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TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
BACKGROUND	3
OBJECTIVES	3
METHODS	3
RESULTS	6
Figure 1.	7
DISCUSSION	7
AUTHORS' CONCLUSIONS	8
ACKNOWLEDGEMENTS	8
REFERENCES	9
CHARACTERISTICS OF STUDIES	12
ADDITIONAL TABLES	15
APPENDICES	17
FEEDBACK	20
WHAT'S NEW	21
HISTORY	21
CONTRIBUTIONS OF AUTHORS	22
DECLARATIONS OF INTEREST	22
SOURCES OF SUPPORT	22
DIFFERENCES BETWEEN PROTOCOL AND REVIEW	22
INDEX TERMS	23

[Intervention Review]

Oral H1 antihistamines as monotherapy for eczema

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ABSTRACT

Background

Eczema is a common skin disease in many countries, and although the majority of cases of eczema occur before the age of five years and often resolve during childhood or adolescence, it can also persist into adulthood. Itch is the most important aspect of eczema, often impacting significantly on the quality of life of an affected individual.

Objectives

To assess the effects of oral antihistamines (H1 antagonists) as monotherapy in children and adults with eczema.

Search methods

We searched the following databases up to March 2012: the Cochrane Skin Group Specialised Register, CENTRAL in *The Cochrane Library* (2012, Issue 3), MEDLINE (from 1946), EMBASE (from 1974), and LILACS (from 1982). We examined the reference lists of excluded studies in order to identify further references to relevant trials. We searched trials registers for ongoing and unpublished trials. We also handsearched the abstracts of the International Research Workshops on eczema, as well as the conference proceedings of the European Academy of Dermatology and Venereology (EADV) and the European Academy of Allergology and Clinical Immunology (EAACI), from 2000 to 2011.

Selection criteria

We sought to include randomised controlled trials that assessed the effects and safety of oral H1 antihistamines as monotherapy in children and adults with eczema. We excluded studies that compared an antihistamine versus another antihistamine and had no placebo control arm. We also excluded topical antihistamines and oral H1 antihistamines as 'add-on' therapy and studies using any concomitant therapy other than emollients or moisturisers, principally because some of these forms of concomitant therapy may be considered treatment modifiers in assessments of the effects of antihistamines on eczema.

Data collection and analysis

Our search retrieved 409 references to studies. Based on assessments of their titles, abstracts, or both, we excluded all except 36 of these studies. After evaluation of the full text of each report, we excluded a further 35 studies, and 1 study is awaiting classification pending a response from the trial investigators. Two review authors independently carried out study assessment.

Main results

No randomised controlled trials met our inclusion criteria.

Authors' conclusions

There is currently no high-level evidence to support or refute the efficacy or safety of oral H1 antihistamines used as monotherapy for eczema. Because most of the studies allowed the use of concomitant medications and involved multi-therapeutic approaches, meaningful assessments of the individual effects of oral H1 antihistamines on eczema were not feasible. Although well-designed randomised controlled trials excluding concomitant medications appear to be needed, consideration should be given to the potential ethical issues raised with the use of antihistamines as monotherapy for the management of eczema by withholding the use of rescue or additional therapies. A further systematic review of studies in which concomitant therapies were permitted might be of value in determining the potential benefits of oral H1 antihistamines as add-on therapy.

PLAIN LANGUAGE SUMMARY

Effects of antihistamines on eczema

Eczema is a common chronic disease. Itch is the most important symptom, and eczema is often accompanied by dry skin. Skin lesions include rash, redness, swelling of the skin, crusts, oozing, and sometimes also bleeding as a consequence of persistent scratching. Although the disease can resolve during childhood, it might also recur in or persist into adult life. The cause of eczema is considered to be a combination of genetic and environmental factors. Moisturisers, topical corticosteroids, and topical immunomodulators are the mainstay during treatment of eczema, while more severe cases might need UV light therapy or systemic immunosuppressants. Itch is very difficult to treat and leads to scratching, which leads to more inflammation of the skin, and often people with eczema end up in a vicious circle of itching and scratching. The role of histamine in itching associated with eczema is not fully elucidated, but oral H1 antihistamines have been used for many years in the treatment of eczema. These might have been used largely for their sedative action, with highly sedative antihistamines, e.g. chlorpheniramine and hydroxyzine. However, oral H1 antihistamines are widely used in the treatment of allergic disorders, such as urticaria, allergic rhinitis, and allergic conjunctivitis, but their efficacy in alleviating itch and eczema remains unclear. This systematic review sought evidence for the effects and safety of the use of oral antihistamines for eczema, to guide their use in clinical practice.

No study matched our inclusion criteria. There is currently no evidence to support the efficacy or safety of the use of oral H1 antihistamines alone in the treatment of eczema. This does not mean that such antihistamines could not be useful as an add-on therapy to the main treatments including topical steroids, which will be the topic of a further review.

BACKGROUND

Description of the condition

For unfamiliar terms, see the 'Glossary of terms' ([Table 1](#)).

The wide and often interchangeable use of the terms 'atopic eczema', 'atopic dermatitis', and 'neurodermatitis' has resulted in some confusion and inconsistency in their application. Therefore, the nomenclature review committee of the World Allergy Organization (WAO) has proposed the use of the term 'eczema' as a unifying term ([Johansson 2004](#)). Eczema is a common skin disease in many countries, with an estimated prevalence ranging from 2% to approximately 20% around the globe ([Odhiambo 2009](#); [Shaw 2011](#); [Williams 2005](#)). The majority of cases of eczema occur before the age of five years, and the condition often resolves during childhood or adolescence, but can also persist into adulthood.

The diagnosis of eczema is made based on a number of major and minor clinical features. Major criteria include itch (pruritus), chronicity of the disease, a personal and family history of atopy, and lesions with a typical morphology and distribution. In children, acute inflammation with exudation occurs commonly on the face and the extensor areas of the arms and legs. Eczema is often accompanied by dry skin. It is thought that eczema arises from an interaction of environmental and genetic factors. Immunopathological findings are characterised by the common occurrence of elevated serum IgE and eosinophilia.

