those in the 0.50 mg/kg bw/d cetirizine dosage group used 6.9 g. On average, those in the placebo group consumed 39.0 g clobetasone butyrate cream and those in the 0.50 mg/kg bw/d cetirizine dosage group consumed 52.0 g of clobetasone butyrate cream. No significant differences emerged when groups were compared with regard to topical anti-inflammatory medication use. No data from the study were available for analysis. We downgraded the quality of evidence by two levels to low: one level for limitations in design due to serious risk of bias (all domains judged as having unclear risk of bias), and one level for reporting bias due to non-publication of results.

Diepgen 2002 reported the results of a long-term intervention (18 months) in children 12 to 24 months of age. Interventions comprised 0.50 mg/kg bw/d cetirizine and placebo. Participants were allowed to use other H1 AH during the study, and study authors reported that a higher percentage in the placebo group used them (Simons 1999).

Primary outcome 1. Mean change in patient-assessed symptoms of eczema

Investigators assessed this outcome as part of the SCORAD assessment. They did not present data separately for pruritus but provided only the total SCORAD score. Thus, no data from the study were available for analysis of this outcome.

Primary outcome 2. Proportion of participants reporting adverse effects and serious adverse events throughout the study period

Data from an earlier publication of the same study show that 37 of 399 in the cetirizine group and 54 of 396 in the placebo group reported the occurrence of adverse events (RR 0.68, 95% CI 0.46 to 1.01; P = 0.06; participants = 795; studies = 1; moderate-quality evidence; Analysis 6.1; Summary of findings for the main comparison) (Simons 1999). The difference was non-significant, and most reported symptoms and events were mild and were attributed to intercurrent (occurring during and modifying the course of another disease) respiratory or gastrointestinal infection or to exacerbations of allergic disorders.

Secondary outcome 1. Mean change in physician-assessed clinical signs

Researchers assessed this outcome by using SCORAD. They found no evidence of a treatment-related reduction in SCORAD scores between baseline and the final visit and reported that the difference between groups was non-significant (from 24.9 to 15.2 in the cetirizine group and from 25.1 to 15.7 in the placebo group; moderate-quality evidence). No data from the study were available for analysis (Summary of findings for the main comparison).

We had stated in the section Subgroup analysis and investigation of heterogeneity that we would compare participants with atopic versus non-atopic dermatitis (i.e. sensitised showing elevated levels of IgE antibodies to inhalant allergens) if data became available. Study authors stated that participants with elevated IgE aeroallergens at baseline showed a decrease in the average SCORAD index during the study period from 30.3 to 22.3 in the placebo group and from 32.6 to 18.8 in the cetirizine group (from baseline to last visit). However, they reported the comparison between groups, and we could extract no data for analysis.

Secondary outcome 3. Number of eczema flares, measured by, for example, 'escalation of treatment' or 'use of topical anti-inflammatory medications'

For this outcome, researchers assessed the use of a variety of topical and systemic medications including oral use of H1 AH. Results show no significant differences between groups, with one exception: participants in the placebo group were more likely to have used H1 AH (P = 0.035; moderate-quality evidence; Summary of findings for the main comparison). No data from this study were available for analysis.

LaRosa 1994 reported the results of a long-term intervention (eight weeks; n = 23) conducted in children six to 12 years of age. Investigators compared 5 mg cetirizine for children ≤ 30 kg and 10 mg for children > 30 kg versus placebo.

Primary outcome 1. Mean change in patient-assessed symptoms of eczema

Study authors stated that cetirizine showed a significant advantage over placebo at week 8 (Chi^2 4.55; P < 0.05) with regard to pruritus assessed by a diary, which favours the intervention group. However, results as presented are not reproducible, as they are shown in figures or are given in a rudimentary way in the text. We could extract no data for analysis from this study. We downgraded the quality of evidence by two levels to low: one level for limitations in design due to unclear judgement for all other domains apart from the domain incomplete outcome data (low risk), and one level due to imprecision (small sample size).

Primary outcome 2. Proportion of participants reporting adverse effects and serious adverse events throughout the study period

Investigators observed no adverse events and provided no study data for analysis. We downgraded the quality of evidence by two levels to low: one level for limitations in design due to unclear judgement for all other domains apart from the domain incomplete outcome data (low risk), and one level due to imprecision (small sample size).

Secondary outcome 1. Mean change in physician-assessed clinical signs

Researchers assessed this outcome by clinical examination at baseline, at four weeks of treatment, and at eight weeks of treatment. Although they observed a significant reduction in scores within groups, they noted no significant differences between groups. No data from this study were available for analysis. We downgraded the quality of evidence by two levels to low: one level for limitations in design due to unclear judgement for all other domains apart from the domain incomplete outcome data (low risk), and one level due to imprecision (small sample size).

Secondary outcome 3. Number of eczema flares, measured by, for example, 'escalation of treatment' or 'use of topical anti-inflammatory medications'

For this outcome, investigators measured the use of concomitant therapy. In all, 18% in the active treatment group and 82% in the placebo group reported use of concomitant therapy (disodium cromoglycate, procaterol, steroids). A Chi^2 test attested to the significance of this difference (P < 0.01). Our analysis confirmed the significance of the reported result (RR 0.22, 95% CI 0.06 to 0.80; P = 0.02; participants = 22; studies = 1; Analysis 7.1), thus favouring the intervention group. We downgraded the quality of evidence by two levels to low: one level for limitations in design due to unclear judgement for all other domains apart from the domain incomplete outcome data (low risk), and one level due to imprecision (small sample size).

Tharp 1998 compared 20 mg/d given to adults in the active treatment group as a long-term intervention versus placebo (12 weeks; n = 106) and published these findings in abstract format.

Primary outcome 1. Mean change in patient-assessed symptoms of eczema

Study authors stated that patient-reported pruritus (no information about scaling provided) improved in the active treatment group significantly more than in the placebo group (P ≤ 0.05) at weeks 3, 5, and 6. The global evaluation of symptoms by patients (no precise information provided on how this was assessed) indicated significantly more improvement for patients treated with cetirizine over placebo (P < 0.05). Both analyses thus favoured the intervention. We could extract no data for analysis from this study. We downgraded the quality of evidence by one level from high to moderate for limitations in design due to serious risk of bias (all domains judged as having unclear risk of bias).

Primary outcome 2. Proportion of participants reporting adverse effects and serious adverse events throughout the study period

Study authors reported no significant differences between groups in the occurrence of this outcome. We could extract no data for analysis from this study. We downgraded the quality of evidence by one level from high to moderate for limitations in design due

to serious risk of bias (all domains judged as having unclear risk of bias).

Secondary outcome 1. Mean change in physician-assessed clinical signs

Researchers reported that the mean improvement in investigator-assessed clinical signs and symptoms was significantly greater in the cetirizine group than in the placebo group (P = 0.04), thus favouring the intervention. Again, no data from this study were available for analysis. We downgraded the quality of evidence by one level from high to moderate for limitations in design due to serious risk of bias (all domains judged as having unclear risk of bias).

Secondary outcome 3. Number of eczema flares, measured by, for example, 'escalation of treatment' or 'use of topical anti-inflammatory medications'

Study authors observed no significant differences between groups in the use of triamcinolone acetonide 0.1% cream (corticosteroid). We could extract no data from this study for analysis. We downgraded the quality of evidence by one level from high to moderate for limitations in design due to serious risk of bias (all domains judged as having unclear risk of bias).

Comparison 4

Chlorpheniramine 12 mg/d versus placebo

We identified one cross-over study that compared this intervention in adults (Frosch 1984). Researchers reported an intermediate-term intervention (four weeks; n = 18).

Primary outcome 1. Mean change in patient-assessed symptoms of eczema

For this outcome, study authors measured pruritus by VAS (100 mm) during the day and during the night, observing no significant differences between groups. No data from this study were available for analysis, and no P values were given. We downgraded the quality of evidence by two levels from high to low due to unclear judgement for most domains and two that were judged low (selection and attrition bias) with imprecision (small sample size).

Primary outcome 2. Proportion of participants reporting adverse effects and serious adverse events throughout the study period

Three participants reported adverse events during treatment with chlorpheniramine; none reported adverse events during the placebo period. No data from this study were available for analysis. We downgraded the quality of evidence by two levels from high to low due to unclear judgement of most domains and two that were judged low (selection and attrition bias) with imprecision (small sample size).

Secondary outcome 1. Mean change in physician-assessed clinical signs

This global assessment reported the numbers of participants with overall improvement, no overall improvement, and overall worsening. Study authors reported no significant differences between groups based on the Kruskal-Wallis test. No data from this study were available for analysis, and no P values were given. We downgraded the quality of evidence by two levels from high to low due to unclear judgement of most domains and two that were judged low (selection and attrition bias) with imprecision (small sample size).

Secondary outcome 3. Number of eczema flares, measured by, for example, 'escalation of treatment' or 'use of topical anti-inflammatory medications'

For this outcome, researchers assessed the amount of betamethasone used in grams. Study authors observed no significant differences between groups. We could extract no data for analysis from this study, and no P values were given. We downgraded the quality of evidence by two levels from high to low due to unclear judgement of most domains and two that were judged low (selection and attrition bias) with imprecision (small sample size).

Comparison 5

Chlorpheniramine maleate BP (2 to 4 mg/d (age dependent) or twice that amount) versus placebo

We included in this comparison one parallel-group study conducted in children (Munday 2002). Researchers reported the results of an intermediate-term (one month) intervention. One group received 2 mg/5 mL chlorpheniramine maleate for those one to five years of age, or 10 mL (4 mg) for six- to 12-year-olds. After two weeks, investigators administered double the bedtime dose (5.0 mL for those aged one to five years, and 10 mL for participants six to 12 years old) to participants who continued to experience sleeplessness. The total dose was 2 or 4 mg (age dependent) or twice that amount after two weeks. The other group received placebo. Study authors concluded that chlorpheniramine maleate is no more effective than placebo for relieving pruritus and controlling symptoms of eczema.

Primary outcome 1. Mean change in patient-assessed symptoms of eczema

Study authors did not assess this outcome as 'Mean change in patient-assessed symptoms', but participants rated the severity of pruritus (ranked) as none, minimal, mild, or moderate between days 1 and 29. Results show no significant differences (P = 0.745 based on the Cochran-Mantel-Haenzsel test) between intervention and placebo groups (stratified for age groups and controlling for baseline differences) in severity of night-time pruritus. Note that modal response is defined as the most common response over a specified period. This combined with the fact that the statistical test used is not very sensitive makes this analysis not very powerful. No data for this outcome were available for analysis. We downgraded the quality of evidence by one level from high to moderate for limitations in design due to serious risk of bias (most domains judged as having unclear risk of bias).

Primary outcome 2. Proportion of participants reporting adverse effects and serious adverse events throughout the study period

Researchers noted no significant differences between groups (RR 0.95, 95% CI 0.49 to 1.82; P = 0.87; participants = 151; studies = 1; Analysis 8.1). We downgraded this outcome by one level from high to moderate because of serious risk of bias (most domains judged as having unclear risk of bias).

Secondary outcome 1. Mean change in physician-assessed clinical signs

Investigators presented this outcome as a composite score consisting of five symptoms (erythema, excoriation, dryness, lichenification, exudation and crusting). Data show no significant differences between groups at day 1 (P = 0.479), day 15 (P =

0.33), or day 29 (P = 0.53). No data were available for analysis. We downgraded the quality of evidence by one level from high to moderate for limitations in design due to serious risk of bias (most domains judged as having unclear risk of bias).

Secondary outcome 3. Number of eczema flares, measured by, for example, 'escalation of treatment' or 'use of topical anti-inflammatory medications'

Study authors assessed this outcome as the amount of 1% hydrocortisone in grams used and analysed data separately for age groups one to five years and six to 12 years. Results show no significant differences between intervention and placebo groups, neither in the age group one to five years (MD -1.30, 95% CI -5.96 to 3.36; P = 0.58; participants = 61; studies = 1; Analysis 8.2) nor in the age group six to 12 years (MD 1.60, 95% CI -2.53 to 5.73; P = 0.45; participants = 90; studies = 1; Analysis 8.2). We downgraded the quality of evidence by two levels from high to low due to serious risk of bias (most domains judged as having unclear risk of bias) with serious imprecision (wide CI due to small sample size or high variability in outcome measurements).

Comparison 6

Fexofenadine 120 mg/d versus placebo

We identified one parallel-group study that compared this intervention in adults (Kawashima 2003). Investigators reported the results of a short-term intervention (one week) and concluded that fexofenadine led to rapid, significant improvement in pruritus associated with eczema, and that the safety profile was similar to that of placebo.

Primary outcome 1. Mean change in patient-assessed symptoms of eczema: pruritus difference between baseline and night of day 6

Researchers measured this outcome as the mean change in patient-assessed pruritus (range 0 to 8) between baseline and the night of day 6. The mean change was significantly larger in the fexofenadine group than in the placebo group; therefore, the comparison favours the intervention group (MD -0.25, 95% CI -0.43 to -0.07; P = 0.006; participants = 400; studies = 1; moderate-quality evidence; Analysis 9.1; Summary of findings 3).

Primary outcome 2. Proportion of participants reporting adverse effects and serious adverse events throughout the study period

In all, 48 of 207 participants in the fexofenadine group and 45 of 204 in the placebo group experienced an adverse event during the trial (RR 1.05, 95% CI 0.74 to 1.50; P = 0.78; participants = 411; studies = 1; moderate-quality evidence; Analysis 9.2; Summary of findings 3). This difference was non-significant, and the most frequently reported adverse events were somnolence and headache.

Secondary outcome 1. Physician-assessed clinical signs

Study authors stated that in terms of investigator-assessed change in the ratio of pruritus area to body surface area, significantly more participants in the fexofenadine group than in the placebo group experienced a reduction in this ratio (P = 0.007). This comparison favours the intervention group (moderate-quality evidence). No data from this study were available for analysis.

Secondary outcome 3. Number of eczema flares/amount of 0.1% hydrocortisone butyrate in grams

Study authors reported no significant differences between groups in the amount of 0.1% hydrocortisone butyrate cream used during the study (moderate-quality evidence). We could extract from this study no data for analysis.

Comparison 7

Hydroxyzine 75 mg/d versus placebo

We identified one parallel-group trial conducted in adults that performed this comparison (Monroe 1992). Researchers reported the results of a short-term (one week) intervention.

Primary outcome 1. Patient-assessed symptoms: global evaluation of the antipruritic effect of treatment: number of participants who reported a marked or complete response

Investigators assessed this outcome not as mean change but as percentage change in pruritus scores (0 to 3) from baseline to endpoint. The daily pruritus score decreased by 38% in the hydroxyzine group and by 33% in the placebo group. Study authors reported that the difference was not significant but gave no P value. According to the global evaluation of the antipruritic effect of treatment, six participants in the hydroxyzine group and three in the placebo group reported a marked or complete response (RR 1.86, 95% CI 0.58 to 5.94; P = 0.30; participants = 27; studies = 1; Analysis 10.1). Fisher's exact test analysis yielded a P value of 0.42. We downgraded the quality of evidence by two levels from high to low due to serious risk of bias (most domains judged as having unclear risk of bias) and due to serious imprecision (wide CI due to small sample size).

Primary outcome 2. Proportion of participants reporting adverse effects and serious adverse events throughout the study period

Study authors did not report occurrence of adverse events separately for participants with eczema but provided data only for the whole sample, including those with urticaria. No data for analysis were available from this study.

Comparison 8

Ketotifen versus placebo

We identified three parallel-group studies for this comparison (Falk 1993; Iikura 1992; Leon 1989).

Ketotifen 2 mg/d versus placebo

We identified two studies that performed this comparison (Falk 1993; Leon 1989).

Falk 1993 reported the results of a long-term intervention in adults (three months; n = 56).

Primary outcome 1. Mean change in patient-assessed symptoms of eczema

Study authors reported a significant reduction in pruritus in both intervention (2 mg/d) and placebo groups but conducted no test to detect differences between groups. It is not possible to extract data from this study for analysis. We downgraded the quality of evidence from high to low due to unclear judgement of most domains and two that were judged low (performance and attrition bias) with imprecision (small sample size).

Secondary outcome 1. Mean change in physician-assessed clinical signs

Researchers assessed this outcome by combining five signs and symptoms (severity of diseased skin, area affected, erythema, lichenification, and pruritus) for a total score ranging from 0 to 4. After treatment, the ketotifen group had a mean score of 2.8 and the placebo group had a mean score of 1.2. Study authors reported the difference to be significant at P < 0.01 and to favour the intervention group. No data from this study were available for analysis. We downgraded the quality of evidence from high to low due to unclear judgement of most domains and two that were judged low (performance and attrition bias) with imprecision (low sample size).

Leon 1989 investigated a long-term intervention (nine weeks) of ketotifen (2 mg/d) in a small sample of children (n = 20).

Primary outcome 1. Mean change in patient-assessed symptoms of eczema

Investigators assessed the intensity of day and night pruritus on a scale from 0 to 3 (absent = 0, mild = 1, moderate = 2, intense = 3). They provided data for the ketotifen group (day pruritus: visit 1: Mean (M) = 2.1 (standard deviation (SD) = 0.74), week 9: M = 0.7 (SD 0.67); night pruritus: visit 1: M = 1.7 (SD = 1.25), week 9: M = 0.2 (SD = 0.42)) but not for the placebo group. Study authors stated that differences in both daytime and night-time pruritus between visit 1 and week 9 were not significant for the placebo group but showed significant improvement for the ketotifen group (P = 0.01 for night-time and P = 0.005 for daytime pruritus comparisons). However, investigators carried out no comparison between groups, and as we could extract no data from the study, no inference could be made about whether ketotifen has an effect on pruritus over placebo. We downgraded the quality of evidence by two levels from high to low due to serious risk of bias (most domains judged as having unclear risk of bias) and imprecision (small sample size).

Ketotifen (0.8 mg/d (< 14 kg) or 1.2 mg/d (≥ 14 kg)) versus placebo

Iikura 1992 investigated the effect of ketotifen (0.8 mg/d (< 14 kg) or 1.2 mg/d (≥ 14 kg)) in a long-term intervention (52 weeks) against the onset of asthma in children.

Primary outcome 2. Proportion of participants reporting adverse effects and serious adverse events throughout the study period

Study authors reported the occurrence of adverse events in 5 of 61 in the ketotifen group and in 0 of 60 in the placebo group (RR 10.82, 95% CI 0.61 to 191.53; P = 0.10; participants = 121; studies = 1; Analysis 11.1); due to the small sample size, Fisher's exact test revealed a significant difference between the two groups (P = 0.04) in favour of placebo. We downgraded the quality of evidence by two levels from high to low because of serious risk of bias (most domains judged as having unclear risk of bias) and serious imprecision (wide CI due to small sample size).

Secondary outcome 1. Mean change in physician-assessed clinical signs

Researchers assessed this outcome by performing a complete physical examination one year after randomisation. They scored data as marked improvement, moderate improvement, slight improvement, unchanged, and aggravated. Fisher's exact test compared the distribution of marked/moderate improvement between groups, and another compared the distribution of marked/moderate/slight improvement between groups. Both analyses favoured ketotifen over placebo (P < 0.05 and P < 0.001). No data from this study were available for analysis. We downgraded the quality of evidence by one level from high to moderate because of serious risk of bias (most domains judged as having unclear risk of bias).

Comparison 9

Levocetirizine versus placebo

Levocetirizine 5 mg/d versus placebo

We identified one parallel-group study that compared this intervention in adults (Kircik 2013). Researchers reported the results of an intermediate-term intervention (four weeks) in 20 participants in the intervention group and 20 participants in the placebo group.

Primary outcome 1. Patient-assessed symptoms of eczema: VAS pruritus

Researchers reported medians and interquartile ranges for baseline, two weeks, and four weeks after randomisation. Baseline values were 7.8 (6.5 to 8.5) for the intervention group and 7.5 (7.00 to 8.00) for the placebo group. At two weeks, the values were 6.10 (1.6 to 7.5) for the intervention group and 5.9 (3.65 to 7.75) for the placebo group. At four weeks, the values were 4.15 (2.4 to 6.9) and 6.4 (2.5 to 7.3). We downgraded the quality of evidence by two levels from high to low due to serious risk of bias (all domains judged as having unclear or high risk of bias) and serious imprecision (due to small sample size).

The same study published an interim report with fewer participants, which yielded data for the analysis of primary outcome 1, showing no significant differences in pruritus between groups two weeks after randomisation (MD -0.79, 95% CI -3.54 to 1.96; P = 0.57; participants = 21; studies = 1; Analysis 12.1) or 4 weeks after randomisation (MD -0.59, 95% CI -3.46 to 2.28; P = 0.69; participants = 21; studies = 1; Analysis 12.1). We downgraded the quality of evidence by two levels from high to low due to serious risk of bias (all domains judged as having unclear or high risk of bias) and serious imprecision (wide CI due to small sample size).

Primary outcome 2. Proportion of participants reporting adverse effects and serious adverse events throughout the study period

Study authors reported that they observed no treatment-related adverse events in either group. We downgraded the quality of evidence by two levels from high to low due to serious risk of bias (all domains judged as having unclear or high risk of bias) and serious imprecision (due to small sample size).

Secondary outcome 2. Mean change in quality of life, as measured by a standardised or validated quality of life measure (e.g. Dermatology Life Quality Index - DLQI)

Study authors reported median DLQI scores and interquartile ranges at baseline, two weeks, and four weeks after randomisation. Baseline values were 7.5 (4.0 to 14.0) for the intervention group and 8.0 (7.0 to 13.0) for the placebo group. Two weeks after randomisation, the values were 3.5 (2.0 to 6.5) for the intervention group and 5.5 (2.0 to 9.0) for the placebo group. Four weeks after randomisation, the values were 2.0 (1.0 to 5.0) for the intervention group and 4.0 (1.0 to 7.5) for the placebo group. Trial authors provided no analysis nor could we extract any data from the study for analysis. We downgraded the quality of evidence by two levels

from high to low due to serious risk of bias (all domains judged as having unclear or high risk of bias) and serious imprecision (due to small sample size).

Levocetirizine 0.25 mg/kg/d versus placebo

We identified one parallel-group study that compared this intervention in children (Simons 2007). Researchers reported the results of a long-term intervention (18 months).

Primary outcome 2. Proportion of participants reporting adverse effects and serious adverse events throughout the study period

Study authors provided a detailed analysis of the occurrence of adverse events during the trial, noting no significant differences between groups in occurrence of one or more adverse events (RR 1.01, 95% CI 0.98 to 1.05; P = 0.48; participants = 510; studies = 1; Analysis 13.1) nor of treatment-attributed adverse events (RR 0.81, 95% CI 0.40 to 1.65; participants = 510; studies = 1; P = 0.57; Analysis 13.1) nor of serious adverse events (RR 0.84, 95% CI 0.54 to 1.31; participants = 510; studies = 1; P = 0.44; Analysis 13.1) nor of treatment-attributed serious adverse events (RR 0.33, 95% CI 0.01 to 8.14; participants = 510; studies = 1; P = 0.50; Analysis 13.1) nor of adverse events that led to discontinuation of the study medication (RR 1.67, 95% CI 0.40 to 6.90; P = 0.48; participants = 510; studies = 1; Analysis 13.1). We downgraded the quality of evidence by one level from high to moderate due to serious risk of bias (all but one domain judged as having unclear risk of bias).

Comparison 10

Loratadine versus placebo

We identified three parallel-group studies - Ruzicka 1998, Monroe 1992, and Kimura 2009 - and one cross-over trial - Langeland 1994 - that compared this intervention.

Ruzicka 1998 reported the results of an intermediate-term intervention (two weeks) in adults. Participants consisted of three groups receiving 5 mg/d, 10 mg/d, or 20 mg/d of loratadine and one placebo group. Baseline values of pruritus were unequally distributed among the groups, with higher baseline values in the 20 mg/d group than in the other groups.

Loratadine 5 mg/d

Primary outcome 1. Mean change in patient-assessed symptoms of eczema: VAS pruritus (difference in pruritus sum between day 0 and day 13)

The difference in the pruritus sum between day 0 and day 13 did not differ significantly between the 5 mg/d group and the placebo group (MD -1.10, 95% CI -2.30 to 0.10; P = 0.07; participants = 72; studies = 1; Analysis 14.1). However, baseline scores were not equally distributed between groups, and this analysis does not account for baseline differences. We downgraded the quality of evidence by two levels from high to low due to unclear judgement in most domains and serious imprecision (wide CI due to small sample size).

Primary outcome 2. Proportion of participants reporting adverse effects and serious adverse events throughout the study period

Study authors reported the occurrence of 16 adverse events in all four groups but failed to report them for each group separately. No data from this study were available for analysis.

Secondary outcome 1. Physician-assessed clinical signs: number of participants for whom treatment success was judged as good or very good 13 days after randomisation

Researchers reported physician-assessed clinical signs not as mean change but as the number of participants for whom treatment success was judged as good or very good. Again, they noted no significant differences in this outcome between groups (RR 1.58, 95% CI 0.73 to 3.42; P = 0.24; participants = 74; studies = 1; Analysis 14.2). We downgraded the quality of evidence by two levels from high to low due to unclear judgement in most domains and serious imprecision (wide CI due to small sample size).

Loratadine 10 mg/d

Primary outcome 1. Mean change in patient-assessed symptoms of eczema: VAS pruritus (difference in pruritus sum between day 0 and day 13)

The difference in the pruritus sum between day 0 and day 13 did not differ significantly between the 10 mg/d group and the placebo group (MD -0.96, 95% CI -2.01 to 0.09; P = 0.07; participants = 71; studies = 1; Analysis 15.1; Summary of findings 5). We downgraded the quality of evidence by two levels from high to low due to unclear judgement in most domains and serious imprecision (wide CI due to small sample size) .

Primary outcome 2. Proportion of participants reporting adverse effects and serious adverse events throughout the study period

Study authors reported the occurrence of 16 adverse events in all four groups but failed to report them for each group separately. No data from this study were available for analysis (Summary of findings 5).

Secondary outcome 1. Physician-assessed clinical signs: number of participants for whom treatment success was judged as good or very good 13 days after randomisation

Researchers reported physician-assessed clinical signs not as mean change but as the number of participants for whom treatment success was judged as good or very good. They noted a marginally significant difference in this outcome between groups (RR 2.04, 95% CI 0.99 to 4.20; P = 0.05; participants = 73; studies = 1; Analysis 15.2; Summary of findings 5). Participants in the 10 mg/d group were about twice as likely to be judged as having good or very good treatment success. The NNTB was 5 (95% CI 2 to 111). We downgraded the quality of evidence by two levels from high to low due to unclear judgement in most domains and serious imprecision (wide CI due to small sample size).

Loratadine 20 mg/d

Primary outcome 1. Mean change in patient-assessed symptoms of eczema: VAS pruritus (difference in pruritus sum between day 0 and day 13)

The difference in the pruritus sum between day 0 and day 13 was significantly larger in the 20 mg/d group than in the placebo group (MD -1.41, 95% CI -2.49 to -0.33; P = 0.01; participants = 72; studies = 1; Analysis 16.1). The comparison favours the intervention group. We downgraded the quality of evidence by two levels from high to low due to unclear judgement in most domains and serious imprecision (wide CI due to small sample size).

Primary outcome 2. Proportion of participants reporting adverse effects and serious adverse events throughout the study period

Study authors reported the occurrence of 16 adverse events in all four groups but failed to report them for each group separately. No data from this study were available for analysis.

***Secondary outcome 1.* Physician-assessed clinical signs: number of participants for whom treatment success was judged as good or very good 13 days after randomisation**

Researchers reported physician-assessed clinical signs not as mean change but as the number of participants for whom treatment success was judged as good or very good. They noted a marginally significant difference in this outcome between groups (RR 2.04, 95% CI 0.99 to 4.20; P = 0.05; participants = 73; studies = 1; Analysis 16.2). Participants in the 20 mg/d group were about twice as likely to be judged as having good or very good treatment success. The NNTB was 5 (95% CI 2 to 111). We downgraded the quality of evidence by two levels from high to low due to unclear judgement in most domains and serious imprecision (wide CI due to small sample size).

Monroe 1992 reported the results of a short-term intervention (one week) in adults consisting of 10 mg/d of loratadine (n = 14) versus placebo (n = 13).

Primary outcome 1. Patient-assessed symptoms of eczema

Investigators did not report this outcome as mean change but measured pruritus as the percentage change in scores (0 to 3) from baseline to endpoint. The daily pruritus score decreased by 57% in the loratadine group and by 33% in the placebo group. Study authors reported that this difference was not significant but gave no P value. According to the global evaluation of the antipruritic effect of treatment, nine participants in the loratadine group and three in the placebo group reported a marked or complete response (RR 2.79, 95% CI 0.96 to 8.09; participants = 27; studies = 1; P = 0.06; Analysis 17.1). The P value from Fisher's exact test was 0.06. This underpowered analysis was not statistically significant but suggested that loratadine may improve pruritus compared to placebo. We downgraded the quality of evidence by two levels from high to low due to limitations in design (most domains judged as having unclear risk of bias) and due to serious imprecision (wide CI due to small sample size).

Primary outcome 2. Proportion of participants reporting adverse effects and serious adverse events throughout the study period

Investigators did not report the occurrence of adverse events separately for participants with eczema but included results for all participants, including those with urticaria. No data from this study were available for analysis.

Kimura 2009 reported the results of an intermediate-term intervention (four weeks) in adults. One group received 10 mg/d loratadine and the other no additional treatment.

Primary outcome 1. Patient-assessed symptoms of eczema: VAS pruritus four weeks after randomisation

For this outcome, study authors assessed pruritus by VAS four weeks after randomisation, noting no significant differences between groups (MD -2.30, 95% CI -20.27 to 15.67; P = 0.80; participants = 28; studies = 1; Analysis 18.1; Summary of findings 4). We downgraded the quality of evidence by two levels to low: one level for limitations of design due to unclear judgement of all but one domain, which we judged as low (selection bias), and one level due to imprecision (small sample size).

Primary outcome 2. Proportion of participants reporting adverse effects and serious adverse events throughout the study period

The occurrence of adverse events did not differ significantly between groups (RR 0.25, 95% CI 0.01 to 5.76; P = 0.39; participants = 28; studies = 1; Analysis 18.2; Summary of findings 4). Fisher's exact test confirmed this analysis (P = 0.429). One participant in the placebo arm reported folliculitis. We downgraded the quality of evidence by two levels to low: one level for limitations of design due to unclear judgement of all but one domain, which we judged as low (selection bias), and one level due to imprecision (small sample size).

Secondary outcome 1. Mean change in physician-assessed clinical signs

For this outcome, researchers assessed the SCORAD after four weeks and found that the difference between groups was not significant (MD -4.10, 95% CI -13.22 to 5.02; P = 0.38; participants = 28; studies = 1; Analysis 18.3; Summary of findings 4). We downgraded the quality of evidence by two levels to low: one level for limitations of design due to unclear judgement of all but one domain, which we judged as low (selection bias), and one level due to imprecision (small sample size)

Langeland 1994 reported the results of an intermediate-term intervention conducted in adults in a complex cross-over trial comparing the effects of 10 mg/d loratadine versus placebo in six consecutive periods, each lasting two weeks (six periods, each lasting two weeks = 12 weeks total duration of study; n = 16). Statistical methods used for analysis were inappropriate, as study authors used methods for independent data and not for related data. Therefore these findings must be interpreted with caution. For instance, Hotelling's T^2 test was specified to compare the effects of loratadine versus placebo. Hence, no control was provided for carry-over and period effects.

Primary outcome 1. Mean change in patient-assessed symptoms of eczema

For this outcome, study authors assessed pruritus during the day and during the night on a 10-cm VAS recorded daily by the participant. Study authors stated that they detected significant effects of loratadine as compared with placebo with regard to this outcome, favouring the intervention. However, the statistical test used was inappropriate, as it did not account for the within-subject design. Reported changes in mean VAS scores varied little across treatment periods. No data from this study were available for analysis. We downgraded the quality of evidence by two levels: one level for limitations of design due to serious risk of bias (all domains judged as having unclear risk of bias), and one level due to imprecision (small sample size).

Primary outcome 2. Proportion of participants reporting adverse effects and serious adverse events throughout the study period

Study authors reported that they noted no adverse effects irrespective of treatment. We downgraded the quality of evidence by two levels from high to low: one level for limitations in design (all domains judged as having unclear risk of bias), and one level due to imprecision (small sample size).

Secondary outcome 3. Number of eczema flares, measured by, for example, 'escalation of treatment' or 'use of topical anti-inflammatory medications'

Study authors reported that the mean number of days with use of local steroids during the six treatment periods and the severity of rash at the end of each treatment period showed a similar pattern to those reported for pruritus during the day and at night. Again, caution is needed in interpreting these findings. We could extract from this study no data for analysis. We downgraded the quality of evidence by two levels from high to low: one level for limitations in design (all domains judged as having unclear risk of bias), and one level due to imprecision (small sample size).

Comparison 11

Olopatadine 10 mg/d versus no additional treatment

We identified one parallel-group study (n = 99) that compared this intervention in adults (Kuniyuki 2009), which reported the results of a long-term intervention (eight weeks).

