H1-antihistamines for chronic spontaneous urticaria

Sharma, M., Bennett, C., Cohen, S,N. and Carter, B.

H1-antihistamines for chronic spontaneous urticaria (Review)

Sharma M, Bennett C, Cohen SN, Carter B

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2014, Issue 11

http://www.thecochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Review]

H1-antihistamines for chronic spontaneous urticaria

Maulina Sharma[1], Cathy Bennett[2a], Stuart N Cohen[3b], Ben Carter[4]

[1]Department of Dermatology, Derby Hospitals NHS Foundation Trust, London Road Community Hospital, Derby, UK. [2]Centre for Technology Enabled Health Research (CTEHR), Coventry University, Coventry, UK. [3]Nottingham University Hospitals NHS Trust, Nottingham, UK. [4]Institute of Primary Care & Public Health, Cardiff University School of Medicine, Cardiff, UK

[a]Joint second author. [b]Joint second author

Contact address: Maulina Sharma, Department of Dermatology, Derby Hospitals NHS Foundation Trust, London Road Community Hospital, London Road, Derby, DE1 2QY, UK. maulinasharma@yahoo.co.uk.

Editorial group: Cochrane Skin Group.
Publication status and date: Edited (no change to conclusions), published in Issue 7, 2015.
Review content assessed as up-to-date: 3 June 2014.

Citation: Sharma M, Bennett C, Cohen SN, Carter B. H1-antihistamines for chronic spontaneous urticaria. *Cochrane Database of Systematic Reviews* 2014, Issue 11. Art. No.: CD006137. DOI: 10.1002/14651858.CD006137.pub2.

ABSTRACT

Background

Chronic spontaneous urticaria (CSU) is characterised by the development of crops of red, itchy, raised weals or hives with no identifiable external cause.

Objectives

To assess the effects of H1-antihistamines for CSU.

Search methods

We searched the following databases up to June 2014: Cochrane Skin Group Specialised Register, CENTRAL (2014, Issue 5), MEDLINE (from 1946), EMBASE (from 1974) and PsycINFO (from 1806). We searched five trials registers and checked articles for references to relevant randomised controlled trials.

Selection criteria

We included randomised controlled trials of H1-antihistamines for CSU. Interventions included single therapy or a combination of H1-antihistamines compared with no treatment (placebo) or another active pharmacological compound at any dose.

Data collection and analysis

We used standard methodological procedures as expected by The Cochrane Collaboration.

Our primary outcome measures were proportion of participants with complete suppression of urticaria: 'good or excellent' response, 50% or greater improvement in quality of life measures, and adverse events. We present risk ratios (RR) with 95% confidence intervals (CIs).

Main results

We identified 73 studies (9759 participants); 34 studies provided data for 23 comparisons. The duration of the intervention was up to two weeks (short-term) or longer than two weeks and up to three months (intermediate-term).

Cetirizine 10 mg once daily in the short term and in the intermediate term led to complete suppression of urticaria by more participants than was seen with placebo (RR 2.72, 95% CI 1.51 to 4.91). For this same outcome, comparison of desloratadine versus placebo in the intermediate term (5 mg) (RR 37.00, 95% CI 2.31 to 593.70) and in the short term (20 mg) (RR 15.97, 95% CI 1.04 to 245.04) favoured desloratadine, but no differences were seen between 5 mg and 10 mg for short-term treatment.

Levocetirizine 20 mg per day (short-term) was more effective for complete suppression of urticaria compared with placebo (RR 20.87, 95% CI 1.37 to 317.60), and at 5 mg was effective in the intermediate term (RR 52.88, 95% CI 3.31 to 843.81) but not in the short term, nor was 10 mg effective in the short term.

Rupatadine at 10 mg and 20 mg in the intermediate term achieved a 'good or excellent response' compared with placebo (RR 1.35, 95% CI 1.03 to 1.77).

Loratadine (10 mg) versus placebo (RR 1.86, 95% CI 0.91 to 3.79) and loratadine (10 mg) versus cetirizine (10 mg) (RR 1.05, 95% CI 0.76 to 1.43) over short-term and intermediate-term treatment showed no significant difference for 'good or excellent response' or for complete suppression of urticaria, respectively.

Loratadine (10 mg) versus desloratadine (5 mg) (intermediate-term) showed no statistically significant difference for complete suppression of urticaria (RR 0.91, 95% CI 0.78 to 1.06) or for 'good or excellent response' (RR 1.04, 95% CI 0.64 to 1.71). For loratadine (10 mg) versus mizolastine (10 mg) (intermediate-term), no statistically significant difference was seen for complete suppression of urticaria (RR 0.86, 95% CI 0.64 to 1.16) or for 'good or excellent response' (RR 0.88, 95% CI 0.55 to 1.42).

Loratadine (10 mg) versus emedastine (2 mg) (intermediate-term) showed no statistically significant difference for complete suppression (RR 1.04, 95% CI 0.78 to 1.39) or for 'good or excellent response' (RR 1.09, 95% CI 0.96 to 1.24); the quality of the evidence was moderate for this comparison.

No difference in short-term treatment was noted between loratadine (10 mg) and hydroxyzine (25 mg) in terms of complete suppression (RR 1.00, 95% CI 0.32 to 3.10).

When desloratadine (5 to 20 mg) was compared with levocetirizine (5 to 20 mg), levocetirizine appeared to be the more effective (P value < 0.02).

In a comparison of fexofenadine versus cetirizine, more participants in the cetirizine group showed complete suppression of urticaria (P value < 0.001).

Adverse events leading to withdrawals were not significantly different in the following comparisons: cetirizine versus placebo at 10 mg and 20 mg (RR 3.00, 95% CI 0.68 to 13.22); desloratadine 5 mg versus placebo (RR 1.46, 95% CI 0.42 to 5.10); loratadine 10 mg versus mizolastine 10 mg (RR 0.38, 95% CI 0.04 to 3.60); loratadine 10 mg versus emedastine 2 mg (RR 1.09, 95% CI 0.07 to 17.14); cetirizine 10 mg versus hydroxyzine 25 mg (RR 0.78, 95% CI 0.25 to 2.45); and hydroxyzine 25 mg versus placebo (RR 3.64, 95% CI 0.77 to 17.23), all intermediate term.

No difference was seen between loratadine 10 mg versus mizolastine 10 mg in the proportion of participants with at least 50% improvement in quality of life (RR 3.21, 95% CI 0.32 to 32.33).

Authors' conclusions

Although the results of our review indicate that at standard doses of treatment, several antihistamines are effective when compared with placebo, all results were gathered from a few studies or, in some cases, from single-study estimates. The quality of the evidence was affected by the small number of studies in each comparison and the small sample size for many of the outcomes, prompting us to downgrade the quality of evidence for imprecision (unless stated for each comparison, the quality of the evidence was low).

No single H1-antihistamine stands out as most effective. Cetirizine at 10 mg once daily in the short term and in the intermediate term was found to be effective in completely suppressing urticaria. Evidence is limited for desloratadine given at 5 mg once daily in the intermediate term and at 20 mg in the short term. Levocetirizine at 5 mg in the intermediate but not short term was effective for complete suppression. Levocetirizine 20 mg was effective in the short term, but 10 mg was not. No difference in rates of withdrawal due to adverse events was noted between active and placebo groups. Evidence for improvement in quality of life was insufficient.

PLAIN LANGUAGE SUMMARY

H1-antihistamines for chronic spontaneous urticaria

Background

Chronic spontaneous urticaria (CSU) is a condition characterised by a rash of red itchy raised weals or hives, which appear for no identifiable reason. Other names include chronic idiopathic or chronic ordinary urticaria. 'Spontaneous' differentiates this type of urticaria from 'inducible' or 'physical' urticaria, for which there are specific triggers such as cold or pressure. 'Chronic' indicates that the condition has continued for at least six weeks. Hives may be intensely itchy, and the appearance may be unsightly and distressing to sufferers. In some cases, hives can be accompanied by deeper swelling, known as angio-oedema, which is most common around the eyes and mouth.

Antihistamine drugs, specifically H1 antihistamines, are the mainstay of treatment for urticaria, although they control the condition rather than cure it. Many antihistamines are available to buy without a prescription, including brand names such as Clarityn, Piriton, Zirtek, Benadryl and Phenergan (brand names may differ by country).

Review question

Which H1-antihistamines are effective and safe for CSU?

Study characteristics

We included 73 randomised controlled trials, with 9759 participants of all ages and looked for complete suppression of urticaria. The duration of the intervention was up to two weeks (short-term) or longer than two weeks and up to three months (intermediate-term).

Key results

We investigated clinical trials in which one therapy was compared against another or against placebo (direct comparisons). We found that for general use, 10 mg once daily of cetirizine for short-term and intermediate-term duration was effective in completely suppressing urticaria, although not in all individuals. Some benefit may be associated with use of desloratadine at 5 mg for at least an intermediate term and at 20 mg in the short term. Levocetirizine at 5 mg was effective for complete suppression in the intermediate term but not in the short term. A higher dose of 20 mg was effective in the short term, but 10 mg was not.

Adverse events, such as headache or dry mouth, are tolerable with most antihistamines. Evidence is less clear for improvement in quality of life (e.g. reduction in sleep disturbance from itching, less distress from the appearance of hives) as many studies did not address this.

We cannot say whether one antihistamine works better than all the rest, as we did not have head-to-head evidence for every possible treatment comparison.

Quality of the evidence

The overall quality of the evidence found for most outcomes was low. Further well-designed and carefully reported comparative studies are required, if we are to find out how well these medicines work, and if any adverse effects are reported, especially over periods of up to several months.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Cetirizine 10 to 20 mg versus placebo for chronic spontaneous urticaria

Patient or population: patients with chronic spontaneous urticaria
Setting: research clinic
Intervention: cetirizine 10 to 20 mg versus placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control (placebo)	Cetirizine 10 to 20 mg				
Complete suppression of urticaria Global assessment of symptom scores	**Study population**		**RR 2.72** (1.51 to 4.91)	178 (2 studies)	⊕⊕◯◯ **Low**[a,b]	Favours cetirizine
	133 per 1000	**363 per 1000** (201 to 655)				
	Moderate					
	146 per 1000	**397 per 1000** (220 to 717)				
Adverse events leading to withdrawal	**Study population**		**RR 3** (0.68 to 13.22)	389 (3 studies)	⊕⊕◯◯ **Low**[a,b]	Favours neither intervention nor control
	10 per 1000	**30 per 1000** (7 to 132)				
	Moderate					
	14 per 1000	**42 per 1000** (10 to 185)				

*The basis for the **assumed risk** (e.g. 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] Design limitation (risk of bias).
[b] Relatively few participants and few events and/or wide confidence intervals.

BACKGROUND

Description of the condition

Urticaria is a condition characterised by the development of a rash of red itchy raised weals or hives that blanch with pressure. The main associated symptom is itching, which may be intense. Although individual weals typically come and go within 24 hours, the overall condition may persist, with fresh crops of weals occurring on other areas of the body, even as the original lesions resolve. In some cases, the weals are accompanied by deeper swelling, known as angio-oedema. If recurrent crops of urticaria continue to occur for longer than six weeks, the condition is known as chronic urticaria (to distinguish this from the more common acute urticaria, for which a cause is more often identified) (James 2011; Sarbijt 2014). Chronic spontaneous urticaria may occur at any age (Hellgren 1972). Recent publications show a female-to-male predominance of 2:1 (Gaig 2004) with a prevalence of between 0.5% and 1% (Maurer 2011).

Causes

A careful history and physical examination are important, but an underlying cause is never identified in most individuals with chronic urticaria (Grattan 2001; Charlesworth 2002). In such cases, the condition has also been called 'chronic idiopathic urticaria.' This term was replaced by 'chronic ordinary urticaria' to include the subset of people who appear to have autoimmune disease, with a circulating antibody that is able to bind to mast cells, thereby causing histamine release and weal formation. This group makes up about 30% of those with chronic urticaria, but such individuals tend to respond in the same way to treatment as those with non-autoimmune urticaria (Hauser 2003). Current consensus is to use the term 'chronic spontaneous urticaria' (Maurer 2013), which describes the behaviour of the disease rather than assuming a particular level of knowledge of its pathogenesis. By contrast, when a trigger for urticaria can be identified, the term 'inducible' is now preferred. In practice, chronic spontaneous urticaria covers the population of individuals who were previously labelled as having chronic idiopathic or ordinary urticaria. Most of the extant literature employs these outmoded terms. We therefore deemed it appropriate to include such studies, whilst adhering to the term 'chronic spontaneous urticaria (CSU)' throughout our review.

Impact

The severity of urticaria varies between individuals. Some of those with the condition have several attacks each day for many months; others may have an attack every week or every month. This can be a very debilitating condition, particularly if the attacks are frequent. The inability to predict an attack and the lack of an identifiable cause are often sources of great frustration. Historically it has been reported that after 10 years, at least 20% of those with urticaria still suffer from it (Champion 1969; Humphreys 1998) and that half of those with chronic urticaria and angio-oedema still had chronic urticaria at five years (Champion 1969). However, the condition is rarely permanent, and recent surveys suggest a higher chance of disease remission (Kozel 2001).

Description of the intervention

The aim of treatment is to suppress urticarial activity completely. In some individuals, only symptomatic improvement can be achieved by reducing the severity and frequency of attacks. H1-antihistamines (commonly called 'antihistamines,' which are available over the counter for various complaints, including hay fever and allergies) form the basis of treatment, providing symptomatic relief for many affected individuals. Older (or 'first-generation') H1-antihistamines (e.g. hydroxyzine) are no longer recommended for use in chronic urticaria, as they are more sedating than the newer 'second generation' of antihistamines (e.g. cetirizine) and carry a higher risk of side effects such as dry mouth, blurred vision, headache, glaucoma and urinary retention.

Antihistamines may have to be taken over extended periods of time to control the disease. High doses of H1-antihistamines may be required to obtain sufficient symptom control in urticaria. Adverse effects of H1-antihistamines vary between individuals, and some of those with the condition may tolerate one antihistamine better than another (Nolen 1997). Terfenadine and astemizole have been associated with cardiac arrhythmias (DuBuske 1999) in a small proportion of people and have been withdrawn from the market. Oral corticosteroids have an occasional role as rescue therapy in severe exacerbations of chronic urticaria.

Other treatments for difficult to control CSU include H2-antihistamines (also known as H2-receptor antagonists, or H2RAs) such as ranitidine (these are not commonly referred to as antihistamines and are usually used for acid-related stomach conditions). (This class of medications was systematically reviewed in Fedorowicz 2012.) Other interventions include the leukotriene receptor antagonist montelukast, immunosuppressive agents (e.g. ciclosporin), diets and food avoidance, doxepin and the anti-immunoglobulin E (IgE) monoclonal antibody omalizumab.

Why it is important to do this review

Patients with chronic spontaneous urticaria can be difficult to treat. Many of those with the condition do not respond to initial treatment, and clear guidance is needed on which antihistamines to use, appropriate dosing regimens and likely responses. As treatment is usually aimed at reducing symptoms and improving the lives of people with CSU, evidence regarding quality of life was sought so an important outcome for this review could be assessed.

Many randomised controlled trials (RCTs) related to the use of antihistamines in CSU have been conducted. We sought to investigate:

- whether one antihistamine is superior to another;
- if combination therapy is superior to monotherapy;
- whether high-dose therapy is superior to standard doses;
- the duration of benefit from H1-antihistamines;
- risks and side effects of H1-antihistamines when used in the treatment of individuals with chronic urticaria; and
- the effects of treatment on quality of life.

We have provided an assessment of the level and quality of currently available evidence, and we have identified areas that require further research on this important condition.

OBJECTIVES

To assess the effects of H1-antihistamines for chronic spontaneous urticaria (CSU).

METHODS

Criteria for considering studies for this review

Types of studies

We included only RCTs that evaluated the effectiveness of H1-antihistamines compared with placebo or another active treatment (including another H1-antihistamine) and those that compared different doses. We did not include studies of other designs.

Types of participants

Participants were individuals of any age (children and adults) who had been clinically diagnosed with CSU. The following were excluded.

- Participants with urticaria of less than six weeks' duration;
- Participants with immune complex urticaria (urticarial vasculitis or serum sickness), papular urticaria, angio-oedema without weals or contact urticaria; and
- Participants with predominantly physical or cholinergic urticaria, or other urticaria with a clearly identifiable causative agent (e.g. medication), and those with auto-inflammatory syndromes (e.g. Muckle-Wells syndrome, Schnitzler's syndrome).

Types of interventions

Any first-generation ('sedating') or second-generation ('non-sedating') H1-antihistamines in current use, given at any dose (including topical interventions and H2RAs given concomitantly). We specifically excluded studies that would yield comparison data only for terfenadine and astemizole, as these drugs have been withdrawn because of safety issues. Interventions could be given as single therapy or combination therapy. Comparators consisted of no treatment (i.e. placebo) or another active compound.
Duration of the intervention was categorised as follows: up to two weeks (short-term), longer than two weeks and up to three months (intermediate-term) and longer than three months (long-term).

Types of outcome measures

Primary outcomes

- Proportion of participants with complete suppression of urticaria whilst taking H1-antihistamines.
- Proportion of participants with 'good' or 'excellent' response to H1-antihistamines whilst taking H1-antihistamines.
- Proportion of participants with 50% or greater improvement in quality of life measurements whilst taking H1-antihistamines.

The above measures were based predominantly on participant self-reporting because of the transient nature of urticaria. We looked at participant and clinician assessments separately and in combination.

Secondary outcomes

- Serious adverse events (i.e. serious enough to require withdrawal of treatment).
- Minor participant-reported adverse events not requiring withdrawal of treatment.
- Proportion of participants who relapse within one month of stopping H1-antihistamines.

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

We revised our draft search strategy to update the names of specific H1-antihistamines used to treat urticaria.
We searched the following databases up to 3 June 2014.

- Cochrane Skin Group Specialised Register (strategy in Appendix 1).

- Cochrane Central Register of Controlled Trials (CENTRAL) (2014, Issue 5) (strategy in Appendix 2).
- MEDLINE via OVID (from 1946) (strategy in Appendix 3).
- EMBASE via OVID (from 1974) (strategy in Appendix 4).
- PsycINFO via OVID (from 1806) (strategy in Appendix 5).