Itch (pruritus) is defined as an unpleasant sensation eliciting the urge to scratch. It is such an important aspect of eczema that the diagnosis "cannot be made if there is no history of pruritus" ([Hanifin 1980](#)). This sensation is not constant but comes in attacks, which can be very severe and disruptive to a person's quality of life ([Thestrup-Pedersen 2000](#); [Weisshaar 2006](#)). Two recent studies reported that pruritus occurred on a daily basis in 87% to 91% of people with eczema ([Dawn 2009](#); [Yosipovitch 2002](#)). Itching leads to scratching, resulting in further skin damage. Scratching produces additional inflammation of the skin, which can induce further itching and initiate a vicious "itch-scratch" cycle often resulting in further exacerbation of the eczema lesions ([Engman 1936](#)). Itch is often perceived as being worse than the pain that results from scratching. The pathophysiology of itch in eczema is not yet fully understood.

Description of the intervention

Antihistamines are among the most widely used drugs in the world and are frequently prescribed for several dermatological conditions other than atopic eczema. Histamine is naturally occurring in the body and is a potent locally-acting substance, and its release is mediated and controlled through three types of histamine receptors in the body (H1, H2, and H3). H1 blockers are the class of antihistamines that continue to be widely used, and they have been recommended in many treatment protocols for the management of eczema ([Klein 1999](#)). A range of alternative interventions are available that include skin care measures, corticosteroids, topical immunomodulators, and dietetic measures.

How the intervention might work

There is evidence both for and against histamine involvement in the pathogenesis of eczema ([Greaves 2001](#)). It is most likely that various non-histamine mechanisms and central mechanisms may pro-

vide a suitable explanation of the intense and disruptive quality of pruritus in eczema ([Reitamo 2001](#)). The exact role of histamine in pruritus associated with eczema remains to be determined, as the group of factors mediating itch, e.g. neuropeptides, is large ([Rukwied 2000](#)).

Side-effects of some of the antihistamines can include daytime drowsiness, dryness of the mouth, fatigue, cardiovascular side-effects, and weight gain ([Yanai 2012](#)). Drowsiness and reduced productivity associated with antihistamines of the first generation, such as diphenhydramine or chlorpheniramine, were the reasons why these agents were not widely used during the day ([Greaves 2005](#)). The aim of the development of second-generation antihistamines was to make drugs available that were as effective as first-generation antihistamines, but did not show sedative effects ([Kay 2000](#)). They are associated with less impairment in terms of cognitive and motor function ([Herman 2003](#); [Zuberbier 2012](#)). Terfenadine and astemizole were found to cause potentially serious arrhythmias, by prolongation of the QT interval by drugs, particularly when they were given in combination with compounds that inhibited their metabolism, such as grapefruit juice ([Woosley 1996](#)). This serious side-effect in-part contributed to the development of the third generation of antihistamines that contain therapeutically active metabolites without any cardiac toxicity ([Handley 1998](#)).

Why it is important to do this review

Although antihistamines are often used in the treatment of eczema, little objective evidence exists to demonstrate relief of either pruritus or skin lesions by this category of medication. There are flaws in many studies investigating the effects of these interventions in terms of sample size and study design. Further evaluation of the efficacy of antihistamines in eczema is necessary.

It is unclear if oral antihistamines are effective in the management of eczema (skin changes, pruritus, quality of life) or if they demonstrate undesirable side-effects.

OBJECTIVES

To assess the effects of oral antihistamines (H1 antagonists) as monotherapy in children and adults with eczema.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials (RCTs). We excluded studies where itch had been experimentally induced (e.g. by histamine iontophoresis) in healthy individuals or participants with eczema.

Types of participants

People (children and adults) with a clinical diagnosis of eczema, identified as 'atopic eczema' or 'eczema', which was made by either 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](#)).

Types of interventions

Oral antihistamines (H1-antagonists) of all classes (sedating, nonsedating) as monotherapy compared to the following:

- a) placebo; or
- b) alternative treatment (e.g. topical corticosteroids or topical immunomodulators).

We excluded studies investigating the following interventions and comparisons: one antihistamine versus another antihistamine, topical antihistamines, or H1 antihistamines as 'add-on' therapy other than emollients/moisturisers. For further details, see the 'Differences between protocol and review' section.

Types of outcome measures

Primary outcomes

1. Reduction of subjectively perceived itch, as determined by validated rating scales (e.g. visual analogue scales).
2. Global improvement in eczema, as measured by reduction in an eczema severity score, such as SCORAD (European Task Force on Atopic Dermatitis 1993; Schmitt 2007).

Secondary outcomes

1. Percentage of participants reporting adverse effects or adverse events.
2. Improvement in quality-of-life measures.

By definition, the person with eczema can only assess the itch sensation. However, parental report of rubbing may measure something important to carers of children with eczema if the children are too young to report the symptoms. We aimed to examine these data if available.

Search methods for identification of studies

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

Electronic searches

The Trials Search Co-ordinator of the Cochrane Skin Group searched the following databases up to 13 March 2012:

- the Cochrane Skin Group Specialised Register using the search strategy in [Appendix 1](#);
- the Cochrane Central Register of Controlled Trials (CENTRAL) in *The Cochrane Library* using the strategy in [Appendix 2](#);
- MEDLINE via OVID (from 1946) using the strategy in [Appendix 3](#);
- EMBASE via OVID (from 1974) using the strategy in [Appendix 4](#); and
- LILACS (Latin American and Caribbean Health Science Information Database, from 1982) using the strategy in [Appendix 5](#).

Trials databases

Two reviewers (UM and EvZ) searched for ongoing and unpublished trials in the following databases between 20 and 25 July 2012:

1. The metaRegister of Controlled Trials (www.controlled-trials.com).
2. The US National Institutes of Health Ongoing Trials Register (www.clinicaltrials.gov).
3. The Australian New Zealand Clinical Trials Registry (www.anzctr.org.au).
4. The World Health Organization International Clinical Trials Registry platform (www.who.int/trialsearch).
5. The Ongoing Skin Trials register (www.nottingham.ac.uk/ongoingskintrials).

Searching other resources

References from published studies

One review author (EvZ) examined the bibliographies of the excluded studies for further references to potentially eligible randomised controlled trials.

Conference proceedings

One review author (UM) handsearched the abstracts from the International Research Workshops on eczema, as well as the conference proceedings of the European Academy of Dermatology and Venereology (EADV) and of the European Academy of Allergology and Clinical Immunology (EAACI), from 2000 to 2011, in order to identify further potentially relevant RCTs. EvZ checked the retrieved abstracts of studies for eligibility.