Primary outcome 1. Mean change in patient-assessed symptoms of eczema

For this outcome, researchers assessed pruritus once by VAS (0 to 100) scale, and once by the 5-point Likert scale (Shiratori scale) (0 = none to 4 = severe). Both instruments were found to be significantly different between groups at weeks 2, 4, and 8. Study authors reported significantly lower values for the olopatadine group than for those given no additional treatment. The comparison thus favours the intervention group. We could extract no data from this study for analysis. We downgraded the quality of evidence from high to moderate due to limitations in design (all domains judged as having unclear or high risk of bias).

Primary outcome 2. Proportion of participants reporting adverse effects and serious adverse events throughout the study period

Investigators reported that 8% (4/49) of those in the olopatadine group and 0% (0/50) in the no additional treatment group reported mild sleepiness (RR 9.18, 95% CI 0.51 to 166.10; P = 0.13; participants = 99; studies = 1; Analysis 19.1). We downgraded the quality of evidence from high to low due to limitations in design (all domains judged as having unclear or high risk of bias) and serious imprecision (wide CI due to low sample size).

Secondary outcome 1. Mean change in physician-assessed clinical signs

For this outcome, researchers measured results by SCORAD. At week 8, they observed significantly lower values in the olopatadine group than in the no additional treatment group. The comparison thus favours the intervention group. No data from this study were available for analysis. We downgraded the quality of evidence from high to moderate due to limitations in design (all domains judged as having unclear or high risk of bias).

Secondary outcome 3. Number of eczema flares, measured by, for example, 'escalation of treatment' or 'use of topical anti-inflammatory medications'

Investigators assessed this outcome by using a topical steroid score. Its respective potency (0.5 to 3) and the amount (g) of topical steroids applied were multiplied to obtain the score. Study authors reported that the decrease in score was significantly lower in the olopatadine group than in the no additional treatment group (P < 0.05) eight weeks after randomisation. The comparison thus favours the intervention group. No data from this study were available for analysis. We downgraded the quality of evidence from high to moderate due to limitations in design (all domains judged as having unclear or high risk of bias).

Comparison 12

Terfenadine versus placebo

We identified three studies that performed this comparison. One study used a parallel-group design (Doherty 1989), and two used a cross-over design (Berth Jones 1989; Hjorth 1988).

Doherty 1989 reported an intermediate-term intervention (10 days) of 180 mg/d in adults but assessed primary outcome 1 seven days after baseline (short-term).

Primary outcome 1. Patient-assessed symptoms of eczema: VAS pruritus seven days after baseline

VAS pruritus scores (seven days after baseline and adjusted for baseline scores as a covariate; range 0 to 100) were higher in the placebo group than in the terfenadine group, but the 95% CI was wide and included one showing uncertainty (MD -15.20, 95% CI -33.03 to 2.63; P = 0.09; participants = 27; studies = 1; Analysis 20.1). We downgraded the quality of evidence by two levels from high to low because of unclear risk of bias for most domains and because of imprecision (wide CI due to small sample size or high variability in outcome measurement).

Secondary outcome 1. Mean change in physician-assessed clinical signs

This study provided data not in the form of mean change but as the number of participants for whom treatment helped itching (physician-assessed). Study authors reported more events in the intervention group but showed no significant difference between terfenadine and placebo groups due to the wide 95% CI, including 1 (RR 2.19, 95% CI 0.88 to 5.44; P = 0.09; participants = 30; studies = 1; Analysis 20.2). We downgraded the quality of evidence by two levels from high to low because of unclear judgement for most domains and serious imprecision (wide CI due to small sample size).

Berth Jones 1989 reported the results of a short-term intervention (one week) of 240 mg/d of terfenadine versus placebo in adults using a cross-over design. Researchers used appropriate statistical tests to attempt to account for possible carry-over and period effects (Wilcoxon rank test = paired text accounting for within-subject design) and as such was an exception among the cross-over trials considered for inclusion in this review.

Primary outcome 1. Patient-assessed symptoms of eczema: VAS pruritus after one week

Study authors reported no evidence of differences between intervention and placebo. Mean scores were 23.95 (standard error (SE) = 4.9) in the terfenadine group and 23.13 (SE = 5.1) in the placebo group. Study authors reported no significant differences between groups based on a Wilcoxon signed rank matched-pair test. We downgraded the quality of evidence by two levels from high to low due to limitations in design (unclear judgement for most domains) and imprecision (small sample size). No data from this study were available for analysis.

Primary outcome 2. Proportion of participants reporting adverse effects and serious adverse events throughout the study period

One participant given placebo and one taking terfenadine reported drowsiness. We downgraded the quality of evidence by two levels from high to low due to limitations in design (unclear judgement for most domains) and imprecision (small sample size).

Secondary outcome 1. Mean change in physician-assessed clinical signs

This study assessed the severity of excoriations and found no significant differences between intervention and placebo groups. No data from this study were available for analysis. We downgraded the quality of evidence by two levels from high to low due to limitations in design (unclear judgement for most domains) and imprecision (small sample size).

Another cross-over trial conducted in adults reported the results of an intermediate-term intervention (two weeks) of 120 mg/d terfenadine versus placebo (Hjorth 1988).

Primary outcome 1. Mean change in patient-assessed symptoms of eczema

Researchers assessed this outcome as severity of itch (no further details given). They stated that terfenadine reduced the severity of itch in approximately 52% of participants; 34% reported no change, and 14% reported increased severity of itch. However, study authors provided no test for significance and no data for placebo. Hence, we could extract no data from this study for analysis. We downgraded the quality of evidence by two levels from high to low due to serious risk of bias (all domains judged as having unclear or high risk of bias) and imprecision (small sample size).

Comparison 13

LN2974 (tazifylline) 15 mg/d versus placebo

We identified one cross-over study that compared this intervention in adults (Savin 1986). Study authors reported a short-term intervention upon randomising participants to receive placebo for seven days, placebo or tazifylline for three days, placebo for seven days, and placebo or tazifylline for three days.

Primary outcome 1. Mean change in patient-assessed symptoms of eczema

For this outcome, researchers assessed pruritus by VAS, noting no significant differences between treatment and placebo. No data from this study were available for analysis. We judged the quality of evidence to be low, as we downgraded the outcome by one level due to serious risk of bias (all domains judged as having unclear risk of bias) and one level due to imprecision (small sample size).

Comparison 14

One single-patient trial compared in a cross-over fashion the effects of chlorpheniramine and terfenadine versus placebo (Nuovo 1992). The trial consisted of four periods, each lasting two weeks, during which placebo, chlorpheniramine 16 mg/d, chlorpheniramine 24 mg/d, or terfenadine 240 mg/d was administered. We downgraded the quality of evidence from high to very low due to very serious imprecision (single-patient trial = small sample size) for all comparisons.

Primary outcome 1. Mean change in patient-assessed symptoms of eczema

For this outcome, researchers assessed pruritus on a 7-point Likert scale. Mean scores during placebo were 1.7, during chlorpheniramine 16 mg/d 0.7, during chlorpheniramine 24 mg/d 0.7, and during terfenadine 240 mg/d 1.4. Results show a marginally significant difference (P = 0.06). No data from this study were available for analysis.

For this outcome, researchers also assessed the severity of symptoms on 7-point Likert scale. Mean scores during placebo were 2.0, during chlorpheniramine 16 mg/d 2.6, during chlorpheniramine 24 mg/d 3.0, and during terfenadine 240 mg/d 1.5. Study authors observed no significant differences (P = 0.10). No data from this study were available for analysis.

Primary outcome 2. Proportion of participants reporting adverse effects and serious adverse events throughout the study period

For this outcome, investigators assessed the severity of drowsiness on a 7-point Likert scale. Mean scores during placebo were 2.6, during chlorpheniramine 16 mg/d 1.9, during chlorpheniramine 24 mg/d 2.7, and during terfenadine 240 mg/d 3.1. Study authors observed no significant differences (P = 0.30). No data from this study were available for analysis.

Secondary outcome 3. Number of eczema flares, measured by, for example, 'escalation of treatment' or 'use of topical anti-inflammatory medications'

For this outcome, investigators assessed the number of daily applications of the topical steroid triamcinolone. Mean scores during placebo were 0.8, during chlorpheniramine 16 mg/d 0.9, during chlorpheniramine 24 mg/d 0.3, and during terfenadine 240 mg/d 0.3. Study authors observed a marginally significant difference (P = 0.06). No data from this study were available for analysis.

DISCUSSION

It is assumed that about 40 different H1 antihistamines (AH) have been developed (Simons 2004; Simons 2011). How many of these have been applied orally to relieve the symptoms and signs of eczema is not known, and little is known about their efficacy and safety despite the fact that oral H1 AH are widely prescribed for patients with eczema.

Summary of main results

We identified 25 randomised controlled trials (RCTs) that tested oral H1 AH as an 'add-on' treatment for eczema against placebo or no add-on treatment; these trials randomised 3285 participants with eczema. Here, we summarise results for the four main comparisons.

For the comparison 'Cetirizine 0.5 mg/kg/d versus placebo' (18-month intervention) in 795 children (Summary of findings for the main comparison), researchers assessed the outcome 'Patient-assessed symptom reduction' as part of the SCORing Atopic Dermatitis index (SCORAD) assessment but did not present data separately for pruritus. Adverse events (mainly mild) were probably less frequent in the intervention group than in the placebo group, but this finding is based on moderate-quality evidence. With regard to the outcome 'Physician-assessed clinical signs', moderate-

quality evidence indicates there is probably no difference in treatment-related reduction in SCORAD scores between baseline and the final visit (only change scores were provided, without standard deviations). For the outcome 'Number of eczema flares, measured by, for example, 'escalation of treatment' or 'use of topical anti-inflammatory medications', study authors assessed the use of a variety of topical and systemic medications, yielding moderate-quality evidence to show that the intervention probably leads to slightly less additional H1 AH use to prevent flares.

For the comparison 'Cetirizine 10 mg/d versus placebo' (four-week intervention) in 84 adults (Summary of findings 2), investigators provided low-quality evidence for 'Patient-assessed symptom reduction'; thus, we are uncertain whether cetirizine 10 mg/d improves pruritus. It is noteworthy that the values reported in Table 2 of the publication actually increased from baseline to the last visit, although the legend stated that "lower values indicate less pruritus". We tried to contact the study authors to inquire about this but were not successful in doing so. Low-quality evidence suggests that adverse events may be slightly higher in the intervention group than in the placebo group, but this result was highly imprecise (due to the small number of participants; n = 84). Adverse events reported included sedation, other skin-related problems, respiratory symptoms, and headache. Low-quality evidence suggests no difference in 'physician-assessed signs' between the cetirizine and placebo groups (but no numerical data were provided). With regard to the outcome 'Number of eczema flares, measured by, for example, 'escalation of treatment' or 'use of topical anti-inflammatory medications'', low-quality evidence suggests no difference in the amount of local rescue therapy (emollient or 1% hydrocortisone) nor in the number of applications observed among groups.

For the comparison 'Fexofenadine 120 mg/d versus placebo' (1-week intervention) in 411 adults (Summary of findings 3), moderate-quality evidence shows there is probably a larger 'patient-assessed symptom reduction' (pruritus) in the fexofenadine group than in the placebo group. Moderate-quality evidence shows there is probably little or no difference between groups in occurrence of adverse events (mostly somnolence and headache) nor in the number of eczema flares, measured by the amount of 0.1% hydrocortisone butyrate cream used during the study. Moderate-quality evidence also shows probably a greater reduction in 'physician-assessed clinical signs' with fexofenadine, in terms of investigator-assessed change in the ratio of pruritus area to body surface area, where significantly more participants in the fexofenadine group than in the placebo group experienced a reduction in pruritus. We could not ascertain the magnitude of this effect because study authors reported no coefficient. The clinical meaningfulness of the effect was small, however.

For the comparison 'Loratadine 10 mg/d versus placebo' (four-week intervention) in 28 adults (Summary of findings 4), the quality of evidence was low for all outcomes. The outcome 'Patient-assessed symptom reduction' may be slightly higher in the intervention group, but the result was very imprecise. Study authors reported only one adverse event (folliculitis), and it occurred in the placebo group. The mean change in physician-assessed clinical signs (SCORAD) was greater in the intervention group, but again, this was based on imprecise data. Investigators did no assess the number of eczema flares.

Additional summary of results

Results show no significant differences in patient-assessed symptoms for acrivastine, azelastine, chlorpheniramine and chlorpheniramine maleate BP, hydroxyzine, ketotifen, levocetirizine, LN2974 (tazifylline), and terfenadine. For most comparisons of cetirizine, low- to moderate-quality evidence shows no significant differences in patient-assessed symptoms. For an eight-week intervention in children (low-quality evidence) and a two-week intervention in adults (moderate-quality evidence), cetirizine significantly improved patient-assessed symptoms compared to placebo. In four comparisons of loratadine, researchers observed non-significant differences, and for the other two comparisons - loratadine (low-quality evidence) and olopatadine (moderate-quality evidence) - patient-assessed symptoms were significantly better in the intervention group than in the placebo group.

Results show significantly more adverse events in the intervention group than in the placebo group for one ketotifen comparison (low-quality evidence), but two others did not measure adverse events. For one cetirizine comparison (40 mg/d; low-quality evidence), results show significantly more adverse events in the intervention group; for all other cetirizine comparisons, researchers observed no significant differences, or we could extract no data. For comparisons of acrivastine, azelastine, chlorpheniramine or chlorpheniramine maleate BP, hydroxyzine, levocetirizine, olopatadine, LN2974 (tazifylline), olopatadine, and terfenadine, study authors observed no significant differences, or we could extract no data.

Investigators reported significantly greater improvement in physician-assessed signs in the intervention groups for the comparison acrivastine (low-quality evidence) and olopatadine (moderate-quality evidence), and two ketotifen comparisons (low- or moderate-quality evidence) but not for the others, and for two cetirizine comparisons (both-low quality evidence) but not for the others. Results show no significant differences in physician-assessed signs, or investigators did not assess this difference for azelastine, chlorpheniramine or chlorpheniramine maleate BP, hydroxyzine, levocetirizine, loratadine, LN2974 (tazifylline), or terfenadine.

Results show significantly better flare control with the intervention for one cetirizine (low-quality evidence) and one olopatadine (moderate-quality evidence) comparison. For all other comparisons, differences were non-significant, or we could extract no data.

Overall completeness and applicability of evidence

Applicability of the evidence described in this review may be restricted by a variety of factors.

Most studies considered in this review were conducted in high-income countries; thus, the generalisability of study findings may need to be considered in light of socioeconomic issues related to education or access to health care.

Even within the scope of socioeconomically restricted populations, it is not clear whether study findings can be generalised to all groups within the population from which the specific sample was drawn. Little information on sociodemographic features was available from most included studies, and very rarely did study

authors attempt to establish that no differences in these features were apparent between groups before commencement of the intervention. However, compliance with therapeutic regimens or adherence to medication is, for instance, associated with sociodemographic variables such as old age, male gender, low education level, physical and mental status, and health literacy (Jin 2016). Health behaviour in general is also affected by sociodemographic and socioeconomic variables (Wang 2011).

Populations from which samples were drawn may have differed across studies with regard to diagnostic characteristics, as a standardised approach to obtaining the diagnosis of eczema based on established criteria such as the Hanifin and Rajka definitions or the UK modification was not evident in all studies (Hanifin 1980; Williams 1994). All trials were conducted in secondary settings. However, a large proportion of trials recruited their sample from within the setting of university hospitals. These are not distributed evenly across countries, and it is likely that patients with more severe cases of eczema may attend clinics there. Thus, these trials may have investigated samples with different clinical features compared to samples recruited in dermatology or general practitioner practices. Further, most trials appear to have used convenience samples rather than random samples.

Although trials have studied many interventions (such as acrivastine, azelastine, cetirizine, chlorpheniramine, chlorpheniramine maleate, fexofenadine, hydroxyzine, ketotifen, levocetirizine, loratadine, olopatadine, tazifylline LN2974, and terfenadine) as oral add-on treatments for eczema, other H1 AH have not been investigated as add-on eczema treatments. For instance, ebastine, rupatadine, desloratadine, diphenhydramine, dimetindene, clemastine, cyproheptadine, mizolastine, and promethazine are H1 AH that are used in clinical practice for treatment of eczema, although their efficacy and safety have not yet been examined.

Duration of treatment in the included studies ranged between three days and 18 months, which allowed us to assess the effects of H1 AH over a variety of time frames. However, for many specific H1 AH, only one study considered the effect of the specific H1 AH medication and dose, but for others, such as loratadine and cetirizine, several studies provided data over a variety of time frames. Overall, the duration of treatment may have been insufficient in some studies to establish treatment effects, especially for long-term eczema control. The quality of most evidence was low, so caution should be applied when attempting to generalise observed effects.

Conclusions drawn from these studies should apply only to short-term relief and consideration of potential adverse events, respectively, in this short time frame or observational period.

Many studies were conducted in small samples, thus reducing the statistical power associated with the likelihood of increased type II error, and some used a cross-over design with sometimes undefined washout periods. Although we would have liked to conduct meta-analyses to arrive at effect sizes over many studies, it was not possible to do so, as researchers used 13 different H1 AH and applied widely varying dosages and intervention durations.

Most included studies assessed our primary outcomes of interest well but did not evaluate our secondary outcomes as well: less than half of the included studies measured the number of eczema flares, and only one study measured ‘mean change in quality of life, as measured by a standardised or validated quality of life measure'.

Although we had planned to analyse cross-over data adequately by accounting for the correlation of data points measured within participants, lack of respective coefficients in the publication and our inability to contact study authors meant that we could provide only narrative accounts of these results.

Additionally, we had intended to pursue the study of H1 AH interventions in patients with eczema with allergic comorbidity as assessed by allergic sensitisations (known as "atopic" eczema). However, no data were available, and we were not able to do so.

Quality of the evidence

Our overall judgement of the quality of the body of evidence based on the GRADE approach was low or very low (Higgins 2011). In a few instances, we believed a moderate judgement was merited. We felt that downgrading was necessary most often because of incomplete outcome data, selection bias, unclear judgement of several or all other risk of bias domains, or serious imprecision. These reasons in addition to the details provided below may impact the quality of the evidence and must be considered when conclusions are drawn on the basis of study findings considered in this review.

Limitations in study design and implementation

Assessment of risk of bias according to Cochrane's 'Risk of bias' tool showed that no single study was at low risk of bias across all domains (Figure 3; Figure 4). Most studies failed to provide sufficient information to allow a comprehensive assessment of the seven domains of risk of bias. Hence, we judged that many studies were at unclear risk of bias for most or all domains. We judged only a few studies to be at low risk of bias for one or more domains. We rated five (25%) included studies as having high risk of bias for at least one domain. In two instances, this referred to incomplete outcome data (attrition bias), in two others, to selection bias, and once, to selective outcome reporting (reporting bias). For all other studies, we judged at least one domain to be at unclear risk of bias. Across studies, we obtained the information collated in this review from studies with overall high risk of bias (25%) or overall unclear risk of bias (75%).

With regard to general quality of the experimental design, further problems arose. No single study reported that a manipulation check had been carried out (e.g. blood samples to check whether the experimental group took H1 AH or used other means to observe compliance).

Another issue deserving discussion revolves around the question of whether intervention and placebo groups were balanced with regard to important clinical and sociodemographic characteristics. Although several study investigators analysed their study data to demonstrate that groups did not differ at baseline, this could not be taken as evidence that allocation bias was absent. First of all, the variables used to analyse any differences were often based on very basic sociodemographic data - not on relevant clinical variables - or study authors reported no differences but did not provide data, or it is not clear on what variable(s) the comparison was based.

Inconsistency of results

Most of the comparisons included in this review were performed in single studies, which did not allow us to assess consistency

of results across studies for different H1 AH treatments. When several single studies investigated the same H1 AH, the duration, the dosage, or the population differed. Differences also occurred with regard to concomitant topical treatment. This heterogeneity meant that we were unable to conduct any meta-analyses.

Indirectness of evidence

In addition, the quality of outcome measures cannot be said to be of high quality across trials. Some measures such as the SCORAD have been used widely and have undergone more rigorous attempts to establish their measurement quality than others (Gerbens 2017; Rehal 2011; Schmitt 2013).

Nonetheless, the quality of several of the other measures summarised under secondary outcome 1 ('Mean change in physician-assessed clinical signs') remains questionable, as study authors failed to provide information on their measurement properties.

Researchers often use the visual analogue scale (VAS) to assess pruritus (Pereira 2017). However, little is known about its measurement properties, particularly responsiveness, when used in trials of patients with eczema because validation studies have not been conducted or measurement properties remain unclear (Gerbens 2017). In the most comprehensive systematic review evaluating the measurement properties of symptom measurement instruments for eczema, review authors put the VAS into category D (A highest, D lowest). Category D meant that the VAS has (almost) not been validated at all (Gerbens 2017). Kido-Nakahara 2015 was referred to as providing limited evidence for indeterminate construct validity of VAS pruritus.

Nine of the 23 included studies providing a measure of pruritus utilised a VAS. The remainder used a variety of measures, most of which failed to report on their measurement properties.

Neither was a standardised assessment of eczema control (Secondary outcome 3. 'Number of eczema flares, measured by, for example, ‘escalation of treatment’ or ‘use of topical anti-inflammatory medications'') used in any of the studies considered in this review. International consensus suggests that long-term control of eczema flares should be included as a core outcome domain in future eczema trials (Schmitt 2012). However, it is unclear how this should be defined and measured (Langan 2006; Langan 2014); included studies varied in terms of individual assessment.

In summary, the validity of outcome measures continues to be an important consideration for the present evidence base, given the variety of tools utilised and their unclear quality. Although many studies reported the validity of their measurement tools, many others did not.

Imprecision of results

Many studies were conducted with small samples, thus reducing the statistical power associated with increased likelihood of type II error; some used a cross-over design with sometimes undefined washout periods.

Publication bias

Publication bias was difficult to assess because few published studies have assessed the same H1 AH, the same dosage, similar treatment duration, and comparable concomitant treatment. However, because we were also able to include the results of unpublished studies, we were able to minimise any existent publication bias. We remain uncertain about whether this review was able to include all data that have been accumulated so far.

Potential biases in the review process

Studies that met our criteria for inclusion in this review were carried out all over the world. We believe we have searched exhaustively and comprehensively and have identified studies conducted in geographically diverse populations, including those from the USA, Australia, South Africa, several European countries, Central America, and Japan. We also searched abstracts from the International Research Workshops on eczema (George Rajka International Symposia on Atopic Dermatitis (ISAD)) and conference proceedings of the European Academy of Dermatology and Venereology (EADV) from 2000 to 2017, the European Academy of Allergy and Clinical Immunology (EAACI) from 2010 to 2015, and the American Academy of Dermatology (AAD) from 2012 to 2015, to identify further potentially relevant RCTs. We searched for reports on clinical trials in progress and for data from completed but unpublished clinical trials, and we checked (handsearched) the reference sections of included and excluded studies for further relevant trials. Our ongoing trials search yielded unpublished studies - Jung 1989 and Cambazard 2001 - that had not been included in previous systematic reviews on the topic - Hoare 2000 and Klein 1999 - nor were these detected in a comprehensive literature review that occurred before these reviews (Sidbury 2014). We did all of this to minimise the risk of potential publication bias in this review.

We included only randomised trials; thus addressing all possible outcomes that may have been investigated in uncontrolled trials was not possible within the constraints of this review. Choice of outcomes was based on both clinical meaningfulness and the core outcome set consented to by the Harmonising Outcome Measures in Eczema (HOME) initiative (clinician-reported signs, patient-reported symptoms, quality of life, and long-term control) (Schmitt 2012; Schmitt 2014). Selection of RCTs for inclusion, however, was not based on prespecified outcomes, but rather on types of studies, participants, and interventions.

Although we assessed risk of bias for all studies, it was often impossible to determine whether studies were at high or low risk of bias due to insufficient reporting of information necessary for the respective risk of bias judgement. Contacting study authors for additional information proved difficult, as all contacted authors failed to respond to our queries. Hence, we judged a large number of studies in this review as having unclear risk of bias for many, sometimes even all, domains.

Agreements and disagreements with other studies or reviews

We identified several literature reviews and systematic reviews (Hoare 2000; Klein 1999; Sidbury 2014), and our findings are in concordance with them. However, although one review stated that the efficacy of antihistamines remains to be adequately investigated (Klein 1999), our recommendations are slightly different (see Implications for practice). We found that there is now a significant body of clinical trial evidence on this topic, and we concluded that trials of antihistamines were unable to

demonstrate a clear benefit of the intervention. A recent study analysing secondary data concluded that H1 AH, although widely prescribed, especially by non-dermatologists, are not effective in reducing pruritus in eczema (He 2018). These findings are consistent with the findings of this review.

AUTHORS' CONCLUSIONS

Implications for practice

We found little conclusive evidence to establish the effectiveness of H1 AH as add-on therapy to topical treatment for eczema. We derived this conclusion from careful consideration of the quality of included trials and their reporting, as well as the wide variation in comparisons and the fact that we found no opportunities to combine results in meta-analyses.

Details of the specific dose and regimen of the interventions described in this section are found in Effects of interventions. All interventions in this section were compared against placebo.

With regard to the primary outcome 'Patient-assessed symptoms', which we narrow here specifically to participant-assessed pruritus, we found no evidence that cetirizine 10 mg/d or loratadine makes a difference in this outcome (both low-quality evidence). Fexofenadine probably slightly improves this outcome (moderate-quality evidence), but the clinical meaning of this slight improvement is uncertain. Trials assessing cetirizine 0.5 mg/kg/d did not report this outcome.

Fexofenadine probably makes little or no difference in the occurrence of adverse effects, and cetirizine 0.5 mg/kg/d is probably associated with fewer adverse events (both moderate-quality evidence). We found no evidence that cetirizine 10 mg or loratadine makes a difference in this outcome (both low-quality evidence).

In terms of physician-assessed clinical signs, we found no evidence that loratadine or cetirizine 10 mg/d or 0.5 mg/kg/d makes a difference (low-quality evidence). Fexofenadine probably improves this outcome (moderate-quality evidence), but the clinical meaning of this improvement is uncertain.

Fexofenadine probably makes little or no difference in terms of the number of eczema flares (measured by 'escalation of treatment' or 'use of topical anti-inflammatory medications') (moderate-quality evidence). We found no evidence that cetirizine 10 mg makes a difference in the amount of treatment required (low-quality evidence), but less cetirizine 0.5 mg/kg/d is probably needed, hence reducing the number of eczema flares (moderate-quality evidence). Trials assessing loratadine did not report this outcome.

We could draw no conclusions about effects on quality of life as only one study assessed this outcome. The data provided by this single study were insufficient for statistical analysis.

Implications for research

One general implication of this review is that some uncertainty remains with regard to the question of whether H1 AH are effective in the treatment of eczema. Further, review findings are not robust. In light of these limitations, little evidence from the 25 included trials suggests that H1 AH have a clinically significant impact on eczema.

As the quality of evidence was often low and our risk of bias assessment arrived frequently at a judgement of unclear, we would like to recommend several methodological requirements for future studies, which should be randomised controlled trials. First, research would benefit from a clear definition of the condition examined, including its course and severity. In intervention studies, it is important to know who exactly was studied, which is why a standardised assessment should be carried out and appropriately reported. Many of the reviewed studies failed to provide this important information. Other relevant baseline data should be obtained and reported. For instance, a clear sociodemographic description should be provided. In our review, most studies failed to do so.

Second, we often noted insufficient detail on how randomisation was implemented, how allocation concealment was achieved, and how incomplete outcome data (attrition) were dealt with. Adherence to guidelines, such as the CONSORT (Consolidated Standards of Reporting Trials) statement (Moher 1998), would help in ensuring complete reporting. For example, to safeguard against incomplete outcome data, investigators need to routinely anticipate attrition and incorporate various measures to minimise dropouts during trial design (Hui 2013). Study participants should be well informed, and expectations with respect to study procedures should be realistic (Matsui 2012). Should substantial attrition occur, it is of paramount importance to assess whether attrition may have affected any effect estimates (Hui 2013). To ensure that intervention and placebo groups are balanced with regard to important clinical and demographic variables, investigators should employ and report adequate randomisation procedures and should check the distribution of these variables between groups.

Third, future research would benefit from a standardised assessment of outcomes. Guidance for choice of reliable and valid outcome measures may be obtained from the HOME initiative (Schmitt 2014). Future availability of more trials using the same standardised outcome measurement, similar intervention periods, and comparable dosages may allow pooling of data - something we could not do. We also recommend that future studies should be conducted in a multi-arm fashion with regard to dosages, such that several different dosages of the same H1 AH are compared against placebo. Further, concomitant treatment should be applied in a standardised way. For instance, studies should mimic clinical practice in accordance with existing guidelines, consisting of moisturisers and/or emollients in combination with either corticosteroids or other immunomodulatory agents (such as tacrolimus or pimecrolimus) (Werfel 2016). Additionally, we suggest that H1 AH interventions should be studied in patients with eczema with allergic comorbidity as assessed by allergic sensitisations (known as 'atopic' eczema).

Several of the included trials studied small or very small samples. As a consequence, we downgraded the quality of the evidence from such trials. Future studies should state what effect is considered clinically useful and should base the sample size calculation on this effect to achieve adequate power. This would greatly enhance confidence in effect estimates.

An important issue pertains to the generalisability of reported findings. Most studies appear to have based their selection rationale on easy availability of potential participants in clinical settings. In other words, the samples can be said to be convenience

samples - a fact that greatly limits the extent to which findings can be generalised to the population of patients with eczema on the whole. Authors of high-quality intervention studies should design their trials to maximise the generalisability of study findings.

Moreover, although the duration of the intervention and of follow-up was as long as 18 months for cetirizine and levocetirizine, up to 52 weeks for ketotifen, or eight weeks for olopatadine, only short- or medium-term interventions and follow-ups were available for acrivastine, azelastine, chlorpheniramine, fexofenadine, hydroxyzine, loratadine, terfenadine, or tazifylline. Future research should ensure a sufficient duration of the intervention to assess impact on eczema severity.

However, as current guidelines recommend the use of H1 AH as add-on to conventional topical treatment during acute flares only (Werfel 2016), future studies could greatly benefit from comparing H1 add-on treatment in groups of patients with acute flares that are comparable.

Only one study assessed quality of life, but the data it provided were insufficient for statistical analysis. It must be borne in mind though that many studies were conducted at a time when health-related patient-reported outcomes were given minor credence compared to today. It is recommended that future trials should include one such measure, in line with the consented core outcome set of the HOME initiative (Heinl 2016; Heinl 2017; Schmitt 2012).

There is scope for replication studies. For instance, olopatadine and fexofenadine were found to have positive effects, albeit of little clinical significance. Further confirmatory trials may be informative. There is also scope for investigating other H1 AH as oral add-on interventions for eczema. For instance, other H1 AH, such as ebastine, rupatadine, desloratadine, diphenhydramine, dimetindene, clemastine, cyproheptadine, mizolastine, and promethazine, are used in clinical practice for the treatment of eczema. However, the efficacy and safety of these agents have not yet been studied in clinical trials.

Should future studies establish more robust evidence for specific H1 AH treatment effects on eczema and adequate safety, subsequent trials could try to compare H1 AH among each other.

In light of recent findings that not only histamine-related pathways lead to mediation of pruritus (Ständer 2002; Tominaga 2016; Yosipovitch 2008), it may be worthwhile to study combination treatments in the future.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Berth Jones 1989

Methods	**Study design:** randomised controlled trial **Study grouping:** cross-over
Participants	**Baseline characteristics** Terfenadine • *Number of participants randomised*: 28 • *Losses to follow-up*: 4 • *Age*: M = 28.6 years • *Duration of condition*: not reported • *Severity of condition*: not reported • *Male/Female*: not reported Placebo • *Number of participants randomised*: 28 • *Losses to follow-up*: 4 • *Age*: M = 28.6 years • *Duration of condition*: not reported • *Severity of condition*: not reported • *Male/Female*: not reported **Inclusion criteria:** (1) diagnostic: eczema as defined by Hanifin and Rajka (1980); (2) severity of condition: not specified; (3) duration of condition: not specified; (4) site evaluated (e.g. face/back): physician-assessed over entire body **Exclusion criteria:** not reported **Group differences:** cross-over study
Interventions	**Intervention characteristics**

Berth Jones 1989 *(Continued)*

	Terfenadine • *Presentation*: tablets • *Dose and frequency*: 120 mg twice daily • *Total dose*: 240 mg/d • *Duration given for*: 1 week • *Supplier and trade name if relevant*: not reported Placebo • *Presentation*: matched • *Dose and frequency*: matched • *Total dose*: matched • *Duration given for*: matched • *Supplier and trade name if relevant*: not reported
Outcomes	*Primary outcome: patient-assessed symptoms: pruritus VAS (0 to 10)* • **Outcome type:** continuous outcome • **Reporting:** fully reported • **Direction:** lower is better • **Data value:** endpoint *Primary outcome 2: adverse events* • **Outcome type:** adverse event *Secondary outcome 1: physician-assessed clinical signs* • **Outcome type:** continuous outcome • **Notes:** severity of excoriations at end of treatment; no exact numbers given nor results of significance tests
Identification	**Sponsorship source:** not stated **Country:** UK **Setting:** secondary **Comments:** not specified, presumably outpatient hospital (i.e. secondary care), probably Leicester Royal Infirmary as affiliation of main study author **Author's name:** Berth-Jones, John, Dr. **Institution:** Department of Dermatology, University Hospitals Coventry and Warwickshire NHS Trust **Email:** johnberthjones@aol.com **Address:** Department of Dermatology, University Hospitals Coventry and Warwickshire NHS Trust, Coventry CV2 2DX, UK
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: study authors merely state 'in randomised order'. Insufficient information about the sequence generation process to permit judgement of low risk or high risk

Berth Jones 1989 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement of low risk or high risk
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: Although study authors state that they report "the results of a double-blind, placebo-controlled" study, whether the placebo was identically matched to the terfenadine tablets remains unclear
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: apart from stating "double-blind", information is insufficient to permit judgement of low risk or high risk
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: loss to follow-up: 4/28; no ITT analysis. Attrition less than 20%, so not substantial
Selective reporting (reporting bias)	Low risk	Comment: no comparison possible with protocol, as study protocol is not available, but it is clear that the published report includes all expected outcomes, including those that were prespecified
Other bias	Unclear risk	Comment: there may be further risk of bias but information is insufficient to judge whether additional bias exists (e.g. no conflict of interest statement provided, no provision of information regarding origin of drugs, Was study initiated by pharmacological company? Did study authors receive funding from any source?)