Trials registers

We searched the following trials registers on 9 June 2014.
For the first three registers listed, we used the following search string: 'chronic idiopathic urticaria AND anti-histamine AND placebo.' For the EU Clinical Trials Register and the World Health Organization International Clinical Trials Registry, we used the phrase 'chronic idiopathic urticaria.'

- metaRegister of Controlled Trials (www.controlled-trials.com).
- US National Institutes of Health Ongoing Trials Register (www.clinicaltrials.gov).
- Australian New Zealand Clinical Trials Registry (www.anzctr.org.au).
- World Health Organization International Clinical Trials Registry platform (www.who.int/trialsearch).
- EU Clinical Trials Register (https://www.clinicaltrialsregister.eu/).

Searching other resources

References from published papers

We checked the bibliographies of reviews on treatment of individuals with CSU to look for additional references to relevant RCTs.

Adverse effects

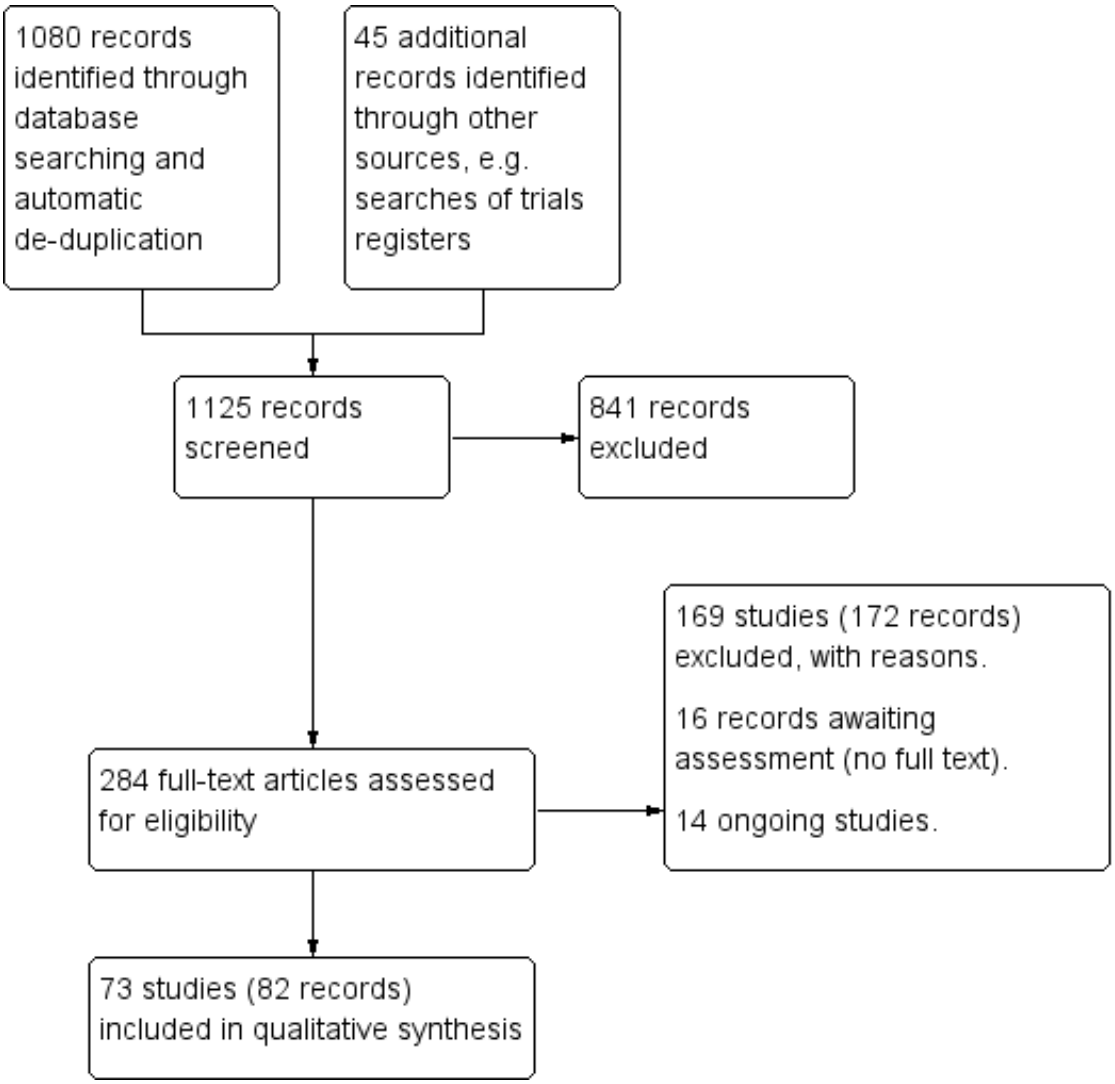
We did not perform a separate search for adverse effects of the target intervention. We considered adverse and side effects described in the included studies. We checked the bibliographies of review articles to look for additional references to relevant reports of adverse effects.

Data collection and analysis

Selection of studies

We included in this review only RCTs evaluating H1-antihistamines for chronic urticaria. We sought advice from translators when the study report was written in a language other than English. At least two review authors (MS, CB and SNC) assessed all titles and abstracts identified by the searches. These review authors independently assessed each included study to determine whether the predefined selection criteria had been met, and they resolved differences of opinion through discussion within the review team. We listed the excluded studies and the reasons for their exclusion in the Characteristics of excluded studies section of the review and presented the study flow chart in PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) (Figure 1).

Figure 1. Study flow diagram.



Data extraction and management

Three review authors (MS, CB and SNC) extracted data independently using a data extraction form, and disagreements on data extraction were resolved by consensus. In the case of studies written in Chinese, German or another foreign language, a translator extracted data, and MS and SNC checked the numerical outcomes. We contacted principal investigators of trials and asked them to provide missing data when possible. Review authors (MS, CB and BC) checked and entered the data (numerical outcomes data and non-numerical data) into RevMan 2014.

Assessment of risk of bias in included studies

At least two review authors (MS, CB and SNC) independently assessed the risk of bias in included studies using the risk of bias assessment tool provided in Chapter 8 of the*Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We compared the evaluations and discussed and resolved inconsistencies between review authors' decisions.

We rated the following domains separately 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. These assessments are reported in the 'Risk of bias' table for each individual study in the Characteristics of included studies section of the review.

- Allocation sequence was adequately generated ('sequence generation').
- Allocation was adequately concealed ('allocation concealment').
- Knowledge of allocated interventions was adequately prevented during the study ('blinding').
- Incomplete outcome data were adequately addressed.
- Reports of the study were free of suggestions of selective outcome reporting.
- The study was apparently free of other sources of bias that could put it at high risk of bias (i.e. potential conflicts of interest, pharmaceutical funding/support or both).

We also categorised and reported 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 were met.
- Unclear risk of bias: plausible bias that raises some doubt 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 one or more criteria were not met.

We reported these assessments in the Risk of bias in included studies section of this review.

Measures of treatment effect

We planned to present continuous outcomes on the original scale as reported in each individual study. We will report standardised mean differences (SMDs) for continuous data in future updates (i.e. if similar outcomes are reported using different scales, we will standardise these by dividing the estimated coefficient by its standard deviation (SD) to permit comparisons between scales).
We presented dichotomous outcomes data as risk ratios (RRs) along with their associated 95% confidence intervals (CIs); we analysed these in RevMan using the Mantel-Haenszel test, unless stated otherwise.

Unit of analysis issues

Cross-over studies

We planned to analyse cross-over studies using first period data only, unless an adequate washout between periods took place and baseline data were presented for each period.

Multi-armed studies

To ensure that analyses from these studies were not falsely powered, we partitioned the number of participants analysed in the comparison arm into each pair-wise comparison; thus a three-arm study with 30 participants in each arm that resulted in two pair-wise comparisons of placebo versus A and placebo versus B was allocated the following numbers of participants: 15 versus 30, and 15 versus 30. Mean and standard deviation summary statistics for comparator participants remained unchanged.

Dealing with missing data

We attempted to contact investigators to retrieve missing data. We reanalysed data according to a treatment by allocation principle when possible, and in accordance with Section 16.2.2 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). If data were not reported and study authors had conducted a per-protocol analysis, we assessed whether there was any imbalance in the dropout rate between trial arms to determine the potential impact of bias. In the absence of intention-to-treat data, we used available case population data (per protocol) and reported these accordingly.

Assessment of heterogeneity

We assessed clinical heterogeneity by examining trial conditions (i.e. characteristics of the studies, similarity between types of participants and the interventions). We assessed the degree of statistical heterogeneity between studies using the I^2 statistic. We reported heterogeneity as important if it was at least moderate to substantial by the I^2 statistic > 60% (Higgins 2011). If this could be explained by clinical reasoning and a coherent argument could be made for combining the studies, we conducted a meta-analysis. In many cases, heterogeneity could not be adequately explained, and we did not pool the data.
Clinical diversity among the studies included in this review, as well as the limited number of studies that could be combined for each intervention, allowed us to assess heterogeneity between studies for only one of the comparisons.

Assessment of reporting biases

We planned to carry out assessments of reporting bias when at least 10 studies were included in a meta-analysis, according to the recommendations on testing for funnel plot asymmetry as described in Section 10.4.3.1 of the *Cochrane Handbook for systematic Reviews of Interventions* (Higgins 2011). We planned to explore possible sources of asymmetry by performing an additional sensitivity analysis.

Data synthesis

Review authors (MS, CB and BC) analysed the data in RevMan 2014 and reported them in accordance with the advice provided in Chapter 9 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). If we were able to identify more than one study that was clinically similar and exhibited not less than moderate heterogeneity, we pooled the data into a meta-analysis using a random-effects model, and we carried out a sensitivity

analysis using a fixed-effect model to assess the degree of heterogeneity.
For some comparisons, we carried out reanalysis using Fisher's exact test because of the small number of participants,

Subgroup analysis and investigation of heterogeneity

We conducted subgroup analyses based on the duration of the intervention. Duration of the intervention was categorised as follows: up to two weeks (short-term) and longer than two weeks up to three months (intermediate-term).

Sensitivity analysis

We planned to conduct sensitivity analyses for primary outcome measures to assess the effects of including only those studies with low risk of bias and to assess the robustness of the results of this review. Included studies with low risk of bias were too few to permit this analysis.

RESULTS

Description of studies

Results of the search

We identified 1080 records in total through our electronic database searches up to June 2014. We identified an additional 45 potential study reports from databases of clinical trials in progress and from bibliographical searches. In total we screened 1125 records and excluded 841 on the basis of examination of titles and abstracts. We examined the remaining 284 records in detail. Sixteen records could not be obtained in full text, and we list these in the Characteristics of studies awaiting classification tables. Fourteen studies were listed as ongoing (see Characteristics of ongoing studies), and we will include these in future updates if the results become available (Figure 1). We excluded 169 studies accounting for 172 records. The remaining 82 records described 73 studies, which were included.
At each stage of the selection process, at least two review authors independently reviewed the search results and selected trials for inclusion. The final list was agreed upon by two review authors (MS and SNC), with involvement of a third review author (CB) if necessary to resolve disagreements.

Included studies

Design

All included studies were randomised, and none was of quasi-randomised design.
Some unusual designs were reported: Garavaglia 1995 reported a randomised trial in which dropouts were replaced with new recruits. It was unclear whether the new participants were randomly assigned or were simply assigned to the intervention group of the most recent dropout. Thompson 2000 Study 1 and Thompson 2000 Study 2 reported two trials within the same study report; it is unclear why the results from both studies were not aggregated and presented as a single two-centre trial, as trial conditions were the same. Wang 2012 was a dose reduction study, and Weller 2013 selected a single body area for each participant. Staevska 2014 employed a cross-over trial design but after randomisation and initial in-hospital treatment assessment tested the effectiveness and tolerability of levocetirizine versus hydroxyzine in an alternate-day regimen. After five days, participants from arms 1 and 2 were crossed over to the alternative treatment without washout between phases.
Twenty-six of the included trials were multi-centre in design (Belaich 1990; Breneman 1995; Breneman 1996; Bronsky 2001; Brostoff 1996; Dubertret 1999; Finn 1999; Gale 1989; Gimenez-Arnau 2007; Godse 2007; Grant 1988; Gu 2002; Hao 2003; Kalivas 1990; Kaplan 2005; Kint 1989; Monroe 1988; Monroe 2003; Nelson 2000; Ollert 1999; Ortonne 2007; Paul 1998; Peyri 1991; Pons-Guiraud 2006; Potter 2009; Zuberbier 2010).
Fourteen included studies were of a cross-over design. However, none of these contributed data to the meta-analyses in this review, although we discuss the results narratively below (Commens 1978; Gale 1989; Go 1989; Goh 1991; Harvey 1981; Hjorth 1988; Juhlin 1987; Juhlin 1991; Kint 1989; Leyh 1989; Liu H-N 1990; Marks 1980; Salo 1989; Staevska 2014).

Sample sizes

We included 73 studies with a total of 9759 randomly assigned participants. Details of all included studies are provided in the Characteristics of included studies tables. Sample sizes ranged from several hundred, for example, 886 (Potter 2009), 525 (Zuberbier 2010), 468 (Nelson 2000), 334 (Gimenez-Arnau 2007) and 314 NCT00536380) to fewer than 25 (Gale 1989; Harvey 1981; Juhlin 1987; Leyh 1989; Liu H-N 1990; Marks 1980; Salo 1989).

Setting

Most studies were carried out in a secondary care setting, including hospital clinics, research clinics and dermatology centres. None were based in primary care.
Studies were carried out mostly, but not exclusively, in Europe and the USA. Outside these continents, Anuradha 2010; Dakhale 2014; Ghosh 1990; Godse 2007; Handa 2004 and Maiti 2011 were undertaken in India. Gu 2002; Hao 2003; Liu 2003; Wang 2012; Wu 2008; Yin 2003a; Yin 2003b and Zou 2002 were undertaken in China, and Makino 2012 in Japan. Garavaglia 1995

and Zuberbier 2010 were carried out in Argentina, Goh 1991 in Singapore and Liu H-N 1990 and Wan 2009 in Taiwan. Marks 1980 took place in Australia, Monroe 2003 in the USA and Chile and Phanuphak 1987 in Thailand. The location was not stated for Patel 1997, although the study authors worked in American and Canadian research centres.

Participants

The total number of participants randomly assigned was 9759. Participants consisted of adults (i.e. over 18 years old) or mixed groups including adolescents (i.e. over 12 years old). Most participants were female.

The inclusion criteria were tightly defined as CSU, alternatively described as chronic idiopathic or ordinary urticaria, of at least six weeks' duration. In Hjorth 1988, the diagnosis was not clearly defined, and investigators may have included some participants with atopic dermatitis. In Wang 2012, disease duration and symptoms were comparable but were not defined clearly in the study. Dakhale 2014; Finn 1999; Grant 1988; Kaplan 2005; Monroe 2003; Nelson 2000; Ortonne 2004 and Pons-Guiraud 2006 excluded participants who were previously unresponsive to antihistamines, and in the Ghosh 1990 study, all participants were previously refractory to antihistamine treatment.

Interventions and comparisons

Intervention

H1-antihistamines usually are classified as first or second generation, according to their chemical structure and properties. First-generation antihistamines may cause sedation and can be useful for treating sleep disturbance 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 without the possibility of sedative effects, and some (particularly terfenadine and astemizole) may also 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 accepted, as such agents do not differ sufficiently from earlier drugs in terms of desirable and undesirable effects (Holgate 2003). In our analyses (of those trials that yielded outcome data), we included the following.

First-generation antihistamines

- Hydroxyzine.
- Pheniramine.

Second-generation antihistamines

- Cetirizine.
- Desloratadine.
- Ebastine.
- Emedastine.
- Fexofenadine.
- Levocetirizine.
- Loratadine.
- Ketotifen.
- Mizolastine.
- Rupatadine.

Other interventions

Di Lorenzo 2004 used montelukast, a non-H1-antihistamine intervention, as the comparator with desloratadine. Montelukast is a leukotriene receptor antagonist (LTRA). Ghosh 1990 used as a comparator doxepin, a sedative tricyclic antidepressant that has antihistaminic properties.

Duration of intervention

Interventions were categorised by duration as follows: up to two weeks (short-term), longer than two weeks and up to three months (intermediate-term) and longer than three months (long-term). Seventeen studies were short-term (Commens 1978; Go 1989; Goh 1991; Harvey 1981; Hjorth 1988; Juhlin 1987; Juhlin 1991; Kint 1989; Leyh 1989; Leynadier 2000; Locci 1991; Monroe 1992; Patel 1997; Peyri 1991; Phanuphak 1987; Salo 1989; Staevska 2014); the duration of intervention was not explicitly stated in Hoxha 2011, but we categorised this as short-term on the basis of information given in the abstract report. One study (Weller 2013) was of very short duration (five hours). The remaining 55 studies were categorised as having an intermediate-term duration of intervention. None of the studies had an intervention period categorised as long-term.

Comparisons

A total of 73 trials met our inclusion criteria. Of these, only 34 trials provided outcome data for the following comparisons.

- Loratadine 10 mg versus placebo (Belaich 1990; Monroe 1992).
- Loratadine 10 mg versus cetirizine 10 mg (Patel 1997; Yin 2003b).
- Loratadine 10 mg versus desloratadine 5 mg (Gu 2002; Hao 2003; Zou 2002).
- Loratadine 10 mg versus mizolastine 10 mg (Guo 2003; Leynadier 2000; Liu 2003; Yin 2003b).
- Loratadine 10 mg versus emedastine 2 mg (Pons-Guiraud 2006).

- Loratadine 10 mg versus hydroxyzine 25 mg (Monroe 1992).
- Cetirizine 10 mg versus placebo (Breneman 1995; Breneman 1996; Go 1989; Kalivas 1990)..
- Cetirizine 10 mg versus hydroxyzine 25 mg (Breneman 1996; Kalivas 1990).
- Cetirizine 10 mg versus fexofenadine 180 mg (Handa 2004).
- Cetirizine 10 mg versus levocetirizine 5 mg (Yin 2003a).
- Cetirizine 10 mg versus mizolastine 10 mg (Yin 2003b).
- Desloratadine 5 mg to 20 mg versus placebo (Di Lorenzo 2004; Hoxha 2011; Monroe 2003; Nettis 2004; Ortonne 2007; Ring 2001).
- Hydroxyzine 25 mg versus placebo (Breneman 1996; Kalivas 1990; Monroe 1992).
- Levocetirizine 5 mg to 20 mg versus placebo (Hoxha 2011; Nettis 2006).
- Rupatadine 10 mg to 20 mg versus placebo (Gimenez-Arnau 2007).
- Desloratadine 5 mg to 20 mg versus levocetirizine 5 to 20 mg (Hoxha 2011; Potter 2009).
- Ebastine 10 mg versus placebo (Peyri 1991).
- Desloratadine 5 mg versus montelukast 10 mg (Di Lorenzo 2004).
- Fexofenadine 180 mg versus placebo (Kaplan 2005).
- Ketotifen 1 mg versus placebo (Phanuphak 1987).
- Cetirizine 5 mg and hydroxyzine 25 mg versus placebo (Wan 2009).
- Azelastine 2 mg versus azelastine 4 mg (Wu 2008).
- Doxepin 10 mg versus pheniramine 22.5 mg (Ghosh 1990).