Correspondence

We contacted trial investigators and requested that they provide missing data or clarify study details (see [Table 2](#)).

Data collection and analysis

Selection of studies

Four review authors (CJA, AJ, ZF, and EvZ) carried out study selection independently. If it was clear that the study did not refer to a randomised controlled trial on eczema, we excluded it. Four authors (CJA, AJ, ZF, and EvZ) independently assessed each study to determine whether it met the predefined selection criteria, and resolved any differences through consensus.

Table of methods archived for use in future updates

Issue method	Description
Data extraction and management	<p>Two review authors will independently extract the data and check and enter it into a piloted data collection form. They will resolve disagreements by discussion.</p> <p>We will enter study details into the 'Characteristics of included studies' tables in Review Manager (Revman 2011).</p>
Assessment of risk of bias in included studies	Two review authors will independently assess the risk of bias in the included studies following the domain-based evaluation described in Chapter 8, Section 8.5 of the <i>Cochrane Handbook for System-</i>

atic Reviews of Interventions (Higgins 2011). We will compare evaluations and discuss and resolve inconsistencies between the review authors.

We will rate separately the following domains for each of the included studies as 'low risk of bias', 'high risk of bias', and 'unclear' if the risk of bias was uncertain or unknown:

- (a) sequence generation (was the allocation sequence adequately generated?);
- (b) allocation concealment (was allocation adequately concealed?);
- (c) blinding of participants, personnel, and outcome assessors (was knowledge of the allocated intervention adequately prevented during the study?);
- (d) incomplete outcome data (were incomplete outcome data adequately addressed?);
- (e) selective outcome reporting (are reports of the study free of suggestion of selective outcome reporting?); and
- (f) other sources of bias (was the study apparently free of other problems that could put it at a high risk of bias?).

We will report these assessments in the 'Risk of bias' table for each individual study in the 'Characteristics of included studies' section of the review.

We will also categorise and report the overall risk of bias of each of the included studies according to the following:

- low risk of bias (plausible bias unlikely to seriously alter the results) if all criteria will be met;
- unclear risk of bias (plausible bias that raises some doubt about the results) if 1 or more criteria will be assessed as unclear; or
- high risk of bias (plausible bias that seriously weakens confidence in the results) if 1 or more criteria will not be met.

Measures of treatment effect

We will consider data reported for periods of less than 6 weeks to reflect short-term benefit, and we will analyse such data separately from data covering 6 weeks or longer, which we consider to reflect a minimum time-period to capture any longer-term benefit. We will consider the long-term data as the primary end point, but we will also include the short-term data in order to detect rapid onset of improvement. We will report any adverse effects in the included studies qualitatively.

Dealing with missing data

We will make attempts to retrieve missing data from investigators in the included trials and document these in Table 2. When dealing with missing data, we will follow the advice provided in Section 16.1.2 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Assessment of heterogeneity

We shall assess clinical heterogeneity by examining the characteristics of the studies, the similarity between the types of participants, the interventions, and the outcomes as specified in the criteria for included studies. We will assess statistical heterogeneity using a Chi² test and the I² statistic where I² statistic values of 30% to 60% indicate moderate to high heterogeneity, and 50% to 90% indicate substantial heterogeneity (Higgins 2011).

Assessment of reporting bias

If we identify sufficient numbers of trials (> 10) investigating similar interventions for inclusion in the review, we will assess publication bias according to the recommendations on testing 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). And if asymmetry is identified, we will try to assess other possible causes, which we will explore in the discussion if appropriate.

Data synthesis

Two review authors will analyse the data and report them as specified in Chapter 9 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We will only undertake pooling of data to provide estimates of the effects of the interventions if the included studies have similar interventions received by similar participants.

We will accept as being of clinical importance a relative treatment difference of at least 50% for comparison between active treatment versus placebo or at least 20% between 2 or more active treatments. Smaller differences are unlikely to be clinically significant.

We will analyse cross-over studies using appropriate techniques for paired designs, and we will not pool these with studies of other designs.

For studies with a similar type of intervention, we will perform a meta-analysis to calculate a weighted treatment effect across trials, using a random-effects model. We will express the results as risk ratios (RR) with 95% confidence intervals (CI) for dichotomous outcomes; we will use number needed to treat (NNT) to express the relative benefit (or otherwise) of the various treatment options where appropriate, for a range of plausible control event rates. We will use mean differences (MD) with 95% CI to express results for continuous outcomes where the same measurement scales have been used across trials, and we will use standardised mean differences (SMD) to express results for continuous outcomes where different, but comparable, measurement scales have been used across trials.

Where there are multiple intervention groups within a trial, we will make pair-wise comparisons of similar active interventions versus no treatment, placebo, or another active intervention.

Where it will not be possible to perform a meta-analysis, we will summarise the data for each trial.

Subgroup analysis and investigation of heterogeneity

If we identify a sufficient number of studies with moderate, substantial, or considerable heterogeneity (as defined above), we will carry out the following subgroup analyses: atopic versus nonatopic participants (i.e. sensitised showing elevated levels of IgE antibodies to inhalant allergens) and children versus adults.

Sensitivity analysis

If we include sufficient studies examining similar interventions, we plan to conduct sensitivity analyses to assess the robustness of our review results by repeating the analysis with the following adjustments: exclusion of studies with unclear or inadequate allocation concealment, unclear or inadequate blinding of outcomes assessment, and completeness of follow-up.

RESULTS

Description of studies

Results of the search

The electronic searches retrieved 409 references to studies, which after removal of any duplicates provided a total of 400 citations. After examination of the titles and abstracts of these references, we eliminated a further 364 ineligible studies. We obtained full text copies of the remaining 36 studies and subjected them to further evaluation. We translated several studies that were not published in the English language, i.e. Chinese (Sheng 2009) and Polish (Tarchalska 1988), prior to assessment for eligibility.

The searches of the WHO International Clinical Trials Registry Platform, the Current Controlled Trials ISRCTN Register, and the ClinicalTrials.gov databases did not identify any ongoing trials that matched our inclusion criteria. Screening of the conference proceedings did not retrieve additional eligible studies.