Cambazard 2001

Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group
Participants	**Baseline characteristics** Cetirizine 0.25; 0.50; 0.75 mg/kg bw/d • *Number of participants randomised*: not reported • *Losses to follow-up*: not reported • *Age*: not reported • *Duration of condition*: not reported • *Severity of condition*: not reported • *Male/Female:* not reported Placebo • *Number of participants randomised*: not reported • *Losses to follow-up*: not reported • *Age*: not reported • *Duration of condition*: not reported • *Severity of condition: not reported* • *Male/Female*: not reported Total • *Number of participants randomised*: 223 • *Losses to follow-up*: not reported

Cambazard 2001 *(Continued)*

- *Age*: M = 30.8 months (range 11 to 71 months)
- *Duration of condition*: not reported
- *Severity of condition:* not reported
- *Male/Female*: 59% male

Inclusion criteria: (1) diagnostic: children, male or female, 1 to 5 years old, who suffer from atopic dermatitis, with written consent to participate in the trial obtained from parents/legal representatives, who satisfy all inclusion/exclusion criteria; (2) severity of condition: not reported; (3) duration of condition: not reported; (4) site evaluated (e.g. face/back): not reported

Exclusion criteria: not reported

Group differences: not reported

Interventions	**Intervention characteristics** Cetirizine 3 groups • *Presentation*: oral drops • *Dose and frequency*: 0.25; 0.50; 0.75 mg/kg bw/d • *Total dose*: 0.50 mg/kg bw/d • *Duration given for*: 8 weeks • *Supplier and trade name if relevant*: UCB Pharma Placebo • *Presentation*: oral drops • *Dose and frequency*: matched • *Total dose:* n/a • *Duration given for*: 8 weeks • *Supplier and trade name if relevant*: UCB Pharma
Outcomes	*Primary outcome 1: mean change in patient-assessed symptoms:* not reported *Primary outcome 2: adverse events* • **Outcome type:** adverse event *Secondary outcome 1: physician-assessed clinical signs: modified SCORAD* • **Outcome type:** continuous outcome *Secondary outcome 3: number of eczema flares, measured by, for example, 'escalation of treatment' or 'use of topical anti-inflammatory medications'* • Amount of hydrocortisone 1% and clobetasone cream in grams
Identification	**Sponsorship source:** UCB Pharma, Belgium **Country:** 26 centres: France (10), Russia (8), Germany (4), Belgium (2), The Netherlands (1), United Kingdom (1) **Setting:** secondary **Comments:** **Author's name:** F. Cambazard **Institution:** not reported **Email:** not reported

Cambazard 2001 *(Continued)*

	Address: Professor F. Cambazard, 42055 Saint-Etienne, France
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Information about the sequence generation process insufficient to permit judgement of low risk or high risk
Allocation concealment (selection bias)	Unclear risk	Information insufficient to permit judgement of low risk or high risk
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Information insufficient to permit judgement of low risk or high risk
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Information insufficient to permit judgement of low risk or high risk
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Information insufficient to permit judgement of low risk or high risk. Number lost to follow-up not reported
Selective reporting (reporting bias)	Unclear risk	Information insufficient to permit judgement of low risk or high risk
Other bias	Unclear risk	Further risk of bias is possible, but information is insufficient to judge whether additional bias exists (e.g. no conflict of interest statement provided); also, the study was funded in part by UCB, SA (Brussels, Belgium), and study medication was provided by that company

Diepgen 2002

Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group
Participants	**Baseline characteristics** Cetirizine • *Number of participants randomised*: 398 • *Losses to follow-up*: 48 • *Age*: M = 16.8 months (SD = 4.2) • *Duration of condition*: not reported • *Severity of condition*: SCORAD: M = 24.9 (SD = 14.7) • *Male/Female*: 61.8% male Placebo • *Number of participants randomised*: 397 • *Losses to follow-up*: 51 • *Age*: M = 17.2 months (SD = 4.1)

Diepgen 2002 *(Continued)*

- *Duration of condition*: not reported
- *Severity of condition*: SCORAD: M = 25.1 (SD = 14.0)
- *Male/Female*: 62.5% male

Inclusion criteria: (1) diagnostic: AD, infants (1 to 2 years of age), at least 1 parent or sibling with history of AD, allergic rhinitis or asthma; (2) severity of condition: active symptoms; (3) duration of condition: at least 1 month; (4) site evaluated (e.g. face/back): not reported

Exclusion criteria: infants with asthma, or with a history (beyond the age of 6 months) of 1 or more episodes of wheezing or nocturnal cough, as well as any conditions that might obscure the diagnosis of asthma (14), were excluded from the study. Further exclusion criteria were the following: weight below the third percentile, chronic pulmonary disease, severe neurological or psychological disorder, any third disease likely to interfere with the study drug, clinically relevant cardiac disease, any anomaly of the Q–T interval on electrocardiogram (ECG) tracing, history of sleep apnoea in the participant or in siblings, neonatal distress, prior desensitisation or immunotherapy, prior treatment with medicines interfering with the immune system, hypersensitivity to cetirizine or other piperazines or parabens, participation in a clinical study within 3 months before randomisation

Group differences: groups were comparable at baseline according to study authors

Interventions

Intervention characteristics

Cetirizine

- *Presentation*: oral solution
- *Dose and frequency*: 0.25 mg cetirizine per kg bodyweight twice daily
- *Total dose*: 0.5 mg/kg bw/d
- *Duration given for*: 18 months
- *Supplier and trade name if relevant*: UCB SA Pharma Sector (Brussels, Belgium)

Placebo

- *Presentation*: matched
- *Dose and frequency*: matched
- *Total dose*: matched
- *Duration given for*: 18 months
- *Supplier and trade name if relevant*: UCB SA Pharma Sector (Brussels, Belgium)

Outcomes

Primary outcome 1: mean change in patient-assessed symptoms: pruritus as part of SCORAD

- **Outcome type:** continuous outcome
- **Notes:** pruritus as a subscale of SCORAD was not individually reported

Primary outcome 2: adverse events

- **Outcome type:** adverse event
- **Reporting:** fully reported
- **Notes:** data were obtained from Simons 1999: P = 0.053; NB: N in Simons 1999 slightly larger; any events occurring during the 18-month study period, including potential side effects (adverse events), were carefully recorded by parents/guardians on diary cards and discussed with the investigator at each visit; serious adverse events (e.g. any hospitalisations) had to be reported immediately

Secondary outcome 1: physician-assessed clinical signs

- **Outcome type:** continuous outcome
- **Reporting:** fully reported
- **Data value:** change from baseline
- **Notes:** SCORAD by trained investigator

Diepgen 2002 *(Continued)*

Secondary outcome 3: number of eczema flares, measured by, for example, 'escalation of treatment' or 'use of topical anti-inflammatory medications'

- **Outcome type:** continuous outcome
- **Notes:** Table 2 - some significant differences in numbers using other topical and systemic medications; Table 3 - no significant difference in duration of use of variety of topical and systemic medications (apart from H1 AH; P = 0.035) between groups

Identification	**Sponsorship source:** UCB, SA, Pharma sector (Brussels, Belgium) **Country:** 12 European countries and Canada **Setting:** dermatological or paediatric centres in 12 countries (i.e. secondary) **Comments:** **Author's name:** Thomas L. Diepgen **Institution:** University Hospital Heidelberg **Email:** thomas.diepgen@med.uni-heidelberg.de **Address:** not reported
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Informatio about the sequence generation process insufficient to permit judgement of low risk or high risk
Allocation concealment (selection bias)	Unclear risk	Information insufficient to permit judgement of low risk or high risk
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Information insufficient to permit judgement of low risk or high risk
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Information insufficient to permit judgement of low risk or high risk
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: incomplete outcome data, as 817 were randomised but ITT population consists of only 795 participants. 12.45% further unaccounted attrition. However, attrition was less than 30% (long-term trial) so was considered to be low risk
Selective reporting (reporting bias)	Unclear risk	Information insufficient to permit judgement of low risk or high risk. No comparison with protocol possible, as a study protocol is not available
Other bias	Unclear risk	There may be further risk of bias, but information is insufficient to judge whether additional bias exists (e.g. no conflict of interest statement provided); also, the study was funded in part by UCB, SA (Brussels, Belgium), and study medication was provided by that company

Doherty 1989

Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group
Participants	**Baseline characteristics** Overall • *Number of participants randomised*: 49 (acrivastine: n = 13; terfenadine: n = 16; placebo: n = 14 (as per protocol)) • *Losses to follow-up*: 5 (but 5 + 43 = 48, not 49) • *Age*: M = 26.8 years (range 16 to 58 years) • *Duration of condition*: not reported • *Severity of condition*: not reported • *Male/Female*: N = 49 (male = 20, female = 29) **Inclusion criteria:** (1) diagnostic: clinical diagnosis of AD; (2) severity of condition: not reported; (3) duration of condition: not reported; (4) site evaluated (e.g. face/back): not reported **Exclusion criteria:** not reported **Group differences:** not reported
Interventions	**Intervention characteristics** Acrivastine • *Presentation*: oral • *Dose and frequency*: 8 mg 3×/d • *Total dose*: 24 mg/d • *Duration given for*: 10 days • *Supplier and trade name if relevant*: not reported Terfenadine • *Presentation*: oral • *Dose and frequency*: 60 mg 3×/d • *Total dose*: 180 mg/d • *Duration given for*: 10 days • *Supplier and trade name if relevant*: not reported Placebo • *Presentation*: oral • *Dose and frequency*: 3×/d • *Total dose*: n/a • *Duration given for*: 10 days • *Supplier and trade name if relevant*: not reported
Outcomes	*Primary outcome 1: mean change in patient-assessed symptoms: pruritus VAS* • **Outcome type:** continuous outcome • **Range:** 0 to 100 • **Direction:** lower is better • **Data value:** change from baseline *Primary outcome 2: adverse events* • **Outcome type:** adverse event

Doherty 1989 *(Continued)*

- **Notes:** adverse events not reported

Primary outcome 2: adverse events: number of flares

- **Outcome type:** adverse event
- **Notes:** not reported

Secondary outcome 1: physician-assessed clinical signs: no. for whom treatment helped itching

- **Outcome type:** dichotomous outcome
- **Direction:** higher is better
- **Data value:** endpoint

Identification	**Sponsorship source:** not reported **Country:** UK **Setting:** secondary **Comments:** UK outpatient hospital **Author's name:** Valerie Doherty **Institution:** Royal Infirmary, Edinburgh **Email:** val.doherty@nhslothian.scot.nhs.uk. **Address:** Valerie Doherty, Consultant Dermatologist, Royal Infirmary, Edinburgh EH3 9YW
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Information about the sequence generation process insufficient to permit judgement of low risk or high risk
Allocation concealment (selection bias)	Unclear risk	Information insufficient to permit judgement of low risk or high risk
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Information insufficient to permit judgement of low risk or high risk
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Apart from stating "double-blind", information is insufficient to permit judgement of low risk or high risk
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: 'as-treated' analysis done with departure of the intervention received from that assigned at randomisation. Attrition (10.2%) and no statement of analysis based on ITT principles. Cases with missing data were deleted from analyses. However, attrition was below 20% and medium-term duration intervention, so considered as low risk
Selective reporting (reporting bias)	Unclear risk	Information insufficient to permit judgement of low risk or high risk. No comparison with protocol possible, as a study protocol is not available
Other bias	Unclear risk	Further risk of bias is possible, but information is insufficient to judge whether additional bias exists (e.g. no conflict of interest statement provided, no provi-

Doherty 1989 *(Continued)*

	sion of information regarding origin of drugs, Was study initiated by pharmacological company? Did study authors receive funding from any source?)

Falk 1993

Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group
Participants	**Baseline characteristics** Ketotifen • *Number of participants randomised*: 30 • *Losses to follow-up*: 2 • *Age*: not reported for groups, only total given (M = 25 years) • *Duration of condition*: not reported • *Severity of condition*: not reported • *Male/Female*: 34/26 total Placebo • *Number of participants randomised*: 30 • *Losses to follow-up*: 2 • *Age*: not reported for groups, only total given (M = 25 years) • *Duration of condition*: not reported • *Severity of condition*: not reported • *Male/Female*: 34/26 total **Inclusion criteria:** (1) diagnostic: eczema according to Hanifin and Rajka (1980); (2) severity of condition: not reported; (3) duration of condition: not reported; (4) site evaluated (e.g. face/back): not reported **Exclusion criteria:** pregnant women and patients concurrently using drugs or vaccines (hyposensitisation) that could influence the disease **Group differences:** "...and the two parallel groups were comparable as to age, sex, severity and duration of the disease"
Interventions	**Intervention characteristics** Ketotifen • *Presentation*: capsules • *Dose and frequency*: 1 mg twice daily • *Total dose*: 2 mg/d • *Duration given for*: 3 months • *Supplier and trade name if relevant*: not stated • *Were instructions given to patients adequate? Give details*: unsure Placebo • *Presentation*: matched • *Dose and frequency*: matched • *Total dose*: matched • *Duration given for*: matched • *Supplier and trade name if relevant*: not reported

Falk 1993 *(Continued)*

	• *Were instructions given to patients adequate? Give details*: unsure
Outcomes	*Primary outcome 1: mean change in patient-assessed symptoms: pruritus* • **Outcome type:** continuous outcome • **Reporting:** partially reported • **Range:** 0 to 3 • **Direction:** lower is better • **Data value:** change from baseline • **Notes:** no significance test between groups given, only within groups (pruritus) *Primary outcome 2: adverse events* • **Outcome type:** adverse event • **Reporting:** not reported • **Notes:** "none of the patients had any drug-related complaints other than a slight drowsiness…" *Secondary outcome 1: physician-assessed clinical signs* • **Outcome type:** continuous outcome • **Reporting:** partially reported • **Range:** 0 to 4 • **Direction:** higher is better • **Data value:** endpoint • **Notes:** P < 0.01
Identification	**Sponsorship source:** not reported **Country:** Norway **Setting:** secondary **Comments:** likely secondary setting, probably outpatient university hospital **Author's name:** Falk, Edvard S **Institution:** Department of Dermatology, University Hospital, Tromso, Norway **Email:** not reported **Address:** Professor Dr. med Edvard S. Falk, Hudlegekontoret Akutten,Skippergata 7A, 9008 Tromsø; Tel.: 77 68 52 87
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Information about the sequence generation process insufficient to permit judgement of low risk or high risk
Allocation concealment (selection bias)	Unclear risk	Information insufficient to permit judgement of low risk or high risk
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "In a double blind study...., patients received placebo capsules identical to ketotifen capsules...." Comment: no further information provided about personnel, but it is unlikely that their blinding could have been broken

Falk 1993 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Information insufficient to permit judgement of low risk or high risk
Incomplete outcome data (attrition bias) All outcomes	Low risk	No intention-to-treat analysis, but as per protocol, dropouts = 4 (2 in each group) due to increased severity during the study. Dropout rate 6.6% in each group, which is fairly low
Selective reporting (reporting bias)	Unclear risk	Comment: no comparison between protocol and article possible
Other bias	Unclear risk	Further risk of bias is possible, but information is insufficient to judge whether additional bias exists (e.g. no conflict of interest statement provided, no provision of information regarding origin of drugs, Was study initiated by pharmacological company?)

Frosch 1984

Methods	**Study design:** randomised controlled trial **Study grouping:** cross-over
Participants	**Baseline characteristics** Overall • *Number of participants randomised*: 18 • *Losses to follow-up*: 2 • *Age*: of 16 who completed, M = 23 years (range 14 to 43 years) • *Duration of condition*: of 16 who completed, M = 17 years (range 3 to 40) • *Severity of condition*: not reported • *Male/Female*: of 16 who completed, 13 female, 3 male **Inclusion criteria:** (1) diagnostic: history of AD of at least 3 years (however, neither according to Hanifin and Rajka nor UK criteria) but study conducted in Department of Dermatology; (2) severity of condition: not specified; (3) duration of condition: at least 3 years; (4) site evaluated (e.g. face/back): not specified **Exclusion criteria:** treatment with systemic corticosteroids or ACTH within the last 2 months; change in topical medication in the last month; history of very distinct seasonal variations in atopic dermatitis; presence of any non-atopic dermatitis-related pathological finding, detected by routine laboratory screening; pregnancy or lactation **Group differences:** not reported but cross-over
Interventions	**Intervention characteristics** Chlorpheniramine • *Presentation*: tablets • *Dose and frequency*: 4 mg 3×/d • *Total dose*: 12 mg/d • *Duration given for*: 4 weeks • *Supplier and trade name if relevant*: Smith, Kline, and Dauelsberg (Göttingen, FRG) Placebo

Frosch 1984 *(Continued)*

- *Presentation*: tablets
- *Dose and frequency*: identical with each active substance
- *Total dose*: n/a
- *Duration given for*: 4 weeks
- *Supplier and trade name if relevant*: Smith, Kline, and Dauelsberg (Göttingen, FRG)

Outcomes	*Primary outcome 1: mean change in patient-assessed symptoms: VAS pruritus* • **Outcome type:** continuous outcome • **Range:** 0 to 100 • **Direction:** lower is better • **Data value:** endpoint • **Notes:** study authors report no significant differences between groups based on Friedman's test *Primary outcome 2: adverse events* • **Outcome type:** adverse event • **Data value:** endpoint *Secondary outcome 1: global assessment: number of patients with overall improvement, no overall improvement, or overall worsening* • **Outcome type:** ordinal outcome • **Notes:** study authors report no significant differences between groups based on Kruskal-Wallis test *Secondary outcome 3: amount of betamethasone used in grams* • **Outcome type:** continuous outcome • **Direction:** lower is better • **Data value:** endpoint
Identification	**Sponsorship source:** not reported **Country:** Germany **Setting:** secondary **Comments:** not stated, but likely outpatients treated at hospital **Author's name:** P.J. Frosch **Institution:** Department of Dermatology, University of Münster **Email:** not reported **Address:** Department of Dermatology, University of Münster, D-4400 Münster, Federal Republic of Germany
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The randomisation was conducted according to a Latin square design" Comment: randomisation procedure was adequate and unlikely to introduce selection bias

Frosch 1984 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Information insufficient to permit judgement of low risk or high risk
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: although placebo tablets were identical with intervention 1, and placebo tablets were identical with intervention 2 (i.e. 2 types of placebo), whether study personnel were blinded remains unclear
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Information insufficient to permit judgement of low risk or high risk
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: as-treated analysis done with departure of the intervention received from that assigned at randomisation (11.11% attrition)
Selective reporting (reporting bias)	Unclear risk	Information insufficient to permit judgement of low risk or high risk. No comparison with protocol possible, as a study protocol is not available
Other bias	Unclear risk	Further risk of bias is possible, but information is insufficient to judge whether additional bias exists (e.g. no conflict of interest statement provided, Did study authors receive funding from any source?) Statement was made regarding receipt of technical assistance and support from Smith, Kline, and Dauelsberg (Göttingen, FRG)

Hannuksela 1993

Methods	**Study design:** randomised controlled trial **Study grouping:** parallel
Participants	**Baseline characteristics** Overall (not given for groups) • *Number of participants randomised*: 178 • *Losses to follow-up*: 20 • *Age*: M = 29.7 years, SD = 8.9 • *Duration of condition*: not reported • *Severity of condition*: moderate to severe AD needing oral therapy and defined by the presence of pruritus and typical atopic dermatitis morphology and typical cutaneous lesion distribution and chronicity • *Male/Female*: not reported **Inclusion criteria:** (1) diagnostic: adults with AD (18 years and older); (2) severity of condition: moderate to severe AD needing oral therapy and defined by the presence of pruritus and typical atopic dermatitis morphology and typical cutaneous lesion distribution and chronicity; (3) duration of condition: not reported; (4) site evaluated (e.g. face/back): not reported **Exclusion criteria:** pregnancy, pregnancy potential and lactation, renal or hepatic sufficiency, known allergy to piperazines, atopic dermatitis requiring systemic treatment other than antihistamines, severe infection complicating atopic dermatitis, systemic infection requiring antibacterial treatment, any diseases that may interfere with treatment such as dermal mycoses, use of antidepressants, needing a specific treatment for asthma, starting hyposensitisation, UVA or UVB therapy, use of depot corticosteroids during the last month, antimicrobial drugs during the last 7 days, topical or systemic antihistamines during the last 7 days (exceptions: astemizole, 6 weeks, and ketotifen, 2 weeks)

Hannuksela 1993 *(Continued)*

	Group differences: all groups were comparable in terms of sex, age, weight, and prior use of emollients and hydrocortisone. They were also comparable at baseline for symptom scores
Interventions	**Intervention characteristics** Cetirizine 3 groups • *Presentation*: tablets • *Dose and frequency*: 10, 20, or 40 mg per day in 2 doses • *Total dose*: group A: 10 mg/d; group B: 20 mg/d; group C: 40 mg/d • *Duration given for*: 4 weeks • *Supplier and trade name if relevant*: UCB Pharmaceutical Sector, Belgium Placebo • *Presentation*: tablets • *Dose and frequency*: identical with each active substance • *Total dose*: n/a • *Duration given for*: 4 weeks • *Supplier and trade name if relevant*: UCB Pharmaceutical Sector, Belgium
Outcomes	*Primary outcome 1a: mean change in patient-assessed symptoms: pruritus as part of SCORAD* • **Outcome type:** continuous outcome • **Range:** 0 to 100 • **Direction**: lower is better • **Notes:** Table 2 says lower values indicate less pruritus, but there was actually an increase in presented values between visits 1 and 2 *Primary outcome 1b: mean change in patient-assessed symptoms: pruritus assessed by patient CRF* • **Outcome type:** continuous outcome • **Range:** 0 to 100 • **Direction:** lower is better • **Notes:** Table 2 says lower values indicate less pruritus, but there was actually an increase in presented values between visits 1 and 2 *Primary outcome 2: adverse events* • **Outcome type:** adverse event • **Direction:** lower is better • **Data value:** endpoint *Secondary outcome 1: physician-assessed clinical signs* • **Outcome type:** continuous outcome • **Direction:** lower is better *Secondary outcome 3: number of eczema flares, measured by, for example, 'escalation of treatment' or 'use of topical anti-inflammatory medications'* • **Outcome type:** continuous outcome • **Direction:** lower is better
Identification	**Sponsorship source:** UCB Pharmaceutical Sector, Belgium **Country:** Finland **Setting:** secondary

Hannuksela 1993 *(Continued)*

	Comments: likely outpatients treated at University Hospital Turku and Tampere, Finland **Author's name:** Matti Hannuksela **Institution:** The Allergy and Asthma Federation, Helsinki, Finland **Email:** not reported **Address:** not reported
Notes	The direction of change appears reversed; study authors were contacted to clarify the nature of this, but we received no reply

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: study authors state that they had randomised by blocks of 4, but it is unclear what this means. Information about the sequence generation process was insufficient to permit judgement of low risk or high risk
Allocation concealment (selection bias)	Low risk	Comment: sealed envelopes were used, so unlikely to introduce selection bias
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: in a double-blind study...., "indistinguishable tablets of either cetirizine ...or placebo were administered"...no further information about personnel
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Information insufficient to permit judgement of low risk or high risk
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: 'as-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation'; attrition was 28.7%, and no ITT was stated
Selective reporting (reporting bias)	Unclear risk	Information insufficient to permit judgement of low risk or high risk. No comparison with protocol possible, as a study protocol is not available
Other bias	Unclear risk	Further risk of bias is possible, but information is insufficient to judge whether additional bias exists (e.g. no conflict of interest statement provided), although statement was made that study was funded by UCB Pharma. However, whether this may have affected authors' decisions remains unclear

Henz 1998

Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group
Participants	**Baseline characteristics** Azelastine • *Number of participants randomised*: n = 45 (imputed) • *Losses to follow-up*: not reported • *Age*: adults - age not reported

Henz 1998 *(Continued)*

- *Duration of condition*: not reported
- *Severity of condition*: not reported
- *Male/Female*: not reported

Cetirizine

- *Number of participants randomised*: 18 (imputed)
- *Losses to follow-up*: not reported
- *Age*: adults - age not reported
- *Duration of condition*: not reported
- *Severity of condition*: not reported
- *Male/Female*: not reported

Placebo

- *Number of participants randomised*: 11 (imputed)
- *Losses to follow-up*: not reported
- *Age*: adults - age not reported
- *Duration of condition*: not reported
- *Severity of condition*: not reported
- *Male/Female*: not reported

Inclusion criteria: (1) diagnostic: AD accompanied by moderate to severe pruritus (not according to Hanifin and Rajka or UK criteria) but study conducted in department of dermatology; (2) severity of condition: not reported; (3) duration of condition: not reported; (4) site evaluated (e.g. face/back): not reported

Exclusion criteria: not reported

Group differences: not reported

Interventions	**Intervention characteristics** Azelastine • *Presentation*: capsule • *Dose and frequency*: 4 mg 1×/d • *Total dose*: 4 mg/d • *Duration given for*: 2 weeks • *Supplier and trade name if relevant*: not reported Cetirizine • *Presentation*: capsules • *Dose and frequency*: 10 mg 1×/d • *Total dose*: 10 mg/d • *Duration given for*: 2 weeks • *Supplier and trade name if relevant*: not reported Placebo • *Presentation*: capsules • *Dose and frequency*: 1×/d • *Total dose*: n/a • *Duration given for*: 2 weeks • *Supplier and trade name if relevant*: not reported
Outcomes	*Primary outcome 1: mean change in patient-assessed symptoms: pruritus reduction assessed at night on diary card*

Henz 1998 *(Continued)*

- **Outcome type:** continuous outcome
- **Data value:** change from baseline
- **Notes:** reduction was less than 1 score point in eczema; no tests for significance were reported

Primary outcome 2: adverse events

- **Outcome type:** adverse event
- **Data value:** endpoint
- **Notes:** only percentages given for whole sample consisting of patients with several distinctly different dermatoses, but not for subgroups

Secondary outcome 1: physician-assessed clinical signs: mean overall response rate

- **Outcome type:** dichotomous outcome

Secondary outcome 2: secondary outcome 3: number of eczema flares, measured by, for example, 'escalation of treatment' or 'use of topical anti-inflammatory medications'

- **Outcome type:** adverse event
- **Data value:** endpoint
- **Notes:** no numbers for patients with AD given, only for whole sample; all groups same amount (28% to 30%)

Identification	**Sponsorship source:** not reported **Country:** Austria and Germany **Setting:** secondary **Comments:** 30 centres in Austria and Germany (i.e. outpatient hospitals) **Author's name:** B.M. Henz **Institution:** Charite-Virchow Klinikum **Email:** henz@prolink.de **Address:** Prof. Dr. med. Beate M. Henz, Charite-Virchow Klinikum, Medizinische Fakultiit der Humboldt-Universität zu Berlin, Dermatologische Universitiitsklinik und Poliklinik Augustenburger Platz 1, D-13353 Berlin, Germany
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: study authors state that randomisation was done centrally, but it is not clear what this means. Information about the sequence generation process insufficient to permit judgement of low risk or high risk
Allocation concealment (selection bias)	Unclear risk	Information insufficient to permit judgement of low risk or high risk
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Information insufficient to permit judgement of low risk or high risk Comment: study authors state "double-blind", but whether placebo was identical to azelastine or cetirizine remains unclear
Blinding of outcome assessment (detection bias)	Unclear risk	No information given as to how assessor was blinded (i.e. information insufficient to permit judgement of low risk or high risk)

Henz 1998 *(Continued)*
All outcomes

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: as it is not clear how many participants were randomised, we cannot judge whether any attrition bias occurred
Selective reporting (reporting bias)	Unclear risk	Information insufficient to permit judgement of low risk or high risk. No comparison with protocol possible, as a study protocol is not available
Other bias	Unclear risk	Further risk of bias is possible, but information is insufficient to judge whether additional bias exists (e.g. no conflict of interest statement provided, no provision of information regarding origin of drugs, Was study initiated by pharmacological company? Did study authors receive funding from any source?)

Hjorth 1988

Methods	**Study design:** randomised controlled trial **Study grouping:** cross-over
Participants	**Baseline characteristics** Overall • *Number of participants randomised*: 30 • *Losses to follow-up*: none reported • *Age*: adults - age not reported • *Duration of condition*: not reported • *Severity of condition*: not reported • *Male/Female*: not reported **Inclusion criteria:** (1) diagnostic: no information given on how atopic dermatitis was diagnosed; (2) severity of condition: not really defined, just “patients with atopic dermatitis whose history indicated contact urticaria”; (3) duration of condition: not reported; (4) site evaluated (e.g. face/back): not reported **Exclusion criteria:** not reported **Group differences:** not applicable
Interventions	**Intervention characteristics** Terfenadine • *Presentation*: oral • *Dose and frequency*: 60 mg 2×/d • *Total dose*: 120 mg/d • *Duration given for*: 2 weeks • *Supplier and trade name if relevant*: not reported Placebo • *Presentation*: oral • *Dose and frequency*: not reported • *Total dose*: n/a • *Duration given for*: 2 weeks • *Supplier and trade name if relevant*: not reported

Hjorth 1988 *(Continued)*

Outcomes	*Primary outcome 1: mean change in patient-assessed symptoms: pruritus* • **Outcome type:** continuous outcome • **Direction:** lower is better • **Notes:** "terfenadine reduced severity of itch in approximately 52% of patients; 34% reported no change and 14% reported increased severity of itch"; no test for significance was provided
Identification	**Sponsorship source:** not reported **Country:** Denmark **Setting:** secondary **Comments:** dermatologist's practice **Author's name:** Niels Hjorth **Institution:** Department of Dermatology, KAS Gentofte, Copenhagen, Denmark **Email:** not reported **Address:** not reported
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Information about the sequence generation process insufficient to permit judgement of low risk or high risk
Allocation concealment (selection bias)	Unclear risk	Information insufficient to permit judgement of low risk or high risk
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: apart from "a double-blind..." study, only insufficient information to permit judgement of low risk or high risk. Study authors did not declare whether medication was identical in appearance and dosage to placebo
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information given as to how assessor was blinded (i.e. insufficient information to permit judgement of low risk or high risk)
Incomplete outcome data (attrition bias) All outcomes	High risk	It is stated that 30 participants were randomised, assuming 16/30 reported reduced itching. Assumed an ITT was not carried out
Selective reporting (reporting bias)	Unclear risk	Information insufficient to permit judgement of low risk or high risk. No comparison with protocol possible, as a study protocol is not available
Other bias	Unclear risk	Further risk of bias is possible, but information is insufficient to judge whether additional bias exists (e.g. no conflict of interest statement provided, no provision of information regarding origin of drugs, Was study initiated by pharmacological company? Did authors receive funding from any source?)