A number of studies compared interventions that could not be included in our analyses because the outcomes measured did not fit our inclusion criteria.

- Acrivastine 4 mg, placebo, clemastine 1 mg (Leynadier 2000).
- Acrivastine 8 mg, chlorphen(ir)amine maleate 4 mg (Gale 1989).
- Acrivastine 8 mg, clemastine 1 mg, placebo (Juhlin 1987).
- Acrivastine 8 mg, hydroxyzine hydrochloride 20 mg (Salo 1989).
- Azelastine 2 mg, azelastine 4 mg, azelastine and cimetidine (H2RA) 2 mg (Wu 2008).
- Cetirizine 10 mg, placebo (Juhlin 1991).
- Cetirizine 10 mg plus placebo, terfenadine 60 mg, placebo (Go 1989; Kint 1989).
- Cetirizine 10 mg, terfenadine 120 mg, placebo (Garavaglia 1995).
- Cetirizine 10 mg, placebo (cross-over) (Goh 1991); non-cross-over (Alomar 1990a).
- Cetirizine 10 mg versus rupatadine 10 mg (Dakhale 2014).
- Chlorphen(ir)amine 4 mg, chlorphen(ir)amine 4 mg plus cimetidine 400 mg (H1 + H2 antagonist), placebo (Marks 1980)
- Cimetidine 200 mg plus chlorphen(ir)amine 4 mg, chlorphen(ir)amine 4 mg plus placebo, placebo (Commens 1978).
- Desloratadine 5 mg, placebo (Bronsky 2001; Monroe 2003; Ortonne 2004; Ortonne 2007Ring 2001).
- Desloratadine 5 mg, desloratadine 10 mg, desloratadine 20 mg (NCT00536380).
- Desloratadine 5 mg, desloratadine 20 mg (Weller 2013).
- Desloratadine 5 mg and placebo, desloratadine 5 mg and montelukast 10 mg, placebo (Nettis 2004).
- Fexofenadine 60 mg, 120 mg, 180 mg and 240 mg; placebo (Paul 1988).
- Fexofenadine 60 mg, placebo (Thompson 2000 Study 1; Thompson 2000 Study 2).
- Fexofenadine HCl 180 mg, levocetirizine 5 mg (Godse 2007).
- Fexofenadine HCl 20 mg, 60 mg,120 mg and 240 mg; placebo (Finn 1999; Nelson 2000).
- Fexofenadine 180 mg, placebo (Degonda 2002).
- Hydroxyzine plus terbutaline (beta agonist) (25 mg plus 5 mg), hydroxyzine plus cyproheptadine (25 mg plus 4 mg), hydroxyzine plus chlorphen(ir)amine (25 mg plus 4 mg), hydroxyzine plus cimetidine (H2RA) (25 mg plus 300 mg), hydroxyzine plus placebo (25 mg) (Harvey 1981).
- Ketotifen 1 mg, fluoxetine 20 mg (selective serotonin reuptake inhibitor-type antidepressant) (Sener 1999).
- Levocetirizine 5 mg, bilastine 20 mg (Zuberbier 2010).
- Levocetirizine 5 mg, desloratadine 5 mg (Potter 2009).
- Levocetirizine 20 mg, levocetirizine 15 mg plus hydroxyzine 50 mg (Staevska 2014).
- Loratadine 10 mg, levocetirizine 5 mg (Anuradha 2010).
- Loratadine 10 mg, placebo (Monroe 1988).
- Mizolastine 10 mg, loratadine 10 mg, placebo (Dubertret 1999).
- Mizolastine 10 mg, placebo (Brostoff 1996; Ollert 1999).
- Mizolastine 10 mg in decreasing dose, mizolastine 10 mg daily (Wang 2012).
- Nifedipine 10 mg, chlorphen(ir)amine 4 mg (Liu H-N 1990).
- Olopatadine 10 mg, olopatadine 5 mg, no medication (Makino 2012).
- Oxatomide 30 mg, clemastine 1 mg (Beck 1985).
- Oxatomide gel 5%, dechlorpheniramine cream (Locci 1991).
- Rupatadine 10 mg, levocetirizine 5 mg (Maiti 2011).
- Rupatadine 10 mg, rupatadine 20 mg, placebo (Gimenez-Arnau 2007).
- Rupatadine 5 mg, rupatadine 10 mg, rupatadine 20 mg, placebo (Dubertret 2007).
- Terfenadine 60 mg, clemastine 1 mg, placebo (Hjorth 1988).
- Terfenadine 60 mg, chlorphen(ir)amine 4 mg, placebo

(Grant 1988).

Outcomes

Timing of outcome assessment varied considerably. Studies reported outcomes assessed at baseline and at the end of the intervention period, with interim outcome assessments performed in some studies. If a study reported serial times of duration of intervention for the same participants, to reduce bias, we summarised these only at the latest time point.

Nine studies reported outcomes measured after the treatment period had ended (Di Lorenzo 2004; Ghosh 1990; Go 1989; Nettis 2006; Pons-Guiraud 2006; Potter 2009; Thompson 2000 Study 1; Thompson 2000 Study 2; Yin 2003b).

Outcomes included measures of weals, redness and itching assessed through both participant diaries or reports and clinician assessments, as well as size of weals and assessment of redness based on visual analogue scales. Numbers of participants experiencing improvement or cessation of symptoms were also reported.

Few of the studies directly reported our prespecified review outcomes (Objectives).

Few studies reported quality of life measures: Degonda 2002 provided participant-assessed summaries of changes in quality of life, and Maiti 2011 provided modified Dermatology Life Quality Index (DLQI) scores. Nettis 2004 and Nettis 2006 also provided quality of life assessment based on the DLQI. Potter 2009 reported the results of a self-administered DLQI questionnaire; Staevska 2014 and Zuberbier 2010 also reported DLQI results. Ortonne 2007 reported disruption of sleep and daily activities, and Staevska 2014 reported effects on quality of nighttime sleep. Thompson 2000 Study 1 and Thompson 2000 Study 2 commented on significant improvements in DLQI with fexofenadine.

Excluded studies

We excluded 169 studies. These consisted of studies that described only chronic urticaria unless the text mentioned or provided details that confirmed a diagnosis of chronic spontaneous or idiopathic or ordinary urticaria. Studies that were conducted with only terfenadine or astemizole were excluded because the medications had already been withdrawn for safety reasons. Further details can be found in Characteristics of excluded studies.

Ongoing studies and studies awaiting assessment

We identified 14 ongoing studies through our searches of clinical trials databases. Further details may be found in the Characteristics of ongoing studies tables. Data from these studies if available will be included in future updates of the review.

We identified 16 studies awaiting assessment, because we were unable to obtain full-text copies at the time of writing of this review. Further details are available in the tables of Characteristics of studies awaiting classification.

Risk of bias in included studies

In this review, we included 'Risk of bias' assessments. Please see Figure 2, which shows our judgements about each 'Risk of bias' item expressed as percentages of included studies in each category of risk, and Figure 3, which shows the judgement for each domain by study. When 'Risk of bias' information was missing from the trial report, we contacted the principal investigators of studies published from 2001 onwards to ask for missing information.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

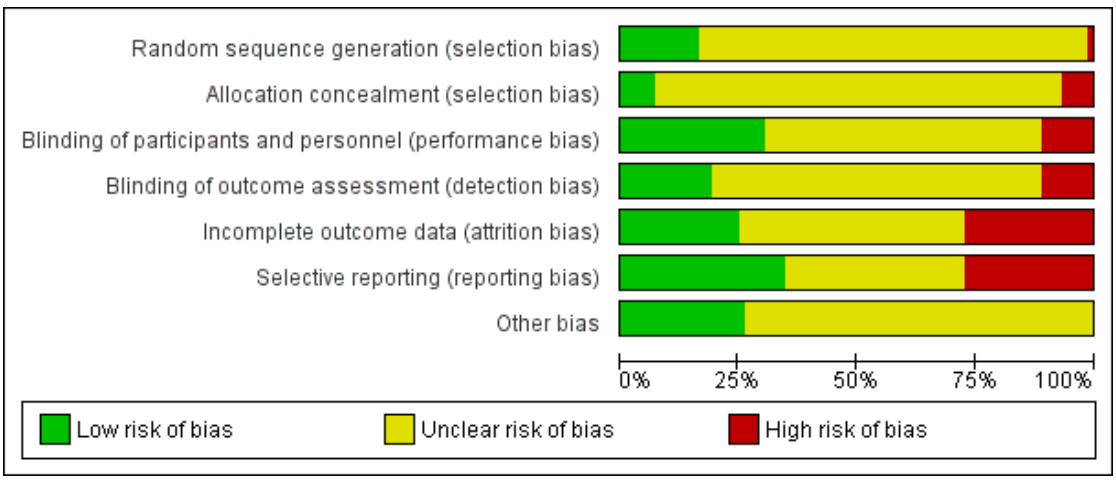
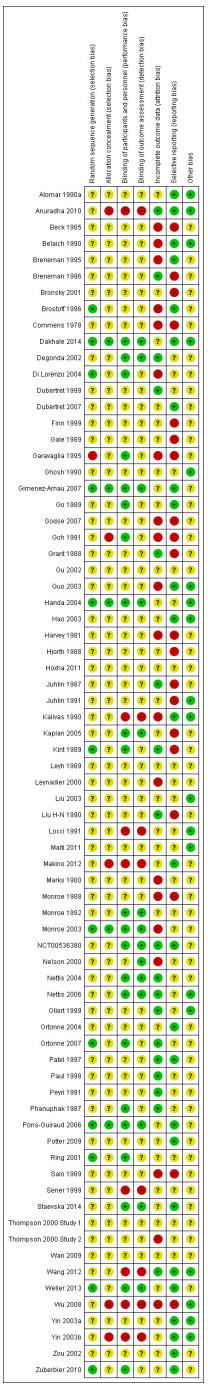


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



For studies with items judged as 'unclear,' we requested clarification from trial investigators, but no further information was forthcoming at the time that this review was prepared. No study provided complete clarity on every item in our 'Risk of bias' assessment, indicating widespread suboptimal reporting of methodology or results. Of the 73 included studies, 37 (50%) had at least one domain that we rated as at high risk of bias.

Allocation

The randomisation process and concealment of allocation are the most important and sensitive indicators that bias has been minimised in clinical trials. In one of the included studies (Garavaglia 1995), we assessed risk of bias as high, as the report of the study stated that the participant group was "randomly divided (by triplets) into three groups," using a preestablished randomisation list. As participants who dropped out were replaced with new participants, it is unclear whether the trial design is truly randomised, and whether new participants were randomly assigned de novo or were assigned to the group of the most recent dropout. We were unable to obtain further information from trial investigators to clarify this. Among all 73 included studies, only 12 (Brostoff 1996; Dakhale 2014; Di Lorenzo 2004; Gimenez-Arnau 2007; Handa 2004; Kint 1989; Monroe 2003; Ortonne 2007; Pons-Guiraud 2006; Ring 2001; Weller 2013; Zuberbier 2010) clearly described adequate randomisation methods. For the rest, the method of randomisation was not described or was unclear, and either we were unable to obtain further information or the trial was published before 2001 and we did not attempt to do so.

Five studies demonstrated adequate concealment of allocation using codes sealed within envelopes (Dakhale 2014; Gimenez-Arnau 2007; Handa 2004; Monroe 2003; Pons-Guiraud 2006). We assessed five of the studies to be at high risk of bias, as no attempt to conceal allocation was made (Anuradha 2010; Goh 1991; Makino 2012; Wu 2008; Yin 2003b). (Of these, Anuradha 2010; Wu 2008 and Yin 2003b were explicitly open-label trials).

Blinding

Eight studies (Anuradha 2010; Kalivas 1990; Locci 1991; Makino 2012; Sener 1999; Wang 2012; Wu 2008; Yin 2003b) did not blind participants or personnel to the intervention being studied so were classed at high risk of bias. Twenty-two studies (Dakhale 2014; Degonda 2002; Di Lorenzo 2004; Garavaglia 1995; Gimenez-Arnau 2007; Go 1989; Goh 1991; Handa 2004; Kaplan 2005; Kint 1989; Monroe 1992; Monroe 2003; NCT00536380; Nettis 2004; Nettis 2006; Ortonne 2007; Phanuphak 1987; Pons-Guiraud 2006; Ring 2001; Staevska 2014; Weller 2013; Zuberbier 2010) adequately blinded participants and personnel to the intervention so were judged at low risk of bias. In the remaining 45, it was unclear whether blinding was adequate. In Goh 1991, participants appear to have been adequately blinded as to the identity of the medication studied.

Only 14 of the included trials demonstrated adequate blinding of outcome assessment (Dakhale 2014; Degonda 2002; Di Lorenzo 2004; Gimenez-Arnau 2007; Handa 2004; Kaplan 2005; Monroe 1992; Monroe 2003; Nelson 2000; Nettis 2004; Nettis 2006; Pons-Guiraud 2006; Staevska 2014; Weller 2013); eight studies did not attempt this and were judged at high risk of bias (Anuradha 2010; Kalivas 1990; Locci 1991; Makino 2012; Sener 1999; Wang 2012; Wu 2008; Yin 2003b). For the remaining 51 studies, we rated risk of bias due to blinding of outcome assessment as unclear.

Incomplete outcome data

Some study investigators analysed their study data to show that the numbers of participants who dropped out or were withdrawn were not significantly different from the numbers analysed, but this did not mean that bias was absent, as there may have been imbalance between groups, or the reasons for dropout might have differed between groups (e.g. adverse events, lack of efficacy).

The high rate of attrition in the included trials was a problem and a potential source of bias. In 20 trials, the distribution or high number of dropouts or losses to follow-up could have introduced bias (Beck 1985; Belaich 1990; Breneman 1995; Brostoff 1996; Commens 1978; Di Lorenzo 2004; Garavaglia 1995; Godse 2007; Goh 1991; Guo 2003; Harvey 1981; Kalivas 1990; Leynadier 2000; Marks 1980; Monroe 1988; Monroe 2003; Nelson 2000; Salo 1989; Thompson 2000 Study 2; Wu 2008); we rated these as at high risk).

A high level of dropout was a feature of seven of the included studies. In Brostoff 1996 51% of participants failed to complete the study, and Breneman 1995 had 27.3% dropouts; in Commens 1978 24% dropped out. In the four-arm study of Di Lorenzo 2004, 38.8% of participants overall dropped out after randomisation with high losses to follow-up, particularly in the placebo group (88%) and the montelukast group (68%). Garavaglia 1995 experienced high levels of dropout and recruited additional participants into the trial in an attempt to compensate. In Monroe 2003 19% dropped out of the desloratadine group and 31% from the placebo group. A total of 34% dropped out from the Salo 1989 study.

Eighteen studies were rated as having low risk of attrition bias (Anuradha 2010; Breneman 1996; Degonda 2002; Dubertret 1999; Grant 1988; Juhlin 1987; Kint 1989; Liu H-N 1990; NCT00536380; Nettis 2004; Nettis 2006; Ollert 1999; Ortonne 2007; Patel 1997; Paul 1998; Peyri 1991; Phanuphak 1987; Wang 2012). In many trials, attrition data were poorly reported or were

absent; despite our attempts to request further information from trial investigators, we judged the remaining 35 as having unclear risk of bias.

Selective reporting

We judged that 24 studies were at low risk of bias (Alomar 1990a; Anuradha 2010; Belaich 1990; Breneman 1995; Brostoff 1996; Dakhale 2014; Dubertret 2007; Gimenez-Arnau 2007; Go 1989; Guo 2003; Hao 2003; Kalivas 1990; Makino 2012; NCT00536380; Nettis 2004; Nettis 2006; Ortonne 2007; Patel 1997; Phanuphak 1987; Pons-Guiraud 2006; Ring 2001; Staevska 2014; Weller 2013; Zuberbier 2010).

We judged that 20 studies could have introduced an element of bias through selective outcome reporting (Beck 1985; Breneman 1996; Bronsky 2001; Commens 1978; Finn 1999; Gale 1989; Garavaglia 1995; Godse 2007; Goh 1991; Grant 1988; Harvey 1981; Hjorth 1988; Juhlin 1987; Juhlin 1991; Kaplan 2005; Kint 1989; Liu H-N 1990; Monroe 1988; Salo 1989; Wu 2008). Specifically, in Beck 1985 and in Breneman 1996, outcomes were reported only in graph form or by percentage and statistical difference (with no participant numbers stated). Similarly, in Commens 1978, Gale 1989 and Godse 2007, the results for numbers of participants in each group were not reported-only mean scores with standard deviations. In Grant 1988 and Hjorth 1988, results were presented in graph form only. In Monroe 1988 only percentages and P values were given, and the origin of the P values was not stated. Salo 1989 provided only mean scores, and investigators offered a subjective judgement as to the best treatment. In Bronsky 2001 scores were given on different days; Harvey 1981 did not report adverse event results; and in Finn 1999 the analysis included results only for participants with baseline and at least one post-baseline mean pruritus score, thus a true intention-to-treat analysis was not provided. Juhlin 1987 states that both physician and participant self-assessments were carried out, but the study report provides only participant perceptions with no objective data. In Juhlin 1991, extensive laboratory tests were carried out (for adverse events) but were not reported. Kaplan 2005 combined DLQI score results from two weeks and four weeks and did not provide separate scores for each time point; as we were unable to obtain the disaggregated data, we could not use these conflated interim and endpoint outcome results. Kint 1989 did not report results clearly, and as rescue medication was permitted, we could not be sure that any benefits were due to the study medications. We were unable to determine the duration of follow-up in Liu H-N 1990, and it was unclear whether concomitant medications were permitted, or whether study participants were compliant. Garavaglia 1995 reported no results for the placebo arm.