Finally, we excluded 35 of the remaining studies (see the '[Characteristics of excluded studies](#)' section), and 1 study is awaiting further assessment pending a response from the trial investigators (see the '[Characteristics of studies awaiting classification](#)' section).

For further details, see the Study Flow Diagram '[Figure 1](#)'.

Figure 1. Flow diagram.

Included studies

We did not include any studies.

Excluded studies

We excluded 35 studies only after assessment of the full text of the report and documented the reasons for their exclusion in the '[Characteristics of excluded studies](#)' tables. The majority of these studies allowed the use of certain concomitant treatments (18), which were prespecified as exclusion criteria for study eligibility in this systematic review. We excluded a further eight studies as these compared one antihistamine versus another antihistamine, which was another prespecified exclusion criterion. We excluded the remainder (9) for other reasons (e.g. not in people with eczema or not a RCT).

Risk of bias in included studies

We did not include any studies.

Effects of interventions

We found no randomised controlled trials that fulfilled the inclusion criteria for this systematic review.

DISCUSSION

Summary of main results

We could not include any randomised controlled trials addressing the efficacy and safety of oral H1 antihistamines used as monotherapy in the treatment of eczema in this review (see [Table 3](#)). Most of the studies identified in the searches had evaluated oral H1 antihis-

tamines as 'add-on' therapy to other topical or systemic treatment, and as these can be considered composite interventions, they did not permit us to make reliable assessments of the individual effects of H1 antihistamines. Eczema and the often-associated pruritus can have a significant effect on the quality of life of an individual, and although H1-sedating antihistamines continue to be prescribed for the relief of pruritus, the results of this systematic review indicate that there is currently no high-level evidence to support or refute the benefits of H1 antihistamines used alone in the management of eczema.

Overall completeness and applicability of evidence

The absence of any studies addressing the objectives of this review illustrates that the evidence for the efficacy and safety of oral H1 antihistamines for eczema is unclear and incomplete. All of the studies retrieved in the searches had assessed the effects of oral H1 antihistamines but also permitted the use of concomitant topical or systemic therapies, which we had prespecified as exclusion criteria for this review. These forms of additional treatment should be viewed as effect modifiers of the interventions under investigation, i.e. H1 antihistamines, and therefore considered to be potential modifiers in assessments of their effects.

A further systematic review including studies that allow the use of concomitant therapies might assist with filling the gaps in the evidence and, in particular, by illustrating the benefit or otherwise of oral H1 antihistamines used as an add-on therapy.

Potential biases in the review process

We made every attempt to limit bias in the review process by ensuring a comprehensive search for potentially eligible studies. The authors' independent assessments of eligibility of studies for inclusion in this review minimised the potential for additional bias.

Agreements and disagreements with other studies or reviews

We identified two relevant reviews, only one of which clearly specified the inclusion criteria for the review and carried out a full and comprehensive literature search (Klein 1999). The review authors' objective was to appraise the evidence for the efficacy of H1 antihistamines in relieving pruritus in atopic dermatitis. They undertook assessments of the methodological quality of the selected trials with a modified version of Sackett's criteria for clinical evidence (Sackett 1989) and reported that the majority of the trials were underpowered and suffered from flawed study designs. Although they did not segregate any studies evaluating oral H1 antihistamines as monotherapy from those using combined treatments, they did conclude that at the time there was little objective evidence to demonstrate the efficacy of antihistamines for the relief of pruritus in people with eczema.

The more recent and broader literature review (Herman 2003) reached similar conclusions, in that the evidence was inconclusive. However, the authors failed to provide any indication of how they selected, evaluated, or critically appraised the primary research studies on which they based their conclusions, or how they could designate them as reliable sources of evidence.

Whilst we are in agreement with both of these previous reviews with regard to the lack of reliable evidence for the efficacy of H1 antihistamines in alleviating the symptoms of pruritus, we express some unease with what appears to be a general lack of acknowledgement of the likely impact of certain concomitant medications and their potential role as modifiers of treatment effect. However, it would be prudent to set these concerns against the findings of these two prior reviews, which concluded that there was uncertainty of benefit in terms of a reduction of symptoms of pruritus, even when H1 antihistamines were combined with these additional medications.

AUTHORS' CONCLUSIONS

Implications for practice

Current recommendations and practices for the management of eczema continue to be largely based on clinicians' judgement and patients' preferences. However, the results of this review demonstrate that there is at present no high-level objective evidence to support clinical decision-making regarding the use of oral H1 antihistamines as monotherapy in people with eczema.

Implications for research

Although we make no specific recommendations for further randomised controlled trials, the fact that clinicians continue to pre-

scribe oral H1 antihistamines in spite of the lack of evidence for the efficacy of this category of medication for eczema suggests the necessity for further primary research based on randomised controlled trials that exclude concomitant treatment. However, whilst we recognise that conducting 'clean' primary studies may present ethical challenges by restricting the use of rescue or concomitant medications, it is conceivable that these studies may help elucidate the questionable role - if any - of oral H1 antihistamines in reducing pruritus (Reitamo 2001), the cardinal symptom of eczema. As oral H1 antihistamines have been used extensively as an add-on therapy, we will conduct a subsequent review on 'oral H1 antihistamines as 'add-on' therapy to topical treatment for eczema', that might fill the gaps in evidence.

Any future randomised controlled trials must be well-designed, well-conducted, and adequately delivered with subsequent reporting, including high-quality descriptions of all aspects of methodology. Reporting should conform to the Consolidated Standards of Reporting Trials (CONSORT) statement (<http://www.consort-statement.org/>), which will enable appraisal and interpretation of results and accurate judgements to be made about the risk of bias and the overall quality of the evidence.

Although it is uncertain whether reported quality mirrors actual study conduct, it is noteworthy that studies with unclear methodology have been shown to produce biased estimates of treatment effects (Schulz 1995).

For further research recommendations based on the EPICOT (evidence, population, intervention, comparison, outcome, and time) format (Brown 2006), see Table 4.

The degree of uncertainty of the efficacy of H1 antihistamines when combined with other medications, which was highlighted in two previous reviews (Herman 2003; Klein 1999), would appear to strengthen the requirement for a further systematic review evaluating their additive benefits, if any.