Iikura 1992

Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group
Participants	**Baseline characteristics** Ketotifen • *Number of participants randomised*: 61 • *Losses to follow-up*: not clear (data given for n = 48) • *Age*: children; frequency of age groups provided • *Duration of condition*: M (months) = 7.55, SE = 1.52 • *Severity of condition*: more than moderate dermal symptoms • *Male/Female*: 36/25 Placebo • *Number of participants randomised*: 60 • *Losses to follow-up*: not clear (data given for n = 43) • *Age*: frequency of age groups provided • *Duration of condition*: M (months) = 6.66, SE = 0.73 • *Severity of condition*: more than moderate dermal symptoms • *Male/Female*: 36/24 **Inclusion criteria:** (1) diagnostic: those having more than moderate dermal symptoms of AD in both groups; (2) duration: for at least 1 month; (3) severity: more than moderate dermal symptoms; (4) site evaluated: at least 2 sites on the body **Exclusion criteria:** history of or displaying recurrent cough and/or wheezing or with condition diagnosed as asthma; cardiac, hepatic, or renal disorders; patients considered unsuitable by the examining physician for some other reason **Group differences:** study authors report that based on their statistical analyses, there were no significant differences in age, sex. weight, allergic family history, onset of AD, duration of AD, or laboratory tests between groups
Interventions	**Intervention characteristics** Ketotifen • *Presentation*: oral (syrup) • *Dose and frequency*: 0.4 mg 2×/d (< 14 kg); 0.6 mg 2×/d (≥ 14 kg) • *Total dose*: 0.8 mg/d (< 14 kg); 1.2 mg/d (≥ 14 kg) • *Duration given for*: 52 weeks • *Supplier and trade name if relevant*: not reported Placebo • *Presentation*: oral (syrup) • *Dose and frequency*: matched • *Total dose*: n/a • *Duration given for*: 52 weeks • *Supplier and trade name if relevant*: not reported
Outcomes	*Secondary outcome 1: physician-assessed clinical signs obtained from complete physical examination* • **Outcome type:** dichotomous outcome *Primary outcome 2: adverse events*

Iikura 1992 *(Continued)*

- **Outcome type:** adverse event

Identification	**Sponsorship source:** not reported **Country:** Brazil and Japan **Setting:** secondary **Comments:** **Author's name:** Yoji Iikura **Institution:** Department of Allergology, National Pediatric Hospital, Tokyo, Japan **Email:** not reported **Address:** not reported
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Information about the sequence generation process insufficient to permit judgement of low risk or high risk
Allocation concealment (selection bias)	Unclear risk	Information insufficient to permit judgement of low risk or high risk
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: although study authors stated that "a placebo syrup indistinguishable from the active syrup was administered", how personnel were blinded remains unclear
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Information insufficient to permit judgement of low risk or high risk
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: study authors report to have studied 121 children but report data for only 91 in their final evaluation. No information is given as to how these missing data came about or how they were treated, respectively. Although attrition was 25%, this was a long-term study so was considered to be at low risk
Selective reporting (reporting bias)	Unclear risk	Information was insufficient to permit judgement of low risk or high risk. No comparison with protocol possible, as a study protocol is not available
Other bias	Unclear risk	Further risk of bias is possible, but information is insufficient to judge whether additional bias exists (e.g. no conflict of interest statement provided, no provision of information regarding origin of drugs, Was study initiated by pharmacological company? Did study authors receive funding from any source?)

Jung 1989

Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group

Jung 1989 *(Continued)*

Participants	**Baseline characteristics** Cetirizine 5 mg/d • *Number of participants randomised*: 33 • *Losses to follow-up*: none reported • *Age*: 3 to 6 years • *Duration of condition*: not reported • *Severity of condition*: chronic or chronically relapsing condition • *Male/Female*: not reported Cetirizine 10 mg/d • *Number of participants randomised*: 36 • *Losses to follow-up*: none reported • *Age*: 3 to 6 years • *Duration of condition*: not reported • *Severity of condition*: chronic or chronically relapsing condition • *Male/Female*: not reported Placebo • *Number of participants randomised*: 29 • *Losses to follow-up*: none reported • *Age*: 3 to 6 years • *Duration of condition*: not reported • *Severity of condition*: chronic or chronically relapsing condition • *Male/Female*: not reported Total • *Number of participants randomised*: 98 • *Losses to follow-up*: none reported • *Age*: M = 4, SD = 1 (range 3 to 6 years) • *Duration of condition*: not reported • *Severity of condition*: chronic or chronically relapsing condition • *Male/Female*: not reported **Inclusion criteria:** (1) diagnostic: atopic dermatitis with the following symptoms: pruritus or a burning sensation; morphology and distribution of skin lesions typical for children over 2 years of age (i.e. occurring at the flexure of the arms and legs, nape and sides of the neck, retro-auricular groove, hands, and perioral area). A minimum score of 4 for the 2 main symptoms - pruritus and erythema - and of 6 for the symptoms considered as a whole, both main and accessory (i.e. vesicles, lichenification, and crusting required for inclusion in the study). This score was obtained based on a 5-point scale where 0 = “none” to 4 = “very severe”, for the main symptoms, and on a 2-point scale, where 0 = “none” and 1 = “present”, for the accessory symptoms; (2) severity of condition: chronic or chronically relapsing condition; (3) duration of condition: not reported; (4) site evaluated (e.g. face/back): see above **Exclusion criteria:** children with a non-atopic dermatitis or dermatitis so severe that recourse to systemic therapy with a drug other than an antihistamine was necessary; all generalised or local (e.g. impetigo, herpes) infection requiring antibiotics; known allergy to piperazines; chronic renal, hepatic cardiovascular, or haematological problems **Group differences:** comparison of groups at the time of the start of the study did not reveal any statistically significant differences regarding age (…), weight (…), height or sex distribution
Interventions	**Intervention characteristics** Cetirizine 5 mg/d

Jung 1989 *(Continued)*

- *Presentation*: oral
- *Dose and frequency*: 2.5 mg 2×/d
- *Total dose*: 5 mg/d
- *Duration given for*: 1 week
- *Supplier and trade name if relevant*: UCB Pharmaceutical Sector

Cetirizine 10 mg/d

- *Presentation*: oral
- *Dose and frequency*: 5 mg 2×/d
- *Total dose*: 10 mg/d
- *Duration given for*: 1 week
- *Supplier and trade name if relevant*: UCB Pharmaceutical Sector

Placebo

- *Presentation*: oral
- *Dose and frequency*: matched
- *Total dose*: n/a
- *Duration given for*: 1 week
- *Supplier and trade name if relevant*: UCB Pharmaceutical Sector

Outcomes	*Primary outcome 1: mean change in patient-assessed symptoms: pruritus measured on 5-point Likert scale (0 = none, 4 = severe)* • **Outcome type:** continuous outcome • **Data value:** change from baseline *Primary outcome 2: adverse events (number of patient-reported adverse events)* • **Outcome type:** adverse event • **Direction:** lower is better • **Data value:** endpoint *Secondary outcome 1: physician-assessed clinical signs: global evaluation measured on 5-point Likert scale (0 = none, 4 = severe)* • **Outcome type:** continuous outcome
Identification	**Sponsorship source:** UCB Pharmaceutical Sector **Country:** Germany, Belgium, and France **Setting:** secondary **Comments:** multi-centre study **Author's name:** Prof. E. G. Jung **Institution:** not reported **Email:** not reported **Address:** not reported
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement

Jung 1989 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Quote: "The patients were allocated, in each centre, according to a randomisation list to one of the 3 following treatment groups..." Comment: no other information available
Allocation concealment (selection bias)	Unclear risk	Information insufficient to permit judgement of low risk or high risk
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Information insufficient to permit judgement of low risk or high risk
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Information insufficient to permit judgement of low risk or high risk
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Information insufficient to permit judgement of low risk or high risk Comment: although study authors report no missing outcome data, whether all randomised participants contributed to data collection remains unclear
Selective reporting (reporting bias)	Unclear risk	Information insufficient to permit judgement of low risk or high risk. No comparison with protocol possible, as a study protocol could not be obtained
Other bias	Unclear risk	Further risk of bias is possible, but information is insufficient to judge whether additional bias exists (e.g. no conflict of interest statement provided); also, the study was funded in part by UCB, SA (Brussels, Belgium), and study medication was provided by that company

Kawashima 2003

Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group
Participants	**Baseline characteristics** Fexofenadine • *Number of participants randomised*: 207 • *Losses to follow-up*: reported only for total • *Age*: M = 26.9 years • *Duration of condition*: 17.8 years • *Severity of condition*: not reported • *Male/Female*: 105/96 Placebo • *Number of participants randomised*: 204 • *Losses to follow-up*: reported only for total • *Age*: M = 26.3 years • *Duration of condition*: 17.2 years • *Severity of condition*: not reported • *Male/Female*: 109/90 Total

Kawashima 2003 *(Continued)*

- *Number of participants randomised*: 411
- *Losses to follow-up*: study authors report 27 but report data for n = 400

Inclusion criteria: (1) diagnostic: male and female outpatients aged 16 years or older who had a diagnosis of atopic dermatitis based on the criteria of the Japanese Dermatological Association (similar to those of Hanifin and Rajka); (2) severity of condition: self-assessed mean pruritus score ≥ 4 points and < 8 points for the last 3 days of the placebo lead-in period (baseline); (3) duration of condition: not specified; (4) site evaluated (e.g. face/back): not specified

Exclusion criteria: using a topical steroid preparation other than 0.1% hydrocortisone butyrate twice daily within the 1-week placebo lead-in period; had taken antiallergic agents, antihistamines, non-steroidal anti-inflammatory agents, gamma-globulin preparations, anticholinergics, tranquillisers, hypnotics, antipsychotic drugs, cold remedies containing antihistamine agents, and any other antiallergic or antipruritic drugs in the 6 days preceding the day of enrolment; use of steroids and immunosuppressive agents not allowed for 2 weeks before and during the 3-day participant selection period; sustained-release steroid depot preparations and astemizole not allowed for 4 weeks before and during the 3-day participant selection period; if pruritus was associated only with the face and head; history of contact dermatitis induced by a topical steroid; history of complications including severe hepatic disorder, renal disorder, cardiopathy, or blood disease; prolonged QTc interval; non-compliance during the 3-day participant selection period; a change in the method of use or in the class of topical preparation during the 1-week placebo run-in period; skin infection induced by bacteria, fungi, or viruses; history of epileptic attacks or organic brain lesions; history of drug allergy to antihistamines and antiallergic agents; receiving specific hyposensitisation, immunomodulation, or light therapy; had participated in other clinical studies in the past 3 to 6 months; history of fexofenadine use; pregnant or nursing women

Group differences: no statistically significant differences between groups in terms of baseline characteristics (Table 2) or symptom assessments. However, analyses were based on n = 400 after exclusion of 11 participants

Interventions

Intervention characteristics

Fexofenadine

- *Presentation*: oral
- *Dose and frequency*: 60 mg 2×/d
- *Total dose*: 120 mg/d
- *Duration given for*: 1 week
- *Supplier and trade name if relevant*: Aventis Pharma Ltd. (Japan)

Placebo

- *Presentation*: oral
- *Dose and frequency*: not reported
- *Total dose*: n/a
- *Duration given for*: 1 week
- *Supplier and trade name if relevant*: Aventis Pharma Ltd. (Japan)

Outcomes

Primary outcome 1: mean change in patient-assessed symptoms: pruritus

- **Outcome type:** continuous outcome
- **Range:** 0 to 8
- **Data value:** change from baseline

Primary outcome 2: adverse events (number of patient-reported adverse events)

- **Outcome type:** adverse event
- **Direction:** lower is better
- **Data value:** endpoint

Secondary outcome 1: physician-assessed clinical signs

Kawashima 2003 *(Continued)*

- **Outcome type:** continuous outcome
- **Notes:** in terms of investigator-assessed change in the ratio of pruritus area to body surface area, significantly more participants in the fexofenadine group than in the placebo group experienced a reduction in their pruritus area (P = 0.007)

Secondary outcome 3: number of eczema flares/amount of 0.1% hydrocortisone butyrate in grams

- **Outcome type:** continuous outcome
- **Data value:** endpoint
- **Notes:** most participants used 0.1% hydrocortisone butyrate every day during lead-in and treatment periods, and no differences in the use of 0.1% hydrocortisone butyrate or any other concomitant drugs and treatments between fexofenadine and placebo groups were observed

Identification	**Sponsorship source:** Aventis Pharma Ltd. (Japan) **Country:** Japan **Setting:** secondary **Comments:** 52 centres in Japan (i.e. outpatient hospitals) **Author's name:** M. Kawashima **Institution:** Department of Dermatology, Tokyo Women's Medical University **Email:** m-kawash@derm.twmu.ac.jp **Address:** Department of Dermatology, Tokyo Women's Medical University, 8-1, Kawada-cho, Shinjuku-ku, Tokyo, 162-8666, Japan
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Comment: randomisation was performed with a uniform block size of 8
Allocation concealment (selection bias)	Low risk	Comment: treatment was allocated using an "ordinal pre-printed schedule", and code listing was secured in a sealed envelope
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "In order to maintain a double-blind protocol, different individuals in the same Clinical Research Organization (CRO) department acted as the generator and executor of assignment. The similarity of treatment characteristics was confirmed by the CRO. Successful blinding was guaranteed by the CRO's standard operating practice (code listing was secured in a sealed envelope stored in the CRO). The emergency code was also stored in the CRO" Comment: blinding was done
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information given as to how assessor was blinded (i.e. insufficient information to permit judgement of low risk or high risk)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: in the fexofenadine group, 6 (2.9%) of 207, and in the placebo group, 5 (2.5%) of 204 dropped out

Kawashima 2003 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Information insufficient to permit judgement of low risk or high risk. No comparison with protocol possible, as a study protocol is not available
Other bias	Unclear risk	Although study authors disclose receipt of payments from the study sponsor (Aventis Pharma Ltd. - Japan) for conducting and publicising this study and state that they have no commercial associations that might pose a conflict of interest, we do not know whether this may have impacted the process of conducting the study

Kimura 2009

Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group
Participants	**Baseline characteristics** Loratadine • *Number of participants randomised*: 16 • *Losses to follow-up*: not reported • *Age*: not reported (> 15 years) • *Duration of condition*: not reported • *Severity of condition*: not reported • *Male/Female*: not reported No additional treatment • *Number of participants randomised*: 12 • *Losses to follow-up*: not reported • *Age*: not reported (> 15 years) • *Duration of condition*: not reported • *Severity of condition*: not reported • *Male/Female*: not reported **Inclusion criteria:** (1) diagnostic: atopic dermatitis; (2) severity of condition: mild to moderate, aged 15 or older; (3) duration of condition: not reported; (4) site evaluated (e.g. face/back): whole body **Exclusion criteria:** pregnant or in lactation; treated with systemic corticosteroids; epilepsy or other brain disorders **Group differences:** study authors report no differences, but the data are not shown
Interventions	**Intervention characteristics** Loratadine • *Presentation*: oral • *Dose and frequency*: 10 mg 1×/d • *Total dose*: 10 mg/d • *Duration given for*: 4 weeks • *Supplier and trade name if relevant*: Claritin® MSD No additional treatment • *Presentation*: oral • *Dose and frequency*: 1×/d

Kimura 2009 *(Continued)*

- *Total dose*: n/a
- *Duration given for*: 4 weeks
- *Supplier and trade name if relevant*:

Outcomes	*Primary outcome 1: mean change in patient-assessed symptoms: VAS (0 to 100)* • **Outcome type:** continuous outcome • **Direction:** lower is better • **Data value:** change from baseline *Primary outcome 2: adverse events* • **Outcome type:** adverse event *Secondary outcome 1: physician-assessed clinical signs: SCORAD after 4 weeks* • **Outcome type:** continuous outcome • **Direction:** lower is better • **Data value:** change from baseline
Identification	**Sponsorship source:** not reported **Country:** Japan **Setting:** secondary **Comments:** dermatological clinic at the university hospital in Japan (a single centre) **Author's name:** Utako Kimura **Institution:** Department of Dermatology and Allergology, Juntendo University, Tokyo, Japan **Email:** not reported **Address:** not reported
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quote: "Participants were allocated to each group whether the clinical ID number was odd (Group A) or even (Group B)" Comment: randomisation method likely to introduce selection bias
Allocation concealment (selection bias)	Unclear risk	Information insufficient to permit judgement of low risk or high risk
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Information insufficient to permit judgement of low risk or high risk
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Informaiton insufficient to permit judgement of low risk or high risk
Incomplete outcome data (attrition bias)	Unclear risk	Comment: although study authors report no missing outcome data, whether all randomised participants contributed to data collection remains unclear

Kimura 2009 *(Continued)*

All outcomes

Selective reporting (reporting bias)	Unclear risk	Information insufficient to permit judgement of low risk or high risk
Other bias	Unclear risk	Information insufficient to permit judgement of low risk or high risk

Kircik 2013

Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group
Participants	**Baseline characteristics** Overall • *Number of participants randomised*: 40 • *Losses to follow-up*: 7 • *Age*: M = 41.1 (19.5 to 68.1) • *Duration of condition*: not reported • *Severity of condition*: not reported ("subjects with uncomplicated atopic dermatitis") • *Male/Female*: 13/26 (1 missing value for gender) **Inclusion criteria:** (1) diagnostic: no information given on how atopic dermatitis was defined; (2) severity of condition: "subjects with uncomplicated atopic dermatitis"; (3) duration of condition: no information given; (4) site evaluated (e.g. face/back); no information given **Exclusion criteria:** not reported **Group differences:** information from interim report: "the treatment groups were balanced with respect to all demographic and baseline characteristics"
Interventions	**Intervention characteristics** Levocetirizine • *Presentation*: tablets • *Dose and frequency*: 5 mg 1×/d • *Total dose*: 5 mg/d • *Duration given for*: 4 weeks • *Supplier and trade name if relevant*: Xyzal Placebo • *Presentation*: tablets • *Dose and frequency*: 1×/d • *Total dose*: n/a • *Duration given for*: 4 weeks • *Supplier and trade name if relevant*: not reported
Outcomes	*Primary outcome 1: mean change in patient-assessed symptoms: pruritus* • **Outcome type:** continuous outcome • **Direction:** lower is better *Primary outcome 2: adverse events*

Kircik 2013 *(Continued)*

- **Outcome type:** adverse event
- **Notes:** "no treatment related AEs were noted in either group"

Secondary outcome 2: mean change in quality of life, as measured by a standardised or validated quality of life measure (e.g. Dermatology Life Quality Index - DLQI (Finlay 1994))

- **Outcome type:** continuous outcome
- **Direction:** lower is better

Identification	**Sponsorship source:** UCB Pharmaceuticals **Country:** USA **Setting:** secondary **Comments:** single-centre **Author's name:** Leon Kircik **Institution:** Mount Sinai Health System **Address:** 1169 Eastern Pkwy # 2310, Louisville, KY 40217, United States
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Information about the sequence generation process insufficient to permit judgement of low risk or high risk
Allocation concealment (selection bias)	Unclear risk	Information insufficient to permit judgement of low risk or high risk
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Information insufficient to permit judgement of low risk or high risk Comment: it is not clear whether medication was identical in appearance to placebo
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information given as to how assessor was blinded (i.e. information insufficient to permit judgement of low risk or high risk)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient reporting of attrition/exclusions to permit judgement of low risk or high risk. No information given about attrition given. Although study authors report no missing outcome data, whether all randomised participants contributed to data collection remains unclear
Selective reporting (reporting bias)	High risk	Comment: reporting of data was rudimentary in the report and did not allow us to run necessary analyses. Contacting the study author failed as the study author did not respond
Other bias	Unclear risk	Further risk of bias is possible, but information is insufficient to judge whether additional bias exists (e.g. no conflict of interest statement provided, but study was funded by UCB Pharmaceuticals)

Kuniyuki 2009

Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group
Participants	**Baseline characteristics** Olapatadine • *Number of participants randomised*: 49 • *Losses to follow-up*: unclear • *Age*: M = 63.6 years, SD 18.3 • *Duration of condition*: longer than 1 month • *Severity of condition*: not reported • *Male/Female*: 28/21 No additional treatment • *Number of participants randomised*: 50 • *Losses to follow-up*: unclear • *Age*: M = 62.8 years, SD 15.9 • *Duration of condition*: longer than 1 month • *Severity of condition*: not reported • *Male/Female*: 29/21 **Inclusion criteria:** (1) diagnostic: chronic eczema/dermatitis; (2) severity of condition: not mentioned; (3) duration of condition: longer than 1 month; (4) site evaluated (e.g. face/back): not reported **Exclusion criteria:** severe systemic disorders; treated with systemic corticosteroids, immune modulators, or antihistamine within 2 weeks; hepatic or nephrotic disorder; pregnant or in lactation **Group differences:** groups appear comparable from the figures
Interventions	**Intervention characteristics** Olapatadine • *Presentation*: oral • *Dose and frequency*: 5 mg 2×/d • *Total dose*: 10 mg/d • *Duration given for*: 8 weeks • *Supplier and trade name if relevant*: Allelock® by Kyowa Hakko Kirin Co. Ltd. No additional treatment • *Presentation*: oral • *Dose and frequency*: • *Total dose*: n/a • *Duration given for*: 8 weeks • *Supplier and trade name if relevant*:
Outcomes	*Primary outcome 1: mean change in patient-assessed symptoms: VAS and 5-grade scale* • **Outcome type:** continuous outcome • **Notes:** mean ± SE was shown in Figure 3, but no detail data were described. VAS and 5-grade scales on 2, 4, and 8 weeks were significantly different between groups *Primary outcome 2: adverse events* • **Outcome type:** adverse event

Kuniyuki 2009 *(Continued)*

Secondary outcome 1: physician-assessed clinical signs

- **Outcome type:** continuous outcome
- **Notes:** mean ± SE was shown in Figure 2, but no detail data were described. Scores on 8 weeks were significantly different

Identification	**Sponsorship source:** not reported **Country:** Japan **Setting:** secondary **Comments:** A dermatology clinic at the general hospital and 5 private dermatology clinics in Japan (6 centres) **Author's name:** Shuichi Kuniyuki **Institution:** Division of Dermatology, Osaka City General Hospital **Email:** ga28547@wa2.so-net.ne.jp; kuniyuki@ocgh.hospital.city.osaka.jp **Address:** Miyakojima-Hondori 2-13-22, Miyakojima-ku, 534-0021, Osaka, Japan
Notes	Data fully extracted by 2 native speakers

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Comment: participants were allocated to each group according to their age: odd to olopatadine and even to placebo
Allocation concealment (selection bias)	Unclear risk	Comment: although age was used to allocate individuals to groups, we do not know whether this action was concealed
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Information insufficient to permit judgement of low risk or high risk
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Information insufficient to permit judgement of low risk or high risk
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: final numbers of evaluable participants not stated
Selective reporting (reporting bias)	Unclear risk	No comparison possible with protocol, as a study protocol is not available, but it is clear that the published report includes all expected outcomes, including those that were prespecified
Other bias	Unclear risk	Further risk of bias is possible, but information is insufficient to judge whether additional bias exists (e.g. no conflict of interest statement provided, no provision of information regarding origin of drugs, Was study initiated by pharmacological company? Did study authors receive funding from any source?)

Langeland 1994

Methods	**Study design:** randomised controlled trial **Study grouping:** cross-over
Participants	**Baseline characteristics** Overall • *Number of participants randomised*: 16 • *Losses to follow-up*: none reported • *Age*: M = 24.8 years (range 19.5 to 37.3 years) • *Duration of condition*: M = 24 years (range 12 to 37 years) • *Severity of condition*: moderate to severe AD • *Male/Female*: 9 male/7 female **Inclusion criteria:** (1) diagnostic: pruritus caused by moderate to severe AD according to Rajka and Langeland (1989); (2) severity of condition: moderate to severe; (3) duration of condition: mean = 24 years; (4) site evaluated (e.g. face/back): not reported **Exclusion criteria:** pregnant or lactating women; patients receiving concomitant medication expected to interfere with skin disorders or with known mechanisms of pruritus **Group differences:** n/a since cross-over trial
Interventions	**Intervention characteristics** Loratadine • *Presentation*: tablets • *Dose and frequency*: 10 mg 1×/d • *Total dose*: 10 mg/d • *Duration given for*: 2 weeks/6 period cross-over = 12 weeks • *Supplier and trade name if relevant*: not reported Placebo • *Presentation*: tablets • *Dose and frequency*: 1×/d • *Total dose*: n/a • *Duration given for*: 2 weeks/6 period cross-over = 12 weeks • *Supplier and trade name if relevant*: not reported
Outcomes	*Primary outcome 1: mean change in patient-assessed symptoms: pruritus during the night on 10 cm VAS daily recorded by patient* • **Outcome type:** continuous outcome • **Notes:** inappropriate statistical analyses *Primary outcome 2: proportion of participants reporting adverse effects and serious adverse events throughout the study period* • **Outcome type:** categorical *Secondary outcome 3: number of eczema flares, measured by, for example, 'escalation of treatment' or 'use of topical anti-inflammatory medications'* • **Outcome type:** continuous
Identification	**Sponsorship source:** not reported

Langeland 1994 *(Continued)*

	Country: Norway
	Setting: probably secondary (i.e. outpatient university hospital (Oslo, Norway))
	Comments:
	Author's name: Dr. med. Tor Langeland
	Institution: Department of Dermatology, National Hospital, Rikshospitalet, Oslo
	Email: torl@online.no
	Address: St. Olavs plass 3, 0165 Oslo, Norway
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: information about the sequence generation process insufficient to permit judgement of low risk or high risk, although a 'block-randomised' design is mentioned
Allocation concealment (selection bias)	Unclear risk	Information about the sequence generation process insufficient to permit judgement of low risk or high risk
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: “a block-randomised, double blind…” Comment: participants received identical placebo tablets...no further information about personnel, but it is unlikely that their blinding could have been broken
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: apart from: "double blind ...", no information given as to how outcome assessor was blinded; however it is unlikely that blinding could have been broken
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: although study authors report no missing outcome data, whether all randomised participants contributed to data collection remains unclear
Selective reporting (reporting bias)	Unclear risk	Comment: no comparison possible with protocol, as a study protocol is not available, but it is clear that the published report includes all expected outcomes, including those that were prespecified
Other bias	Unclear risk	Further risk of bias is possible, but information is insufficient to judge whether additional bias exists (e.g. no conflict of interest statement provided, no provision of information regarding origin of drugs, Was study initiated by pharmacological company? Did study authors receive funding from any source?)

LaRosa 1994

Methods	**Study design:** randomised controlled trial
	Study grouping: parallel group
Participants	**Baseline characteristics**
	Cetirizine

LaRosa 1994 *(Continued)*

- *Number of participants randomised*: 12
- *Losses to follow-up*: 1
- *Age*: total: M = 7 years; SD = 2 (range 6 to 12 years)
- *Duration of condition*: not reported
- *Severity of condition*: not reported
- *Male/Female*: not reported

Placebo

- *Number of participants randomised*: 11
- *Losses to follow-up*: 0
- *Age*: total: M = 7 years; SD = 2 (range 6 to 12 years)
- *Duration of condition*: not reported
- *Severity of condition*: not reported
- *Male/Female*: not reported

Inclusion criteria: (1) diagnostic: diagnosis of AD based on presence of at least 3 major and minor criteria according to Hanifin and Rajka; (2) severity of condition: not reported; (3) duration of condition: not reported; (4) site evaluated (e.g. face/back): not reported

Exclusion criteria: chronic kidney disease; liver or cardiovascular disease; treatment with parenteral steroids, ketotifen, oxatomide, other histamines; cutaneous or other infection

Group differences: "the randomisation procedure resulted in a balancing of the two groups with respect to" ...age, weight, height, and sex. However, there were differences in clinical parameters between groups (e.g. family history of allergy)

Interventions

Intervention characteristics

Cetirizine

- *Presentation*: ampules
- *Dose and frequency*: 20 mL ampules containing 5 mg cetirizine for children ≤ 30 kg and 10 mg for those > 30 kg
- *Total dose*: 5 mg/d or 10 mg/d depending on weight
- *Duration given for*: 8 weeks
- *Supplier and trade name if relevant*: UCB Pianezza (Turin), Italy

Placebo

- *Presentation*: ampules
- *Dose and frequency*: matched
- *Total dose*: n/a
- *Duration given for*: 8 weeks
- *Supplier and trade name if relevant*: UCB Pianezza (Turin), Italy

Outcomes

Primary outcome 1: mean change in patient-assessed symptoms: pruritus

- **Outcome type:** continuous outcome
- **Notes:** presentation of results not reproducible, as in figures or only rudimentary in text. “With regard to pruritus, the differences between the two groups were significant from the first day until the second week (P < 0.05; P < 0.01)”, then not anymore…”there were more days of stable resolution of pruritus in the group treated with cetirizine with respect to the control group (P < 0.05) (Fig. 3)”

Primary outcome 2: adverse events

- **Outcome type:** adverse event
- **Notes:** no adverse effects of cetirizine were noted

Secondary outcome 1: physician-assessed clinical signs

LaRosa 1994 *(Continued)*

- **Outcome type:** continuous outcome
- **Notes:** no actual numbers reported in text, somehow in Figure 1; however, they are not exactly reproducible. Several differences within groups between baseline means and weeks 4 and 8 were reported for the intervention group ($P < 0.01$) and for the placebo group, where less pronounced; however, differences between groups were not statistically significant (according to study authors)

Secondary outcome 3: number of eczema flares, measured by, for example, 'escalation of treatment' or 'use of topical anti-inflammatory medications'

- **Outcome type:** adverse event
- **Notes:** "in the group receiving placebo, concomitant anti-allergic therapy (disodium cromoglycate and nasal topical steroids) was required significantly more often than in the treated group ($P < 0.01$)"; 2 of 11 (18%) children in the cetirizine group received disodium cromoglycate and procaterol. In the placebo group: 9 participants (82%) received other drugs (mainly disodium cromoglycate aerosol and nasal and cutaneously administered topic steroids). Differences between the 2 groups were highly significant

Identification	**Sponsorship source:** not reported **Country:** Italy **Setting:** secondary **Comments:** Day Hospital of the Pediatric Clinic of Catania, University (i.e. secondary setting) (outpatients at university hospital) **Author's name:** M. LaRosa **Institution:** Department of Pediatrics, University of Catania, Italy **Email:** not reported **Address:** not reported
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Information about the sequence generation process insufficient to permit judgement of low risk or high risk
Allocation concealment (selection bias)	Unclear risk	Information insufficient to permit judgement of low risk or high risk
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "double blind study"; "the therapy consisted of identical 20-ml ampules containing placebo or cetirizine" Comment: no further information provided about personnel, but it is unlikely that their blinding could have been broken
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "double-blind study" Comment: no information given as to how outcome assessor was blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: only 1 participant randomised to cetirizine group withdrew "voluntarily"; no other reason for dropout given - but risk of attrition bias considered low

LaRosa 1994 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Information insufficient to permit judgement of low risk or high risk. No comparison with protocol possible, as a study protocol is not available
Other bias	Unclear risk	Further risk of bias is possible, but information is insufficient to judge whether additional bias exists (e.g. no conflict of interest statement provided; although provision of information regarding origin of drugs is reported, we do not know whether study was initiated by pharmacological company? Did study authors receive funding from any source?)

Leon 1989

Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group
Participants	**Baseline characteristics** Ketotifen • *Number of participants randomised*: 10 • *Losses to follow-up*: 0 • *Age*: mean = 5.95 years; SD = 3.41 • *Duration of condition*: not reported • *Severity of condition*: not reported • *Male/Female*: 2 male/8 female Placebo • *Number of participants randomised*: 10 • *Losses to follow-up*: 0 • *Age*: M = 5.92 years; SD = 2.70 • *Duration of condition*: not reported • *Severity of condition*: not reported • *Male/Female*: 3 male/7 female **Inclusion criteria:** (1) diagnostic: clinical diagnosis of atopic eczema; (2) severity of condition: not reported; (3) duration of condition: not reported; (4) site evaluated (e.g. face/back): whole body **Exclusion criteria:** chronic disease of the gastrointestinal system, liver, or kidneys that could influence the absorption, metabolism, and excretion of medication; diabetes mellitus, heart disease, or pre-existing or intermittent pneumopathy **Group differences:** not reported
Interventions	**Intervention characteristics** Ketotifen • *Presentation*: oral solution • *Dose and frequency*: 1 mg twice daily • *Total dose*: 2 mg/d • *Duration given for*: 9 weeks • *Supplier and trade name if relevant*: not reported Placebo • *Presentation*: oral solution

Leon 1989 *(Continued)*

- *Dose and frequency*: matched
- *Total dose*: n/a
- *Duration given for*: 9 weeks
- *Supplier and trade name if relevant*: not reported

Outcomes	*Primary outcome 1: mean change in patient-assessed symptoms: pruritus during the day and the night* • **Outcome type:** continuous outcome • **Notes:** the intensity of each was assessed according to the following evaluation scale: absent = 0, mild = 1, moderate = 2, intense = 3 *Primary outcome 2: adverse events* • **Outcome type:** adverse event • **Notes:** at each visit at weeks 3, 5, and 9 of the study, side effects that were presented, their intensity, and the need to stop treatment were noted *Secondary outcome 1: physician-assessed clinical signs* • **Outcome type:** continuous outcome • **Notes:** the intensity of each was assessed according to the following evaluation scale: absent = 0, mild = 1, moderate = 2, intense = 3
Identification	**Sponsorship source:** not reported **Country:** Mexico **Setting:** secondary **Comments:** **Author's name:** Gladys Leon **Institution:** Oficina Farmacologia Clinica, Servicio de Investigacion Clinica Hospitalaria. Adscrita al Servicio de Dermatologigia del Hospital General de México, S.S. y Dermatologia de la UNAM y Universidad La Salle **Email:** not reported **Address:** Oficina Farmacologia Clinica, Servicio de Investigacion Clinica Hospitalaria. Adscrita al Servicio de Dermatologigia del Hospital General de México, S.S. y Dermatologia de la UNAM y Universidad La Salle; Petén 316 Col. Navarte. México, DF 03020
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Information about the sequence generation process insufficient to permit judgement of low risk or high risk
Allocation concealment (selection bias)	Unclear risk	Information insufficient to permit judgement of low risk or high risk
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Information insufficient to permit judgement of low risk or high risk Comment: although study authors stated that placebo medication was identical in appearance and taste to the ketotifen medication, they failed to elucidate the blinding procedure for personnel

Leon 1989 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information given as to how assessor was blinded (i.e. information insufficient to permit judgement of low risk or high risk)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: the number of participants randomised equals the number of participants evaluated
Selective reporting (reporting bias)	Unclear risk	Information insufficient to permit judgement of low risk or high risk. No comparison with protocol possible, as a study protocol is not available
Other bias	Unclear risk	Further risk of bias is possible, but information is insufficient to judge whether additional bias exists (e.g. no conflict of interest statement provided, no provision of information regarding origin of drugs, Was study initiated by pharmacological company? Did study authors receive funding from any source?)