For the remaining 29 studies, information was insufficient to allow a judgement to be reached; we rated these as having unclear risk of bias for this domain.

Other potential sources of bias

We assessed whether each study appeared to be free of other sources of bias that could put it at high risk of bias (e.g. potential conflicts of interest, pharmaceutical funding or support). We judged studies as having unclear risk when the extent to which other factors may have introduced bias could not be determined. Of the 73 included studies, most reports were unclear in terms of other bias (Figure 2). This was the result of insufficient information to assess whether risk of bias existed in some studies (Bronsky 2001; Hoxha 2011; Marks 1980; Monroe 1988; Ortonne 2004; Sener 1999; Staevska 2014), or it reflected baseline imbalance between groups (e.g. Breneman 1995; Finn 1999). In the remaining studies judged as unclear, potential bias may have been present in the form of industry sponsorship and funding.

A total of 19 studies for which no funding or sponsorship was declared were assessed as having low risk of bias, as we detected no other bias.

Effects of interventions

See: **Summary of findings for the main comparison** Cetirizine 10 to 20 mg versus placebo for chronic spontaneous urticaria; **Summary of findings 2** Desloratadine 5 to 20 mg versus placebo for chronic spontaneous urticaria; **Summary of findings 3** Levocetirizine 5 to 20 mg versus placebo for chronic spontaneous urticaria; **Summary of findings 4** Rupatadine 10 to 20 mg versus placebo for chronic spontaneous urticaria; **Summary of findings 5** Loratadine 10 mg versus placebo for chronic spontaneous urticaria; **Summary of findings 6** Loratadine 10 mg versus cetirizine 10 mg for chronic spontaneous urticaria; **Summary of findings 7** Loratadine 10 mg versus desloratadine 5 mg for chronic spontaneous urticaria; **Summary of findings 8** Loratadine 10 mg versus mizolastine 10 mg for chronic spontaneous urticaria; **Summary of findings 9** Loratadine 10 mg versus emedastine 2 mg for chronic spontaneous urticaria; **Summary of findings 10** Loratadine 10 mg versus hydroxyzine 25 mg for chronic spontaneous urticaria; **Summary of findings 11** Cetirizine 10 mg versus hydroxyzine 25 mg for chronic spontaneous urticaria; **Summary of findings 12** Hydroxyzine 25 mg versus placebo for chronic spontaneous urticaria

We have indicated in this section when our 23 comparisons of interventions addressed our prespecified outcomes (for details of outcomes, please see Types of outcome measures).

Numbers given show the total numbers of participants included in the analysis. When it was possible to calculate an effect size, we reported this with the 95% confidence interval. When the calculated effect size was statistically significant (P value < 0.05), we stated whether the result favoured the intervention group or the control condition. In the text below, an I^2 statistical value for heterogeneity is reported as high if it exceeds 50%.

We have summarised the results of included studies that could not be combined in meta-analyses because of differences between

studies in terms of design. We present the results of studies that could not be pooled in meta-analyses using data and information derived from the reports of individual studies (along with P values when applicable).

Comparison 1

Loratadine 10 mg versus placebo

Two studies that compared these interventions were identified (Belaich 1990; Monroe 1992). Both studies reported short-term and intermediate-term interventions that favoured loratadine.

Primary outcome 2: proportion of participants with 'good' or 'excellent' response whilst taking H1-antihistamines

Short-term duration of intervention

In this subgroup we found only one relevant trial (Monroe 1992) (n = 12, risk ratio (RR) 3.0, 95% confidence interval (CI) 0.42 to 21.3; Analysis 1.1) (no statistically significant difference).

Intermediate-term duration of intervention

In this subgroup we found only one relevant trial (Belaich 1990) (n = 112, RR 1.73, 95% CI 0.81 to 3.72) (no statistically significant difference). The study report states that 22/60 (loratadine) and 5/52 (placebo) participants experienced complete cessation of urticaria following an intermediate-term duration of the intervention and that loratadine was significantly more effective than placebo (P value < 0.01).

Our meta-analysis of Monroe 1992 and Belaich 1990, combining data from short- and intermediate-term durations of intervention (n = 124), found that loratadine may increase the chance that a participant will experience a good response, expressed as RR of 1.86 (95% CI 0.91 to 3.79; P value 0.09; I^2 = 0%; Analysis 1.1), but this difference was not statistically significant.

Comparison 2

Loratadine 10 mg versus cetirizine 10 mg

Two studies that compared these interventions were identified (Patel 1997; Yin 2003b) (n = 103). The individual studies reported similar proportions of participants with complete suppression of urticaria.

Primary outcome 1: proportion of participants with complete suppression of urticaria whilst taking H1-antihistamines

Short-term duration of intervention

In this subgroup we found only one relevant trial (Patel 1997). No statistically significant difference between groups was noted (RR 1.13, 95% CI 0.64 to 2.01; participants = 37; I^2 = 0%); Analysis 2.1).

Intermediate-term duration of intervention

In this subgroup we found only one relevant trial (Yin 2003b). No statistically significant difference between groups was noted (RR 1.01, 95% CI 0.69 to 1.47; participants = 66; I^2 = 0%; Analysis 2.1).

Overall, combining data from both studies (RR 1.05, 95% CI 0.76 to 1.43; n = 103; I^2 = 0%); Analysis 2.1) yielded no evidence of a difference in rates of complete cessation of urticaria. Data from Yin 2003b showed that an additional proportion of participants experienced at least a good response following treatment with either drug (10/32 in the loratadine arm and 11/34 in the cetirizine arm).

Comparison 3

Loratadine 10 mg versus desloratadine 5 mg

Three studies that compared these interventions were identified (Gu 2002; Hao 2003; Zou 2002). Zou 2002 reported no significant differences in efficacy between desloratadine 5 mg once daily for four weeks and loratadine 10 mg once daily for four weeks.

Primary outcome 1: proportion of participants with complete suppression of urticaria whilst taking H1-antihistamines

Intermediate-term duration of intervention

Individual studies reported similar proportions of participants with complete suppression of urticaria. Comparing loratadine with desloratadine (Gu 2002; Hao 2003) revealed no significant differences between loratadine 10 mg and desloratadine 5 mg for complete suppression of disease (RR 0.91, 95% CI 0.78 to 1.06; P value 0.22; I^2 = 0%; Analysis 3.1).

Primary outcome 2: proportion of participants with 'good' or 'excellent' response whilst taking H1-antihistamines

Intermediate-term duration of intervention

In this subgroup we found three relevant trials (Guo 2003; Hao 2003; Zou 2002) (n = 410). Individual studies reported similar proportions of participants with at least good response to treatment. No significant differences between loratadine 10 mg and desloratadine 5 mg were noted (RR 1.04, 95% CI 0.64 to 1.71; Analysis 3.2), and moderate heterogeneity was exhibited (I^2 = 40%; P value 0.191).

Primary outcome 3: proportion of participants with 50% or greater improvement in quality of life measurements whilst taking H1-antihistamines

Hao 2003 reported that at four weeks, 16/106 (loratadine) and 9/105 (desloratadine) participants described at least 50% improvement in quality of life (QoL) (P value 0.25).

Secondary outcome 2: minor participant-reported adverse events not requiring withdrawal of treatment

All three studies (Guo 2003; Hao 2003; Zou 2002) individually concluded that desloratadine was a safe and effective treatment for CSU. However, we were unable to pool data on adverse events in a meta-analysis. Desloratadine was found to be at least as effective as loratadine in each individual study but was not compared with placebo. Therefore it may be the case that desloratadine is as effective as loratadine, but this is assumed through speculative non-superiority to loratadine.

We were unable to combine adverse effect data in a meta-analysis because the study reports are unclear about the number of participants presenting with adverse effects in each group at each time point. Zou 2002 reported that in the desloratadine group, four participants had side effects: one severe headache, one dry mouth and two sleepiness. In the loratadine group, one participant had dry mouth and three experienced sleepiness. Hao 2003 reported that adverse effect rates of desloratadine and loratadine were 11.32% and 13.21%, respectively. The main side effects included dry mouth, dizziness and headache. Gu 2002 reported that no serious adverse effects were recorded for the duration of the study.

Comparison 4

Loratadine 10 mg versus mizolastine 10 mg

Four studies that compared these interventions were identified (Guo 2003; Leynadier 2000; Liu 2003; Yin 2003b).

The authors of Guo 2003 reported that scores for pruritus and weal number, size and persistence in the mizolastine group were much lower than those in the loratadine group (P value < 0.05). They concluded that mizolastine could be considered the preferred treatment for CSU (Guo 2003).

Primary outcome 1: proportion of participants with complete suppression of urticaria whilst taking H1-antihistamines

Intermediate-term duration of intervention

In this subgroup we found three relevant trials (Guo 2003; Liu 2003; Yin 2003b) (n = 316). These studies reported similar proportions of participants with complete suppression of urticaria, and no significant difference between loratadine 10 mg and mizolastine 10 mg was noted (RR 0.86, 95% CI 0.64 to 1.16; Analysis 4.1); heterogeneity was substantial (I^2 = 55%; P value 0.11; Analysis 4.1).

Primary outcome 2: proportion of participants with 'good' or 'excellent' response whilst taking H1-antihistamines

These three studies also reported the proportions of participants experiencing at least a good response to treatment. In comparing loratadine with mizolastine, we found no significant differences between loratadine 10 mg and mizolastine 10 mg (RR 0.88, 95% CI 0.55 to 1.42; Analysis 4.2; P value 0.78; I^2 = 0%).

Primary outcome 3: proportion of participants with 50% or greater improvement in quality of life measurements whilst taking H1-antihistamines

Intermediate-term duration of intervention

In this subgroup we found two relevant trials (Guo 2003; Liu 2003) (n = 252). These studies reported the proportions of participants who experienced improvement in QoL of at least 50%. This amounted to 26/125 and 13/127 (loratadine and mizolastine, respectively). No significant difference between loratadine 10 mg and mizolastine 10 mg was reported in either study; when data were pooled (RR 3.21, 95% CI 0.32 to 32.33; Analysis 4.3), important levels of heterogeneity were noted (Chi^2 = 2.86; df = 1; P value 0.091; I^2 = 65%).

Secondary outcome 1: serious adverse events (i.e. serious enough to require withdrawal of treatment)

Liu 2003 reported that the incidences of adverse events for mizolastine and loratadine were 28.6% and 25.5%, respectively; no statistically significant differences between the two groups were noted (Chi^2 = 0.25; P value 0.62).

Leynadier 2000 reported minor adverse events requiring withdrawal: in the mizolastine group, fatigue (n = 2) and drowsiness (n = 1); in the loratadine group, drowsiness (n = 1), dizziness (n = 1) and rhinitis (n = 1).

Guo 2003 reported that data on one participant were excluded from the analysis, but it is unclear whether this occurred because of withdrawal due to adverse effects. No clear data about adverse effects were presented, although study authors noted that no differences between the two groups were noted. Adverse effects included dry mouth, sleepiness and lethargy, but the numbers in each group experiencing these effects were not stated.

Intermediate-term duration of intervention

Two studies (Leynadier 2000; Liu 2003) reported the numbers of participants who experienced an adverse event that led to withdrawal: One participant in the mizolastine group in Liu 2003 had severe diarrhoea, and one in Leynadier 2000 had painful erythema of the hands. In comparing loratadine with mizolastine in 267 participants, we found no significant differences between loratadine 10 mg and mizolastine 10 mg (RR 0.38, 95% CI 0.04 to 3.6; P value 0.40; I^2 value 0%; Analysis 4.4) in terms of the numbers of participants withdrawing because of an adverse event.

Comparison 5

Loratadine 10 mg versus emedastine 2 mg

We report the results of our analysis of a single study for this comparison (Pons-Guiraud 2006).

The study report states that the key finding was that no significant differences between treatments at four weeks were noted by investigators or participants. Mean symptom scores improved significantly from baseline in both groups. The study authors state: "Also the proportion of patients with no symptoms at the end of treatment was similar (emedastine 52.4% versus loratadine 54.5% P = 0.41) and so was the proportion of patients with mild symptoms (total score $\leq$ 8) (emedastine 92.9% versus loratadine 96.1% P = 0.37)"; they also comment: "After 28 days of treatment mean symptom scores recorded in patients improved significantly versus baseline both with emedastine and loratadine (both P < 0.00005, t test for paired samples). No significant difference between groups was found (P = 0.48 for intensity of erythema, P = 0.30 for number of hives, P = 0.39 for size of the largest hive, P = 0.45 for the extent of the skin area involved and P = 0.19 for the overall assessment of urticaria symptoms)."

Primary outcome 1: proportion of participants with complete suppression of urticaria whilst taking H1-antihistamines

Intermediate-term duration of intervention

Among 161 participants after four weeks of therapy in Pons-Guiraud 2006, no difference between loratadine 10 mg and emedastine 2 mg was noted for complete cessation of urticaria (RR 1.04, 95% CI 0.78 to 1.39; Analysis 5.1).

Primary outcome 2: proportion of participants with 'good' or 'excellent' response whilst taking H1-antihistamines

Intermediate-term duration of intervention

Among 160 participants after four weeks of therapy in Pons-Guiraud 2006, no difference between loratadine 10 mg and emedastine 2 mg was noted for good or excellent response (RR 1.09, 95% CI 0.96 to 1.24; Analysis 5.2).

Secondary outcome 1: serious adverse events (i.e. serious enough to require withdrawal of treatment)

Intermediate-term duration of intervention

In an analysis of 161 participants in total, one participant in each group withdrew because of adverse effects. The study report states: "Two patients were withdrawn because of serious adverse events: a suicide attempt not related to study treatment (loratadine) and a bilateral fracture of the calcaneum following a fall, which led to hospitalisation, in the emedastine group. Although the patient who fell was taking a number of medicinal products besides emedastine (paracetamol, hydroxyzine, enoxaparin, ketoprofen and omeprazole), the causal relationship with emedastine was not ruled out and considered possible."

In our analysis, no statistically significant differences between groups were noted (RR 1.09, 95% CI 0.07 to 17.14; Analysis 5.3).

Comparison 6

Loratadine 10 mg versus hydroxyzine 25 mg

Primary outcome 1: proportion of participants with complete suppression of urticaria whilst taking H1-antihistamines

Short-term duration of intervention

One study that compared these interventions was identified (Monroe 1992). The number of participants who experienced marked or complete relief of symptoms was 3/6 with loratadine and 3/6 with hydroxyzine (RR 1.00, 95% CI 0.32 to 3.10; Analysis 6.1).

This study reported that total symptoms score value decreased by 43% in the loratadine group and by 47% in the hydroxyzine group, although actual mean scores for each group were not reported.

Secondary outcome 2: minor participant-reported adverse events not requiring withdrawal of treatment

Overall in Monroe 1992, eight of 20 participants in the hydroxyzine group and one of 20 in the loratadine group (some with dermatitis rather than CSU) reported sedation, a minor adverse event that did not require withdrawal of the drug; the study report states that differences between groups were significant (P value 0.02).

Comparison 7

Cetirizine 10 mg versus placebo

Four studies that compared these interventions were identified (Breneman 1995; Breneman 1996; Go 1989; Kalivas 1990).

Primary outcome 1: proportion of participants with complete suppression of urticaria whilst taking H1-antihistamines

Short-term duration of intervention

In this subgroup we found only one relevant trial (Go 1989) (n = 56). A statistically significant difference between cetirizine 10 mg to 20 mg and placebo was reported (RR 2.80, 95% CI 1.17 to 6.73; Analysis 7.1).

Intermediate-term duration of intervention

In this subgroup we found only one relevant trial (Breneman 1995) (n = 122). A statistically significant difference between cetirizine 10 mg to 20 mg and placebo was reported (RR 2.66, 95% CI 1.2 to 5.9; Analysis 7.1).

Meta-analysis

Combining the results of two studies across short-term and Intermediate-term durations of intervention revealed that 32/88 and 12/90 participants experienced complete cessation of urticaria following treatment (cetirizine and placebo, respectively) (RR 2.72, 95% CI 1.51 to 4.91; P value < 0.001; I^2 = 0%; Analysis 7.1). Thus, strong evidence showed that cetirizine increased the chance of complete cessation of disease.

Primary outcome 2: proportion of participants with 'good' or 'excellent' response whilst taking H1-antihistamines

One study (Breneman 1995) reported that at least a good response following treatment was seen in 45/60 and 29/62 participants (cetirizine and placebo, respectively) (P value 0.001).

Secondary outcome 1: serious adverse events (i.e. serious enough to require withdrawal of treatment)

Intermediate-term duration of intervention

In this subgroup we found two relevant trials (Breneman 1995; Breneman 1996) (n = 247). No significant differences between cetirizine 10 mg to 20 mg and placebo were reported (RR 4.6, 95% CI 0.79 to 26.67; Analysis 7.2).

Intermediate-term duration of intervention

In this subgroup we found only one relevant trial (Kalivas 1990) (n = 142). No significant differences between cetirizine 10 mg to 20 mg and placebo were reported (RR 1.06, 95% CI 0.07 to 16.59; Analysis 7.2).

Meta-analysis

These three studies (Breneman 1995; Breneman 1996; Kalivas 1990) of 389 participants in total, reported that seven participants withdrew because of adverse events whilst taking cetirizine, and two withdrew whilst taking placebo (RR 3.00, 95% CI 0.68 to 13.22; P value 0.15; I^2 = 0%; Analysis 7.2). This does not constitute adequate evidence to suggest that cetirizine is associated with increased risk of withdrawal due to an adverse event.

Comparison 8

Cetirizine 10 mg versus hydroxyzine 25 mg

Efficacy was not reported in a form commensurate with the outcome measures of our review in either of the two studies that compared these interventions (Breneman 1996; Kalivas 1990).

Secondary outcome 1: serious adverse events (i.e. serious enough to require withdrawal of treatment)

Intermediate-term duration of intervention (cetirizine 10 mg)

In this subgroup we found only one relevant trial (Breneman 1996) (n = 123). No significant differences between cetirizine 10 mg and hydroxyzine 25 mg were noted (RR 1.05, 95% CI 0.27 to 4.01; Analysis 8.1).

Intermediate-term duration of intervention (cetirizine 5 mg to 25 mg)

In this subgroup we found only one relevant trial (Kalivas 1990) (n = 138). No significant differences between cetirizine 10 mg and hydroxyzine 25 mg were noted (RR 0.33, 95% CI 0.04 to 3.13; Analysis 8.1).