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CHARACTERISTICS OF STUDIES

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Baraf 1976	This was a comparison of 2 different antihistamines (cyproheptadine versus hydroxyzine). It did not include a placebo arm.
Berth-Jones 1989	All participants received topical steroids to maintain their dermatitis in a stable condition.
Castro Torres 1987	This study included participants with different pruritic skin diseases, varying from insect bites to psoriasis. However, it did not give clear indications that it included participants with eczema.
Doherty 1989	All participants were concomitantly treated with a standardised regimen of topical treatment consisting of a twice daily application of 0.05% clobetasone butyrate ointment.
Falk 1993	All participants received concomitant 1% hydrocortisone cream and 2 mg dexchlorpheniramine maleate (Polaramine) twice a day systemically.
Foulds 1981	This was a comparison of 2 different antihistamines (cimetidine versus promethazine). It did not include a placebo arm.
Hamada 1996	This evaluated the efficacy of terfenadine with 0.1% alclometasone dipropionate ointment (A group) in comparison with 0.12% betamethasone 17-valerate ointment only (B group).
Henz 1998	This used rescue medication, i.e. hydrocortisone cream, in all 3 treatment groups.
Hjorth 1988	This paper evaluated the effect of H1 antihistamines on chronic urticaria and contact urticaria associated with atopic dermatitis; therefore, it did not meet the inclusion criteria prespecified for this review.
Kawashima 2003	This used 0.1% hydrocortisone butyrate twice a day, in addition to other topical agents necessary for the treatment of atopic dermatitis, including preparations containing heparinoids and zinc oxide ointment.

Study	Reason for exclusion
Kawashima 2011	This was a comparison of 2 different antihistamines (olopatadine versus ketotifen fumarate). It did not include a placebo arm.
Kimura 2009	Group A used betamethasone valerate ointment or with loratadine tablet as add-on in B group.
Klein 1980	This was a comparison of 2 different antihistamines (hydroxyzine versus cyproheptadine). It did not include a placebo arm.
Kuniyuki 2009	This study allowed topical corticosteroids.
La Rosa 1994	The 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.
Michel 1990	After evaluation of the full text of the report, we found that the trial did not include participants with eczema.
Monroe 1992	This study permitted, but did not specify, concomitant treatment.
Munday 2002	This study allowed concomitant therapy with 1% hydrocortisone.
Nakagawa 2006	This was a comparison of 2 different antihistamines (fexofenadine versus ketotifen fumarate). It did not include a placebo arm.
Nakayama 1980	This was a comparison of 2 different antihistamines (azatadine maleate syrup versus d-chlorpheniramine maleate). It did not include a placebo arm.
Nuovo 1992	This was a single-participant trial. After discussion with the CSG Statistical Editor, we agreed to exclude.
Patel 1997	This was a comparison of 2 different antihistamines (loratadine versus cetirizine). It did not include a placebo arm.
Ruzicka 1998	This study permitted, but did not specify, concomitant treatment.
Savin 1979	They did not make changes in the topical treatment of the eczema (not specified).
Savin 1986	Participants continued routine topical treatment (not specified).
Sheng 2009	There was additional treatment with dyclonine cream. It was translated by Dr Edwin Chan, Director of the Singapore Branch of the Australasian Cochrane Centre (see Acknowledgements).
Simons 2007	This evaluated the effect of levocetirizine on the prevention of urticaria in participants with atopic dermatitis (and the prevention of asthma), but there was no evaluation of the effect of levocetirizine on atopic dermatitis.
Sugai 2003	There was additional use of topical tacrolimus.
Tarchalska 1988	This was a literature review. It was translated from the Polish language by Zbys Fedorowicz and checked by Dr Malgorzata Bala of Jagiellonian University Medical College, Kraków, Poland (see Acknowledgements).
Tharp 1998	The study allowed triamcinolone acetonide.
Tholen 1989	This was a comparison of 2 different antihistamines (terfenadine versus ketotifen). It did not include a placebo arm.

Study	Reason for exclusion
Wahlgren 1990	This trial experimentally induced flare and itch; therefore, it did not match our inclusion criteria.
Wolfram 1967	After evaluation of the full text of the report, we found that this was a non-RCT.
Zhang 1998	There was additional use of interferon gamma.
Zimmermann 1981	After evaluation of the full text of the report, we found that the trial did not include participants with eczema.

RCT = randomised controlled trial

CCT = controlled clinical trial (quasi-randomised)

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

Kircik 2010

Methods	<p>This was a randomised double-blind placebo-controlled study</p> <p>The paper did not specify the single-centre setting.</p> <p>The date of the study, which was 4 weeks in duration, was not specified.</p>
Participants	<p>The study included 40 participants (mean age = 40.8 years (SD 11.2)).</p> <p><u>Inclusion criteria of the trial</u></p> <ul style="list-style-type: none"> • > 18 years • Moderate to severe pruritus associated with uncomplicated atopic dermatitis <p><u>Exclusion criteria of the trial</u></p> <ul style="list-style-type: none"> • Not specified <p>40 participants were randomised: 20 to each group.</p> <p>Withdrawals/losses to follow up were not specified.</p>
Interventions	<p><u>Intervention</u></p> <ul style="list-style-type: none"> • Levocetirizine dihydrochloride 5 mg once daily <p><u>Comparator</u></p> <ul style="list-style-type: none"> • Placebo once daily <p>It was unclear if the study allowed additional topical or systemic treatment for atopic dermatitis.</p>
Outcomes	<p><u>Outcomes as reported in the trial</u></p> <ol style="list-style-type: none"> 1. Pruritus scores (visual analogue scale) 2. Reporting of adverse events
Notes	<p>The abstract for the conference proceedings reported interim analysis, but with limited data. We made several attempts at contacting this author (by electronic mail and phone) without response.</p>