Monroe 1992

Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group
Participants	**Baseline characteristics** Overall • *Number of participants randomised*: 41 (loratadine: n = 14; hydroxyzine: n = 14; placebo n = 13) • *Losses to follow-up*: not reported • *Age*: 18 to 65 years • *Duration of condition*: the skin condition had to be in an active stage for at least 2 weeks before the study • *Severity of condition*: "with at least moderate itching and skin lesions present on the day of entry into the study" • *Male/Female*: 10/31 **Inclusion criteria:** (1) diagnostic: atopic dermatitis diagnosed by a physician (department of dermatology); (2) severity of condition: atopic dermatitis with at least moderate itching and skin lesions; (3) duration of condition: skin condition had to be “in an active state at least 3 weeks prior to the study”; (4) site evaluated (e.g. face/back): whole body **Exclusion criteria:** "patients were excluded from the study if they were totally unresponsive to previous treatment with AH or they had taken AH in the previous 24 h, oral corticosteroids in the previous 10 days, or depot corticosteroids in the previous 28 days, or were taking any medication that could have a clinical effect on the course of the skin disorder" **Group differences:** not reported
Interventions	**Intervention characteristics** Loratadine • *Presentation*: oral • *Dose and frequency*: 10 mg 1×/d + placebo 2×/d • *Total dose*: 10 mg/d • *Duration given for*: 1 week • *Supplier and trade name if relevant*: not reported

Monroe 1992 *(Continued)*

	Hydroxyzine • *Presentation*: oral • *Dose and frequency*: 25 mg 3×/d • *Total dose*: 75 mg/d • *Duration given for*: 1 week • *Supplier and trade name if relevant*: not reported Placebo • *Presentation*: oral • *Dose and frequency*: 3×/d • *Total dose*: n/a • *Duration given for*: 1 week • *Supplier and trade name if relevant*: not reported
Outcomes	*Primary outcome 1: mean change in patient-assessed symptoms: pruritus (percentage change in scores (0 to 3) from baseline to endpoint* • **Outcome type:** continuous outcome • **Range:** 0 to 3 • **Direction:** lower is better • **Notes:** daily pruritus score decreased by 57% in the loratadine group, by 38% in the hydroxyzine group, and by 33% in the placebo group. Differences in decrease were not significant. According to the global evaluation of the antipruritic effect of treatment, a marked or complete response was reported by nine in the loratadine group, by 6 in the hydroxyzine group, and by 3 in the placebo group. The difference between loratadine and placebo groups was marginally significant (P = 0.05) *Primary outcome 2: adverse events: somnolence or sedation during treatment* • **Outcome type:** adverse event • **Direction:** lower is better
Identification	**Sponsorship source:** not reported **Country:** USA **Setting:** secondary **Comments:** outpatients at Department of Dermatology, Milwaukee Medical Clinic, and Medical College of Wisconsin, Milwaukee, Wisonsin **Author's name:** Eugene W. Monroe **Institution:** Department of Dermatology, Milwaukee Medical Clinic, and Medical College of Wisconsin, Milwaukee, Wisonsin **Email:** not reported **Address:** not reported
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Information about the sequence generation process insufficient to permit judgement of low risk or high risk

Monroe 1992 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Information insufficient to permit judgement of low risk or high risk
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: although "all drugs were supplied as identical capsules" the frequency of usage varied across the 3 groups. Thus whether participants could have shared this knowledge among one other remains unclear
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information given as to how assessor was blinded (i.e. information insufficient to permit judgement of low risk or high risk)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: number randomised was the number analysed
Selective reporting (reporting bias)	Unclear risk	Information insufficient to permit judgement of low risk or high risk. No comparison with protocol possible, as a study protocol is not available
Other bias	Unclear risk	Further risk of bias is possible, but information is insufficient to judge whether additional bias exists (e.g. no conflict of interest statement provided, no provision of information regarding origin of drugs, Was study initiated by pharmacological company? Did study authors receive funding from any source?)

Munday 2002

Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group
Participants	**Baseline characteristics** Overall • *Number of participants randomised*: 151 • *Losses to follow-up*: 21 • *Age*: median: 7 years (range 1 to 12 years) • *Duration of condition*: not reported • *Severity of condition*: not reported • *Male/Female*: not reported **Inclusion criteria:** (1) diagnostic: established AD with nocturnal itching and scratching (not stated whether according to Hanifin & Rajka or UK criteria) but study group consisted of dermatologists; (2) severity of condition: not reported; (3) duration of condition: not reported; (4) site evaluated (e.g. face/back): not reported **Exclusion criteria:** had received therapy with any systemic antihistamines within the 2-week period before the date of screening (day 1); history of epilepsy, glaucoma, or hepatic disease; hypersensitivity or contraindications to the study medication (including hydrocortisone and Unguentum Merck emollient); any other clinical abnormalities that the investigator felt were likely to affect participation in the trial **Group differences:** no statistically significant difference in relation to duration of condition, condition status, or prior use of eczema therapies
Interventions	**Intervention characteristics**

Munday 2002 *(Continued)*

Chlorpheniramine maleate BP

- *Presentation*: elixir
- *Dose and frequency*: 2 mg/5 mL chlorpheniramine maleate for those 1 to 5 years of age, and 10 mL (4 mg) for 6-to 12-year-olds (after 2 weeks, participants continuing to experience sleeplessness were permitted to receive double the bedtime dose (5.0 mL for participants 1 to 5 years old, and 10 mL for those 6 to 12 years old)
- *Total dose*: 2 or 4 mg (age dependent) or twice that amount after 2 weeks
- *Duration given for*: 1 month
- *Supplier and trade name if relevant*: not reported

Placebo

- *Presentation*: elixir
- *Dose and frequency*: not reported
- *Total dose*: n/a
- *Duration given for*: 1 month
- *Supplier and trade name if relevant*: not reported

Outcomes

Primary outcome 1: mean change in patient-assessed symptoms: severity of pruritus (none, minimal, mild, moderate) between days 1 and 29

- **Outcome type:** dichotomous outcome
- **Notes:** Table 1b: Cochran-Mantel-Haenzsel test: P = 0.745; stratified for age groups between placebo and intervention with control for baseline difference. Note that modal response was defined as the most common response over a specified period. This combined with the fact that the statistical test used is not very sensitive makes this analysis not very powerful

Primary outcome 2: adverse events

- **Outcome type:** adverse event
- **Notes:** study authors state no difference but not tested for significance

Secondary outcome 1: physician-assessed clinical signs

- **Outcome type:** continuous outcome
- **Notes:** reported as median scores with 95% CIs and P values. Composite score at baseline, day 15, and day 29. Analyses based on Wilcoxon rank sum test not appropriate, and study authors state no differences between groups but differences within groups over time

Secondary outcome 3: number of eczema flares/amount of 1% hydrocortisone in grams

- **Outcome type:** continuous outcome
- **Data value:** endpoint

Identification

Sponsorship source: not reported

Country: UK and Poland

Setting: secondary

Comments: multi-centre trial; 3 outpatient centres in UK and Poland (i.e. secondary setting)

Author's name: James Munday

Institution: Pharmax Ltd., Bexley

Email: imunday@intercern.com

Address: James Munday, 18 Brockley Park, Forest Hill, London SE23 1PS (UK)

Munday 2002 *(Continued)*

Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Information about the sequence generation process insufficient to permit judgement of low risk or high risk
Allocation concealment (selection bias)	Unclear risk	Information insufficient to permit judgement of low risk or high risk
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Information insufficient to permit judgement of low risk or high risk. Study authors failed to state whether placebo elixir was identical in appearance and taste to chlorpheniramine maleate BP
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Information insufficient to permit judgement of low risk or high risk
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "all analyses were performed using the intention-to-treat (ITT) population"
Selective reporting (reporting bias)	Unclear risk	Information insufficient to permit judgement of low risk or high risk. No comparison with protocol possible, as no study protocol appears to have been registered
Other bias	Unclear risk	Further risk of bias is possible, but information is insufficient to judge whether additional bias exists (e.g. no conflict of interest statement provided, no provision of information regarding origin of drugs, Was study initiated by pharmacological company? Did study authors receive funding from any source?) Main study author worked for Pharmax Ltd.

Nuovo 1992

Methods	**Study design:** single-patient randomised trial **Study grouping:** cross-over single-patient
Participants	**Baseline characteristics** Overall • *Number of participants randomised*: 1 • *Losses to follow-up*: n.a. • *Age*: 32 years • *Duration of condition*: lifelong • *Severity of condition*: not reported • *Male/Female*: 1 male **Inclusion criteria:** (1) diagnostic: (2) severity of condition: not reported; (3) duration of condition: lifelong; (4) site evaluated (e.g. face/back): not reported **Exclusion criteria:** n.a.

Nuovo 1992 *(Continued)*

	Group differences: n.a.
Interventions	**Intervention characteristics** Chlorpheniramine 16 mg/d • *Presentation*: oral • *Dose and frequency*: 8 mg chlorpheniramine twice daily • *Total dose*: 16 mg/d • *Duration given for*: 2 weeks • *Supplier and trade name if relevant*: not reported Chlorpheniramine 24 mg/d • *Presentation*: oral • *Dose and frequency*: 12 mg chlorpheniramine twice daily • *Total dose*: 24 mg/d • *Duration given for*: 2 weeks • *Supplier and trade name if relevant*: not reported Terfenadine 240 mg/d • *Presentation*: oral • *Dose and frequency*: 120 mg terfenadine twice daily • *Total dose*: 240 mg/d • *Duration given for*: 2 weeks • *Supplier and trade name if relevant*: not reported Placebo • *Presentation*: oral • *Dose and frequency*: not reported • *Total dose*: n/a • *Duration given for*: 2 weeks • *Supplier and trade name if relevant*: not reported
Outcomes	*Primary outcome 1: mean change in patient-assessed symptoms: pruritus assessed on 7-point Likert scale* • **Outcome type:** dichotomous outcome *Primary outcome 1: mean change in patient-assessed symptoms: patient-assessed severity of symptoms assessed on 7-point Likert scale* • **Outcome type:** dichotomous outcome *Primary outcome 2: adverse events (severity of drowsiness) on 7-point Likert scale* • **Outcome type:** adverse event *Secondary outcome 3: number of eczema flares/frequency of triamcinolone applications* **Outcome type:** continuous outcome • **Data value:** endpoint
Identification	**Sponsorship source:** the paper was supported by a grant (HS06006) from the National Center for Health Services Research-OASH **Country:** USA **Setting:** secondary

Nuovo 1992 *(Continued)*

	Comments: **Author's name:** James Nuovo **Institution:** Departments of Family Medicine, Pharmacy Practice, and Medicine, Schools of Medicine and Phannacy, University of Washington, Seattle **Email:** not reported **Address:** Department of Family Medicine, RF-30, University of Washington, Seattle, WA 98195
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "the order of treatment was determined by random allocation" Comment: no further information given (i.e. information about the sequence generation process insufficient to permit judgement of low risk or high risk)
Allocation concealment (selection bias)	Unclear risk	Information insufficient to permit judgement of low risk or high risk
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "the patient and the investigator were blinded to the treatment sequence"; "A pharmacist prepared all study medications to appear identical as pink capsules and maintained the drug code" Comment: participants and personnel were blinded to study groups
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: information insufficient to permit judgement of low risk or high risk
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: all data from the cross-over trial were reported
Selective reporting (reporting bias)	Unclear risk	Information insufficient to permit judgement of low risk or high risk. No comparison with protocol possible, as a study protocol is not available
Other bias	Unclear risk	Further risk of bias is possible, but information is insufficient to judge whether additional bias exists (e.g. no conflict of interest statement provided, no provision of information regarding origin of drugs, Was study initiated by pharmacological company?) However, a source of funding was provided

Ruzicka 1998

Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group
Participants	**Baseline characteristics** Overall • *Number of participants randomised*: 159/160

Ruzicka 1998 *(Continued)*

- *Losses to follow-up*: 28 (numbers do not add up, as there is a discrepancy between number lost to follow up and reported number of participants completing the study (n =138))
- *Age*: mean age in groups ranged from 36.0 to 39.2 years (age range 18 to 65 years)
- *Duration of condition*: group means ranged between 7.0 and 14.1 years (total range 1 month to 51 years)
- Duration of current episodes ranged between 2 days and 72 months
- *Severity of condition*: pruritus on VAS moderate (4 to 7) (10-cm VAS) at baseline; EASI: subtotal score A ≥ 18 and ≤ 40, and B ≥ 2 and ≤ 10
- *Male/Female*: 51/98

Inclusion criteria: (1) diagnostic AD according to Hanifin and Rajka, age 18 to 65 years; (2) severity of condition: pruritus score 4 to 7 (VAS), moderate severity of condition according to EASI score (Eczema Area and Severity Index) subtotal score A ≥ 18 and ≤ 40, and B ≥ 2 and ≤ 10; (3) duration of condition: not reported; (4) site evaluated (e.g. face/back): not reported

Exclusion criteria: cardiovascular disease; neurological and other systemic diseases; administration of depot corticosteroids within previous 3 months, systemic corticosteroids within previous 28 days, or topical corticosteroids within previous 7 days

Group differences: no baseline comparisons were provided; however, study authors report that baseline pruritus was not equally distributed among groups

Interventions

Intervention characteristics

Loratadine 5 mg

- *Presentation*: oral
- *Dose and frequency*: 5 mg 1×/d
- *Total dose*: 5 mg/d
- *Duration given for*: 2 weeks
- *Supplier and trade name if relevant*: not reported

Loratadine 10 mg

- *Presentation*: oral
- *Dose and frequency*: 10 mg 1×/d
- *Total dose*: 10 mg/d
- *Duration given for*: 2 weeks
- *Supplier and trade name if relevant*: not reported

Loratadine 20 mg

- *Presentation*: oral
- *Dose and frequency*: 20 mg 1×/d
- *Total dose*: 20 mg/d
- *Duration given for*: 2 weeks
- *Supplier and trade name if relevant*: not reported

Placebo

- *Presentation*: oral
- *Dose and frequency*: not reported
- *Total dose*: n/a
- *Duration given for*: 2 weeks
- *Supplier and trade name if relevant*: not reported

Outcomes

Primary outcome 1: mean change in patient-assessed symptoms: VAS pruritus (0 to 10 cm) (difference in pruritus sum between day 0 and day 13)

- **Outcome type:** continuous outcome

Ruzicka 1998 *(Continued)*

- **Direction:** lower is better
- **Notes:** VAS on a scale from 0 to 10 cm; from Table 2, it appears as if the absolute difference between VAS pruritus day 0 and day 13 was calculated (i.e. not a difference in pruritus sums but difference in VAS 0 to 10, day 0 and day 13

Patient-assessed symptoms: VAS pruritus: sum of days 7 to 13

- **Outcome type:** continuous outcome
- **Direction:** lower is better
- **Notes:** respective VAS pruritus values were summed over days 7 to 13. Study authors did not provide possible minimum and maximum values for this outcome, but it seems as if they could range from 0 to 70. Significant differences between groups (Jonckheer-Terpstra Test) in Table 4, and all post-hoc comparisons with placebo significant, but baseline not considered (i.e. should have been done with differences between t0 and t2)

Primary outcome 2: adverse events

- **Outcome type:** adverse event
- **Data value:** endpoint
- **Notes:** 16.2% of 160 randomised participants reported adverse events. However, study authors failed to describe or analyse, respectively, the number of AE across groups.

Secondary outcome 1: physician-assessed clinical signs: no. for whom treatment success was judged as good or very good

- **Outcome type:** dichotomous outcome
- **Notes:** again, comparisons not considering baseline differences, as only days 7 and 13; significance in Table 5 (not sure whether based on therapy success or global efficacy evaluation, or whether study authors meant they are the same)

Identification	**Sponsorship source:** not reported **Country:** Germany **Setting:** secondary **Comments:** 8 centres **Author's name:** T. Ruzicka **Institution:** Klinik und Poliklinik für Dermatologie und Allergologie, Frauenlobstraße 9–11, 80337 München **Email:** Marion.Michl@med.uni-muenchen.de **Address:** Klinik und Poliklinik für Dermatologie und Allergologie, Frauenlobstraße 9–11, 80337 MünchenKlinikum München Thalkirchner Straße, Thalkirchner Straße 48, 80337 München
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Information about the sequence generation process insufficient to permit judgement of low risk or high risk
Allocation concealment (selection bias)	Unclear risk	Information insufficient to permit judgement of low risk or high risk

Ruzicka 1998 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Information insufficient to permit judgement of low risk or high risk Comment: whether medication was identical in appearance to placebo remains unclear
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Information insufficient to permit judgement of low risk or high risk
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: of 160 participants randomised, only 138 were assessed at the end of the study (i.e. attrition rate was 13.7%). Study authors did not provide reasons for these dropouts and did not describe the missing data - but the risk of attrition bias was considered low based on the attrition rate
Selective reporting (reporting bias)	Unclear risk	Information insufficient to permit judgement of low risk or high risk Comment: no comparison with protocol possible, as a study protocol is not available
Other bias	Unclear risk	Further risk of bias is possible, but information is insufficient to judge whether additional bias exists (e.g. no conflict of interest statement provided, no provision of information regarding origin of drugs, Was study initiated by pharmacological company? Did study authors receive funding from any source?)

Savin 1986

Methods	**Study design:** randomised controlled trial **Study grouping:** cross-over
Participants	**Baseline characteristics** Overall • *Number of participants randomised*: 10 • *Losses to follow-up*: not reported • *Age*: adults - age not reported • *Duration of condition*: long-standing • *Severity of condition*: not reported • *Male/Female*: 10/0 **Inclusion criteria:** (1) diagnostic: not reported which diagnostic criteria were used for the definition of atopic dermatitis; (2) severity of condition: not reported; (3) duration of condition: long-standing (not further defined); (4) site evaluated (e.g. face/back): not reported **Exclusion criteria:** not reported **Group differences:** no baseline group differences (cross-over design)
Interventions	**Intervention characteristics** LN2974 (tazifylline) • *Presentation*: oral • *Dose and frequency*: 15 mg 2×/d • *Total dose*: 30 mg/d

Savin 1986 *(Continued)*

- *Duration given for*: days 1 to 7: placebo; days 8 to 10: placebo or LN2974; days 11 to 17: placebo; days 18 to 20: placebo or LN2974
- *Supplier and trade name if relevant*: not reported

Placebo

- *Presentation*: oral
- *Dose and frequency*: 2×/d
- *Total dose*: n/a
- *Duration given for*: days 1 to 7: placebo; days 8 to 10: placebo or LN2974; days 11 to 17: placebo; days 18 to 20: placebo or LN2974
- *Supplier and trade name if relevant*: not reported

Outcomes

Primary outcome 1: mean change in patient-assessed symptoms: pruritus

- **Outcome type:** continuous outcome
- **Direction:** lower is better
- **Notes:** "The difference in mean scores of the visual analogue assessment of itching between placebo and LN2974 did not reach statistical significance..."

Identification

Sponsorship source: not reported

Country: UK

Setting: secondary

Comments:

Author's name: John Andrew Savin

Institution: Department of Dermatology, The Royal Infirmary, Edinburgh, Scotland

Notes

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Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Information about the sequence generation process insufficient to permit judgement of low risk or high risk
Allocation concealment (selection bias)	Unclear risk	Informationn insufficient to permit judgement of low risk or high risk
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "in a double blind ....trial" Comment: whether medication was identical remains unclear. No information given regarding blinding of clinician
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information given as to how assessor was blinded (i.e. information insufficient to permit judgement of low risk or high risk)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Reporting of attrition/exclusions insufficient to permit judgement of low risk or high risk
Selective reporting (reporting bias)	Unclear risk	Information insufficient to permit judgement of low risk or high risk. No comparison with protocol possible, as a study protocol is not available

Savin 1986 *(Continued)*

Other bias	Unclear risk	Further risk of bias is possible, but information is insufficient to judge whether additional bias exists (e.g. no conflict of interest statement provided, no provision of information regarding origin of drugs, Was study initiated by pharmacological company? Did study authors receive funding from any source?)

Simons 2007

Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group
Participants	**Baseline characteristics** Levocetirizine • *Number of participants randomised*: 255 • *Losses to follow-up*: 36 • *Age*: M = 19.3 months • *Duration of condition*: not reported • *Severity of condition*: not reported • *Male/Female*: 60.8% male Placebo • *Number of participants randomised*: 255 • *Losses to follow-up*: 39 • *Age*: M = 19.4 months • *Duration of condition*: not reported • *Severity of condition*: not reported • *Male/Female*: 64.3% male **Inclusion criteria:** (1) diagnostic: atopic dermatitis (no further details given); (2) severity of condition: not specified; (3) duration of condition: not specified; (4) site evaluated (e.g. face/back): not reported **Exclusion criteria:** children with asthma or any other systemic disease; height or body mass below the 5th percentile; any severe neurological or psychological disorder requiring medical treatment; known to be intolerant of levocetirizine or any other piperazine antihistamine, or to the parabens used as preservatives in H1 antihistamine liquid formulations; personal history or sibling history of sleep apnoea; renal insufficiency or any metabolic condition that might affect elimination of levocetirizine **Group differences:** -
Interventions	**Intervention characteristics** Levocetirizine • *Presentation*: drops • *Dose and frequency*: 0.125 mg/kg twice daily • *Total dose*: 0.25 mg/kg/d • *Duration given for*: 18 months • *Supplier and trade name if relevant*: not reported Placebo • *Presentation*: matched • *Dose and frequency*: matched • *Total dose*: matched

Simons 2007 *(Continued)*

- *Duration given for*: matched
- *Supplier and trade name if relevant*: not reported

Outcomes	*Primary outcome 2: adverse events* • **Outcome type:** adverse event
Identification	**Sponsorship source:** UCB Pharma (information obtained from trial registration site) **Country:** Multi-centre: 10 European countries, Australia, and South Africa **Setting:** secondary **Comments:** **Author's name:** Simons F.E.R. **Institution:** Children's Hospital Research Institute of Manitoba **Email:** lmcniven@hsc.mb.ca **Address:** Children's Hospital Research Institute of Manitoba, 513 – 715 McDermot Avenue, Winnipeg MB R3E 3P4
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: although assignment to treatment was made according to preselected randomisation factors at baseline, including status of sensitisation to grass pollen or house dust mite, sensitisation to egg, maternal history of asthma, and country of residence, whether this eliminated selection bias remains unclear
Allocation concealment (selection bias)	Unclear risk	Information insufficient to permit judgement of low risk or high risk
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Information insufficient to permit judgement of low risk or high risk
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Information insufficient to permit judgement of low risk or high risk
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: ITT analyses were conducted for presented outcomes
Selective reporting (reporting bias)	Low risk	All outcomes stated in the trial registration were reported
Other bias	Unclear risk	Further risk of bias is possible, but information is insufficient to judge whether additional bias exists (e.g. no conflict of interest statement provided, no provision of information regarding origin of drugs, Was study initiated by pharmacological company? Did study authors receive funding from any source?)

Simons 2007 *(Continued)*

	Acknowledgement to UCB is made, but no further details are given

Tharp 1998

Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group
Participants	**Baseline characteristics** Overall • *Number of participants randomised*: 106 • *Losses to follow-up*: not reported • *Age*: adults - age not reported • *Duration of condition*: not reported • *Severity of condition*: patients with atopic dermatitis involving 20% to 50% of total body surface area and located at 2 or more non-contiguous areas • *Male/Female*: not reported **Inclusion criteria:** (1) diagnostic: no information given on how atopic dermatitis was defined; (2) severity of condition: patients with atopic dermatitis involving 20% to 50% of total body surface area and located at 2 or more non-contiguous areas; (3) duration of condition: not reported; (4) site evaluated (e.g. face/back): whole body **Exclusion criteria:** not reported **Group differences:** not reported
Interventions	**Intervention characteristics** Cetirizine • *Presentation*: oral • *Dose and frequency*: 20 mg 1×/d • *Total dose*: 20 mg/d • *Duration given for*: 12 weeks • *Supplier and trade name if relevant*: not reported Placebo • *Presentation*: oral • *Dose and frequency*: 1×/d • *Total dose*: n/a • *Duration given for*: 12 weeks • *Supplier and trade name if relevant*: not reported
Outcomes	*Primary outcome 1: mean change in patient-assessed symptoms: pruritus* • **Outcome type:** continuous outcome • **Notes:** pruritus reported by patients improved in cetirizine group compared to placebo group at visits 3, 5, and 6 ($P \leq 0.05$) *Primary outcome 2: adverse events* • **Outcome type:** adverse event • **Notes:** "The most reported adverse event in cetirizine group were headache and somnolence, which was not statistically significant from placebo group"

Tharp 1998 *(Continued)*

Secondary outcome 1: physician-assessed clinical signs

- **Outcome type:** continuous outcome
- **Notes:** "Mean improvement in investigator assessment of combined signs and symptom scores in cetirizine group was significantly greater than in placebo group (P = 0.04)"

Secondary outcome 3: secondary outcome 3: number of eczema flares, measured by, for example, 'escalation of treatment' or 'use of topical anti-inflammatory medications'

Amount of triamcinolone used

- **Outcome type:** continuous outcome
- **Notes:** "use of triamcinolone did not differ statistically between groups"

Identification	**Sponsorship source:** not reported, but because the last author of the abstract was an employee of Pfizer Inc., this pharmaceutical company might be the funding body for this study **Country:** USA **Setting:** secondary **Comments:** multi-centre study **Author's name:** Michael D. Tharp **Institution:** Rush University Medical Center **Email:** not reported **Address:** 1725 W. Harrison St., Suite 264, Chicago, IL 60612 USA. Phone: (312) 942-2195; fax: (312) 563-2263
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Information about the sequence generation process insufficient to permit judgement of low risk or high risk
Allocation concealment (selection bias)	Unclear risk	Information insufficient to permit judgement of low risk or high risk
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Information insufficient to permit judgement of low risk or high risk Comment: whether medication was identical in appearance to placebo remains unclear
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Information insufficient to permit judgement of low risk or high risk
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient reporting of attrition/exclusions to permit judgement of low risk or high risk. No information regarding dropouts was given
Selective reporting (reporting bias)	Unclear risk	Information insufficient to permit judgement of low risk or high risk. No comparison with protocol possible, as a study protocol is not available

Tharp 1998 *(Continued)*

Other bias	Unclear risk	Further risk of bias is possible, but information is insufficient to judge whether additional bias exists (e.g. no conflict of interest statement provided, no provision of information regarding origin of drugs, Was study initiated by pharmacological company? Did study authors receive funding from any source?)

ACTH: adrenocorticotropic hormone; AD: atopic dermatitis; AE: adverse event; bw/d: body weight each day; CRO: clinical research organisation; EASI: Eczema Area and Severity Index; ECG: electrocardiogram; ITT: intention-to-treat; M: mean; n.a.: not applicable; SCORAD: SCORing Atopic Dermatitis index; SD: standard deviation; SE: standard error; UVA: ultraviolet A; UVB: ultraviolet B; VAS: visual analogue scale.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Anton'ev 1988	Wrong study design: study not described as randomised
Balabolkin 1983	Wrong study design: study not described as randomised
Bogdaszewska 1968	Wrong study design: study not described as randomised
CastroTorres 1987	Wrong indication/wrong patient population: study included participants with different pruritic skin diseases, varying from insect bites to psoriasis. However, study authors did not give clear indications that the study included participants with eczema
Eberhartinger 1969	Wrong study design: study not described as randomised
Foulds 1981	Wrong comparator/wrong intervention: Cimetidene vs promethazine hydrochloride but not vs placebo
Furue 2009	Wrong study design: study not described as randomised
Grabner 1970	Wrong study design: study not described as randomised
Imaizumi 2003	Wrong study design: study not described as randomised
Kawakami 2006	Wrong comparator/wrong intervention: comparison of fexofenadine combined with emollient vs fexofenadine combined with steroid treatment
Kleine Natrop 1970	Wrong study design: study not described as randomised
Kori Lindner 1997	Review article
Korossy 1972	Wrong study design: study not described as randomised
Liu 2008	Wrong study design: study not described as randomised
Lutsky 1993	Wrong comparator/wrong intervention: comparison of loratadine vs terfenadine but not vs placebo
May 1966	Wrong study design: study not described as randomised
Mensing 1991	Wrong comparator/wrong intervention: comparison of loratadine vs dimethindene but not vs placebo

Study	Reason for exclusion
Mesquita 1994	Wrong comparator/wrong intervention: comparison of dimethindene vs astemizole but not vs placebo
Miller 1963	Wrong study design: study not described as randomised
Nitzschner 1970	Wrong study design: study not described as randomised
Ohsawa 2014	Review article
Ohtani 2004	Wrong comparator/wrong intervention: comparison of cetirizine vs epinastine hydrochloride vs vitamin B2 but not vs placebo
Pacor 1992	Wrong comparator/wrong intervention: comparison of oxatomide vs cromoglycate but not vs placebo
Patel 1997	Wrong comparator/wrong intervention: comparison of loratadine vs cetirizine but not vs placebo
Pfab 2012	Wrong study design: comparison of effects of several interventions on magnitude of experimentally induced itch
Rajka 1965	Wrong study design: study not described as randomised
Rajka 1968a	Wrong study design: study not described as randomised
Rajka 1968b	Wrong study design: study not described as randomised
Schmoeckel 1992	Wrong study design: observational drug safety study (i.e. study not described as randomised)
Sheng 2009	Wrong comparator/wrong intervention: comparison of mizolastine in combination with dyclonine cream vs cetirizine and dyclonine cream vs vitamin C and dyclonine cream
Simons 1984	Wrong comparator/wrong intervention: comparison of hydroxyzine 0.7 mg/kg 3 times daily vs hydroxyzine 1.4 mg/kg 3 times daily but not vs placebo
Sugai 2003	Wrong comparator/wrong intervention: comparison of tacrolimus ointment alone for 2 weeks followed by complementary use of cetirizine for another 2 weeks vs tacrolimus ointment and cetirizine for 2 weeks followed by tacrolimus alone for 2 weeks
Tarchalska 1988	Review article: a literature review
Veien 1995	Wrong patient population: sample consisted of patients with current hand eczema who had or previously had eczema
Voigtlander 1989	Wrong study design: study not described as randomised
Wahlgren 1990	Wrong study design: study not described as randomised
Wahlgren 1991	Wrong study design: study not described as randomised
Weitgasser 1967	Wrong comparator/wrong intervention: comparison of tavegyl vs another unspecified antihistamine
Wolfram 1967	Wrong study design: study not described as randomised

Study	Reason for exclusion
Zhang 1998	Wrong comparator/wrong intervention: comparison of oral terfenadine, injection of interferon gamma (up to 7 to 11 weeks), and rinse with calamine lotion vs cyproheptadine tablets and rinse with calamine lotion
Zhang 2010	Wrong comparator/wrong intervention: comparison of Qushi decoction oral and bathed vs oral chlorpheniramine 0.35 mg/kg 3×/d combined with Kangfu ointment
Zuluaga de Cadena 1989	Wrong study design: study not described as randomised

Wrong study design (e.g. lack of randomisation); wrong comparator (e.g. one H1 AH vs one or several other H1 AH but not vs placebo); wrong patient population (e.g. participants with no diagnosis of eczema); review article (e.g. not a trial but an article discussing several trials).