Meta-analysis

Both studies reported the numbers of participants who withdrew because of an adverse event. Combining the two (n= 260 participants) (RR of withdrawal 0.78, 95% CI 0.25 to 2.45; P value 0.67; I^2 = 0%; Analysis 8.1) revealed no evidence of a difference.

Comparison 9

Cetirizine 10 mg versus fexofenadine 180 mg

One study that compared these interventions was identified (Handa 2004). No analysis was possible for this comparison.

Primary outcome 1: proportion of participants with complete suppression of urticaria whilst taking H1-antihistamines

The key finding was that at four weeks, 27/59 participants in the cetirizine group had complete suppression of urticaria compared with 2/57 in the fexofenadine group (P value < 0.001). According to the study authors, partial improvement was seen in a further 19 participants in each group. No improvement was noted among six participants in the cetirizine group and 24 in the fexofenadine group.

Secondary outcome 2: minor participant-reported adverse events not requiring withdrawal of treatment

Minor adverse events noted in the cetirizine group included drowsiness (four), constipation (three), epigastric pain (two) and cough (two). In the fexofenadine group, drowsiness was experienced by two participants; headache, swollen feet and abdominal pain were reported by one participant.

Comparison 10

Cetirizine 10 mg versus levocetirizine 5 mg

One study that compared these interventions was identified (Yin 2003a). No analysis was possible for this comparison.

Primary outcome 1: proportion of participants with complete suppression of urticaria whilst taking H1-antihistamines

This study reported that 16/22 and 19/22 participants had complete suppression of urticaria following treatment with cetirizine and levocetirizine, respectively, at 28 days (P value 0.309). A further two participants had at least a good response to cetirizine and one to levocetirizine, but without complete clearance. Overall there was no statistically significant difference in clinical efficacy between the two groups was noted (P value > 0.05).

Secondary outcome 1: serious adverse events (i.e. serious enough to require withdrawal of treatment)

No participants withdrew from this study as the result of an adverse event.

Comparison 11

Cetirizine 10 mg versus mizolastine 10 mg

One study that compared these interventions was identified (Yin 2003b). No analysis was possible for this comparison.

Primary outcome 1: proportion of participants with complete suppression of urticaria whilst taking H1-antihistamines

This study reported that 21/34 and 20/30 participants had complete suppression of urticaria following treatment with cetirizine and mizolastine, respectively (P value 0.600). This study also reported that a further 11/34 and 9/30 had a good response to treatment.

Comparison 12

Desloratadine 5 mg to 20 mg versus placebo

Six studies that compared these interventions were identified (Di Lorenzo 2004; Hoxha 2011; Monroe 2003; Nettis 2004; Ortonne 2007; Ring 2001). Ortonne 2007 did not provide outcome data on efficacy that could be included in our meta-analyses.

Primary outcome 1: proportion of participants with complete suppression of urticaria whilst taking H1-antihistamines

Two studies (Di Lorenzo 2004; Hoxha 2011) reported on complete suppression of urticaria. A short-term duration of intervention was used in one study (Hoxha 2011), which investigated three doses compared with placebo and reported that 4/34, 11/34, 21/34 and 0/36 (desloratadine 5 mg, 10 mg and 20 mg and placebo) achieved resolution of symptoms. Following an intermediate-term duration of intervention, one study (Di Lorenzo 2004) reported complete suppression of urticaria in 18/40 (desloratadine 5 mg) and 0/40 (placebo) (additional data supplied by investigator); the report of the study states that the difference between the total symptom scores for the desloratadine and placebo groups was statistically significant (P value < 0.001).

These data from Hoxha 2011 suggest an association between dosage and an increased chance of complete suppression of urticaria. We did not pool data across all dosages and durations of intervention (Analysis 9.1), but as no participants allocated to placebo exhibited suppression of urticaria, Fisher's exact test was used to compare the two interventions (53/142 desloratadine and 0/76 placebo), resulting in a 95% CI for the odds ratio (OR) of between 7.12 and infinity (P value < 0.001),

Additional data obtained from the principal investigator of Di Lorenzo 2004 revealed that 22/40 in the intervention group and 0/40 in the placebo group experienced an 'excellent' response (P value < 0.001).

Primary outcome 3: proportion of participants with 50% or greater improvement in quality of life measurements whilst taking H1-antihistamines

The numbers of participants who exhibited improvement in QoL (Ortonne 2007) were 34/49 and 23/36 in the desloratadine 5 mg and placebo groups, respectively. The study report states: "Desloratadine treatment was associated with significantly greater improvements from baseline to day 42 compared with placebo in DLQI overall score (-6 versus -2.2 points; P < 0.002) and VQ-Dermato score (18.5 versus 29.1 points; P = 0.009)."

Secondary outcome 1: serious adverse events (i.e. serious enough to require withdrawal of treatment)

Intermediate-term duration of 5 mg of intervention

In this subgroup we found three relevant trials (n = 466).

Three studies (Monroe 2003; Nettis 2004; Ring 2001) of 466 participants, reported similar numbers of participants who withdrew as the result of adverse events, totalling 6/236 and 4/230 (desloratadine 5 mg and placebo, respectively). No significant difference between desloratadine 5 mg and placebo were noted (RR 1.46, 95% CI 0.42 to 5.1; Analysis 9.2).

Differences between the three studies were examined: Monroe 2003 excluded participants with previous lack of response to antihistamines, but this exclusion criterion was not stated in the reports of Nettis 2004 and Ring 2001.

Comparison 13

Hydroxyzine 25 mg versus placebo

Three studies that compared these interventions were identified (Breneman 1996; Kalivas 1990; Monroe 1992). Efficacy was not reported in Breneman 1995 or Kalivas 1990 in a form commensurate with the outcome measures of our review.

Primary outcome 1: proportion of participants with complete suppression of urticaria whilst taking H1-antihistamines

Short-term duration of intervention

One study (Monroe 1992) stated that 3/6 and 1/6 participants exhibited at least a good response (marked or complete relief of symptoms) following treatment (hydroxyzine and placebo, respectively). After a reanalysis using Fisher's exact test because of the small number of participants, no difference between interventions was reported (P value 0.27).

The study report stated that for this outcome, differences between the placebo group and the two treated groups (hydroxyzine and

loratadine) were statistically significant (P value < 0.05). The small number of included participants limits firm conclusions that can be drawn from this outcome.

Secondary outcome 1: serious adverse events (i.e. serious enough to require withdrawal of treatment)

Intermediate-term duration of intervention

In a meta-analysis of Breneman 1996 and Kalivas 1990 (n = 270), the pooled RR was 3.64 (95% CI 0.77 to 17.23; P value 0.10; I^2 = 0%; Analysis 10.1). Therefore little evidence of differences between interventions was found.

Comparison 14

Levocetirizine 5 mg to 20 mg versus placebo

Two studies that compared these interventions were identified (Hoxha 2011; Nettis 2006).

Primary outcome 1: proportion of participants with complete suppression of urticaria whilst taking H1-antihistamines

Following a short-term duration of intervention, Hoxha 2011 reported complete suppression of urticaria as 9/37, 17/37, 30/37 and 0/37 (levocetirizine 5 mg, 10 mg, 20 mg and placebo). In one intermediate-term duration of intervention study (Nettis 2006), complete suppression was noted in 27/51 and 0/51 participants (levocetirizine 5 mg and placebo). No participants in the placebo arm achieved complete suppression of urticaria (Analysis 11.1). Analysis of the total counts was carried out with Fisher's exact test; the 95% CI for the OR was between 11.12 and infinity (P value < 0.001), suggesting that use of levocetirizine at least 5 mg increased the chance of complete suppression of CSU.

Secondary outcome 1: serious adverse events (i.e. serious enough to require withdrawal of treatment)

No withdrawals due to adverse events were seen in either arm following treatment (0/51 and 0/49, levocetirizine 5 mg and placebo; Nettis 2006). No serious adverse events were noted with levocetirizine (at any dose) in the study by Hoxha 2011.
No data are available on the adverse events that followed when a higher than standard dosage (10 mg and 20 mg per day) of levocetirizine was prescribed.

Comparison 15

Rupatadine 10 mg to 20 mg versus placebo

Primary outcome 2: proportion of participants with 'good' or 'excellent' response whilst taking H1-antihistamines

Intermediate-term duration of intervention (rupatadine 10 mg)

In this subgroup we found only one relevant trial (Gimenez-Arnau 2007) (n = 122). No significant difference between rupatadine 10 mg and placebo was reported (RR 1.28, 95% CI 0.86 to 1.91; Analysis 12.1).

Intermediate-term duration of intervention (rupatadine 20 mg)

In this subgroup we found only one relevant trial (Gimenez-Arnau 2007) (n = 123). No significant difference between rupatadine 20 mg and placebo was reported (RR 1.42, 95% CI 0.98 to 2.06; Analysis 12.1).

Meta-analysis

The pooled RR between rupatadine (at both doses) and placebo in 245 participants was 1.35 (95% CI 1.03 to 1.77; P value 0.03; I^2 = 0%; Analysis 12.1); thus rupatadine increased the chance of a good response, but little evidence was found to indicate that 10 mg is more effective than 20 mg.

Comparison 16

Desloratadine 5 mg to 20 mg versus levocetirizine 5 mg to 20 mg

Two studies that compared these interventions were identified (Hoxha 2011; Potter 2009). No meta-analysis was possible for this comparison.

Primary outcome 1: proportion of participants with complete suppression of urticaria whilst taking H1-antihistamines

In Hoxha 2011, a three-arm study, 107 participants were randomly assigned to double-blind treatment with levocetirizine, desloratadine or placebo (37/34/36). Treatment started at a dose of 5 mg

and then was increased weekly to 10 mg and 20 mg. The numbers of participants who exhibited complete suppression of urticaria following a week at each dose were as follows: 9/37, 17/37 and 30/37 (levocetirizine 5 mg, 10 mg and 20 mg) and 4/34, 11/34 and 21/34 (desloratadine 5 mg, 10 mg and 20 mg).

Primary outcome 2: proportion of participants with 'good' or 'excellent' response whilst taking H1-antihistamines

A total of 294/438 and 256/448 participants in Potter 2009 exhibited at least a good response following treatment with levocetirizine 5 mg and desloratadine 5 mg. The report of the study states that levocetirizine "Decreased pruritus duration and the mean CSU composite scores to a significantly greater extent than desloratadine during the first week (P=0.002 and 0.005, respectively) and over the entire study (P=0.009 and P<0.05, respectively)."

Secondary outcome 2: minor participant-reported adverse events not requiring withdrawal of treatment

No serious adverse effects occurred with desloratadine. The authors of Hoxha 2011 concluded that increasing the dose of either drug up to four-fold was beneficial without compromising safety, and that levocetirizine appeared to be more effective than desloratadine (P value < 0.02).

Comparison 17

Ebastine 10 mg versus placebo

One study that compared these interventions was identified (Peyri 1991).

Primary outcome 1: proportion of participants with complete suppression of urticaria whilst taking H1-antihistamines

In this study, 38/91 and 22/86 participants (ebastine and placebo, respectively) exhibited complete suppression of urticaria following an intermediate-term duration of intervention (Fisher's exact test P value 0.13). According to the investigators' assessment, overall efficacy was good or moderate in 76/95 participants (80%) treated with ebastine compared with 52/102 participants (51%) treated with placebo (P value < 0.001). Study investigators concluded that ebastine could be an affective alternative to other non-sedating antihistamines.

Secondary outcome 1: serious adverse events (i.e. serious enough to require withdrawal of treatment)

A similar number of participants in each group withdrew from this study because of an adverse event: 2/91 and 3/86 (ebastine and placebo, respectively; Fisher's exact test P value 0.68).

Comparison 18

Desloratadine 5 mg versus montelukast 10 mg

One study that compared these interventions was identified (Di Lorenzo 2004). No analysis was possible for this comparison.
In the desloratadine group, 18/40 achieved complete suppression of CSU and 22/40 had an excellent response, whilst in the montelukast group, 4/40 achieved remission and 1/40 had an excellent response (P value 0.008 and P value < 0.001). It is interesting to note that 33/40 in the montelukast group showed no change with the intervention, and two individuals actually felt worse. Significant differences in total symptoms score, pruritus, number of hives and size of largest hive were noted (P value < 0.001, P value < 0.001, P value 0.017 and P value 0.003, respectively). Similar significant difference were noted between groups of desloratadine plus montelukast versus montelukast alone (P value < 0.001, P value < 0.001, P value 0.01 and P value 0.003). No difference was found between the group treated with desloratadine alone and the group treated with desloratadine plus montelukast.

Secondary outcome 2: minor participant-reported adverse events not requiring withdrawal of treatment

Adverse events were noted to be of low incidence and mild in all groups. Withdrawals, reported in large numbers in this study, appear to have been due to lack of efficacy in the groups not receiving desloratadine-not to adverse effects.

Comparison 19

Fexofenadine 180 mg versus placebo

One study that compared this intervention was identified (Kaplan 2005). No analysis was possible for this comparison.

Primary outcome 1: proportion of participants with complete suppression of urticaria whilst taking H1-antihistamines

No significant differences in complete suppression were reported between the interventions: 6/91 and 19/162 (placebo and fexofenadine, respectively; P value 0.272).

Primary outcome 2: proportion of participants with 'good' or 'excellent' response whilst taking H1-antihistamines

However, a difference was suggested between the proportions of participants who experienced at least a good response (11/91 and 57/162, placebo and fexofenadine, respectively; P value < 0.001). This study excluded participants who were previously unresponsive to antihistamines, so this result may not be generalisable.

Secondary outcome 2: minor participant-reported adverse events not requiring withdrawal of treatment

Whether any participants required treatment withdrawal as the result of adverse effects was not stated, although one individual in the fexofenadine group required hospital admission for asthma. We conclude that this event is not likely to have been related to the intervention.

Comparison 20

Ketotifen 1 mg versus placebo

One study that compared these interventions was identified (Phanuphak 1987). No analysis was possible for this comparison.

Primary outcome 2: proportion of participants with 'good' or 'excellent' response whilst taking H1-antihistamines

A total of 12/16 (ketotifen) and 2/14 (placebo) participants reported at least a good response (P value < 0.005). Notably, participants were permitted to take a different H1-antihistamine, chlorpheniramine 4 mg as required up to six-hourly, then were randomly assigned to ketotifen or placebo and were still allowed to take chlorpheniramine concomitantly. Investigators recorded the number of chlorpheniramine tablets taken, but this information was not reported explicitly. Study investigators noted that the requirement for chlorpheniramine dropped in significantly more participants taking ketotifen than placebo (94% vs 7%). It is still possible that positive results in the ketotifen group might have been caused by this alone, or by taking a combination of ketotifen and chlorpheniramine.

Secondary outcome 2: minor participant-reported adverse events not requiring withdrawal of treatment

No participants were withdrawn from either treatment as the result of an adverse event.

Comparison 21

Cetirizine 5 mg and hydroxyzine 25 mg (CH) versus placebo

These interventions were compared in one study on the clinical efficacy of a leukotriene receptor antagonist (LRA) plus an H1-antihistamine, an H1-antihistamine plus H2RA, two H1-antihistamines in combination and placebo for treating participants with CSU (Wan 2009). We compared only the H1-antihistamine combination and placebo arms. No analysis was possible for this comparison.

Primary outcome 2: proportion of participants with 'good' or 'excellent' response whilst taking H1-antihistamines

This study reported that 7/30 participants in the CH group and 0/30 in the placebo group experienced at least a good response following treatment after an intermediate-term duration of intervention (P value 0.01). Investigators concluded: "The combination of LRA and H1 receptor antagonist is promising for CSU treatment and is reasonably well tolerated by participants. The combination of H1- and H2-receptor antagonists provided the greatest treatment efficacy by the measures used in this small study."

Comparison 22

Azelastine 2 mg versus azelastine 4 mg

One study that compared these interventions was identified (Wu 2008). No analysis was possible for this comparison.

Primary outcome 1: proportion of participants with complete suppression of urticaria whilst taking H1-antihistamines

This study reported that 21/34 (2 mg) and 27/33 (4 mg) participants experienced complete suppression of CSU following an intermediate intervention (P value 0.103).

Primary outcome 2: proportion of participants with 'good' or 'excellent' response whilst taking H1-antihistamines

A further 6/34 (2 mg) and 4/33 (4 mg) participants exhibited good or excellent response to treatment over the same period (P value 0.637).

Comparison 23

Doxepin 10 mg versus pheniramine 22.5 mg

One study that compared these interventions was identified, although participants previously non-responsive to antihistamines were excluded (Ghosh 1990). No analysis was possible for this comparison.

Primary outcome 1: proportion of participants with complete suppression of urticaria whilst taking H1-antihistamines

Following an intermediate-term duration of intervention, 8/28 and 3/28 participants experienced complete suppression of urticaria (doxepin and pheniramine, respectively; P value < 0.001). Within seven days of treatment cessation, symptoms recurred in three of the participants (37.5%) who had taken doxepin and in all three who had taken pheniramine (P value 1.00).

Secondary outcome 2: minor participant-reported adverse events not requiring withdrawal of treatment

Although drowsiness and dry mouth were commonly reported in both groups (doxepin 37.5% and 64.3%, respectively; pheniramine 60.7% and 46.4%, respectively), no withdrawals from this study were reported.

Sensitivity and subgroup analyses

Only one comparison consisting of two studies (n = 260) compared hydroxyzine first-generation ('sedating') and cetirizine second-generation ('non-sedating') antihistamines individually (see Comparison 8). No difference in adverse effects leading to withdrawal was reported between these two groups (RR 0.78, 95% CI 0.25 to 2.45; Analysis 8.1).