ADDITIONAL TABLES

Table 1. Glossary of terms

Term	Definition
Atopy (atopic syndrome)	A predisposition toward developing certain allergic hypersensitivity reactions. A person with atopy typically presents with 1 or more of the following: eczema (atopic dermatitis), allergic rhinitis (hay fever), allergic conjunctivitis, or allergic asthma
Arrhythmia	Irregular heart beat
Eosinophilia	A condition in which the eosinophil count in the peripheral blood exceeds $0.45 \times 10^9/L$ (450/ μ l). Several causes are known, with the most common being some form of allergic reaction or parasitosis
H1-antihistamine	Pharmaceutical drug that inhibits the action of histamine by blocking it from attaching to the H1 histamine receptors (there are also H2, H3, and H4 histamine receptors)
IgE (Immunoglobulin E)	Immunoglobulin E is a class of antibody. IgE 'recognises' an allergen and elicits an immune response by binding to Fc receptors found on the surface of mast cells and basophils, capable of mediating inflammatory reactions, which cause many of the symptoms we associate with allergy, such as airway constriction in asthma, local inflammation in eczema, and increased mucus secretion in allergic rhinitis. IgE is increased in individuals with an atopic predisposition
Immunomodulators	A class of medication that has an effect on the immune system. Examples of topical immunomodulators are tacrolimus and pimecrolimus
QT interval	This is a measure of the electrical cycle of the heart, beginning with ventricular contraction
Morphology	The form or structure of an individual skin lesion
Neuropeptides	Small protein-like molecules used by neurons to communicate with each other, distinct from the larger neurotransmitters

Table 2. Contact with investigators

Study ID	Trialists contact email/date of contact	Response	Additional comment
Kircik 2010	wedoderm@yahoo.com and called (502) 456 2783 Date of contact: 25 July 2012	No	We were unable to complete assessment; we are awaiting a response from the Principle Investigator (PI). For further details, see the ' Characteristics of studies awaiting classification ' assessment.
Simons 2007	lmcniven@hsc.mb.ca; simons@cc.u-manitoba.ca Date of contact: 26 July 2012	Yes	The PI provided sufficient additional trial detail that the study did not match the prespecified inclusion criteria for this systematic review.

Table 3. Summary of findings table of oral H1 antihistamines compared to placebo or alternative treatment for eczema

Oral H1 antihistamines compared to placebo or alternative treatment for eczema
Patient or population: Patients with eczema

Table 3. Summary of findings table of oral H1 antihistamines compared to placebo or alternative treatment for eczema (Continued)

Intervention: Oral H1 antihistamines

Comparison: Placebo or alternative treatment¹

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 or alternative treatment	Oral H1 antihistamines				
Reduction of subjectively perceived itch, as determined by validated rating scales	-	-	Not estimable	0 (0)	No evidence from RCTs that met our inclusion criteria ²	No RCT could be included
Global improvement in eczema, as measured by reduction in an eczema severity score, such as SCORAD	-	-	Not estimable	0 (0)	No evidence from RCTs that met our inclusion criteria ²	No RCT could be included
Percentage of participants reporting adverse effects/adverse events	-	-	Not estimable	0 (0)	No evidence from RCTs that met our inclusion criteria ²	No RCT could be included
Improvement in quality-of life-measures	-	-	Not estimable	0 (0)	No evidence from RCTs that met our inclusion criteria ²	No RCT could be included

*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.

¹Excluding: one antihistamine versus another antihistamine; topical antihistamines; H1 antihistamines as 'add-on' therapy; and studies using any concomitant therapy other than emollients/moisturisers.

²There might be some evidence coming from studies that allowed concomitant therapies for eczema, but that would not address the singular effect of oral antihistamines on eczema.

Table 4. Research recommendations based on a gap in the evidence of the effects H1 antihistamines for eczema

Core elements	Issues to consider	Status of research for this review
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Oral H1 antihistamines as monotherapy for eczema (Review)

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Table 4. Research recommendations based on a gap in the evidence of the effects H1 antihistamines for

eczema Evidence (E) <i>(Continued)</i>	What is the current state of the evidence?	This systematic review did not identify any RCTs. There is no high-level evidence of efficacy and safety of H1 antihistamines for eczema.
Population (P)	Diagnosis, disease stage, comorbidity, risk factors, gender, age, ethnic group, specific inclusion or exclusion criteria, clinical setting	<p>Inclusion criteria</p> <ul style="list-style-type: none"> Children and adults with a clinical diagnosis of eczema, identified as 'atopic eczema' or 'eczema', which was made by either 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) <p>Exclusion criteria</p> <ul style="list-style-type: none"> Use of concomitant therapy for the treatment of eczema, except for moisturisers or emollients Presence of other diseases requiring immunosuppressants Use of antidepressives with antihistamine activity Other skin disease requiring topical treatment with corticosteroids, calcineurin inhibitors, or both UV light treatment
Intervention (I)	Type, frequency, dose, duration, prognostic factor	<ul style="list-style-type: none"> The study duration should be 1 to 2 weeks assessing oral H1 antihistamines No concomitant therapy was allowed, except moisturisers or emollients
Comparison (C)	Type, frequency, dose, duration, prognostic factor	<ul style="list-style-type: none"> No treatment or placebo treatment No concomitant therapy was allowed, except moisturisers or emollients
Outcome (O)	Which clinical or patient-related outcomes will the researcher need to measure, improve, influence, or accomplish? Which methods of measurement should be used?	<ul style="list-style-type: none"> Reduction of subjectively perceived itch, as determined by validated rating scales (e.g. visual analogue scales) Global improvement in eczema, as measured by reduction in a validated eczema severity score, such as SCORAD (European Task Force on Atopic Dermatitis 1993) Percentage of participants reporting adverse effects or adverse events Improvement in quality-of-life measures using any validated disease-specific or generic instrument
Time stamp (T)	Date of literature search or recommendation	13 March 2012
Study type	What is the most appropriate study design to address the proposed question?	<ul style="list-style-type: none"> Randomised controlled trial (adequately powered/multicentred) Methods: concealment of allocation sequence Blinding: blinding of participants, trialists, and outcomes assessors Setting: hospital/university with adequate follow-up (at least 4 weeks)

APPENDICES

Appendix 1. Specialised Register search strategy

((atopic and dermatitis) or (atopic and 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 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)

Appendix 2. CENTRAL (Cochrane Library) search strategy

#1 (atopic dermatitis)
 #2 (atopic eczema)
 #3 (neurodermatitis) or (atopic ekzema)
 #4 MeSH descriptor Dermatitis, Atopic, this term only
 #5 MeSH descriptor Neurodermatitis, this term only
 #6 MeSH descriptor Eczema, this term only
 #7 (#1 OR #2 OR #3 OR #4 OR #5 OR #6)
 #8 (histamine H1 antagonist*) or (histamine antagonist*)
 #9 MeSH descriptor Histamine H1 Antagonists explode all trees
 #10 (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 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 tivist 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)
 #11 (#8 OR #9 OR #10)
 #12 (#7 AND #11)