Characteristics of studies awaiting assessment *[ordered by study ID]*

Borelli 1969

Methods	Controlled clinical comparison of BP 400 vs placebo
Participants	200 patients with eczema and other pruritogenic skin conditions
Interventions	BP 400 (synonyms: 1-methyl-4-thioxanthen-9-ylidene-piperidine; 9-(1-methyl-4-piperidinylidene)thioxanthene; 9-(N-methyl-4'-piperidylene)thioxanthene; 9-(N-methyl-4'-piperidylidene)-thioxanthene; BP 400S; CGA 123427; Calmixen; Mepithiathene; Pimetixene) vs placebo
Outcomes	Antiprurigogenic and sedative effects of treatment
Notes	Not clear whether this was a randomised study. We contacted study authors but received no response to our queries

Chunharas 2002

Methods	Double-blind placebo controlled trial; however, whether a random allocation took place remains unclear
Participants	48 patients with eczema (children) with a mean age of 73.67 months
Interventions	Oral loratadine (5 mL/30 kg bodyweight/d) vs placebo as add-on to once-a-day topical mometasone fuorate 0.1% ointment
Outcomes	Severity of eczema as measured by SCORAD; physician global assessment of improvement; pruritus
Notes	Not clear whether this was a randomised study. We contacted study authors but received no response to our queries

DeBeule 1974

Methods	This is a randomised controlled trial
Participants	8 patients with eczema; 40 with other dermatological conditions, mainly hay fever

DeBeule 1974 *(Continued)*

Interventions	Oral primalan (mequitazine) (10 mg/d) vs placebo
Outcomes	Clinical signs of eczema
Notes	Although the study was also conducted in patients with eczema, results were not reported separately for these. We tried to contact study authors to request additional information but received no response

Laugier 1978

Methods	This is a randomised controlled trial
Participants	10 patients with eczema, 20 with urticaria, and 10 with other skin conditions
Interventions	Oral mequitazine 10 mg/d vs placebo
Outcomes	Overall clinical assessment of response to treatment
Notes	Although the study was also conducted in patients with eczema, results were not reported separately for these. We tried to contact study authors to request additional information but received no response

NCT00160563

Methods	This is a randomised controlled trial
Participants	Inclusion criteria that must be verified at the end of the first 18 months of treatment (visit 9) Having completed the previous 18-month treatment period of the EPAAC trial - NCT00152464
Interventions	Drug: levocetirizine 5 mg/mL oral drops, 0.125 mg/kg body weight, bid for 18 months; other name: Xyzal® Other: placebo oral drops, bid for 18 months Other: placebo oral drops, bid for 18 months
Outcomes	Primary outcome measures: time to onset of asthma [time frame: 36 months (from randomisation visit to preceding A00309 - NCT00152464 trial onwards)] [designated as safety issue: no] Secondary outcome measures: time to onset of asthma in the subset of subjects still asthma free after first 18 months [time frame: 18 months (from end of the preceding A00309 - NCT00152464 trial onwards)] [designated as safety issue: no]
Notes	Study has been terminated, but we do not know whether this took place before commencement of the study or afterwards

Simons 2003

Methods	This is a randomised controlled trial

Simons 2003 *(Continued)*

Participants	Infants who had a history of H1-antihistamine treatment for allergic rhinitis, urticaria, atopic dermatitis (eczema), or other disorders
Interventions	Drug: oral cetirizine 0.5 mg/d Other: matched placebo
Outcomes	Adverse events and electrocardiographic measurements
Notes	Although the study was also conducted in patients with eczema, results were not reported separately for these. We tried to contact study authors to request additional information but received no response

SCORAD: SCORing Atopic Dermatitis index.

Characteristics of ongoing studies *[ordered by study ID]*

CRT EU 23679

Trial name or title	Prednicarbat and cetirizine dihydrochloride in the treatment of acute stage of atopic eczema in children
Methods	Not reported
Participants	Children with eczema (age 2 to 11 years)
Interventions	Prednicarbat and cetirizine dihydrochloride
Outcomes	Not reported
Starting date	Not reported
Contact information	Not reported
Notes	-

CTR EU 23697

Trial name or title	Effect of long-term treatment with the H1 -receptor antagonist cetirizine in the prevention of urticaria in children with atopic dermatitis
Methods	Not reported
Participants	Children with eczema (age 2 to 11 years)
Interventions	H1-receptor antagonist cetirizine
Outcomes	Not reported
Starting date	Not reported
Contact information	Not reported
Notes	May be related to Simons 2007

CTR EU 29342

Trial name or title	Hydroxyzine: pharmacokinetics and antipruritic effect in children with atopic dermatitis
Methods	Not reported
Participants	Children with eczema (age 2 to 11 years)
Interventions	Hydroxyzine
Outcomes	Not reported
Starting date	Not reported
Contact information	Not reported
Notes	-

CTR EU 39698

Trial name or title	Evaluation of the efficacy and the safety of DCL syrup in childhood atopic dermatitis
Methods	Not reported
Participants	Children with eczema (age range unclear)
Interventions	Desloratadine
Outcomes	Not reported
Starting date	Not reported
Contact information	Not reported
Notes	-

UMIN000010519

Trial name or title	Impact of olopatadine hydrochloride (Allelock(R)) against scratching behavior of atopic dermatitis patients at night
Methods	This is a randomised controlled trial
Participants	Adults suffering from atopic dermatitis Inclusion criteria: • Persons with severe or moderate disease severity classification defined by atopic dermatitis (Japanese Dermatological Association) • 18 years of age or older (at the time of obtaining informed consent) • Unquestioned gender • Outpatient

UMIN000010519 *(Continued)*	• Persons with voluntary documented consent form • With night itching
Interventions	Olapatadine versus placebo
Outcomes	Measurement of the scratching ratio and the depth of sleep Measurement will be performed on days -2, -1, and 7 for patients with atopic dermatitis Measurement on day 7 day can be extended up to 3 additional days, in case the participant is not available on day 7 VAS value of itch and dermatitis score (EASI, ELQI) are measured for patients with atopic dermatitis Medication and measurement on day 7 will not be performed for healthy individuals
Starting date	18/02/2013
Contact information	Keiichi Yamanaka, MD, PhD; Mie University, Graduate School of Medicine; Department of Dermatology; 2-174 Edobashi, Tsu, Mie 514-8507, Japan
Notes	-

DCL: denotes desloratadine; EASI: Eczema Area and Severity Index; ELQI: authors did not provide what ELQI stands for, the abbreviation may contain a spelling mistake and actually refer to DLQI: Dermatology Quality of Life Index.

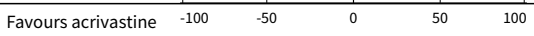
DATA AND ANALYSES

Comparison 1. Acrivastine 24 mg/d versus placebo

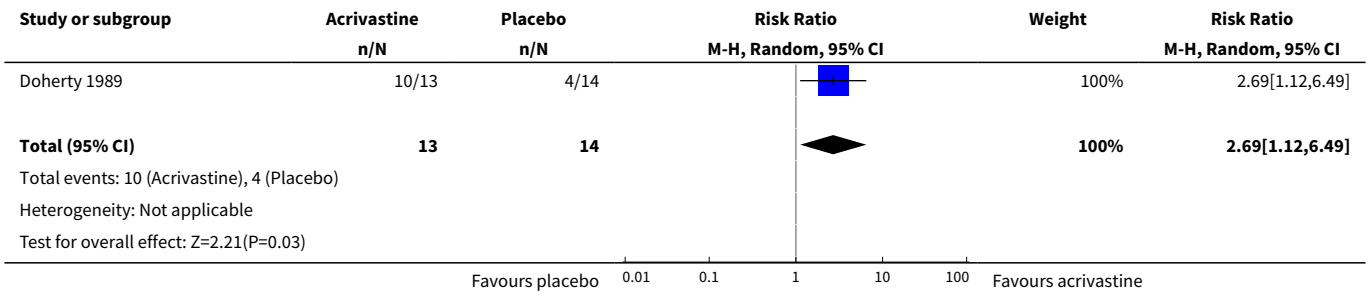
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Primary outcome 1. Mean change in patient-assessed symptoms: VAS pruritus 7 days after baseline adjusted for baseline score as covariate	1	23	Mean Difference (IV, Random, 95% CI)	-11.40 [-29.44, 6.64]
2 Secondary outcome 1. Physician-assessed clinical signs: number of participants for whom treatment helped itching	1	27	Risk Ratio (M-H, Random, 95% CI)	2.69 [1.12, 6.49]

Analysis 1.1. Comparison 1 Acrivastine 24 mg/d versus placebo, Outcome 1 Primary outcome 1. Mean change in patient-assessed symptoms: VAS pruritus 7 days after baseline adjusted for baseline score as covariate.

Study or subgroup	Acrivastine N	Acrivastine Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Doherty 1989	11	35 (21)	12	46.4 (23.2)		100%	-11.4[-29.44,6.64]
Total ***	**11**		**12**			**100%**	**-11.4[-29.44,6.64]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.24(P=0.22)							



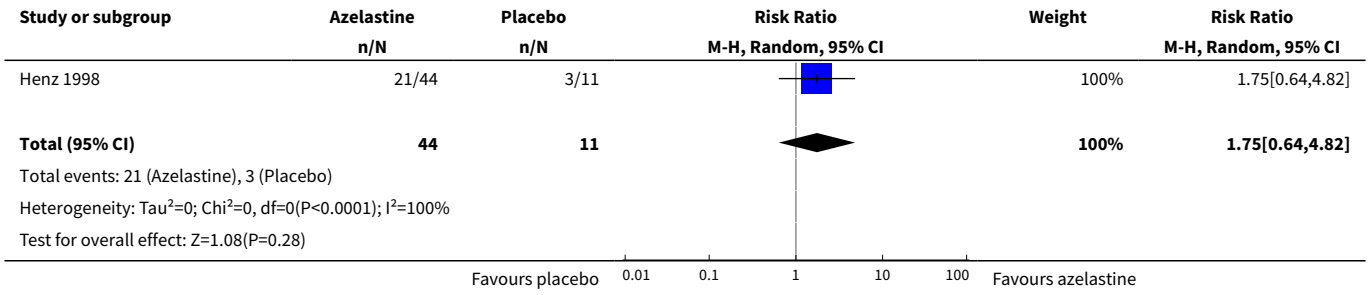
Analysis 1.2. Comparison 1 Acrivastine 24 mg/d versus placebo, Outcome 2 Secondary outcome 1. Physician-assessed clinical signs: number of participants for whom treatment helped itching.



Comparison 2. Azelastine 4 mg/d versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Secondary outcome 1. Physician-assessed clinical signs: mean overall response rate (number of participants who responded to treatment) 2 weeks after baseline	1	55	Risk Ratio (M-H, Random, 95% CI)	1.75 [0.64, 4.82]

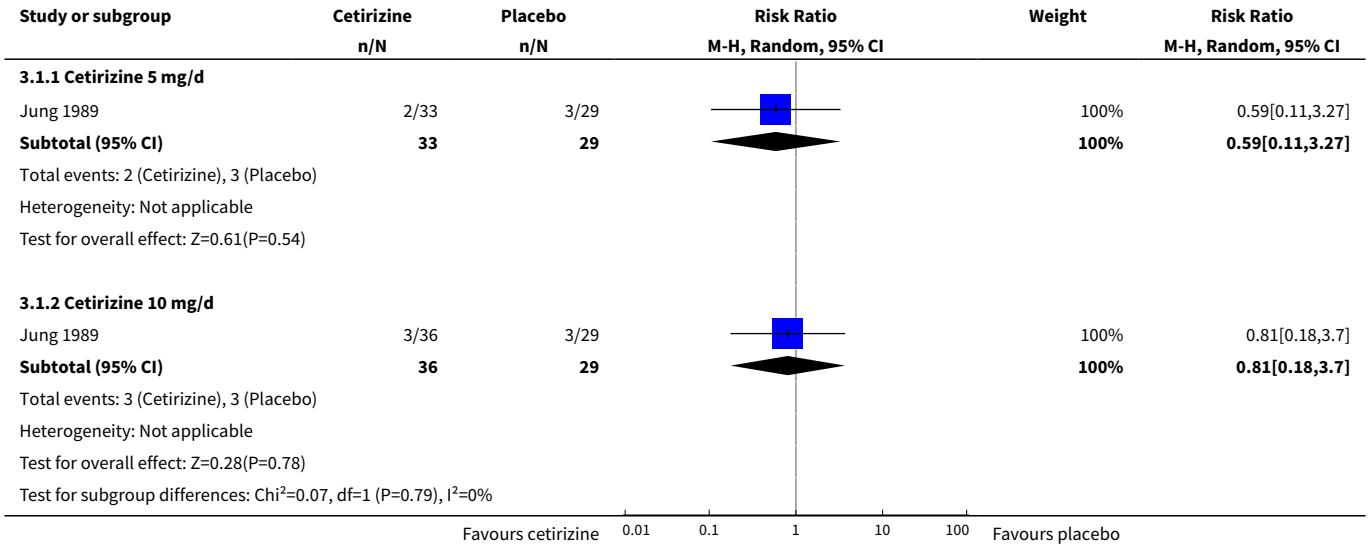
Analysis 2.1. Comparison 2 Azelastine 4 mg/d versus placebo, Outcome 1 Secondary outcome 1. Physician-assessed clinical signs: mean overall response rate (number of participants who responded to treatment) 2 weeks after baseline.



Comparison 3. Cetirizine 5 and 10 mg/d versus placebo (1-week intervention)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Primary outcome 2. Adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Cetirizine 5 mg/d	1	62	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.11, 3.27]
1.2 Cetirizine 10 mg/d	1	65	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.18, 3.70]

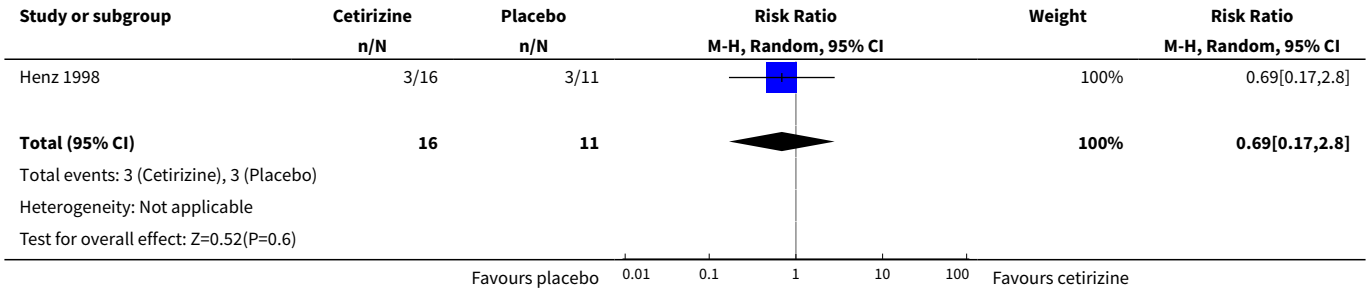
Analysis 3.1. Comparison 3 Cetirizine 5 and 10 mg/d versus placebo (1-week intervention), Outcome 1 Primary outcome 2. Adverse events.



Comparison 4. Cetirizine 10 mg versus placebo (2-week intervention)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Secondary outcome 1. Physician-assessed clinical signs: mean overall response rate (number of participants who responded to treatment) 2 weeks after baseline	1	27	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.17, 2.80]

Analysis 4.1. Comparison 4 Cetirizine 10 mg versus placebo (2-week intervention), Outcome 1 Secondary outcome 1. Physician-assessed clinical signs: mean overall response rate (number of participants who responded to treatment) 2 weeks after baseline.

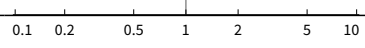


Comparison 5. Cetirizine 10, 20, 40 mg/d versus placebo (4-week intervention)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Primary outcome 2. Proportion of participants reporting adverse effects and serious adverse events throughout the study period	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 10 mg/d vs placebo	1	84	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.50, 2.45]
1.2 20 mg/d vs placebo	1	87	Risk Ratio (M-H, Random, 95% CI)	1.45 [0.70, 3.00]
1.3 40 mg/d vs placebo	1	89	Risk Ratio (M-H, Random, 95% CI)	2.38 [1.25, 4.53]

Analysis 5.1. Comparison 5 Cetirizine 10, 20, 40 mg/d versus placebo (4-week intervention), Outcome 1 Primary outcome 2. Proportion of participants reporting adverse effects and serious adverse events throughout the study period.

Study or subgroup	Cetirizine n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
5.1.1 10 mg/d vs placebo					
Hannuksela 1993	10/42	9/42		100%	1.11[0.5,2.45]
Subtotal (95% CI)	**42**	**42**		**100%**	**1.11[0.5,2.45]**
Total events: 10 (Cetirizine), 9 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.26(P=0.79)					
5.1.2 20 mg/d vs placebo					
Hannuksela 1993	14/45	9/42		100%	1.45[0.7,3]
Subtotal (95% CI)	**45**	**42**		**100%**	**1.45[0.7,3]**
Total events: 14 (Cetirizine), 9 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.01(P=0.31)					
5.1.3 40 mg/d vs placebo					
Hannuksela 1993	24/47	9/42		100%	2.38[1.25,4.53]
Subtotal (95% CI)	**47**	**42**		**100%**	**2.38[1.25,4.53]**
Total events: 24 (Cetirizine), 9 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.65(P=0.01)					
Test for subgroup differences: Chi^2=2.33, df=1 (P=0.31), I^2=14.19%					



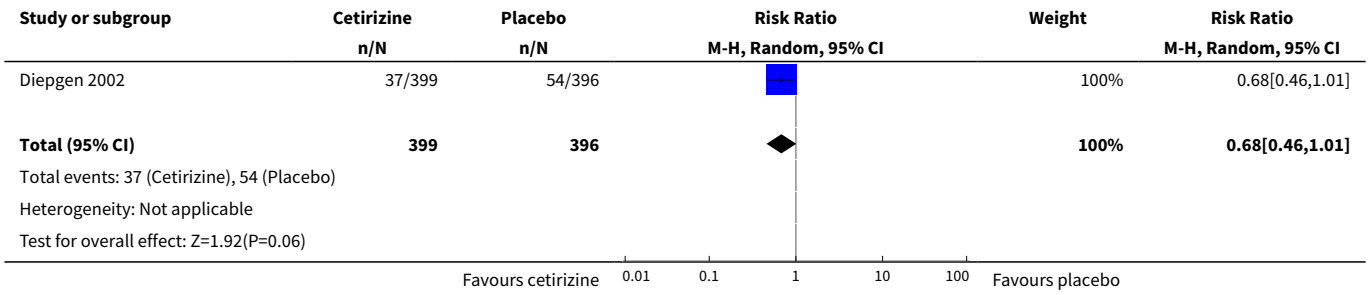
Favours cetirizine

Favours placebo

Comparison 6. Cetirizine 0.5 mg/d per kg versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Primary outcome 2. Proportion of participants reporting adverse effects and serious adverse events throughout the study period	1	795	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.46, 1.01]

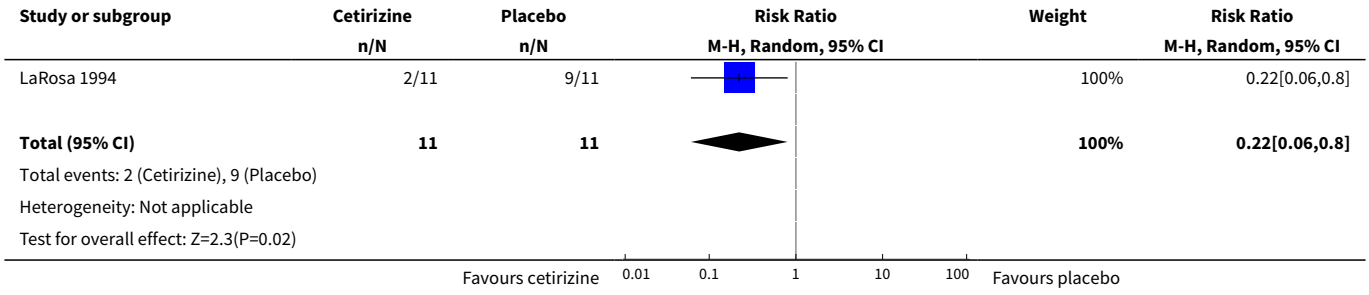
Analysis 6.1. Comparison 6 Cetirizine 0.5 mg/d per kg versus placebo, Outcome 1 Primary outcome 2. Proportion of participants reporting adverse effects and serious adverse events throughout the study period.



Comparison 7. Cetirizine 5 mg/d for children < 30 kg and 10 mg/d for children > 30 kg versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Secondary outcome 3. Use of concomitant therapy (disodium cromoglycate, procaterol, steroids)	1	22	Risk Ratio (M-H, Random, 95% CI)	0.22 [0.06, 0.80]

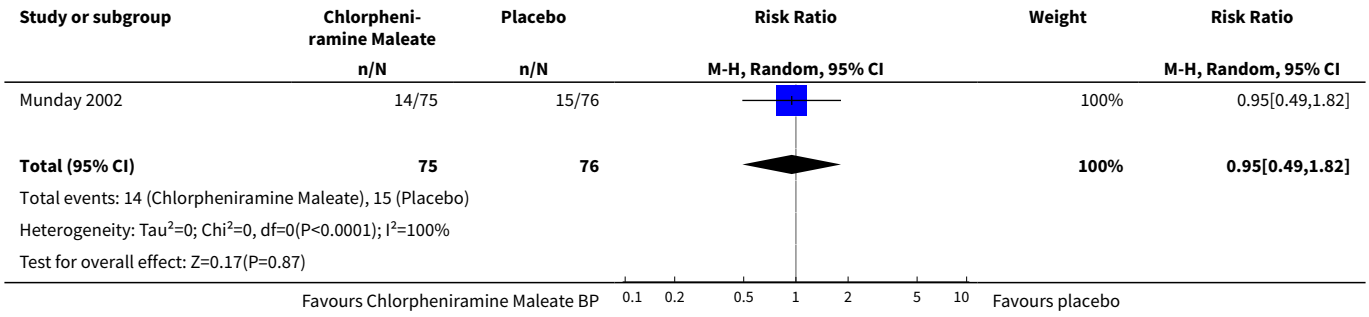
Analysis 7.1. Comparison 7 Cetirizine 5 mg/d for children < 30 kg and 10 mg/d for children > 30 kg versus placebo, Outcome 1 Secondary outcome 3. Use of concomitant therapy (disodium cromoglycate, procaterol, steroids).



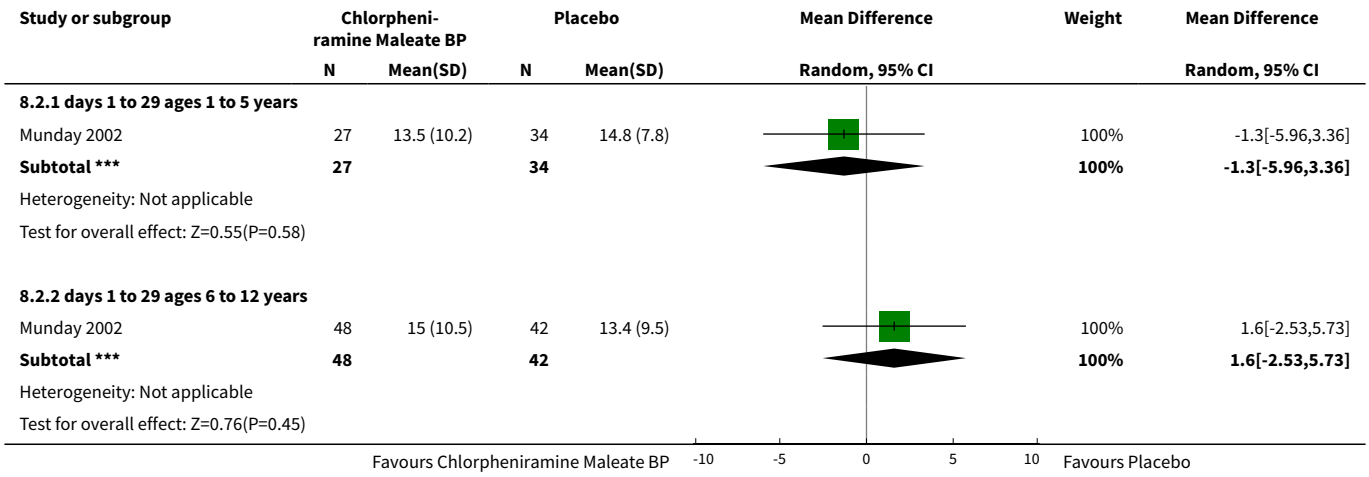
Comparison 8. Chlorpheniramine maleate BP (2 to 4 mg/d (age dependent) or twice that amount) versus placebo

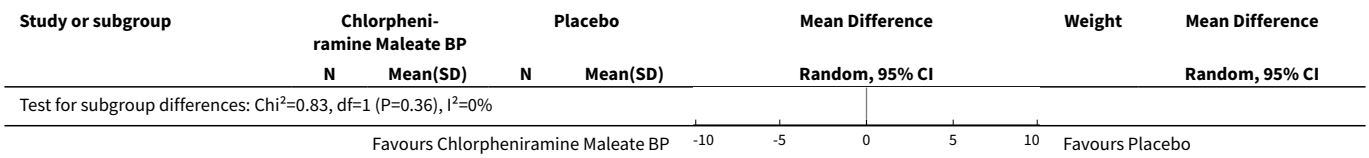
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Primary outcome 2. Proportion of participants reporting adverse effects and serious adverse events throughout the study period	1	151	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.49, 1.82]
2 Secondary outcome 3. Amount of 1% hydrocortisone in grams used	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.1 days 1 to 29 ages 1 to 5 years	1	61	Mean Difference (IV, Random, 95% CI)	-1.30 [-5.96, 3.36]
2.2 days 1 to 29 ages 6 to 12 years	1	90	Mean Difference (IV, Random, 95% CI)	1.60 [-2.53, 5.73]

Analysis 8.1. Comparison 8 Chlorpheniramine maleate BP (2 to 4 mg/d (age dependent) or twice that amount) versus placebo, Outcome 1 Primary outcome 2. Proportion of participants reporting adverse effects and serious adverse events throughout the study period.



Analysis 8.2. Comparison 8 Chlorpheniramine maleate BP (2 to 4 mg/d (age dependent) or twice that amount) versus placebo, Outcome 2 Secondary outcome 3. Amount of 1% hydrocortisone in grams used.

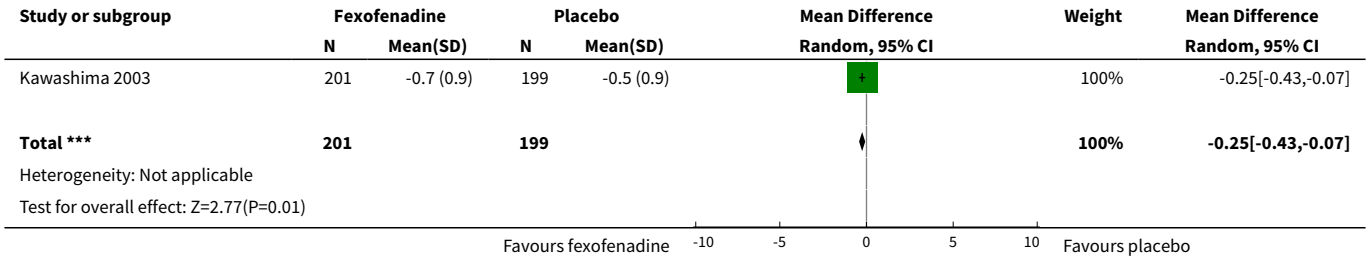




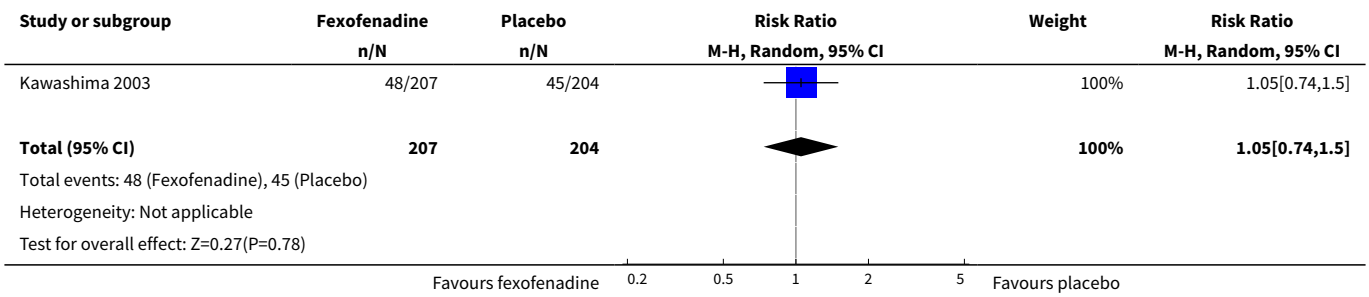
Comparison 9. Fexofenadine 120 mg/d versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Primary outcome 1. Mean change in patient-assessed symptoms: mean pruritus difference (0 to 8) between baseline and night of day 6	1	400	Mean Difference (IV, Random, 95% CI)	-0.25 [-0.43, -0.07]
2 Primary outcome 2. Adverse events	1	411	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.74, 1.50]

Analysis 9.1. Comparison 9 Fexofenadine 120 mg/d versus placebo, Outcome 1 Primary outcome 1. Mean change in patient-assessed symptoms: mean pruritus difference (0 to 8) between baseline and night of day 6.



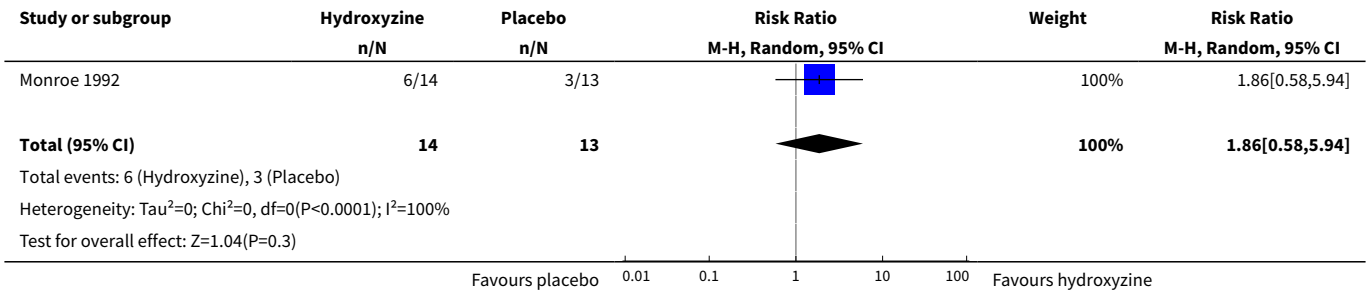
Analysis 9.2. Comparison 9 Fexofenadine 120 mg/d versus placebo, Outcome 2 Primary outcome 2. Adverse events.



Comparison 10. Hydroxyzine 75 mg/d versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Primary outcome 1. Patient-assessed symptoms: global evaluation of the antipruritic effect of treatment: number of participants who reported a marked or complete response	1	27	Risk Ratio (M-H, Random, 95% CI)	1.86 [0.58, 5.94]

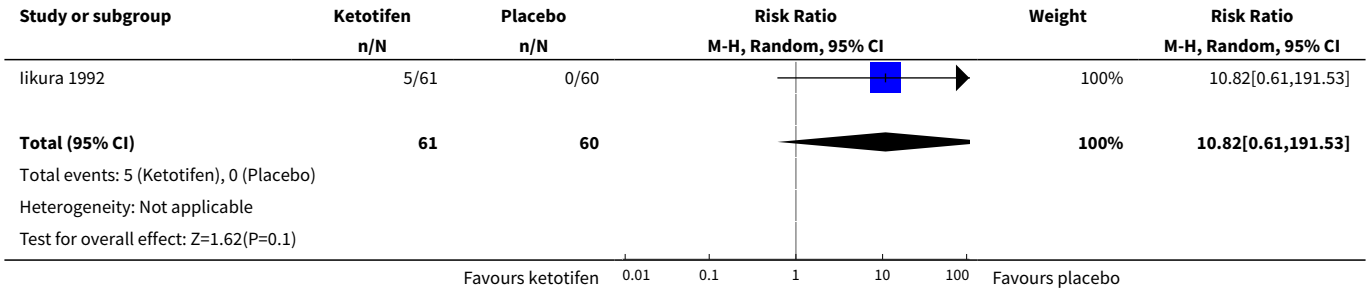
Analysis 10.1. Comparison 10 Hydroxyzine 75 mg/d versus placebo, Outcome 1 Primary outcome 1. Patient-assessed symptoms: global evaluation of the antipruritic effect of treatment: number of participants who reported a marked or complete response.



Comparison 11. Ketotifen 0.8 to 1.2 mg/d versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Primary outcome 2. Adverse events	1	121	Risk Ratio (M-H, Random, 95% CI)	10.82 [0.61, 191.53]

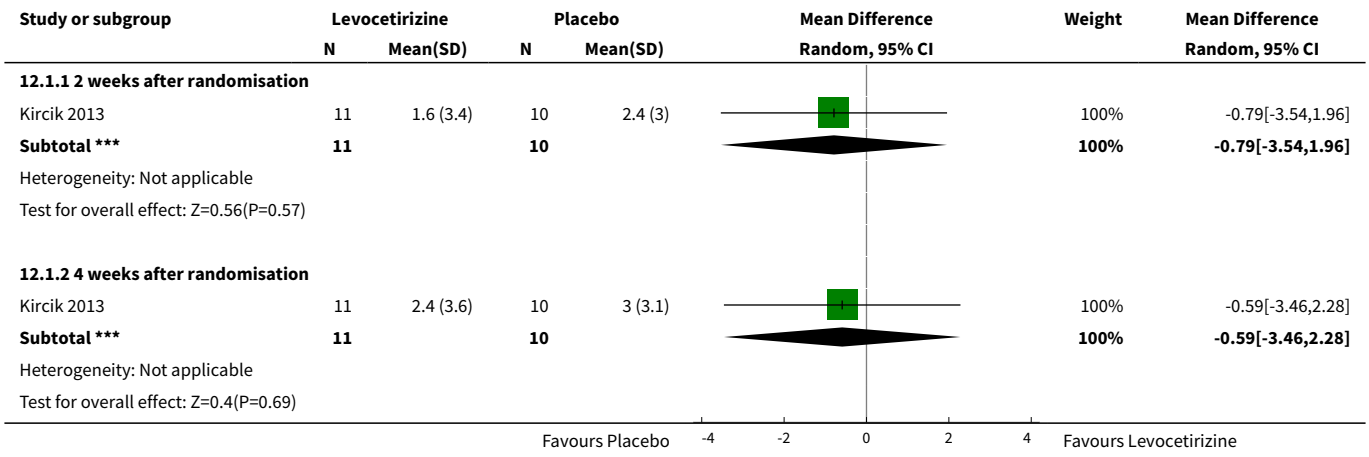
Analysis 11.1. Comparison 11 Ketotifen 0.8 to 1.2 mg/d versus placebo, Outcome 1 Primary outcome 2. Adverse events.