ADDITIONAL SUMMARY OF FINDINGS *[Explanation]*

Desloratadine 5 to 20 mg versus placebo for chronic spontaneous urticaria

Patient or population: patients with chronic spontaneous urticaria
Setting: research clinic
Intervention: desloratadine 5 to 20 mg versus placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control (placebo)	Desloratadine 5 to 20 mg				
Complete suppression of urticaria: short-term duration of intervention (desloratadine 5 mg) Global assessment of symptom scores	See comment	See comment	Not estimable	46 (1 study)	⊕⊕◯◯ **Low**[a,b]	Favours neither intervention nor control Only 1 study, a conference abstract (Hoxha 2011)
Complete suppression of urticaria: short-term duration of intervention (desloratadine 10 mg) Global assessment of symptom scores	See comment	See comment	Not estimable	46 (1 study)	⊕⊕◯◯ **Low**[a,b]	Favours neither intervention nor control Only 1 study, a conference abstract (Hoxha 2011)
Complete suppression of urticaria: short-term duration of intervention (desloratadine 20 mg) Global assessment of symptom scores	See comment	See comment	Not estimable	46 (1 study)	⊕⊕◯◯ **Low**[a,b]	Favours desloratadine Only 1 study, a conference abstract (Hoxha 2011)

Complete suppression of urticaria: intermediate-term duration of intervention (desloratadine 5 mg) Global assessment of symptom scores	See comment	See comment	Not estimable	80 (1 study)	⊕⊕◯◯ **Low**[a,b]	Favours desloratadine Only 1 study (Di Lorenzo 2004)
Adverse effects leading to withdrawal: intermediate-term duration of 5 mg of intervention	**Study population**		**RR 1.46** (0.42 to 5.1)	466 (3 studies)	⊕⊕◯◯ **Low**[a,b]	Favours neither intervention nor control
	17 per 1000	**25 per 1000** (7 to 89)				
	Moderate					
	18 per 1000	**26 per 1000** (8 to 92)				

*The basis for the **assumed risk** (e.g. 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]Design limitation (risk of bias).
[b]Relatively few participants and few events and/or wide confidence intervals.

Levocetirizine 5 to 20 mg versus placebo for chronic spontaneous urticaria

Patient or population: patients with chronic spontaneous urticaria
Setting: research clinic
Intervention: levocetirizine 5 to 20 mg versus placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control (placebo)	Levocetirizine 5 to 20 mg				
Complete suppression of urticaria: short-term duration of intervention (levocetirizine 5 mg) Global assessment of symptom scores	See comment	See comment	Not estimable	49 (1 study)	⊕⊕◯◯ **Low**[a,b]	Favours neither intervention nor control Only 1 study, a conference abstract (Hoxha 2011)
Complete suppression of urticaria: short-term duration of intervention (levocetirizine 10 mg) Global assessment of symptom scores	See comment	See comment	Not estimable	49 (1 study)	⊕⊕◯◯ **Low**[a,b]	Favours neither intervention nor control Only 1 study, a conference abstract (Hoxha 2011)
Complete suppression of urticaria: short-term duration of intervention (levocetirizine 20 mg) Global assessment of symptom scores	See comment	See comment	Not estimable	49 (1 study)	⊕⊕◯◯ **Low**[a,b]	Favours levocetirizine Only 1 study, a conference abstract (Hoxha 2011)

Complete suppression of urticaria: intermediate-term duration of intervention (levocetirizine 5 mg) Global assessment of symptom scores	See comment	See comment	Not estimable	100 (1 study)	⊕⊕◯◯ **Low**[a,b]	Favours levocetirizine Only 1 study (Nettis 2006)

*The basis for the **assumed risk** (e.g. 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.

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]Design limitation (risk of bias).
[b]Relatively few participants and few events and/or wide confidence intervals.

Rupatadine 10 to 20 mg versus placebo for chronic spontaneous urticaria

Patient or population: patients with chronic spontaneous urticaria
Setting: research clinic
Intervention: rupatadine 10 to 20 mg versus placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control (placebo)	Rupatadine 10 to 20 mg				
Good or excellent response Global assessment of symptom scores	**Study population**		**RR 1.35** (1.03 to 1.77)	245 (1 study)	⊕⊕◯◯ **Low**[a,b]	Favours rupatadine
	509 per 1000	**687 per 1000** (524 to 901)				
	Moderate					
	509 per 1000	**687 per 1000** (524 to 901)				

*The basis for the **assumed risk** (e.g. 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] Design limitation (risk of bias).
[b] Relatively few participants and few events and/or wide confidence intervals.

Loratadine 10 mg versus placebo for chronic spontaneous urticaria

Patient or population: patients with chronic spontaneous urticaria
Setting: research clinic
Intervention: loratadine 10 mg versus placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control (placebo)	Loratadine 10 mg				
Good or excellent response Global assessment of symptom scores	**Study population**		**RR 1.86** (0.91 to 3.79)	124 (2 studies)	⊕⊕◯◯ **Low**[a,b]	Favours neither intervention nor control
	155 per 1000	**289 per 1000** (141 to 588)				
	Moderate					
	160 per 1000	**298 per 1000** (146 to 606)				

*The basis for the **assumed risk** (e.g. 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] Design limitation (risk of bias).
[b] Relatively few participants and few events and/or wide confidence intervals.

Loratadine 10 mg versus cetirizine 10 mg for chronic spontaneous urticaria

Patient or population: patients with chronic spontaneous urticaria
Setting: research clinic
Intervention: loratadine 10 mg versus cetirizine 10 mg

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control (cetirizine 10 mg)	Loratadine 10 mg				
Complete cessation of urticaria Global assessment of symptom scores	**Study population**		**RR 1.05** (0.76 to 1.43)	103 (2 studies)	⊕⊕◯◯ **Low**[a,b]	Combined short and intermediate-term duration of intervention Favours neither intervention nor control
	588 per 1000	**618 per 1000** (447 to 841)				
	Moderate					
	574 per 1000	**603 per 1000** (436 to 821)				

*The basis for the **assumed risk** (e.g. 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] Design limitation (risk of bias).
[b] Relatively few participants and few events and/or wide confidence intervals.

Loratadine 10 mg versus desloratadine 5 mg for chronic spontaneous urticaria

Patient or population: patients with chronic spontaneous urticaria
Setting: research clinic
Intervention: loratadine 10 mg versus desloratadine 5 mg

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control (desloratadine 5 mg)	Loratadine 10 mg				
Complete suppression of urticaria: intermediate-term duration of intervention	**Study population**		**RR 0.91** (0.78 to 1.06)	369 (2 studies)	⊕⊕◯◯ **Low**[a,b]	Favours neither intervention nor control
	658 per 1000	**598 per 1000** (513 to 697)				
	Moderate					
	670 per 1000	**610 per 1000** (523 to 710)				
Good or excellent response: intermediate-term duration of intervention Global assessment of symptom scores	**Study population**		**RR 1.04** (0.64 to 1.71)	410 (3 studies)	⊕⊕◯◯ **Low**[a,b]	Favours neither intervention nor control No participants reported a good or excellent response in the loratadine group in Zou 2002 We found low levels of statistical heterogeneity in this analysis I^2 = 40%)

	263 per 1000	**274 per 1000** (169 to 450)	
	Moderate		
	228 per 1000	**237 per 1000** (146 to 390)	

*The basis for the **assumed risk** (e.g. 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] Design limitation (risk of bias).
[b] Relatively few participants and few events and/or wide confidence intervals.

Loratadine 10 mg compared to mizolastine 10 mg for chronic spontaneous urticaria

Patient or population: patients with chronic spontaneous urticaria
Setting: research clinic
Intervention: loratadine 10 mg
Comparison: mizolastine 10 mg

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control (mizolastine 10 mg)	Loratadine 10 mg				
Complete cessation of urticaria: intermediate-term duration of intervention Global assessment of symptom scores	**Study population**		**RR 0.86** (0.64 to 1.16)	316 (3 studies)	⊕◯◯◯ **Very low**[a,b,c]	Overall, favours neither loratadine nor mizolastine In Guo 2003, more participants in mizolastine group had complete cessation of urticaria than in the other 2 studies (Liu 2003 and Yin 2003b)
	675 per 1000	**581 per 1000** (432 to 783)				
	Moderate					
	667 per 1000	**574 per 1000** (427 to 774)				
Good or excellent response: intermediate-term duration of intervention Global assessment of symptom scores	**Study population**		**RR 0.88** (0.55 to 1.42)	314 (3 studies)	⊕⊕◯◯ **Low**[a,c]	Favours neither loratadine nor mizolastine
	187 per 1000	**165 per 1000** (103 to 266)				
	Moderate					
	174 per 1000	**153 per 1000** (96 to 247)				

Adverse events leading to withdrawal: intermediate-term duration of intervention	**Study population**		**RR 0.38** (0.04 to 3.6)	267 (2 studies)	⊕⊕◯◯ **Low**[a,c]	Favours neither loratadine nor mizolastine
	15 per 1000	**6 per 1000** (1 to 53)				
	Moderate					
	19 per 1000	**7 per 1000** (1 to 68)				
Proportion of participants with at least 50% improvement in QoL: intermediate-term duration of intervention Symptom score reducing index (SSRI)	**Study population**		**RR 3.21** (0.32 to 32.33)	252 (2 studies)	⊕◯◯◯ **Very low**[a,b,c]	Favours neither loratadine nor mizolastine No participants in the mizolastine group in Guo 2003 reported at least 50% improvement in QoL
	104 per 1000	**334 per 1000** (33 to 1000)				
	Moderate					
	64 per 1000	**205 per 1000** (20 to 1000)				

*The basis for the **assumed risk** (e.g. 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]Design limitation (risk of bias).
[b]Widely differing estimates of the treatment effect (i.e. heterogeneity or variability in results) across studies.
[c]Relatively few participants and few events and/or wide confidence intervals.

Loratadine 10 mg versus emedastine 2 mg for chronic spontaneous urticaria

Patient or population: patients with chronic spontaneous urticaria
Setting: research clinic
Intervention: loratadine 10 mg versus emedastine 2 mg

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control (emedastine 2 mg)	Loratadine 10 mg				
Complete cessation of urticaria: intermediate-term duration of intervention Global assessment of symptom scores	**Study population**		**RR 1.04** (0.78 to 1.39)	161 (1 study)	⊕⊕⊕◯ **Moderate**[a]	Favours neither loratadine nor emedastine Only 1 study (Pons-Guiraud 2006)
	524 per 1000	**545 per 1000** (409 to 728)				
	Moderate					
	524 per 1000	**545 per 1000** (409 to 728)				
Good or excellent response: intermediate-term duration of intervention Global assessment of symptom scores	**Study population**		**RR 1.09** (0.96 to 1.24)	160 (1 study)	⊕⊕⊕◯ **Moderate**[a]	Favours neither loratadine nor emedastine Only 1 study (Pons-Guiraud 2006)
	819 per 1000	**893 per 1000** (787 to 1000)				
	Moderate					
	819 per 1000	**893 per 1000** (786 to 1000)				

Adverse events leading to withdrawal: intermediate-term duration of intervention	**Study population**		**RR 1.09** (0.07 to 17.14)	161 (1 study)	⊕⊕⊕◯ **Moderate**[a]	Favours neither loratadine nor emedastine Only 1 study (Pons-Guiraud 2006)
	12 per 1000	**13 per 1000** (1 to 204)				
	Moderate					
	12 per 1000	**13 per 1000** (1 to 206)				

*The basis for the **assumed risk** (e.g. 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]Relatively few participants and few events and/or wide confidence intervals.

Loratadine 10 mg versus hydroxyzine 25 mg for chronic spontaneous urticaria

Patient or population: patients with chronic spontaneous urticaria
Setting: research clinic
Intervention: loratadine 10 mg versus hydroxyzine 25 mg

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control (hydroxyzine 25 mg)	Loratadine 10 mg				
Complete suppression of urticaria: short-term duration of intervention Global assessment of symptom scores	**Study population**		**RR 1** (0.32 to 3.1)	12 (1 study)	⊕⊕◯◯ **Low**[a,b]	Favours neither intervention or control Only 1 study (Monroe 1992)
	500 per 1000	**500 per 1000** (160 to 1000)				
	Moderate					
	500 per 1000	**500 per 1000** (160 to 1000)				

*The basis for the **assumed risk** (e.g. 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] Design limitation (risk of bias).
[b] Relatively few participants and few events and/or wide confidence intervals.

Cetirizine 10 mg versus hydroxyzine 25 mg for chronic spontaneous urticaria

Patient or population: patients with chronic spontaneous urticaria
Setting: research clinic
Intervention: cetirizine 10 mg versus hydroxyzine 25 mg

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control (hydroxyzine 25 mg)	Cetirizine 10 mg				
Adverse events leading to withdrawal	Study population		RR 0.78 (0.25 to 2.45)	261 (2 studies)	⊕⊕◯◯ **Low**[a,b]	Favours neither cetirizine nor hydroxyzine
	53 per 1000	41 per 1000 (13 to 130)				
	Moderate					
	54 per 1000	42 per 1000 (14 to 132)				

*The basis for the **assumed risk** (e.g. 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] Design limitation (risk of bias).
[b] Relatively few participants and few events and/or wide confidence intervals.

Hydroxyzine 25 mg versus placebo for chronic spontaneous urticaria

Patient or population: patients with chronic spontaneous urticaria
Setting: research clinic
Intervention: hydroxyzine 25 mg versus placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control (placebo)	Hydroxyzine 25 mg				
Adverse events leading to withdrawal: intermediate-term duration of intervention	**Study population**		**RR 3.64** (0.77 to 17.23)	270 (2 studies)	⊕⊕◯◯ **Low**[a,b]	Favours neither intervention nor control
	14 per 1000	**53 per 1000** (11 to 250)				
	Moderate					
	15 per 1000	**55 per 1000** (12 to 258)				

*The basis for the **assumed risk** (e.g. 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] Design limitation (risk of bias).
[b] Relatively few participants and few events and/or wide confidence intervals.

DISCUSSION

Summary of main results

This review included 73 randomised studies with 9759 participants. For inclusion in our review, we would have preferred all studies to define their inclusion criteria explicitly as individuals with urticaria for a duration of at least six weeks, with the exclusion of those with inducible urticaria. To avoid excluding multiple studies that were likely to be relevant, we included studies that clearly stated the diagnosis under investigation as chronic spontaneous (or idiopathic or ordinary) urticaria, with nothing included in the paper to contradict this.

All studies were carried out in a secondary care setting, which included hospitals, research centres and dermatology centres. Participants were adults or were 12 years of age or older, and most were female.

Seventeen studies looked at short-term response to treatment of up to 2 weeks' duration, whilst 55 assessed intermediate response (longer than two weeks to three months). One study did not mention the duration of treatment or follow-up. No study looked at a long-term response of three months and beyond. Chronic spontaneous urticaria (CSU) can persist for years, and it would be useful for future studies to address whether treatments are effective over a longer period.

Considerable variation was noted in the interventions and comparators used in included studies; this limited the number of analyses that we could carry out. Additionally, pooling of data was not feasible for most of the treatment options, as the outcomes reported were not comparable. Of the 23 comparisons we were able to make, 10 provided outcome data that could be combined in meta-analyses. Thus most of our findings are based on results from individual trials.

Evidence suggests that some antihistamines appear to be more effective than placebo in achieving complete suppression of urticaria. This is the case for cetirizine 10 mg in the short term and in the intermediate term. Levocetirizine 20 mg over the short term also appears to be effective for complete suppression of urticaria (Hoxha 2011); however Hoxha 2011 has been published only as a conference abstract, and a fuller report or further information was unavailable at the time of writing of this review. The Nettis 2006 study found levocetirizine 5 mg to be considerably more likely to lead to complete suppression of urticaria over an intermediate-term duration than Hoxha 2011 over a short duration. Given that this information was derived from only two studies, each with some factors carrying an unclear risk of bias, it may be the case that levocetirizine is more beneficial when used for a longer duration.

Rupatadine in the study of Gimenez-Arnau 2007 was effective (good or excellent response) at 10 mg or 20 mg when compared against placebo. However, no difference was demonstrated between doses.

Meta-analyses assessing response to treatment with loratadine 10 mg indicate that its efficacy was not significantly different from that of placebo in the short and intermediate time frame (intervention for up to three months) for the outcome of 'good or excellent response' (Belaich 1990; Monroe 1992).

Comparisons of desloratadine versus placebo suggested a possible relationship between dose, duration and response: Lower doses (5 mg) with a shorter intervention period led to similar results, but a longer duration of a low dose (5 mg) or a shorter duration of a higher dose (20 mg) led to a higher rate of complete suppression of urticaria. In Hoxha 2011, different doses of desloratadine 5 mg to 20 mg were compared with doses of levocetirizine 5 mg to 20 mg; study investigators concluded: "increasing dose up to four-fold in both active groups was beneficial without compromising safety. Levocetirizine appeared to be more effective than desloratadine" (P value < 0.02).

In comparisons of more than one active intervention, no significant difference was found between loratadine 10 mg and cetirizine 10 mg at short- or intermediate-term durations in bringing about complete suppression of urticaria (Patel 1997; Yin 2003b).

Similarly, for loratadine 10 mg versus desloratadine 5 mg for complete suppression of urticaria and for good or excellent response, no statistically significant difference was noted between groups over an intermediate term of intervention (Gu 2002; Zou 2002).

For loratadine 10 mg versus mizolastine 10 mg, again with an intermediate term of intervention, no statistically significant difference was noted between groups for complete suppression of urticaria and for 'good or excellent response' (Guo 2003; Liu 2003; Liu H-N 1990; Yin 2003b). Loratadine 10 mg versus emedastine 2 mg (one study; n = 161) showed no statistically significant difference for complete suppression or good or excellent response, or for withdrawals due to adverse effects (Pons-Guiraud 2006).

We investigated the frequency with which adverse events led to withdrawal of treatment. No significant differences were observed in efficacy or adverse events compared with placebo in the intermediate term for cetirizine (doses from 5 mg to 20 mg) (Breneman 1995; Breneman 1996; Kalivas 1990), desloratadine (5 mg) (Monroe 2003; Nettis 2004; Ring 2001) or hydroxyzine (25 mg) (Breneman 1996; Kalivas 1990).

For withdrawals in comparisons of two active interventions, no significant differences were noted between loratadine 10 mg and mizolastine 10 mg (Leynadier 2000; Liu 2003), loratadine 10 mg and emedastine 2 mg (Pons-Guiraud 2006), cetirizine 10 mg and hydroxyzine 25 mg (Breneman 1996) and cetirizine 5 mg to 25 mg and hydroxyzine 25 mg (Kalivas 1990).

Quality of life was assessed in one comparison of two trials (Guo 2003; Liu 2003), but no difference was noted between loratadine 10 mg and mizolastine 10 mg in the proportion of participants with at least 50% improvement in quality of life.

Overall completeness and applicability of

evidence

The studies that met our criteria for inclusion in this review were conducted all over the world. We searched exhaustively and identified studies conducted in many disparate populations, including those in the USA, Australia, various European countries, South America, China, Taiwan and India. We also searched for reports on clinical trials in progress and for data from completed but unpublished clinical trials. Translation of all relevant non-English studies was conducted, and data were extracted and included. Most Japanese studies defined CSU as lasting four weeks or longer, and as this differed from our more generally recognised definition of CSU as lasting six weeks or longer, they could not be included. Evidence within this review should be applicable to all populations in which antihistamines are used for the treatment of CSU.