Appendix 3. MEDLINE (OVID) search strategy

1. randomized controlled trial.pt.
 2. controlled clinical trial.pt.
 3. randomized.ab.
 4. placebo.ab.
 5. clinical trials as topic.sh.
 6. randomly.ab.
 7. trial.ti.
 8. 1 or 2 or 3 or 4 or 5 or 6 or 7
 9. (animals not (human and animals)).sh.
 10. 8 not 9
 11. atopic dermatitis.mp. or exp Dermatitis, Atopic/
 12. atopic eczema.mp.
 13. neurodermatitis.mp. or exp Neurodermatitis/
 14. atopic ekzema.mp. or exp Eczema/ or eczema.mp.
 15. histamine H1 antagonists.mp. or exp Histamine H1 Antagonists/
 16. histamine antagonists/ or exp histamine h1 antagonists/
 17. exp Ethanolamine/ or ethanolamine.mp.
 18. diphenhydramine.mp. or exp Diphenhydramine/
 19. clemastine.mp. or exp Clemastine/
 20. dimenhydrinate.mp. or exp Dimenhydrinate/
 21. doxylamine.mp. or exp Doxylamine/
 22. piperazine.mp. or exp Piperazines/
 23. hydroxyzine.mp.
 24. (hydroxyzine or hydroxyzone).mp.
 25. meclizine.mp. or exp Meclizine/
 26. cyclizine.mp. or exp Cyclizine/
 27. chlorcyclizine.mp.
 28. phenothiazine.mp. or exp Phenothiazines/
 29. chlorpromazine.mp. or exp Chlorpromazine/
 30. promethazine.mp. or exp Promethazine/
 31. trimeprazine.mp. or exp Trimeprazine/
 32. ethylenediamine.mp. or exp Ethylenediamines/
 33. mepyramine.mp. or exp Pyrilamine/
 34. tripelenamine.mp.
 35. alkylamine.mp.
 36. brompheniramine.mp. or exp Brompheniramine/
 37. chlorpheniramine.mp. or exp Chlorpheniramine/
 38. carbinoxamine.mp.

39. teldane.mp. or exp Terfenadine/
40. astemizole.mp. or exp Astemizole/
41. hismanal.mp.
42. loratadine.mp. or exp Loratadine/
43. mequitazine.mp.
44. mebhydroline.mp.
45. semprex.mp.
46. fexofenadine.mp.
47. telfast.mp.
48. mizolastine.mp.
49. mizollen.mp.
50. azatadine.mp.
51. cyproheptadine.mp. or exp Cyproheptadine/
52. atosil.mp.
53. norastemizole.mp.
54. dimetapp.mp.
55. tivist.mp.
56. dramamine.mp.
57. benadryl.mp.
58. atarax.mp.
59. vistaril.mp.
60. actifed.mp.
61. thorazine.mp.
62. dimetane.mp.
63. zyrtec.mp. or exp Cetirizine/
64. periactin.mp.
65. claritine.mp.
66. seldane.mp.
67. allegra.mp.
68. 11 or 12 or 13 or 14
69. or/15-67
70. 69 and 68 and 10

Appendix 4. EMBASE (OVID) search strategy

1. random\$.mp.
2. factorial\$.mp.
3. (crossover\$ or cross-over\$).mp.
4. placebo\$.mp. or PLACEBO/
5. (doubl\$ adj blind\$).mp.
6. (singl\$ adj blind\$).mp.
7. (assign\$ or allocat\$).mp.
8. volunteer\$.mp. or VOLUNTEER/
9. Crossover Procedure/
10. Double Blind Procedure/
11. Randomized Controlled Trial/
12. Single Blind Procedure/
13. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
14. atopic dermatitis.mp. or exp Dermatitis, Atopic/
15. atopic eczema.mp.
16. neurodermatitis.mp. or exp Neurodermatitis/
17. atopic ekzema.mp. or exp Eczema/ or eczema.mp.
18. histamine H1 antagonists.mp. or exp Histamine H1 Antagonists/
19. histamine antagonists/ or exp histamine h1 antagonists/
20. exp Ethanolamine/ or ethanolamine.mp.
21. diphenhydramine.mp. or exp Diphenhydramine/
22. clemastine.mp. or exp Clemastine/
23. dimenhydrinate.mp. or exp Dimenhydrinate/
24. doxylamine.mp. or exp Doxylamine/
25. piperazine.mp. or exp Piperazines/
26. hydroxizine.mp.
27. (hydroxizine or hydroxyzine).mp.

28. meclizine.mp. or exp Meclizine/
29. cyclizine.mp. or exp Cyclizine/
30. chlorcyclizine.mp.
31. phenothiazine.mp. or exp Phenothiazines/
32. chlorpromazine.mp. or exp Chlorpromazine/
33. promethazine.mp. or exp Promethazine/
34. trimeprazine.mp. or exp Trimeprazine/
35. ethylenediamine.mp. or exp Ethylenediamines/
36. mepyramine.mp. or exp Pyrilamine/
37. tripelenamine.mp.
38. alkylamine.mp.
39. brompheniramine.mp. or exp Brompheniramine/
40. chlorpheniramine.mp. or exp Chlorpheniramine/
41. carbinoxamine.mp.
42. teldane.mp. or exp Terfenadine/
43. astemizole.mp. or exp Astemizole/
44. hismanal.mp.
45. loratadine.mp. or exp Loratadine/
46. mequitazine.mp.
47. mebhydroline.mp.
48. semprex.mp.
49. fexofenadine.mp.
50. telfast.mp.
51. mizolastine.mp.
52. mizollen.mp.
53. azatadine.mp.
54. cyproheptadine.mp. or exp Cyproheptadine/
55. atosil.mp.
56. norastemizole.mp.
57. dimetapp.mp.
58. tavist.mp.
59. dramamine.mp.
60. benadryl.mp.
61. atarax.mp.
62. vistaril.mp.
63. actifed.mp.
64. thorazine.mp.
65. dimetane.mp.
66. zyrtec.mp. or exp Cetirizine/
67. periactin.mp.
68. claritine.mp.
69. seldane.mp.
70. allegra.mp.
71. 14 or 15 or 16 or 17
72. or/18-70
73. 72 and 71 and 13