Comparison 12. Levocetirizine 5 mg/d versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Primary outcome 1. Mean change in patient-assessed symptoms: mean difference in VAS pruritus between baseline and 2 and 4 weeks after randomisation	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 2 weeks after randomisation	1	21	Mean Difference (IV, Random, 95% CI)	-0.79 [-3.54, 1.96]
1.2 4 weeks after randomisation	1	21	Mean Difference (IV, Random, 95% CI)	-0.59 [-3.46, 2.28]

Analysis 12.1. Comparison 12 Levocetirizine 5 mg/d versus placebo, Outcome 1 Primary outcome 1. Mean change in patient-assessed symptoms: mean difference in VAS pruritus between baseline and 2 and 4 weeks after randomisation.

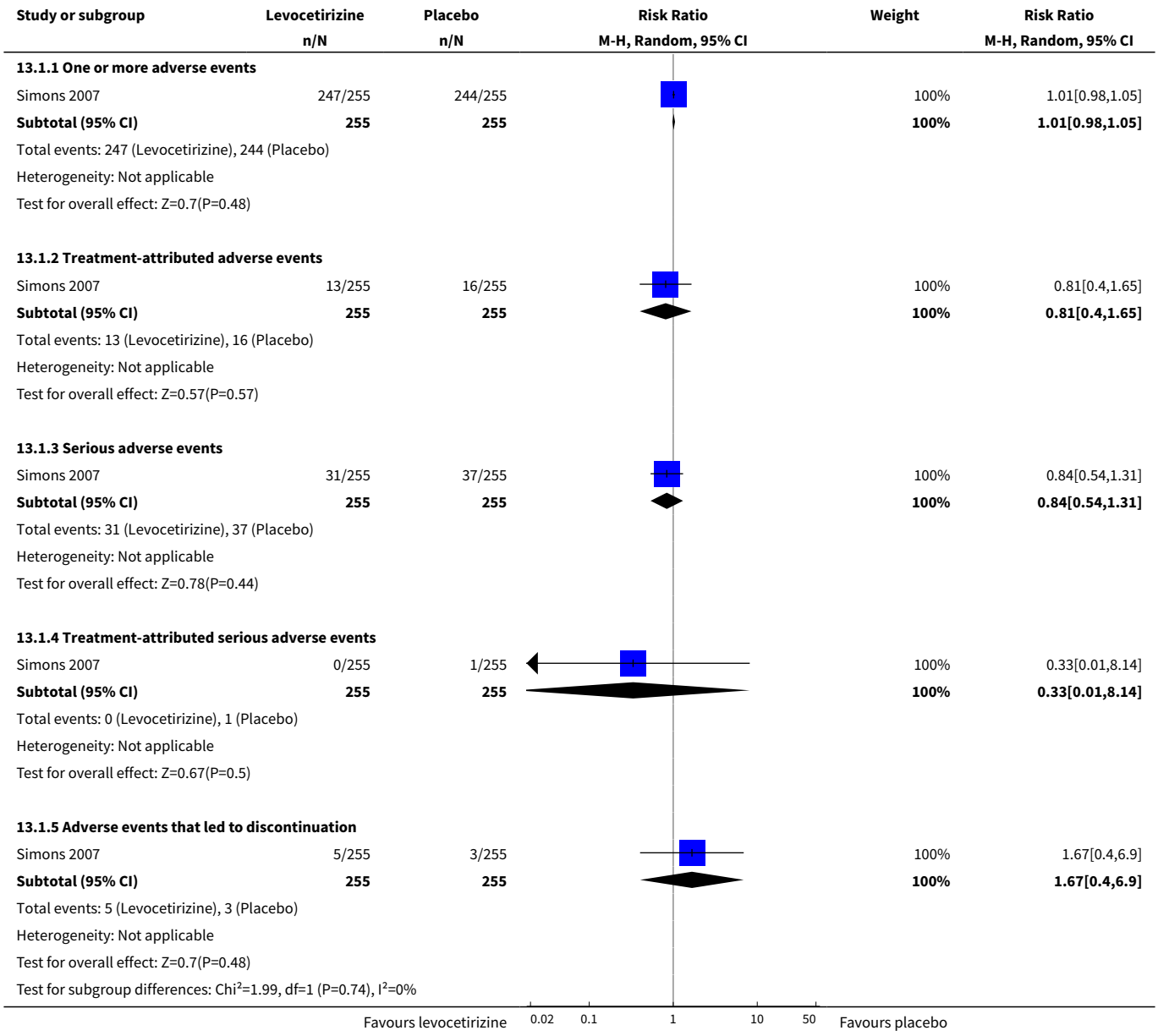


Comparison 13. Levocetirizine 0.25 mg/kg/d

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Primary outcome 2. Adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 One or more adverse events	1	510	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.98, 1.05]
1.2 Treatment-attributed adverse events	1	510	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.40, 1.65]
1.3 Serious adverse events	1	510	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.54, 1.31]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.4 Treatment-attributed serious adverse events	1	510	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.01, 8.14]
1.5 Adverse events that led to discontinuation	1	510	Risk Ratio (M-H, Random, 95% CI)	1.67 [0.40, 6.90]

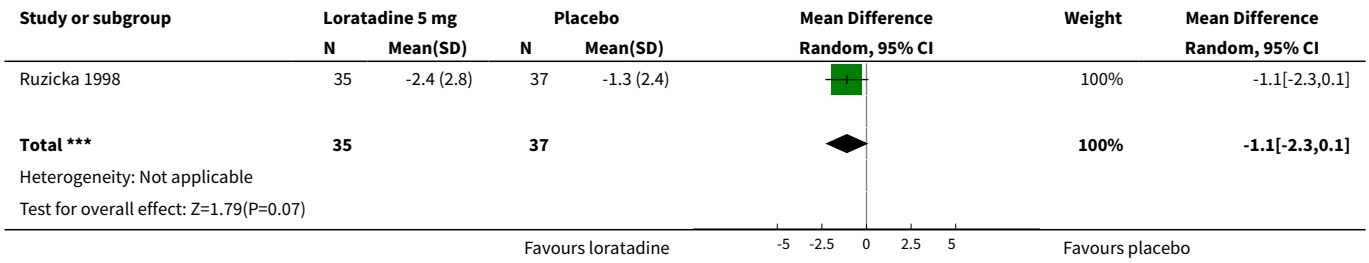
Analysis 13.1. Comparison 13 Levocetirizine 0.25 mg/kg/d, Outcome 1 Primary outcome 2. Adverse events.



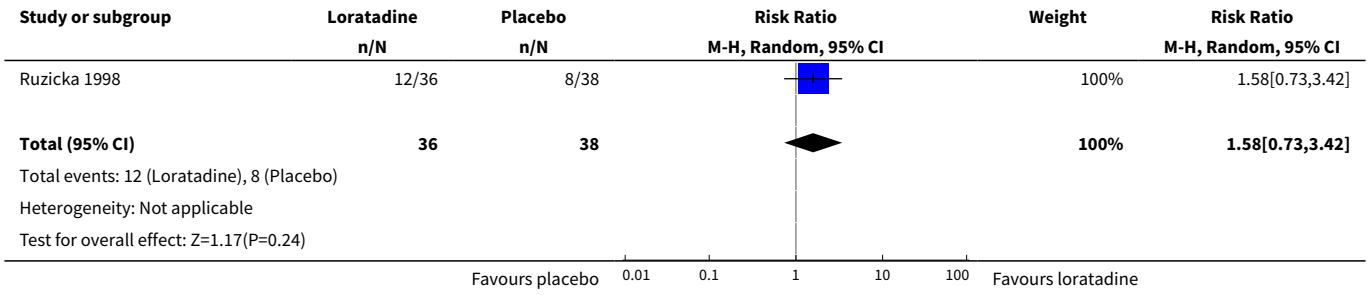
Comparison 14. Loratadine 5 mg/d versus placebo (2-week intervention)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Primary outcome 1. Mean change in patient-assessed symptoms: VAS pruritus (difference in pruritus sum between day 0 and day 13)	1	72	Mean Difference (IV, Random, 95% CI)	-1.10 [-2.30, 0.10]
2 Secondary outcome 1. Physician-assessed clinical signs: number of participants for whom treatment success was judged as good or very good 13 days after randomisation	1	74	Risk Ratio (M-H, Random, 95% CI)	1.58 [0.73, 3.42]

Analysis 14.1. Comparison 14 Loratadine 5 mg/d versus placebo (2-week intervention), Outcome 1 Primary outcome 1. Mean change in patient-assessed symptoms: VAS pruritus (difference in pruritus sum between day 0 and day 13).



Analysis 14.2. Comparison 14 Loratadine 5 mg/d versus placebo (2-week intervention), Outcome 2 Secondary outcome 1. Physician-assessed clinical signs: number of participants for whom treatment success was judged as good or very good 13 days after randomisation.

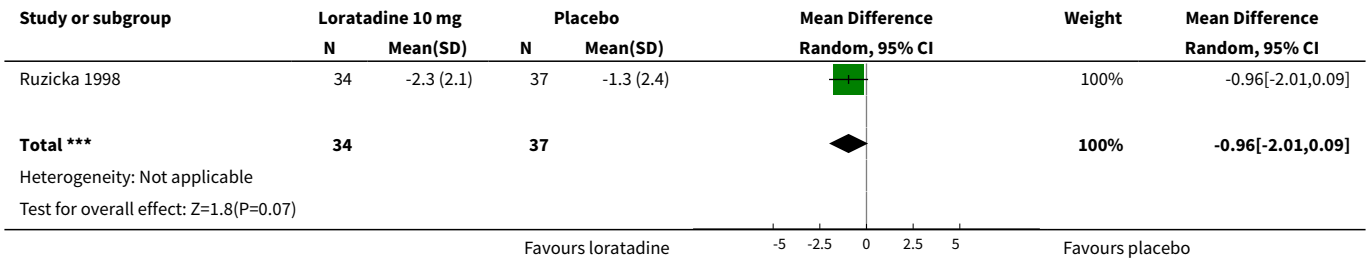


Comparison 15. Loratadine 10 mg/d versus placebo (2-week intervention)

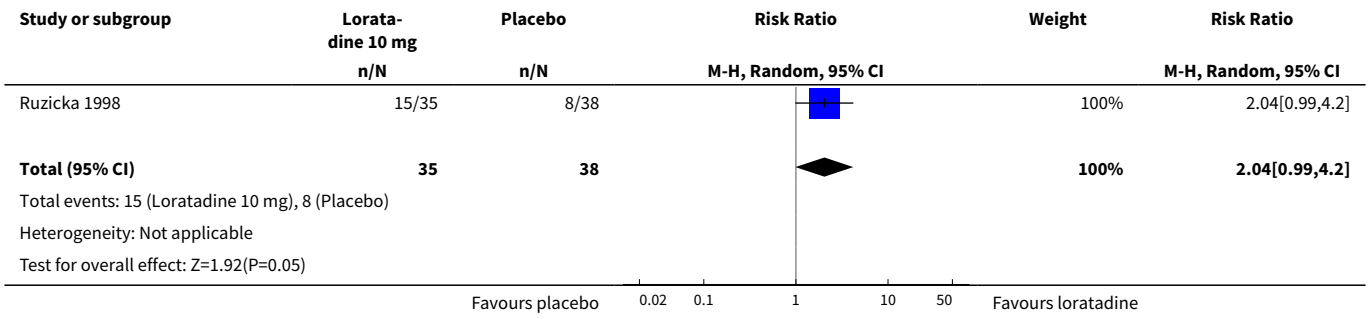
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Primary outcome 1. Mean change in patient-assessed symptoms: VAS pruritus (difference in pruritus sum between day 0 and day 13)	1	71	Mean Difference (IV, Random, 95% CI)	-0.96 [-2.01, 0.09]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Secondary outcome 1. Physician-assessed clinical signs: number of participants for whom treatment success was judged as good or very good 13 days after randomisation	1	73	Risk Ratio (M-H, Random, 95% CI)	2.04 [0.99, 4.20]

Analysis 15.1. Comparison 15 Loratadine 10 mg/d versus placebo (2-week intervention), Outcome 1 Primary outcome 1. Mean change in patient-assessed symptoms: VAS pruritus (difference in pruritus sum between day 0 and day 13).



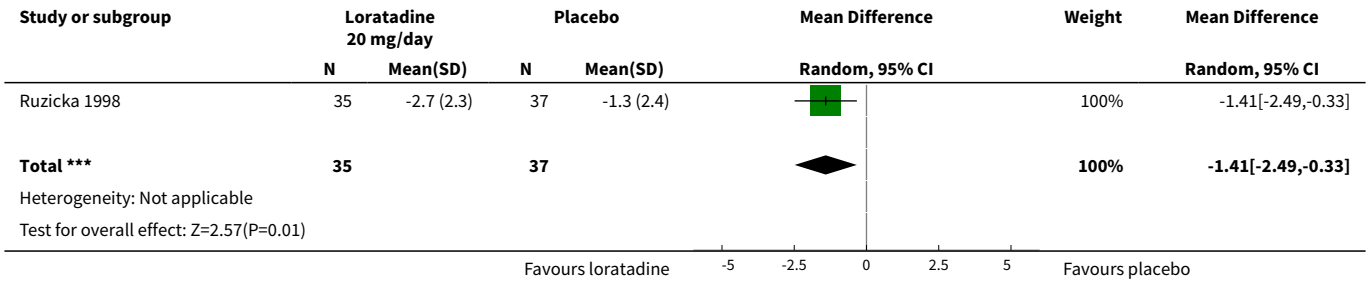
Analysis 15.2. Comparison 15 Loratadine 10 mg/d versus placebo (2-week intervention), Outcome 2 Secondary outcome 1. Physician-assessed clinical signs: number of participants for whom treatment success was judged as good or very good 13 days after randomisation.



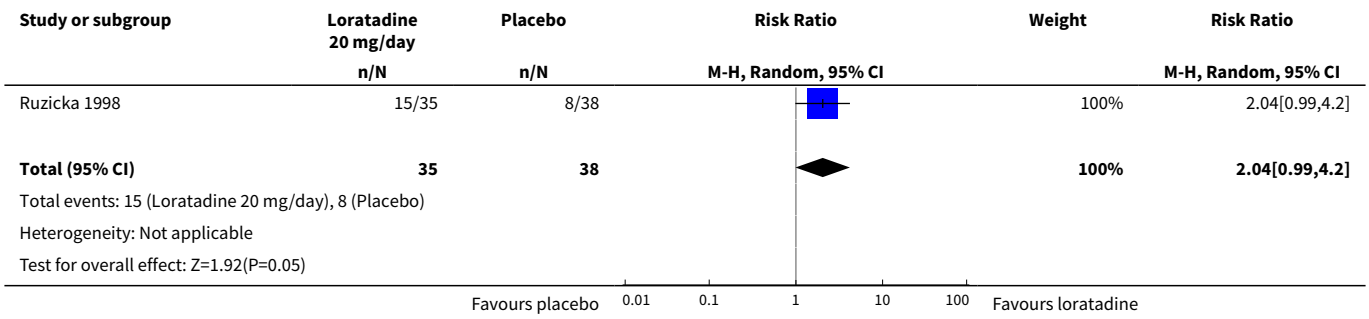
Comparison 16. Loratadine 20 mg/d versus placebo (2-week intervention)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Primary outcome 1. Mean change in patient-assessed symptoms: VAS pruritus (difference in pruritus sum between day 0 and day 13)	1	72	Mean Difference (IV, Random, 95% CI)	-1.41 [-2.49, -0.33]
2 Secondary outcome 1. Physician-assessed clinical signs: number of participants for whom treatment success was judged as good or very good	1	73	Risk Ratio (M-H, Random, 95% CI)	2.04 [0.99, 4.20]

Analysis 16.1. Comparison 16 Loratadine 20 mg/d versus placebo (2-week intervention), Outcome 1 Primary outcome 1. Mean change in patient-assessed symptoms: VAS pruritus (difference in pruritus sum between day 0 and day 13).



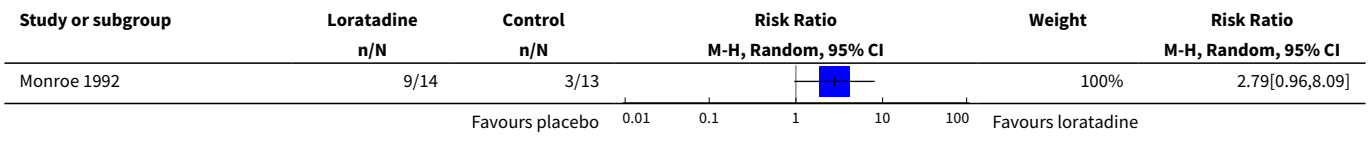
Analysis 16.2. Comparison 16 Loratadine 20 mg/d versus placebo (2-week intervention), Outcome 2 Secondary outcome 1. Physician-assessed clinical signs: number of participants for whom treatment success was judged as good or very good.

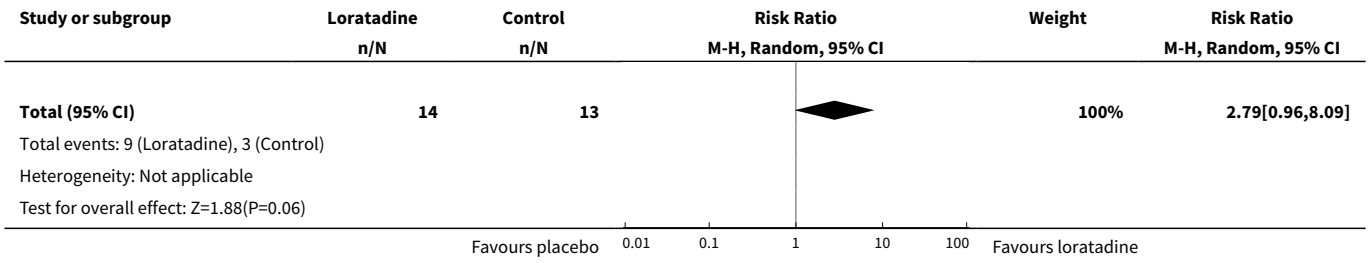


Comparison 17. Loratadine 10 mg/d versus placebo (1-week intervention)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Primary outcome 1. Global evaluation of the antipruritic effect of treatment: number of participants who reported a marked or complete response	1	27	Risk Ratio (M-H, Random, 95% CI)	2.79 [0.96, 8.09]

Analysis 17.1. Comparison 17 Loratadine 10 mg/d versus placebo (1-week intervention), Outcome 1 Primary outcome 1. Global evaluation of the antipruritic effect of treatment: number of participants who reported a marked or complete response.

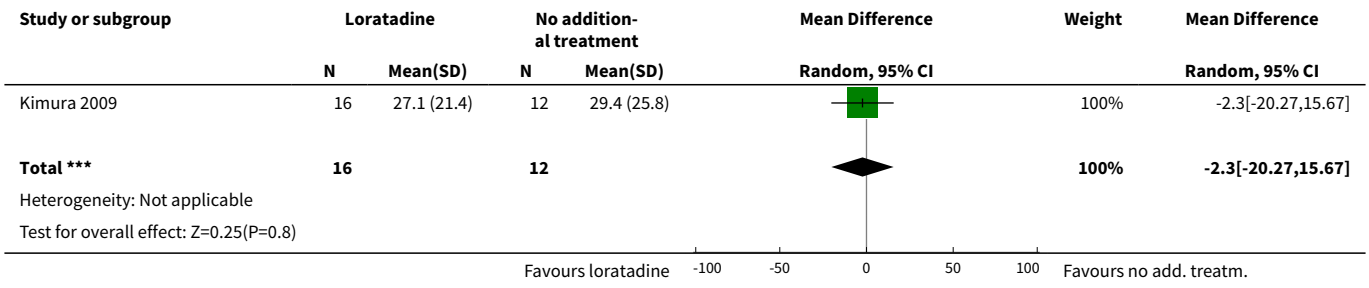




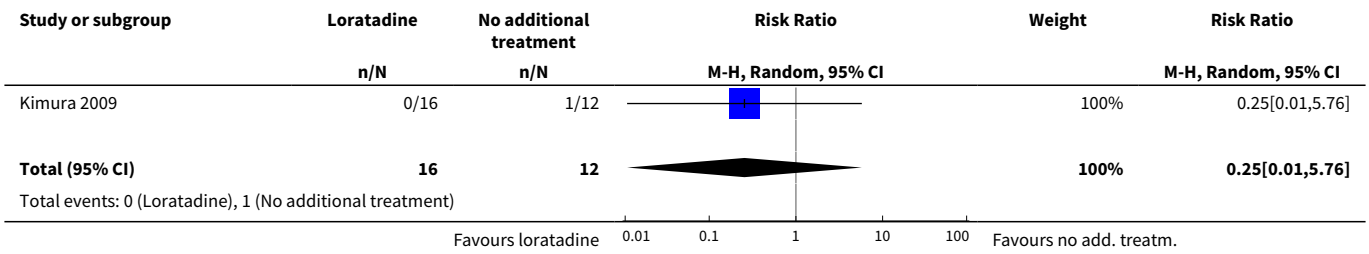
Comparison 18. Loratadine 10 mg/d versus no additional treatment (4-week intervention)

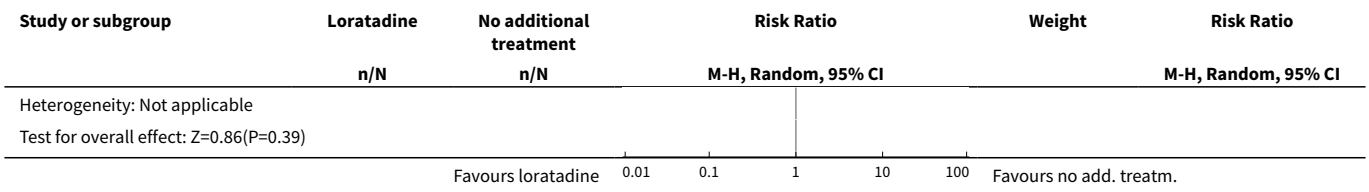
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Primary outcome 1. Patient-assessed symptoms: VAS pruritus 4 weeks after randomisation	1	28	Mean Difference (IV, Random, 95% CI)	-2.30 [-20.27, 15.67]
2 Primary outcome 2. Adverse events	1	28	Risk Ratio (M-H, Random, 95% CI)	0.25 [0.01, 5.76]
3 Secondary outcome 1. Physician-assessed clinical signs: SCORAD after 4 weeks	1	28	Mean Difference (IV, Random, 95% CI)	-4.10 [-13.22, 5.02]

Analysis 18.1. Comparison 18 Loratadine 10 mg/d versus no additional treatment (4-week intervention), Outcome 1 Primary outcome 1. Patient-assessed symptoms: VAS pruritus 4 weeks after randomisation.

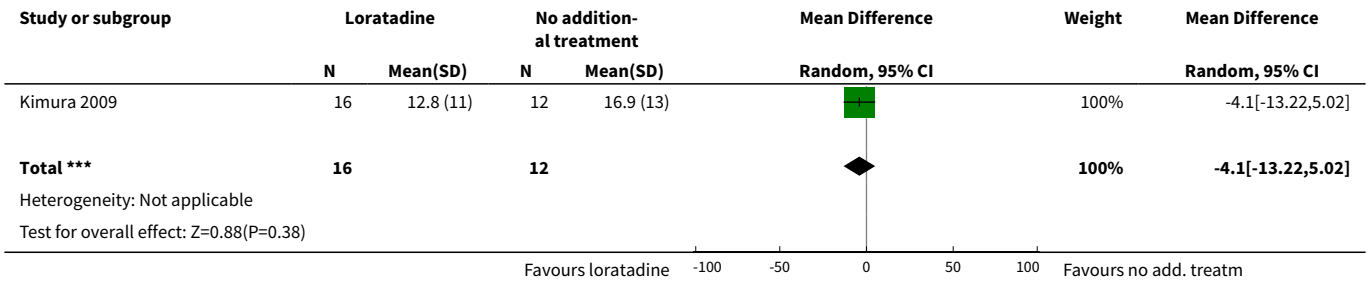


Analysis 18.2. Comparison 18 Loratadine 10 mg/d versus no additional treatment (4-week intervention), Outcome 2 Primary outcome 2. Adverse events.





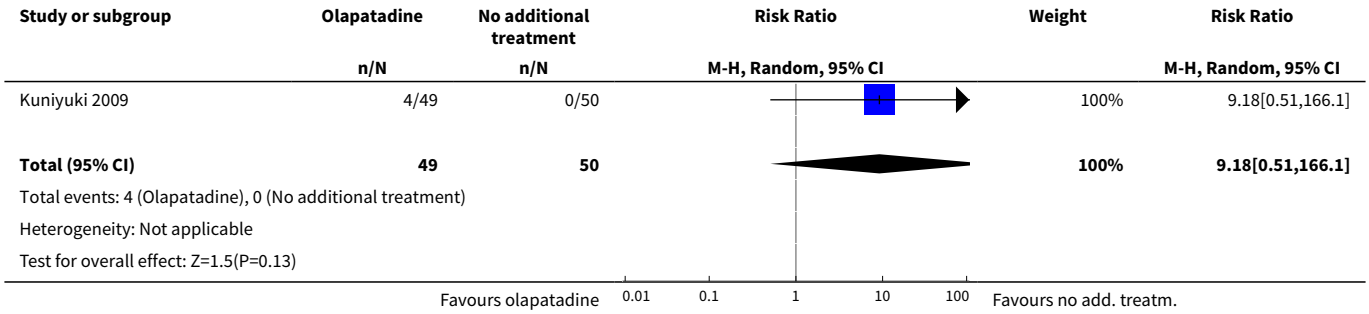
Analysis 18.3. Comparison 18 Loratadine 10 mg/d versus no additional treatment (4-week intervention), Outcome 3 Secondary outcome 1. Physician-assessed clinical signs: SCORAD after 4 weeks.



Comparison 19. Olopatadine 10 mg/d versus no additional treatment

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Primary outcome 2. Adverse events 8 weeks after randomisation	1	99	Risk Ratio (M-H, Random, 95% CI)	9.18 [0.51, 166.10]

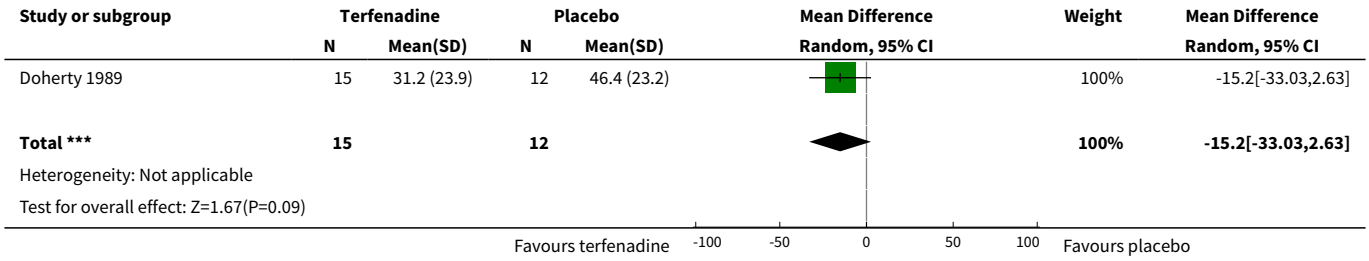
Analysis 19.1. Comparison 19 Olopatadine 10 mg/d versus no additional treatment, Outcome 1 Primary outcome 2. Adverse events 8 weeks after randomisation.



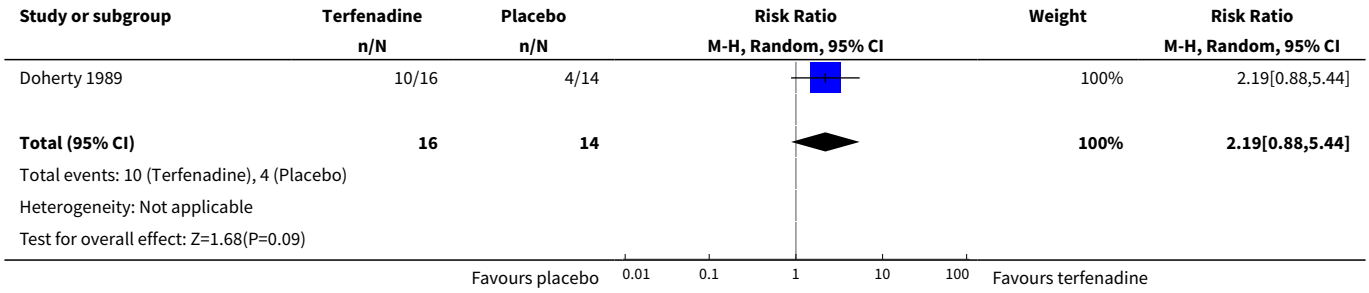
Comparison 20. Terfenadine 180 mg/d versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Primary outcome 1. Mean change in patient-assessed symptoms: VAS pruritus 7 days after baseline adjusted for baseline score as covariate	1	27	Mean Difference (IV, Random, 95% CI)	-15.2 [-33.03, 2.63]
2 Secondary outcome 1. Physician-assessed clinical signs: number of participants for whom treatment helped itching (1 week after randomisation)	1	30	Risk Ratio (M-H, Random, 95% CI)	2.19 [0.88, 5.44]

Analysis 20.1. Comparison 20 Terfenadine 180 mg/d versus placebo, Outcome 1 Primary outcome 1. Mean change in patient-assessed symptoms: VAS pruritus 7 days after baseline adjusted for baseline score as covariate.



Analysis 20.2. Comparison 20 Terfenadine 180 mg/d versus placebo, Outcome 2 Secondary outcome 1. Physician-assessed clinical signs: number of participants for whom treatment helped itching (1 week after randomisation).