After discussion and consensus, we excluded studies that compared terfenadine and astemizole unless other comparison trial arms included interventions. These drugs are no longer in use for the treatment of urticaria because of safety concerns.

It is interesting to note that eight studies excluded participants previously unresponsive to antihistamines. The effect of this is that a subset of those with CSU who were more likely to be refractory to the intervention were screened out. These may be individuals with more severe disease. This could have a large effect on observed efficacy of an antihistamine in this trial, although it does not render in-trial comparisons of different antihistamines completely invalid.

The duration of CSU varies among individuals, although the mean duration may be prolonged (three to five years), and a small proportion of people can have CSU for longer than 20 years (Demera 2001; Kaplan 2005). It was disappointing to note that the duration of interventions used in the studies included in this review was relatively short (up to six weeks), and longer-term data are not available.

It would also have been of interest to analyse each study by itch, weal numbers and angio-oedema separately, as itch is a different symptom from swellings, even though both are mediated by histamine. Some of the original product licences for classical antihistamines were based on itch suppression rather than reduction in wealing. Itch is often the most troublesome symptom for people in terms of impairment of quality of life because of its effect on sleep and its general propensity to cause distress. In clinical practice, patients may refer to improvement in itch but not weals (or the opposite) rather than both, so treatment effects should ideally be reported separately rather than as an overall assessment of improvement. Furthermore, physician-rated scales of itch are a contradiction, as it is only the individual with the symptom who can rate this. In our review, we were unable to look at itch or weal numbers separately because not all of the included studies reported these consistently. and our focus was on urticaria rather than angio-oedema. We were reluctant to undertake further subgroup analyses because the likelihood of false-positive significance tests increases as more subgroup analyses are performed.

Quality of the evidence

The included studies had notable methodological limitations; only 12 were clearly adequately randomised, and the randomisation method used in the rest was unclear or at high risk. Only four described adequate allocation concealment; in the remaining studies, this was unclear or was judged to confer high risk of selection bias. Blinding of participants and personnel was adequate in only 20 studies, and blinding of outcome assessors was adequate in 14. Twenty studies were at risk of bias from incomplete reporting of outcome data (attrition bias), and 20 studies were at high risk of selective reporting bias. We detected other sources of bias including baseline imbalance within groups and potential bias from industry sponsorship or funding in 55 of the included studies, but the extent to which these factors may have introduced bias was unclear. It is therefore important to emphasise that any conclusions that we have drawn are reliant on primary studies with varying degrees of bias. Risk of bias should be considered when these results are interpreted (Figure 2), and findings derived from studies with high or unclear risk of bias should be viewed with caution.

Although we included a large number of studies, only a few for each comparison reported outcome data that could be incorporated in meta-analyses. Several studies included small numbers of participants. We have drawn limited conclusions from single study analyses, or we have reported the results of the trial narratively or we have presented results from small meta-analyses of up to three studies (e.g. loratadine vs desloratadine, n = 410 from three studies; loratadine vs mizolastine, n = 204 from three studies).

Some studies showed some statistical heterogeneity, for example, for the comparison of loratadine versus desloratadine, and loratadine versus mizolastine. We give reasons for downgrading the quality of the body of evidence for each comparison in the 'Summary of findings' tables (Summary of findings for the main comparison; Summary of findings 2; Summary of findings 3; Summary of findings 4; Summary of findings 5; Summary of findings 6; Summary of findings 7; Summary of findings 8; Summary of findings 9; Summary of findings 10; Summary of findings 11; Summary of findings 12) (as described in the footnotes of each table). Overall, the quality of evidence in each comparison was rated as low in most studies or of moderate quality, meaning that further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. The current body of evidence does not, therefore, allow robust conclusions.

Potential biases in the review process

Risk of bias was assessed for all studies. Although we requested additional details of trial conditions from study investigators, in many cases we were unable to determine whether randomisation and allocation concealment methods were adequate. Overall, a high proportion of the included studies were assessed as having

unclear or high risk of bias. Most although not all trials published within the past 10 years provided enough information to enable full assessment of risk of bias. Many studies were at high risk of attrition bias as the result of dropouts and losses to follow-up. This could often be attributed to participants who did not experience symptomatic relief in the placebo arm of trials.

Of the 73 included studies with 9759 randomly assigned participants, 31 were stated to be sponsored by the pharmaceutical industry, and six through research grants or non-profit organisations. It is unclear whether sponsorship was a source of bias in these trials.

We attempted to minimise publication bias by seeking out results of unpublished trials. This review included 73 studies, of which 35 provided outcome data for 23 comparisons. Therefore, even though we have included a large number of studies, clinical diversity and variation in the ways in which results were reported led to only a few meta-analyses. Whilst every effort was made to minimise the introduction of bias in this review, clinically divergent interventions led to wide confidence intervals and potentially imprecise results. Sensitivity analysis was not possible for primary outcomes measures for studies at low risk of bias, as studies were too few to permit assessment of the results of the review in this way.

Although the evidence for cetirizine is somewhat more robust than for other antihistamines, it should be borne in mind that cetirizine was effective in suppressing urticaria completely in only some participants. Bias may be present here because cetirizine has been on the market for a long time and more data are available for this agent in comparison with other drugs.

We were unable to include data from studies of participants with varying types of urticaria if no disaggregated data specific to the participants with CSU were available. Although some such studies may provide valuable information, we excluded them, as any conclusions that we derived from studies with mixed populations may not be applicable to populations with CSU.

The clinical heterogeneity that was present in the included studies in terms of populations, interventions and outcomes contributed to difficulties in pooling data for analysis. In some cases, smaller unpublished studies that reported outcomes that fit our inclusion criteria contributed data to several meta-analyses (e.g. Hoxha 2011).

Agreements and disagreements with other studies or reviews

Kavosh 2011 reviewed second-generation H1-antihistamines and found that limited data on comparisons of antihistamines led to the recommendation to use cetirizine in preference to fexofenadine. In our review, the main finding from the key study (Handa 2004) was that at four weeks, 27/59 participants in the cetirizine group had complete suppression of urticaria as compared with 2/57 in the fexofenadine group (P value < 0.001). However, this result was derived from only 116 participants and no meta-analysis was possible, so the finding may not be wholly conclusive.

The findings of this review are broadly in agreement with those of the Kavosh 2011 review, which recommended use of levocetirizine in preference to desloratadine. In our review, two studies were identified that compared these interventions (Hoxha 2011; Potter 2009). In Hoxha 2011, study investigators concluded: "Increasing dose up to four-fold in both active groups was beneficial without compromising safety. Levocetirizine appeared to be more effective than desloratadine" (P value < 0.02). However, this study was published only as a conference abstract, and we were unable to obtain study data from study investigators. Participants in Potter 2009 demonstrated at least good response following treatment with levocetirizine 5 mg and desloratadine 5 mg. Levocetirizine "...decreased pruritus duration and the mean CSU composite scores to a significantly greater extent than desloratadine during the first week (P=0.002 and 0.005, respectively) and over the entire study (P=0.009 and P<0.05, respectively)." No meta-analysis was possible for this comparison.

Other studies have investigated treatment with H1-antihistamines at higher than recommended licensed doses (e.g. Finn 1999; Nelson 2000; Weller 2013). In our review, one study compared different doses of fexofenadine, but the outcomes did not fit our criteria (Nelson 2000). Furthermore, in this trial, participants previously unresponsive to antihistamines were excluded.

A review by Church 2012 concluded that three clinical studies (Hong 2010; Potter 2009; Staevska 2010) suggested that H1-antihistamines, or at least desloratadine and levocetirizine, are efficacious in the treatment of CSU. However, we excluded Hong 2010 and Staevska 2010 from our review, as they included participants outside our inclusion criteria. We agree with the authors of Church 2012 that an independent multi-centre study could provide valuable information about the relative efficacy of these interventions. Currently available evidence for use of higher doses of H1-antihistamines for CSU is limited, and no long-term data are available for any of the trials.

Guidelines of the British Association of Dermatologists for management of urticaria (Grattan 2007) suggested that patients should be offered the choice of at least two non-sedating H1-antihistamines, and that benefits of increasing the dose to above the licensed limit may outweigh risks, but we found limited evidence in our included studies to support this approach.

AUTHORS' CONCLUSIONS

Implications for practice

This review has found limited quality evidence to establish the efficacy of H1-antihistamines compared with placebo in the treatment of CSU. Several antihistamines were found to be superior to placebo at standard (licensed) doses of treatment. Although the

quality of evidence for adverse events was low, the direction of effects in most of the analyses suggest that users generally found these medicines tolerable.

Symptomatic relief has been demonstrated to a variable extent with different antihistamines. However, only few studies have assessed their effects on quality of life in urticaria.

On the basis of our data collection and analysis, it is evident that a clear message does not emerge regarding whether one antihistamine is better than another. Given the quality of trials and of their reporting, as well as the wide variation in comparisons and few opportunities to combine results in meta-analyses, we must be guarded in putting forward specific treatment algorithms.

For general use, cetirizine at 10 mg once daily for short- and intermediate-term duration was found to be effective in completely suppressing urticaria. However, three of the four trials that compared this treatment against placebo did have factors that we rated as suggesting high risk of bias. The two trials of loratadine 10 mg once daily versus placebo failed to demonstrate efficacy and were also at some risk of bias. Only two trials compared these two drugs: They failed to show a difference in efficacy, although they were not designed to demonstrate equivalence. Cetirizine and loratadine offer the advantages of being cheap and widely available. It would be reasonable to regard cetirizine as a first-line option.

Some benefit (for complete suppression of urticaria) may be derived from using desloratadine at 5 mg once daily for at least an intermediate term of intervention and 20 mg desloratadine in the short term. Once again, risks of bias in trials of this drug were significant.

Levocetirizine at 5 mg once daily in the intermediate term appears to be effective in achieving complete suppression of CSU. This is based on the results of only three trials. We rated two of these as carrying an unclear risk of bias in every domain, although the third, whilst small, was relatively well conducted and reported. Evidence of benefit from increasing the dose to a ceiling of 20 mg per day is limited. It is common practice to use higher than licensed doses of various H1-antihistamines, at least in Europe, where the guidelines recommend this (Zuberbier 2012). We included very few RCTs that assessed the effects of this and found insufficient evidence to support the practice, especially over longer durations. For clarity, the maximum licensed dose for both cetirizine and loratadine is 10 mg once daily, and for both levocetirizine and desloratadine, 5 mg once daily.

Although we included trials on various other drugs, their data are too sparse to allow firm conclusions about their relative efficacy. Furthermore, very few trials assessed combinations of antihistamines at conventional or higher doses; although such prescribing does occur in clinical practice, we have no basis on which to make recommendations.

Implications for research

We found little research on the use of higher doses of H1-antihistamines, and no included studies continued over longer durations. Very few assessed whether responses were sustained after the intervention was stopped; future work should address these gaps.

Study investigators should provide information about the duration of urticaria for each participant before entry into a trial, as it is conceivable that urticaria that has persisted for many years may be more refractory to treatment than urticaria of only six weeks' duration.

We would welcome trials with two (or more) active treatment arms rather than a placebo that performed comparisons of different doses over longer periods. Although trials including a placebo yield useful data, particularly for new compounds, participants receiving placebo may find little benefit from taking part and seem to be more likely to withdraw or to fail to comply with the medication schedule. This can lead to very high levels of dropout and resulting difficulties in interpretation of study results. Trials should preferably be conducted independently of involvement of pharmaceutical companies.

Many dermatologists recommend higher, unlicensed doses of H1-antihistamines in difficult cases of urticaria. Future studies should address whether this is justified in terms of effectiveness and safety.

In this review, primary outcome scores were variable for several of the trials, making it difficult for review authors to draw direct comparisons. This would be enabled by the use of a standardised outcome score such as the Urticaria Activity Score. This instrument is recommended in the European guidelines (Zuberbier 2012) and comprises the sum of 4-point scales (0-3) for number of weals and pruritus over a 24-hour period. In several studies, outcome measures were not clearly defined, and for some measures, it was not clear how improvements in composite scores really correlated with symptomatic relief. For example, level of pruritus is likely to be of far greater importance to an individual with urticaria than the size of the largest weal.

In terms of reporting of results, we find that it is more meaningful to the clinician and to the participant if outcomes can be related to numbers of individuals who achieve a particular response. For example, five out of 10 of those with CSU will attain complete symptom relief, and a further three will experience greater than 50% improvement, rather than a particular drug will, on average, lead to a 3-point reduction in total symptoms score. The latter approach is often accompanied by a P value < 0.05, but clinical significance and the spread of responses may be less clear: Was there some improvement for all participants, or were complete responses noted for a few and no response for others? We favour clear outcomes such as number of participants achieving complete suppression of urticaria, or 75% reduction in itch severity (which could be equated with a good response).

Wider use of standardised and validated quality of life (QoL) scores for trial participants diagnosed with this often disabling condition would provide measurable data to aid treatment decisions. For example, QoL scores would help investigators to monitor change in dosage or drug, or cessation of therapy.

Virtually no long-term studies have looked at treatment and outcomes over much longer periods of time. Longer-term studies should be designed, so that the extent of relief from symptoms from participants' perspective (symptoms, quality of life) and safety and efficacy should be included in the design of such studies. We do recognise that long-term studies may be difficult to perform for reasons including expense and attrition, with fewer participants remaining in the study over long periods of time.

ACKNOWLEDGEMENTS

Many thanks to Dr Gudula Kirtschig and the Cochrane Skin Group for guidance and assistance with this project.

We would also like to thank Dr Chih-Mei Chen, Dr Amy Stanway, Dr Lynda Binney and Dr Conrad Hauser, who were co-authors on the protocol for this review.

Dr Jonathan Batchelor, Dr Carsten Flohr, Dr Marcello Di Bonito and Dr Kim Varma provided assistance with translations. Dr Sujoy Ray provided support with data extraction and risk of bias assessments.

We thank the following study investigators, who provided additional details of study results for included trials: Dr Ana Gimenez-Arneau, Dr Ganesh Dakhale, Dr Gabriele Di Lorenzo, Prof Louis Dubertret, Dr Jean-Jacques Grob, Dr Sanjeev Handa and Dr Arthur Helbling.

The Cochrane Skin Group editorial base wishes to thank Sam Gibbs, who was the Cochrane Dermatology Editor for this review; Jo Leonardi-Bee, who was the Statistical Editor; Ching-Chi Chi, who was Methods Editor; the clinical referees, Clive Grattan and Karsten Weller; and the consumer referee, who wishes to remain anonymous.

REFERENCES

References to studies included in this review

Alomar 1990a *{published data only}*
Alomar A, Puig L, De Moragas JM. Cetirizine in the treatment of chronic urticaria [Tratamiento de la urticaria cronica con dihidrocloruro de cetirizina]. *Actas Dermo-Sifiliograficas* 1990;**81**(3):181–3. [EMBASE: 1990175012]

Anuradha 2010 *{published data only}*
Anuradha P, Maiti R, Jyothirmai J, Mujeebuddin O, Anuradha M. Loratadine versus levocetirizine in chronic idiopathic urticaria: a comparative study of efficacy and safety. Indian Journal of Pharmacology 2010; Vol. 42, issue 1:12–6. [MEDLINE: 20606830]

Beck 1985 *{published data only}*
Beck HI, Cramers M, Herlin T, Sondergaard I, Zachariae H. Comparison of oxatomide and clemastine in the treatment of chronic urticaria. A double blind study. *Dermatologica* 1985;**171**(1):49–51. [MEDLINE: 2863185]

Belaich 1990 *{published data only}*
Belaich S, Bruttmann G, DeGreef H, Lachapelle J M, Paul E, Pedrali P, et al. Comparative effects of loratadine and terfenadine in the treatment of chronic idiopathic urticaria. *Annals of Allergy* 1990;**64**(2 Pt 2):191–4. [MEDLINE: 1967919]

Breneman 1995 *{published data only}*
Breneman D, Bronsky EA, Bruce S, Kalivas JT, Klein GL, Roth HL, et al. Cetirizine and astemizole therapy for chronic idiopathic urticaria: a double-blind, placebo-controlled, comparative trial. *Journal of the American Academy of Dermatology* 1995;**33**(2 Pt 1):192–8. [MEDLINE: 7622644]

Breneman 1996 *{published data only}*
Breneman DL. Cetirizine versus hydroxyzine and placebo in chronic idiopathic urticaria. *Annals of Pharmacotherapy* 1996;**30**(10):1075–9. [MEDLINE: 8893110]

Bronsky 2001 *{published data only}*
Bronsky E, Desloratadine urticaria study group. Desloratadine: a safe and effective therapy for chronic idiopathic urticaria. *Annals of Allergy, Asthma & Immunology* 2001;**86**:109. [CENTRAL: CN–00384995]

Brostoff 1996 *{published data only}*
Brostoff J, Fitzharris P, Dunmore C, Theron M, Blondin P. Efficacy of mizolastine, a new antihistamine, compared with placebo in the treatment of chronic idiopathic urticaria. *Allergy* 1996;**51**(5):320–5. [MEDLINE: 8836336]

Commens 1978 *{published data only}*
Commens CA, Greaves MW. Cimetidine in chronic idiopathic urticaria: a randomized double-blind study. *British Journal of Dermatology* 1978;**99**(6):675–9. [MEDLINE: 367422]

Dakhale 2014 *{published data only}*
Dakhale GN, Shinde AT, Mahatme MS, Hiware SK, Mishra DB, Mukhi JI, et al. Clinical effectiveness and safety of cetirizine versus rupatadine in chronic spontaneous urticaria: a randomized, double-blind, 6-week trial. *International Journal of Dermatology* 2014;**53**(5):643–9. [MEDLINE: 24320728]

Degonda 2002 *{published data only}*

Degonda M, Pichler WJ, Bircher A, Helbling A. Chronic idiopathic urticaria: effectiveness of fexofenadine. A double-blind, placebo controlled study with 21 patients. *Schweizerische Rundschau für Medizin Praxis / Revue Suisse de Médecine Praxis* 2002;**91**(15):637–43. [MEDLINE: 12014063]

Di Lorenzo 2004 *{published data only}*

Di Lorenzo G, Pacor ML, Mansueto P, Esposito Pellitteri M, Lo Bianco C, Ditta V, et al. Randomized placebo-controlled trial comparing desloratadine and montelukast in monotherapy and desloratadine plus montelukast in combined therapy for chronic idiopathic urticaria. *Journal of Allergy & Clinical Immunology* 2004;**114**(3):619–25. [MEDLINE: 15356567]

Dubertret 1999 *{published data only}*

Dubertret L, Murrieta Aguttes M, Tonet J. Efficacy and safety of mizolastine 10 mg in a placebo-controlled comparison with loratadine in chronic idiopathic urticaria: results of the MILOR Study. *Journal of the European Academy of Dermatology & Venereology* 1999;**12**(1):16–24. [MEDLINE: 10188144]

Dubertret 2007 *{published data only}*

Dubertret L, Zalupca L, Cristodoulo T, Benea V, Medina I, Fantin S, et al. Once-daily rupatadine improves the symptoms of chronic idiopathic urticaria: a randomised, double-blind, placebo-controlled study. *European Journal of Dermatology* 2007;**17**(3):223–8. [MEDLINE: 17478385]

Finn 1999 *{published data only}*

Finn A, Kaplan AP, Fretwell R, Qu R, Long J. A double-blind, placebo-controlled trial of fexofenadine HCL in the treatment of chronic idiopathic urticaria CIU. *Annals of Allergy, Asthma and Immunology* 1999;**85**:118. [CENTRAL: CN–00278281]

* Finn AF Jr, Kaplan AP, Fretwell R, Qu R, Long J. A double-blind, placebo-controlled trial of fexofenadine HCl in the treatment of chronic idiopathic urticaria. *Journal of Allergy & Clinical Immunology* 1999;**104**(5):1071–8. [MEDLINE: 10550755]

Gale 1989 *{published data only}*

Gale AE, Harvey SG, Calthrop JG, Gibson JR. A comparison of acrivastine versus chlorpheniramine in the treatment of chronic idiopathic urticaria. *Journal of International Medical Research* 1989;**17**(Suppl 2):25B–7B. [MEDLINE: 2569998]

Garavaglia 1995 *{published data only}*

Garavaglia M, Cavallo A, Goncalvez M, Cassanitti C. Double-blind, comparative, six weeks in duration study to evaluate the efficacy and tolerability of cetirizine vs terfinadine and placebo in the treatment of patients with chronic idiopathic urticaria [Estudio doble ciego, comparativo, de seis semanas de duracion para evaluar la eficacia y tolerancia de la cetirizina vs terfinadina y placebo en el tratamiento de pacientes con urticaria idiopatica cronica]. *Archivos Argentinos de Alergia e Immunologia Clinica* 1995;**26**(3):179–89.