Appendix 5. LILACS search strategy

((Pt RANDOMIZED CONTROLLED TRIAL OR Pt CONTROLLED CLINICAL TRIAL OR Mh RANDOMIZED CONTROLLED TRIALS OR Mh RANDOM ALLOCATION OR Mh DOUBLE-BLIND METHOD OR Mh SINGLE-BLIND METHOD OR Pt MULTICENTER STUDY) OR ((tw ensaio or tw ensayo or tw trial) and (tw azar or tw acaso or tw placebo or tw control\$ or tw aleat\$ or tw random\$ or (tw duplo and tw cego) or (tw doble and tw ciego) or (tw double and tw blind)) and tw clinic\$)) AND NOT ((CT ANIMALS OR MH ANIMALS OR CT RABBITS OR CT MICE OR MH RATS OR MH PRIMATES OR MH DOGS OR MH RABBITS OR MH SWINE) AND NOT (CT HUMAN AND CT ANIMALS)) [Palavras] and ((atopic and dermatitis) or (atopic and eczema) or ((atopic and ekzema) or neurodermatitis) or ((atopica or atopia) and eccema)) [Palavras]

FEEDBACK

Comment on future research, 10 March 2013

Summary

Comment by Andrew Herxheimer:

Congratulations on this ground-clearing review!

However, please make specific suggestions or proposals in the conclusions on what trials or studies should be done next. I agree that the challenge is to design the most useful trial(s) of an add-on oral antihistamine accompanying topical treatment, presumably with a long established corticosteroid ointment.

Perhaps four groups each treated for 3 months but followed up for longer:

- loratadine 10 mg/day + beclomethasone valerate 0.1% ointment;
- placebo + beclomethasone valerate 0.1% ointment;
- loratadine 10 mg/day + hydrocortisone 0.5% ointment; or
- placebo + hydrocortisone 0.5% ointment.

An add-on trial of a sedative H1 antihistamine seems less necessary than one of a non-sedative one, but might be useful in children.

Reply

Response to Andrew Herxheimer:

Thank you very much for your important comments. As concluded in our systematic review, well designed randomised controlled trials investigating benefits and harms of H1 antihistamines as monotherapy appear to be needed. However, it is unlikely that such trials will be conducted due to ethical concerns that arise from withholding concomitant or additional treatment for eczema. In your comment, you refer to the most useful design for a trial investigating the effect of antihistamines as add-on therapy to established treatment. This is a very relevant clinical research question. We are currently preparing a protocol for a further systematic review investigating benefits and harms of antihistamines as add-on therapy. This systematic review will look at both sedative and non-sedative antihistamines.

Contributors

Comment made by Andrew Herxheimer, Emeritus Fellow, UK Cochrane Centre: "I agree with the conflict of interest statement: I certify that I have no affiliations with or involvement in any organisation or entity with a financial interest in the subject matter of my feedback."

Reply by Christian J Apfelbacher, Esther J van Zuuren, Zbys Fedorowicz, Aldrin Jupiter, Uwe Matterne, and Elke Weisshaar, and processed by Hywel Williams and Urbà González.

WHAT'S NEW

Date	Event	Description
18 May 2016	Review declared as stable	A quick search in Medline and Embase in May 2016 did not find any major studies. As there is currently no new data of relevance, and it is unlikely that there will be further research in this area, this review continues to be marked stable.

HISTORY

Protocol first published: Issue 2, 2009

Review first published: Issue 2, 2013

Date	Event	Description
23 March 2015	Review declared as stable	There were no ongoing studies listed in the last published review, and only one study was awaiting assessment (because the review team had not been able to contact the author). A search of MEDLINE and Embase in 2014 found only 2 potentially relevant results, and an additional search of MEDLINE, Embase, and PubMed found only one relevant result. Our Co-ordinating Editor confirmed that there is currently no new data of relevance, and it is unlikely that there will be further research in this area. Thus,

Date	Event	Description
		this review has been marked stable because an update has not been considered necessary for two successive years.
30 April 2013	Feedback has been incorporated	A reader's comment on future research plans acknowledged and addressed by authors.
28 February 2013	Amended	A sentence was added to the 'Data collection and analysis' section within the Abstract.
21 December 2012	Amended	Title changed: "as monotherapy" added to clarify the type of intervention
8 August 2012	Amended	Title changed: "Oral" added to clarify the mode of administration of H1antihistamines. Types of interventions and comparisons; clarification of inclusion and exclusion criteria. See Differences between protocol and review

CONTRIBUTIONS OF AUTHORS

Link with editorial base and co-ordinate contributions from co-reviewers (CJA)
 Screen ongoing trials and congress proceedings (UM, EvZ, and EW)
 Identify relevant titles and abstracts from searches (CJA, AJ, ZF, EvZ, UM, and EW)
 Obtain copies of trials (CJA, AJ, EvZ, EW, and UM)
 Selection of trials (CJA, AJ, ZF, and EvZ)
 Extract data from trials in future updates (CJA, AJ, ZF, and EvZ)
 Enter data into Review Manager in future updates (CJA)
 Carry out analysis in future updates (CJA, ZF, and EvZ)
 Interpret data in future updates (CJA, EvZ, and ZF)
 Draft final review (CJA, EvZ, and ZF)
 Update review (CJA, AJ, EvZ, and ZF)

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- No source of support, Netherlands.
- No source of support, Germany.
- No source of support, Bahrain.

External sources

- No source of support, Netherlands.
- No source of support, Germany.
- No source of support, Bahrain.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In view of the generally acknowledged uncertainty surrounding the efficacy of this class of medication for the management of eczema and following discussions with the Cochrane Skin Group, we made post-hoc amendments to the types of interventions and comparisons examined in this review. We considered that these changes, which recognised concomitant medications as potential treatment-effect modifiers in outcomes assessment, would more likely ensure fairer comparisons of the interventions under investigation.

In the protocol, we stated that we would search for adverse effects of drugs used for the treatment of eczema and that we would conduct additional searches for potentially serious side-effects that the non-randomised studies may have reported. However, as we have already addressed adverse events as secondary outcomes and the potential side-effects of H1 are well-known, we undertook no further searches.

INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Oral; Eczema [*drug therapy]; Histamine H1 Antagonists [*administration & dosage]

MeSH check words

Adolescent; Adult; Child; Humans