ADDITIONAL TABLES

Table 1. Glossary of terms

Term	Definition
Adverse event	The occurrence of an unwanted effect due to a medication or a medical procedure
Antihistamines	Antihistamines (or histamine antagonists/histamine blockers) are drugs that block the action of histamine (an endogenous messenger substance released, e.g. in allergic inflammatory reactions). H1 antihistamines are predominantly used in the treatment of allergies

Table 1. Glossary of terms *(Continued)*

Arrhythmia	Irregular heartbeat
Atopy	Describes a genetic predisposition for hypersensitivity to common antigens (e.g. pollen, house dust, animal dander). Atopy can manifest in atopic diseases such as hay fever, allergic asthma, or eczema. Atopy can be associated with increased immunoglobulin E (IgE) levels
Autonomic nervous system	A division of the peripheral nervous system that regulates smooth muscle and gland functioning. As such, it influences the function of internal organs. This is a control system that acts largely unconsciously and regulates bodily functions such as heart rate, digestion, respiratory rate, pupillary response, urination, and sexual arousal
Axon reflex flare	Vasodilation and increased redness and sensitivity of the skin caused by stimulation of peripheral nerves
Cardiotoxic	Pertaining to the occurrence of heart electrophysiology dysfunction or muscle damage. The heart becomes weaker and is not as efficient in pumping and therefore in circulating blood
Clinical signs	Physician-assessed visible signs of eczema, such as erythema (redness) or dryness
Corticosteroids	A group of naturally occurring hormones or synthetic analogues of hormones. Corticosteroids are produced in the adrenal glands. According to their biological function, corticosteroids can be classified into: (1) mineralocorticoids (hormones that influence the salt and water balance within the body), (2) glucocorticosteroids (=> see below), and (3) androgen/oestrogen (male/female sex hormones)
Cross-over study	A type of clinical trial in which participants under study receive a sequence of different treatments in a randomly selected order
Eosinophils	White blood cells - one of the immune system components - that control mechanisms associated with allergy and asthma as well as parasitosis
Emollients	Emollients (or moisturisers) are complex mixtures of chemical agents designed to soften the epidermis (external layers of the skin)
Epidermal	Referring to the epidermis. The epidermis is the protective outer layer of the skin
Epithelial	Pertaining to the thin tissue forming the outer layer of a body's surface and lining the alimentary canal and other hollow structures
Erythema	Redness of the skin (or mucous membranes) that is caused by increased blood flow into superficial vessels and capillaries. This can occur, for example, with skin injury, infection, or inflammation
Excoriations	Skin lesions caused by repetitive, compulsive scratching of the skin. Of different colours (e.g. yellow or red caused by tissue fluid and light bleeding), they are frequently found in patients suffering from itch
Filaggrin	A protein that binds to keratin fibres in the cells to form a functional barrier at the skin surface. There is defective permeability of the barrier function (skin-protecting function) in eczema. Defects of the filaggrin gene contribute to the defective permeability of the outermost layer of the skin
Flexural	Related to the action of bending or curving (e.g. of the skin or a joint)
Gene polymorphism	A gene is said to be polymorphic if more than 1 allele (1 of 2 or more forms of a gene) occupies that gene's locus (location of a gene on a chromosome) within a population
Glucocorticosteroids	Particular class of corticosteroids. They have various functions within the human body (e.g. in the immune system, in metabolism)

Table 1. Glossary of terms *(Continued)*

IgE	A class of antibodies (immunoglobulins, Ig). The primary function of IgE within the immune system is to fight endoparasites. However, it is also responsible for some allergic reactions (e.g. local inflammation in eczema, airway constriction in asthma). People with an atopic predisposition often have increased IgE levels
IL-31	Belongs to the group of cytokines. These are mediators that communicate between different cell types. IL stands for interleukin
Immunomodulator	Pharmacologically active substance that affects the immune system. Examples of topical immunomodulators used in the treatment of eczema are tacrolimus and pimecrolimus
Lichenification	Describes extensive thickening of the skin accompanied by noticeable skin markings. Lichenification is a symptom of a number of chronic skin diseases (e.g. eczema)
Lipid	An organic compound (e.g. fats, oils, hormones) grouped together because components are not soluble in water
Mediators	Intermediary substances or agents that are released from cells to regulate or cause physiological consequences
Metabolites	Small molecules that are intermediate or final products of metabolism
Neuropeptides	Small molecules that can be found in the nervous tissue. They serve as messenger substances used by nerve cells (neurons) to communicate with one another
Nodule	A palpable solid skin lesion usually 0.5 cm or larger in diameter. Can involve different depths of the skin and can vary in shape and surface
Oedema	Abnormal accumulation of fluid in or under the skin
Papule	A solid elevated palpable lesion usually less than 0.5 cm in diameter. Can have different shapes and surfaces (e.g. flat-topped and rough)
Pimecrolimus	An immunomodulating agent used in the treatment of eczema. Available as a topical cream
Polymorphism	A variation in the DNA that is too common to be due merely to new mutation. A polymorphism must have a frequency of at least 1% in the population
Prurigo	Prurigo and prurigo nodularis may be used synonymously. Prurigo describes a condition of nodular cutaneous lesions that itch intensely (i.e. are pruritic). Prurigo nodules usually reflect a chronic state of itch and eczema
Pruritogen	Any substance that causes pruritus
Psychosomatic	Refers to the processes of psychological factors that influence physiological functioning
Long QT interval	Abnormal pattern seen on the records of the heart's electrical activity measured by electrocardiography (ECG). Long QT-syndrome is a disorder of the heart's electrical activity that can cause fast and chaotic heartbeats, leading to a sudden fainting spell or, in some cases, death
RCT	Randomised controlled trial. A type of scientific study in which participants in the study population are allocated randomly to an experimental, placebo, or control group. RCTs are often conducted to test the effectiveness of a new medication or medical procedure
Somnolence	A state of strong desire for sleep, or sleeping for unusually long periods

Table 1. Glossary of terms *(Continued)*

Symptom	Departure from normal function or feeling that is noticed by a patient, indicating the presence of disease or abnormality (Knol 2011) (e.g. sleep loss, itching)
Tachycardia	A heart rate greater than 100 beats per minute (BPM) in adults. It means that the heart beats too fast
Tacrolimus	An immunosuppressive drug used mainly after organ transplantation to lower the risk of organ rejection. Tacrolimus is also used, among other indications, in a topical preparation for the treatment of eczema
Th2 helper cells	A functionally distinct subclass of T helper cells (lymphocytes, white blood cells) that play an important role in the immune system. They can stimulate IgE synthesis and are critical in favouring the differentiation of eosinophilic granulocytes. They activate the release of local mediators that cause sneezing, coughing, or eczema
Tryptase	A protein-splitting enzyme (proteinase) that is produced by mast cells. These cells are located in the human dermis. Proteinases play a role in regulation of the immune response and cutaneous inflammation
Vasodilation	Refers to widening of blood vessels
Ventricular tachycardia	A type of tachycardia that arises from improper electrical activity in the ventricles of the heart
Vesicle	A cavity (smaller than 0.5 cm) filled with fluid. It may be non-palpable in thicker skin (e.g. palms, soles), breaks easily, and releases its fluid onto the skin

BPM: beats per minute; ECG: electrocardiogram; Ig: immunoglobulin; IL: interleukin; RCT: randomised controlled trial.

Table 2. H1 antihistamines under investigation in the included studies

	# of studies	Study ID	Type of study /grouping	Duration of intervention	Dose	Concomitant treatment	n randomised
Acrivastine	1	Doherty 1989	Parallel	10 days	24 mg/d	Twice-daily application of 0.05% clobetasone butyrate ointment and aqueous cream as a soap substitute	27 adults
Azelastine	1	Henz 1998	Parallel	2 weeks	4 mg/d	Unspecified rescue hydrocortisone cream	56 adults
Cetirizine	7	Hannuksela 1993	Parallel	4 weeks	10, 20, 40 mg/d	"The use of emollients (Aqualan L or Novalan, Orion Pharmaceuticals) [was] allowed when it was felt necessary. Patients were given an emollient supply of 100g/week. In the event of failure hydrocortisone cream 1% ...could be used"	178 adults
		Cambazard 2001	Parallel	8 weeks	0.25 mg/kg bw/d; 0.50 mg/kg bw/d; 0.75 mg/kg bw/d; bw = bodyweight	"Patients were allowed to use 1% hydrocortisone (Cremicor) cream as rescue treatment for facial atopic dermatitis and clobetasone butyrate (Eumovatem) as rescue treatment for atopic dermatitis on other parts of the body"	223 children
		Jung 1989	Parallel	1 week	5 and 10 mg/d	"Throughout the duration of the study the patients were asked to apply an antibiotic ointment (Fucicdin) to all their lesions; a topical corticosteroid (Eumovat) was to be used only when	98 children

Table 2. H1 antihistamines under investigation in the included studies *(Continued)*

					absolutely necessary"	
		LaRosa 1994	Parallel	8 weeks	5 to 10 mg/d	This study used disodium cromoglycate and procaterol, and 9 participants (82%) in the placebo group received other drugs, mainly disodium cromoglycate aerosol and nasal and cutaneous administration of topical steroids	23 children
		Henz 1998	Parallel	2 weeks	10 mg	Unspecified rescue hydrocortisone cream	29 adults
		Tharp 1998	Parallel	12 weeks	20 mg/d	This study allowed triamcinolone acetonide	106 adults
		Diepgen 2002	Parallel	18 months	0.5 mg/kg/d	"All concomitant medications were allowed but had to be recorded by the parents/guardians on the diary card and by the investigator in the case report form"	795 children
Chlorpheniramine or chlorpheniramine maleate	3	Frosch 1984	Cross-over	4 weeks	12 mg/d	"The patients were allowed to use at will a bland greasy ointment which did not contain an antiinflammatory active substance (e.g. vaseline or eucerin). They also received weighed containers of 0.1% betamethasone ointment...."	18 adults
		Munday 2002	Parallel	1 month	2 to 4 mg/d (age dependent) or twice that amount	This study allowed concomitant therapy with 1% hydrocortisone	151 children
		Nuovo 1992*	Cross-over	2 weeks	16 and 24 mg/d	Concomitant therapy with topical corticosteroid	1 adult

Table 2. H1 antihistamines under investigation in the included studies *(Continued)*

Fexofenadine	1	Kawashima 2003	Parallel	1 week	120 mg/d	"In addition to 0.1% hydrocortisone butyrate twice daily, other topical agents necessary as emollients for the treatment of atopic dermatitis, including preparations containing heparinoids and zinc oxide ointment, were also permitted for concomitant use. All topical drugs for use on the face and head were allowed, along with agents that were considered to have no effect on the drug under investigation. Patients recorded in their diaries the use of 0.1% hydrocortisone butyrate and investigators recorded in clinical records the use of topical drugs or concomitant treatment"	411 adults
Hydroxyzine	1	Monroe 1992	Parallel	1 week	75 mg/d	This study permitted, but did not specify, concomitant treatment	27 adults
Ketotifen	3	Leon 1989	Parallel	9 weeks	2 mg/d	"Only the topical application of cold cream and baths with oat colloid were allowed in both groups"	20 children
		Iikura 1992	Parallel	52 weeks	0.8 to 1.2 mg/d	"Beta2 agonists (by inhaled or oral route) and theophylline were permitted. Use of external preparations (nonsteroidal ointments and mild steroid preparations) was allowed"	121 children

Table 2. H1 antihistamines under investigation in the included studies *(Continued)*

		Falk 1993	Parallel	3 months	2 mg/d	All participants received concomitant 1% hydrocortisone cream and 2 mg dexchlorpheniramine maleate (Polaramine) twice a day systemically	60 adults
Levocetirizine	2	Kircik 2013	Parallel	4 weeks	5 mg/d	Not reported	40 adults
		Simons 2007	Parallel	18 months	0.25 mg/kg/d	Not reported	510 children
Loratadine	4	Monroe 1992	Parallel	1 week	10 mg/d	This study permitted, but did not specify, concomitant treatment	27 adults
		Langeland 1994	Cross-over	2 weeks	10 mg/d	"emollients and if needed, mild topical steroid ointment (hydrocortisone 17alpha-butyras)"	16 adults
		Ruzicka 1998	Parallel	2 weeks	5 to 20 mg/d	This study permitted, but did not specify, concomitant treatment	159 adults
		Kimura 2009	Parallel	4 weeks	10 mg/d	This study permitted the use of moisturisers	28 adults
Olopatadine	1	Kuniyuki 2009	Parallel	8 weeks	10 mg/d	Moisturisers were permitted. This study also allowed topical corticosteroids	99 adults
Tazifylline LN 2974	1	Savin 1986	Cross-over	variable (≥ 3 days)	30 mg/d	Unspecified routine topical treatment	10 adults
Terfenadine	4	Hjorth 1988	Cross-over	2 weeks	120 mg/d	Not reported	30 adults
		Doherty 1989	Parallel	10 days	180 mg/d	Twice-daily application of 0.05% clobetasone butyrate ointment and aqueous cream as a soap substitute	30 adults

Table 2. H1 antihistamines under investigation in the included studies *(Continued)*

	Berth Jones 1989	Cross-over	1 week	240 mg/d	Unspecified steroids and emollients	28 adults
	Nuovo 1992[a]	Cross-over	2 weeks	240 mg/d	Concomitant therapy with topical corticosteroid	1 adult

[a]Nuovo 1992 is a single-patient randomised study comparing chlorpheniramine and terfenadine versus placebo.

Table 3. Outcomes

Study ID	Primary outcome 1	Primary outcome 2	Secondary outcome 1	Secondary outcome 2	Secondary outcome 3
Berth Jones 1989	VAS pruritus (0 to 10)	Adverse events	Severity of excoriations	Not assessed	Not assessed
Cambazard 2001	Pruritus as part of SCORAD but only total SCORAD reported	Adverse events	SCORAD	Not assessed	Amount of topical corticosteroid used
Diepgen 2002	Pruritus as part of SCORAD but only total SCORAD reported	Adverse events	SCORAD	Not assessed	Use of a variety of topical and systemic medications including oral use of H1 antihistamines
Doherty 1989	VAS pruritus (0 to 100)	Not assessed	Number of participants for whom treatment helped itching (physician-assessed)	Not assessed	Not assessed
Falk 1993	Pruritus by Likert scale (scaling unclear)	Not assessed	Combination of 5 signs and symptoms (severity of diseased skin, area affected, erythema, lichenification, and pruritus) to a total score	Not assessed	Not assessed
Frosch 1984	Pruritus by VAS (0 to 100)	Adverse events	Number of participants with overall improvement, no overall improvement or overall worsening	Not assessed	Amount of betamethasone used in grams
Hannuksela 1993	Pruritus as part of SCORAD (0 to 100)	Adverse events	Total symptom score	Not assessed	Amount of local rescue therapy (emollient or 1% hydrocortisone)
Henz 1998	Pruritus on 4-point Likert scale	Adverse events	Mean overall response rate (number of participants	Not assessed	Not assessed

Table 3. Outcomes *(Continued)*

		(but not reported)	who responded to treatment)		
Hjorth 1988	Pruritus severity (no further details given)	Not assessed	Not assessed	Not assessed	Not assessed
Iikura 1992	Not assessed	Adverse events	Complete physical examination	Not assessed	Not assessed
Jung 1989	Pruritus by 4-point Likert scale	Adverse events	Percentage of improvement rated as "good or excellent"	Not assessed	Not assessed
Kawashima 2003	Pruritus 0 to 8 score	Adverse events	Investigator-assessed change in the ratio of pruritus area to body surface area	Not assessed	Amount of 0.1% hydrocortisone butyrate cream used during the study
Kimura 2009	Pruritus by VAS (0 to 100)	Adverse events	SCORAD	Not assessed	Not assessed
Kircik 2013	Pruritus by VAS (0 to 100)	Adverse events	Not assessed	Not assessed	Not assessed
Kuniyuki 2009	Pruritus by VAS (0 to 100)	Adverse events	SCORAD	Not assessed	Topical steroid score
Langeland 1994	Pruritus by VAS (0 to 10)	Adverse events	Not assessed	Not assessed	Mean number of days with use of local steroids during the 6 treatment periods and severity of rash at the end of each treatment period
LaRosa 1994	Pruritus by diary (no further details given)	Adverse events	Assessment by clinical examination	Not assessed	Amount of disodium cromoglycate, procaterol, steroids
Leon 1989	Pruritus by 4-point Likert scale	Not assessed	Not assessed	Not assessed	Not assessed

Table 3. Outcomes *(Continued)*

Monroe 1992	Pruritus percentage score	Adverse events (but not reported)	Not assessed	Not assessed	Not assessed
Munday 2002	Pruritus by 4-point Likert scale	Adverse events	Composite score consisting of 5 symptoms (erythema, excoriation, dryness, lichenification, exudation and crusting)	Not assessed	Amount of 1% hydrocortisone used in grams
Nuovo 1992	Pruritus on 7-point Likert scale	Adverse events	Not assessed	Not assessed	Number of daily applications of the topical steroid triamcinolone
Ruzicka 1998	Pruritus by VAS (0 to 10)	Adverse events	Number for whom treatment success was judged as good or very good	Not assessed	Not assessed
Savin 1986	Pruritus by VAS (no further details given)	Not assessed	Not assessed	Not assessed	Not assessed
Simons 2007	Not assessed	Adverse events	Not assessed	Not assessed	Not assessed
Tharp 1998	Pruritus (no further details given)	Adverse events	Clinical signs and symptoms	Not assessed	Use of triamcinolone acetonide 0.1% cream (corticosteroid)

SCORAD: SCORing Atopic Dermatitis index; VAS: visual analogue scale.

Table 4. Registered trials

Study ID	Trial registration number
Berth Jones 1989	unable to obtain or not registered respectively
Cambazard 2001	a protocol number was provided (MPCE97B2501/lV -11 Dec. 97 Amdt 1 (29.01.98) / Amdt 2 (06.03.98)), but we could not find it
Diepgen 2002	unable to obtain or not registered respectively

Table 4. Registered trials *(Continued)*

Doherty 1989	unable to obtain or not registered respectively
Falk 1993	unable to obtain or not registered respectively
Frosch 1984	unable to obtain or not registered respectively
Hannuksela 1993	unable to obtain or not registered respectively
Henz 1998	unable to obtain or not registered respectively
Hjorth 1988	unable to obtain or not registered respectively
Iikura 1992	unable to obtain or not registered respectively
Jung 1989	a protocol number was provided (PCE87F291), but we could not find it
Kawashima 2003	unable to obtain or not registered respectively
Kimura 2009	unable to obtain or not registered respectively
Kircik 2013	NCT00884325 Management of pruritus with Xyzal in atopic dermatitis
Kuniyuki 2009	unable to obtain or not registered respectively
Langeland 1994	unable to obtain or not registered respectively
LaRosa 1994	unable to obtain or not registered respectively
Leon 1989	unable to obtain or not registered respectively
Monroe 1992	unable to obtain or not registered respectively
Munday 2002	unable to obtain or not registered respectively
Nuovo 1992	unable to obtain or not registered respectively
Ruzicka 1998	unable to obtain or not registered respectively
Savin 1986	unable to obtain or not registered respectively
Simons 2007	NCT00152464 Prevention of Asthma With Levocetirizine 18 Month Treatment in Infants (12 - 24 Months) Suffering From Eczema (Atopic Dermatitis) and Sensitized to Grass Pollen and/or House Dust Mite (HDM)
Tharp 1998	unable to obtain or not registered respectively

APPENDICES

Appendix 1. Cochrane Skin Group Specialised Register (CRS) search strategy

((atopic and dermatitis) or eczema or (atopic and ekzema) or neurodermatitis) AND ((histamine and antagonist*) or (H1 and histamine and antagonist*) or (H-1 and histamine and antagonist*) or ethanolamine or diphenhydramine or clemastine or dimenhydrinate or doxylamine or piperazine or hydroxyzine or hydroxyzine or meclizine or cyclizine or chlorcyclizine or phenothiazine or chlorpromazine or promethazine or trimeprazine or ethylenediamine or mepyramine or tripelenamine or alkylamine or brompheniramine or chlorpheniramine or

carbinoxamine or teldane or terfenadine or astemizole or hismanal or loratadine or mequitazine or mebhydroline or semprex or fexofenadine or telfast or mizolastine or mizollen or azatadine or cyproheptadine or atosil or norastemizole or dimetapp or tavist or dramamine or benadryl or atarax or vistaril or actifed or thorazine or dimetane or zyrtec or cetirizine or periactin or claritine or seldane or allegra or desloratadine or aerius or urtimed or rupatadine or acrivastine or promethazine or chlorpromazine or cyproheptadine)

Appendix 2. CENTRAL (the Cochrane Library) search strategy

#1 atopic dermatitis:ti,ab,kw
#2 eczema:ti,ab,kw
#3 neurodermatitis:ti,ab,kw or atopic ekzema:ti,ab,kw
#4 MeSH descriptor: [Dermatitis, Atopic] this term only
#5 MeSH descriptor: [Neurodermatitis] this term only
#6 MeSH descriptor: [Eczema] this term only
#7 {or #1-#6}
#8 histamine H1 antagonist*:ti,ab,kw or histamine antagonist*:ti,ab,kw
#9 MeSH descriptor: [Histamine H1 Antagonists] explode all trees
#10 (ethanoliamine or diphenhydramine or clemastine or dimenhydrinate or doxylamine or piperazine or hydroxizine or hydroxyzine or meclizine or cyclizine or chlorcyclizine or phenothiazine or chlorpromazine or promethazine or trimeprazine or ethylenediamine or mepyramine or tripelenamine or alkylamine or brompheniramine or chlorpheniramine or carbinoxamine or teldane or terfenadine or astemizole or hismanal or loratidine or mequitazine or mebhydroline or semprex or fexofenadine or telfast or mizolastine or mizollen or azatadine or cyproheptadine or atosil or norastemizole or dimetapp or tavist or dramamine or benadryl or atarax or vistaril or actifed or thorazine or dimetane or zyrtec or cetirizine or periactin or claritine or seldane or allegra or desloratadine or aerius or urtimed or rupatadine or acrivastine or promethazine or chlorpromazine or cyproheptadine):ti,ab,kw
#11 [mh Ethanolamine] or [mh Diphenhydramine] or [mh Clemastine] or [mh Dimenhydrinate] or [mh Doxylamine] or [mh Piperazines] or [mh Meclizine] or [mh Cyclizine] or [mh Phenothiazines] or [mh Chlorpromazine] or [mh Promethazine] or [mh Trimeprazine] or [mh Ethylenediamines] or [mh Pyrilamine] or [mh Brompheniramine] or [mh Chlorpheniramine] or [mh Terfenadine] or [mh Astemizole] or [mh Loratadine] or [mh Cyproheptadine] or [mh Cetirizine]
#12 {or #8-#11}
#13 #7 and #12

Appendix 3. MEDLINE (Ovid) search strategy

1. atopic dermatitis.mp.
2. exp Dermatitis, Atopic/
3. neurodermatitis.mp.
4. exp Neurodermatitis/
5. exp Eczema/
6. atopic ekzema.mp.
7. eczema.mp.
8. or/1-7
9. histamine H1 antagonist$.mp.
10. exp Histamine H1 Antagonists/
11. histamine antagonists/
12. exp Ethanolamine/ or ethanolamine.mp.
13. diphenhydramine.mp. or exp Diphenhydramine/
14. clemastine.mp. or exp Clemastine/
15. dimenhydrinate.mp. or exp Dimenhydrinate/
16. doxylamine.mp. or exp Doxylamine/
17. piperazine$.mp. or exp Piperazines/
18. (hydroxizine or hydroxyzine).mp.
19. meclizine.mp. or exp Meclizine/
20. cyclizine.mp. or exp Cyclizine/
21. chlorcyclizine.mp.
22. phenothiazine$.mp. or exp Phenothiazines/
23. chlorpromazine.mp. or exp Chlorpromazine/
24. promethazine.mp. or exp Promethazine/
25. trimeprazine.mp. or exp Trimeprazine/
26. ethylenediamine$.mp. or exp Ethylenediamines/
27. mepyramine.mp. or exp Pyrilamine/
28. tripelenamine.mp.
29. alkylamine.mp.
30. brompheniramine.mp. or exp Brompheniramine/
31. chlorpheniramine.mp. or exp Chlorpheniramine/

32. carbinoxamine.mp.
33. (teldane or terfenadine).mp.
34. exp Terfenadine/
35. astemizole.mp.
36. exp Astemizole/
37. hismanal.mp.
38. loratadine.mp.
39. exp Loratadine/
40. mequitazine.mp.
41. mebhydroline.mp.
42. semprex.mp.
43. fexofenadine.mp.
44. telfast.mp.
45. mizolastine.mp.
46. mizollen.mp.
47. azatadine.mp.
48. cyproheptadine.mp.
49. exp Cyproheptadine/
50. atosil.mp.
51. norastemizole.mp.
52. dimetapp.mp.
53. tavist.mp.
54. dramamine.mp.
55. benadryl.mp.
56. atarax.mp.
57. vistaril.mp.
58. actifed.mp.
59. thorazine.mp.
60. dimetane.mp.
61. (zyrtec or cetirizine).mp.
62. exp Cetirizine/
63. periactin.mp.
64. claritine.mp.
65. seldane.mp.
66. allegra.mp.
67. desloratadine.mp.
68. aerius.mp.
69. urtimed.mp.
70. rupatadine.mp.
71. or/9-70
72. randomized controlled trial.pt.
73. controlled clinical trial.pt.
74. randomized.ab.
75. placebo.ab.
76. clinical trials as topic.sh.
77. randomly.ab.
78. trial.ti.
79. 72 or 73 or 74 or 75 or 76 or 77 or 78
80. exp animals/ not humans.sh.
81. 79 not 80
82. 8 and 71 and 81

[Lines 72-81: Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity- and precision-maximizing version (2008 revision)]

Appendix 4. Embase (Ovid) search strategy

1. exp ECZEMA/
2. eczema.ti,ab.
3. exp atopic dermatitis/
4. exp NEURODERMATITIS/
5. neurodermatitis.ti,ab.

6. atopic dermatitis.mp.
7. atopic ekzema.mp.
8. or/1-7
9. exp histamine H1 receptor antagonist/
10. exp antihistaminic agent/
11. exp diphenhydramine/ or diphenhydramine.mp.
12. ethanolamine.mp. or exp ethanolamine/
13. histamine H1 antagonist$.mp.
14. clemastine.mp. or exp clemastine/
15. dimenhydrinate.mp. or exp dimenhydrinate/
16. doxylamine.mp. or exp doxylamine/
17. exp piperazine/
18. piperazine$.mp.
19. (hydroxizine or hydroxyzine).mp.
20. meclizine.mp. or exp meclozine/
21. exp cyclizine/ or cyclizine.mp.
22. exp chlorcyclizine/ or chlorcyclizine.mp.
23. exp phenothiazine/
24. Phenothiazine$.mp.
25. exp chlorpromazine/ or chlorpromazine.mp.
26. exp promethazine/ or promethazine.mp.
27. trimeprazine.mp. or exp alimemazine/
28. exp ethylenediamine/
29. Ethylenediamine$.mp.
30. exp mepyramine/ or mepyramine.mp.
31. Pyrilamine.mp.
32. tripelenamine.mp. or exp tripelennamine/
33. alkylamine.mp. or exp aliphatic amine/
34. exp brompheniramine/ or brompheniramine.mp.
35. exp chlorpheniramine/ or chlorpheniramine.mp.
36. carbinoxamine.mp. or exp carbinoxamine/
37. (teldane or terfenadine).mp.
38. exp terfenadine/
39. astemizole.mp. or exp astemizole/
40. hismanal.mp.
41. loratadine.mp. or exp loratadine/
42. mequitazine.mp. or exp mequitazine/
43. mebhydroline.mp. or exp mebhydrolin/
44. semprex.mp. or exp acrivastine/
45. exp fexofenadine/ or fexofenadine.mp.
46. telfast.mp.
47. mizolastine.mp. or exp mizolastine/
48. mizollen.mp.
49. exp azatadine/ or azatadine.mp.
50. exp cyproheptadine/ or cyproheptadine.mp.
51. atosil.mp. or exp promethazine/
52. norastemizole.mp. or exp norastemizole/
53. dimetapp.mp. or exp dimetapp/
54. tavist.mp. or exp clemastine fumarate/
55. dramamine.mp.
56. benadryl.mp.
57. atarax.mp.
58. exp hydroxyzine/
59. vistaril.mp. or exp hydroxyzine embonate/
60. actifed.mp. or exp pseudoephedrine plus triprolidine/
61. thorazine.mp. or exp chlorpromazine/
62. dimetane.mp.
63. (zyrtec or cetirizine).mp.
64. exp cetirizine/
65. periactin.mp. or exp cyproheptadine/
66. claritine.mp.
67. seldane.mp.

68. allegra.mp.
69. exp desloratadine/ or desloratadine.mp.
70. aerius.mp.
71. urtimed.mp.
72. rupatadine.mp. or exp rupatadine/
73. or/9-72
74. crossover procedure.sh.
75. double-blind procedure.sh.
76. single-blind procedure.sh.
77. (crossover$ or cross over$).tw.
78. placebo$.tw.
79. (doubl$ adj blind$).tw.
80. allocat$.tw.
81. trial.ti.
82. randomized controlled trial.sh.
83. random$.tw.
84. or/74-83
85. exp animal/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/
86. human/ or normal human/
87. 85 and 86
88. 85 not 87
89. 84 not 88
90. 8 and 73 and 89

CONTRIBUTIONS OF AUTHORS

CA secured funding to carry out this review.
CA, AJ, BC, EW, and MB drafted the protocol.
UM was the contact person with the editorial base.
UM co-ordinated contributions from coauthors.
UM and CA wrote the final draft of the review with contributions from all review authors.
UM, CA, and MB screened papers against eligibility criteria.
UM obtained data on ongoing and unpublished studies.
UM and CA appraised the quality of papers.
UM, CA, MB, and AJ extracted data for the review and sought additional information about papers.
UM, CA, MB, and AJ assessed the risk of bias.
UM entered data into RevMan.
UM, CA, and BC analysed and interpreted data.
UM, CA, and BC worked on the methods sections.
CA, EW, UM, and AJ drafted the clinical sections of the background and responded to the clinical comments of referees.
UM, CA, and BC responded to the methods and statistics comments of referees.
CA is the guarantor of the update.

DECLARATIONS OF INTEREST

Uwe Matterne: none known.
Merle Margarete Böhmer: none known.
Elke Weisshaar: my institution received money from Menlo Therapeutics and Trevi Therapeutics for my participation in advisory board meetings and publication steering committee meetings for itch trials. My institution also received money from Menlo Therapeutics and Trevi Therapeutics for recruiting participants into clinical studies with new antipruritic substances for prurigo nodularis, none of which are relevant to this review. However, antihistamines are a complementary (add-on) treatment, so eczema treatment is not a direct competitor (i.e. relevant) to this review's intervention of interest; thus, this declaration of interest is compliant with the Cochrane Commercial sponsorship policy. The last date funding was received was 18 December 2018.
Aldrin Jupiter: I am a shareholder of Bayer and Novartis.
Ben Carter: none known.
Christian J Apfelbacher: my institution received a grant from Dr. August Wolff GmbH (which produces products that are used for atopic eczema and other forms of dermatitis, such as emollients) for research related to work on patient-reported outcome validation for hyperhidrosis. However, antihistamines are a complementary (add-on) treatment, so eczema treatment is not a direct competitor (i.e. relevant) to this review's intervention of interest; thus, this declaration of interest is compliant with the Cochrane Commercial sponsorship policy. I also received money for consultancy from Dr. August Wolff GmbH, and travel and meeting expenses from LKC Medicine, NTU Singapore, the European Academy of Allergy and Clinical Immunology (EAACI), and the European League Against Rheumatism (EULAR). The last date funding was received was 28 November 2018.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

It was stated in the protocol that "Two review authors (MB and EW) will search for ongoing trials in the following databases using the terms: eczema, atopic eczema, atopic dermatitis", but for this review, UM and CA conducted this search.

It was also stated in the protocol that "Two review authors (EW and MB) will examine the bibliographies of the included and excluded studies for further references to potentially-eligible RCTs", but for this review, UM and CA carried out the examination.

The protocol stated that "Two authors (CA and MB) will independently assess the abstracts of trials resulting from the searches." However, UM carried out the conference proceedings search for this review.

The protocol stated that "Two authors (CA and MB) will independently assess the abstracts of trials resulting from the searches", but UM and CA performed these assessments for this review.

It was stated in the protocol that "Two authors (CA and MB) will independently review the full-text papers and disagreements over eligibility will be resolved by discussion, consensus, or with a third review author (BC)". However, UM, CA, and MB reviewed the full-text papers and resolved disagreements among themselves.

The protocol stated "Two authors (CA and MB) will enter details of the included trials into the 'Characteristics of included studies' tables in RevMan 5.3 (Review Manager (RevMan)", but for this review, UM and CA performed this task.

"Four review authors (CA, MB, AJ, EW) will extract data using a previously developed and piloted data extraction form and will resolve disagreements on data extraction by consensus". UM, CA, and MB actually performed this task for this review.

The protocol stated that "Two authors (CA and MB) will check and enter the data into RevMan 5.3 (Review Manager (RevMan))", but UM and CA performed this task for this review.

We had stated in the protocol that we would search the bibliographies of included studies for further references to potentially eligible randomised controlled trials. We extended this search also to the bibliographies of excluded studies.

The protocol stated that risk of bias would be assessed by CA and MB, but in this review, UM and CA performed this task.

The protocol stated that "any outcomes that are statistically significant ($P < 0.05$) were used to calculate a number needed to treat for an additional beneficial outcome (NNTB)", but we also reported the number needed to treat for an additional harmful outcome (NNTH), for instance, for adverse events.

In the protocol, we had stated that "the 'Mean change in physician-assessed clinical signs' would be based on standardised or validated measures." However, we also considered other measures provided by the respective study for this outcome and described the outcome assessment in detail.

We had stated in the protocol that "If we feel there are several major comparisons or that our findings need to be summarised for different populations, we would include further 'Summary of findings' tables (Higgins 2011)." However, we did not summarise findings for different populations.

The protocol stated that 'Summary of findings' tables would report mean change in eczema symptoms scores. We narrowed this outcome to look only at pruritus in the 'Summary of findings' table because no other eczema symptom score was assessed in the studies summed up in the 'Summary of findings' table.

Because we were unable to pool data in a meta-analysis due to clinical diversity, we could not undertake subgroup and sensitivity analyses to assess heterogeneity, as planned in our protocol. Neither were we able to study H1 AH interventions in patients with eczema with allergic comorbidity as assessed by allergic sensitisations (known as "atopic" eczema), as no data were available.

We had originally planned to analyse cross-over data based on advice provided in Section 16.4.4 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We had particularly planned to assess carry-over and period effects descriptively. The protocol stated that if there was a limited suggestion of these effects and data were adequate, we would carry out a paired analysis. However, for all cross-over trials, data were not adequately reported to allow such analyses. Instead we described narratively the data as reported by study authors.

INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Oral; Administration, Topical; Cetirizine [administration & dosage] [adverse effects]; Chemotherapy, Adjuvant; Eczema [*drug therapy]; Histamine H1 Antagonists [*administration & dosage] [adverse effects]; Loratadine [administration & dosage] [adverse effects]; Outcome Assessment, Health Care; Pruritus [drug therapy] [etiology]; Randomized Controlled Trials as Topic; Terfenadine [administration & dosage] [adverse effects] [analogs & derivatives]

MeSH check words

Adult; Child; Humans