Ghosh 1990 *{published data only}*

Ghosh S, Haldar S. Therapeutic effect of doxepin in chronic idiopathic urticaria. Indian Journal of Dermatology, Venerology & Leprology 1990; Vol. 56, issue 3:218–20. [EMBASE: 1990321412]

Gimenez-Arnau 2007 *{published data only}*

Gimenez-Arnau A, Pujol RM, Ianosi S, Kaszuba A, Malbran A, Poop G, et al. Rupatadine in the treatment of chronic idiopathic urticaria: a double-blind, randomized, placebo-controlled multicentre study. *Allergy* 2007;**62**(5):539–46. [MEDLINE: 17441794]

Go 1989 *{published data only}*

Go MJTH, Wuite J, Arendt C, Bernheim J. Double-blind, placebo controlled comparison of cetirizine and terfenadine in chronic idiopathic urticaria. *Acta Therapeutica* 1989;**15**(1):77–86. [EMBASE: 1989116427]

Godse 2007 *{published data only}*

Godse K, Jain A, Pharande P. Comparative efficacy of fexofenadine and levocetirizine in chronic idiopathic urticaria. *Indian Journal of Dermatology* 2007;**52**(4):212–3. [EMBASE: 2008015145]

Goh 1991 *{published data only}*

Goh CL, Wong WK, Lim J. Cetirizine vs placebo in chronic idiopathic urticaria-a double blind randomised cross-over study. *Annals of the Academy of Medicine, Singapore* 1991;**20**(3):328–30. [MEDLINE: 1681778]

Grant 1988 *{published data only}*

Grant JA, Bernstein DI, Buckley CE, Chu T, Fox RW, Rocklin RE, et al. Double-blind comparison of terfenadine, chlorpheniramine, and placebo in the treatment of chronic idiopathic urticaria. *Journal of Allergy & Clinical Immunology* 1988;**81**(3):574–9. [MEDLINE: 3126220]

Gu 2002 *{published data only}*

Gu J, Wen H, Hu ZJ, Lian S, Guo ZL, Hou J. A study on the efficacy and safety of desloratadine in the treatment of chronic idiopathic urticaria. *Chinese Journal of Dermatovenereology* 2002;**16**(4):227–9. [CENTRAL: CN–00430184]

Guo 2003 *{published data only}*

Guo ZP, Zhang YZ, Chen Y Xiong L, Jiang X, Zhang M, Li Z. Randomized double blind research of mizolastine for the treatment of idiopathic chronic urticaria. *West China Medical Journal* 2003;**18**(4):482–3. [CENTRAL: CN–00517791]

Handa 2004 *{published data only}*

Handa S, Dogra S, Kumar B. Comparative efficacy of cetirizine and fexofenadine in the treatment of chronic idiopathic urticaria. *Journal of Dermatological Treatment* 2004;**15**(1):55–7. [MEDLINE: 14754652]

Hao 2003 *{published data only}*

Hao F, Peng ZH, Chen XP, Bi J, Hi G, Diao Q, et al. A multiple-centre double-blind comparative clinical trial of desloratadine and loratadine for the treatment of chronic idiopathetic urticaria. *Chinese Journal of Dermatovenereology* 2003;**17**(4):233–5. [CENTRAL: CN–00493820]

Harvey 1981 *{published data only}*
Harvey RP, Wegs J, Schocket AL. A controlled trial of therapy in chronic urticaria. *Journal of Allergy & Clinical Immunology* 1981;**68**(4):262–6. [MEDLINE: 6116728]

Hjorth 1988 *{published data only}*
Hjorth N. Terfenadine in the treatment of chronic idiopathic urticaria and atopic dermatitis. *Cutis* 1988;**42** (4A):29–30. [MEDLINE: 2903817]

Hoxha 2011 *{published data only}*
Hoxha, M, Xhani A, Shehu E, Shameti A, Qirko E, Priftanji A. The treatment of severe urticaria with increasing doses of antihistamines [Abstract]. 30th Congress of the European Academy of Allergy and Clinical Immunology Istanbul Turkey. Conference Start: 20110611 Conference End: 20110615. *Allergy: European Journal of Allergy and Clinical Immunology* 2011;**66**:272–3. [EMBASE: 70641059]

Juhlin 1987 *{published data only}*
Juhlin L, Gibson JR, Harvey SG, Huson LW. Acrivastine versus clemastine in the treatment of chronic idiopathic urticaria. A double-blind, placebo-controlled study. *International Journal of Dermatology* 1987;**26**(10):653–4. [MEDLINE: 2892806]

Juhlin 1991 *{published data only}*
Juhlin L. Cetirizine in the treatment of chronic urticaria. *Clinical Therapeutics* 1991;**13**(1):81–6. [MEDLINE: 1827614]

Kalivas 1990 *{published data only}*
Kalivas J, Breneman D, Tharp M, Bruce S, Bigby M. Urticaria: clinical efficacy of cetirizine in comparison with hydroxyzine and placebo. *Journal of Allergy & Clinical Immunology* 1990;**86**(6 Pt 2):1014–8. [MEDLINE: 1979796]

Kaplan 2005 *{published data only}*
Kaplan AP, Spector SL, Meeves S, Liao Y, Varghese ST, Georges G. Once-daily fexofenadine treatment for chronic idiopathic urticaria: a multicenter, randomized, double-blind, placebo-controlled study. *Annals of Allergy, Asthma & Immunology* 2005;**94**(6):662–9. [MEDLINE: 15984599]
Spector SL, Shikiar R, Harding G, Meeves S, Leahy MJ. The effect of fexofenadine hydrochloride on productivity and quality of life in patients with chronic idiopathic urticaria. *Cutis* 2007;**79**(2):157–62. [MEDLINE: 17388220]

Kint 1989 *{published data only}*
Kint A, Constandt L, Arendt C, Bernheim J. Comparative efficacy of cetirizine and terfenadine in the treatment of chronic idiopathic urticaria. *Acta Therapeutica* 1989;**15**(1): 65–75. [EMBASE: 1989116426]

Leyh 1989 *{published data only}*
Leyh F, Harvey SG, Gibson JR, Manna VK. A comparison of acrivastine versus clemastine and placebo in the treatment of patients with chronic idiopathic urticaria. *Journal of International Medical Research* 1989;**17**(Suppl 2):22B–4B. [MEDLINE: 2569997]

Leynadier 2000 *{published data only}*
Leynadier F, Duarte-Risselin C, Murrieta M. Comparative therapeutic effect and safety of mizolastine and loratadine in chronic idiopathic urticaria. URTILOR Study Group. *European Journal of Dermatology* 2000;**10**(3):205–11. [MEDLINE: 10725819]

Liu 2003 *{published data only}*
Liu LL, Zhu XJ, Jiang W, Chen XX, Li M, Peng Z, et al. A multicentre, double-blind, randomized, parallel comparative study on the efficacy and safety of mizolastine versus loratadine in the treatment of chronic urticaria. *Chinese Journal of Dermatology* 2003;**36**(6):306–9. [CENTRAL: CN–00484864]

Liu H-N 1990 *{published data only}*
Liu HN, Pan LM, Hwang SC, Chu TL. Nifedipine for the treatment of chronic urticaria: a double-blind cross-over study. *Journal of Dermatological Treatment* 1990;**1**(4): 187–9. [EMBASE: 1990343405]

Locci 1991 *{published data only}*
Locci F, Del Giacco GS. Treatment of chronic idiopathic urticaria with topical preparations: controlled study of oxatomide gel versus dechlorpheniramine cream. *Drugs Under Experimental & Clinical Research* 1991;**17**(8): 399–403. [MEDLINE: 1688044]

Maiti 2011 *{published data only}*
Maiti R, Jaida J, Raghavendra BN, Goud P, Ahmed I, Palani A. Rupatadine and levocetirizine in chronic idiopathic urticaria: a comparative study of efficacy and safety. Journal of Drugs in Dermatology 2011; Vol. 10, issue 12:1444–50. [MEDLINE: 22134570]

Makino 2012 *{published data only}*
Makino T, Takegami Y, Rehman MU, Yoshihisa Y, Ishida W, Toyomoto T, et al. Maintenance of remission with low-dose olopatadine hydrochloride for itch in well-controlled chronic urticaria. Clinical, Cosmetic and Investigational Dermatology CCID 2012; Vol. 5:141–6. [MEDLINE: 23055763]

Marks 1980 *{published data only}*
Marks R. Treatment of chronic urticaria [letter]. *British Journal of Dermatology* 1980;**102**(2):240. [MEDLINE: 6992835]

Monroe 1988 *{published data only}*
Monroe E, Fox R, Green A. Efficacy and safety of loratadine (10 mg once and daily) in the management of idiopathic chronic urticaria [Abstract no:3]. *Indian Journal of Dermatology, Venerology & Leprology* 1989;**55**:270. [CENTRAL: CN–00692719]
* Monroe EW, Fox RW, Green AW, Izuno GT, Bernstein DI, Pleskow WW, et al. Efficacy and safety of loratadine (10 mg once daily) in the management of idiopathic chronic urticaria. *Journal of the American Academy of Dermatology* 1988;**19**(1 Pt 1):138–9. [MEDLINE: 2900256]

Monroe 1992 *{published data only}*
Monroe EW. Relative efficacy and safety of loratadine, hydroxyzine, and placebo in chronic idiopathic urticaria and atopic dermatitis. *Clinical Therapeutics* 1992;**14**(1): 17–21. [MEDLINE: 1349509]

Monroe 2003 *{published data only}*

Monroe E, Finn A, Patel P, Guerrero R, Ratner P, Bernstein D. Efficacy and safety of desloratadine 5 mg once daily in the treatment of chronic idiopathic urticaria: a double-blind, randomized, placebo-controlled trial. *Journal of the American Academy of Dermatology* 2003;**48**(4):535–41. [MEDLINE: 12664016]

NCT00536380 *{unpublished data only}*

NCT00536380. A study of the efficacy, safety, and quality of life (QOL) in patients with chronic idiopathic urticaria dosed with AERIUS (desloratadine) tablets (5 mg, 10 mg, or 20 mg once daily)-ACCEL. NCT00536380. http://clinicaltrials.gov/show/NCT00536380. Accessed 3 July 2013.

Nelson 2000 *{published data only}*

Nelson HS, Reynolds R, Mason J. Fexofenadine HCl is safe and effective for treatment of chronic idiopathic urticaria. *Annals of Allergy, Asthma & Immunology* 2000;**84**(5):517–22. [MEDLINE: 10831005]

Nettis 2004 *{published data only}*

Nettis E, Colanardi MC, Paradiso MT, Ferrannini A. Desloratadine in combination with montelukast in the treatment of chronic urticaria: a randomized, double-blind, placebo-controlled study. *Clinical & Experimental Allergy* 2004;**34**(9):1401–7. [MEDLINE: 15347373]

Nettis 2006 *{published data only}*

Nettis E, Colanardi MC, Barra L, Ferrannini A, Vacca A, Tursi A. Levocetirizine in the treatment of chronic idiopathic urticaria: a randomized, double-blind, placebo-controlled study. *British Journal of Dermatology* 2006;**154**(3):533–8. [MEDLINE: 16445787]

Ollert 1999 *{published data only}*

Ollert MW, Brockow K, Engst R, Ring J. Successful treatment of chronic urticaria with mizolastine-Results of a placebo-controlled study [Erfolgreiche behandlung der chronischen urtikaria mit mizolastin-Ergebnisse einer plazebokontrollierten doppelblindstudie]. Allergo Journal 1999; Vol. 8, issue Suppl 1:S22–8. [EMBASE: 1999044749]

Ortonne 2004 *{published data only}*

Grob JJ, Stalder JF, Dreyfus I, Ortonne JP. Desloratadine improves quality of life and measures of impaired sleep and daily activity in chronic idiopathic urticaria [Abstract]. American Academy of Allergy Asthma and Immunology, San Francisco, California, March 19-23 2004. *Journal of Allergy & Clinical Immunology* 2004;**113**(2 Suppl):S28. [CENTRAL: CN–00475471]

* Ortonne JP, Dron Gonzalvez M, Brassac I, Guinnepain MT. Desloratadine has a rapid and enduring impact on signs and symptoms in chronic idiopathic urticaria [Abstract]. American Academy of Allergy Asthma and Immunology, San Francisco, California, March 19-23 2004. Journal of Allergy & Clinical Immunology 2004; Vol. 113, issue 2 Suppl:S135. [CENTRAL: CN–00476210]

Ortonne 2007 *{published data only}*

Grob JJ, Auquier P, Dreyfus I, Ortonne JP. Quality of life in adults with chronic idiopathic urticaria receiving desloratadine: a randomized, double-blind, multicentre, placebo-controlled study. *Journal of the European Academy of Dermatology & Venereology* 2008;**22**(1):87–93. [PUBMED: 18181978]

Ortonne JP, Grob JJ, Auquier P, Dreyfus I. Efficacy and safety of desloratadine in adults with chronic idiopathic urticaria: a randomized, double-blind, placebo-controlled, multicenter trial. *American Journal of Clinical Dermatology* 2007;**8**(1):37–42. [MEDLINE: 17298105]

Patel 1997 *{published data only}*

Patel P, Danzig M. Comparative efficacy and safety of loratadine and cetirizine in patients with chronic idiopathic urticaria. Advances in Therapy 1997; Vol. 14, issue 6: 318–22. [EMBASE: 1998034759]

Paul 1998 *{published data only}*

Paul E, Berth Jones J, Ortonne JP, Stern M. Fexofenadine hydrochloride in the treatment of chronic idiopathic urticaria: a placebo-controlled, parallel-group, dose-ranging study. Journal of Dermatological Treatment 1998; Vol. 9, issue 3:143–9. [EMBASE: 1998346160]

Peyri 1991 *{published data only}*

Peyri J, Vidal J, Marron J, Fonseca E, Suarez E, Ledo A, et al. Ebastine in chronic urticaria: a double-blind placebo-controlled study. *Journal of Dermatological Treatment* 1991; **2**(2):51–3. [EMBASE: 1991326012]

Phanuphak 1987 *{published data only}*

Phanuphak P. Double-blind, placebo-controlled study of ketotifen in chronic urticaria. *Immunology & Allergy Practice* 1987;**9**(4):138–43. [EMBASE: 1987132488]

Pons-Guiraud 2006 *{published data only}*

Pons-Guiraud A, Nekam K, Lahovsky J, Costa A, Piacentini A. Emedastine difumarate versus loratadine in chronic idiopathic urticaria: a randomized, double-blind, controlled European multicentre clinical trial. *European Journal of Dermatology* 2006;**16**(6):649–54. [MEDLINE: 17229605]

Potter 2009 *{published data only}*

NCT00264303. CUTE (Chronic Urticaria Treatment Evaluation). //clinicaltrials.gov/show/NCT00264303 (accessed 3 July 2013).

* Potter PC, Kapp A, Maurer M, Guillet G, Jian AM, Hauptmann P, et al. Comparison of the efficacy of levocetirizine 5 mg and desloratadine 5 mg in chronic idiopathic urticaria patients. Allergy 2009; Vol. 64, issue 4: 596–604. [MEDLINE: 19053988]

Ring 2001 *{published data only}*

Hein R, Gauger A, Rikken G, Staudinger H, Ring J. Rapid onset and sustained efficacy of desloratadine in treatment of chronic idiopathic urticaria. *Allergologie* 2000;**23**:427. [CENTRAL: CN–00606999]

Prenner B, Desloratadine urticaria study group. Desloratadine has a rapid onset of action in the treatment

of chronic idiopathic urticaria. *Annals of Allergy, Asthma & Immunology* 2001;**86**:84. [CENTRAL: CN–00385348]
* Ring J, Hein R, Gauger A, Bronsky E, Miller B. Once-daily desloratadine improves the signs and symptoms of chronic idiopathic urticaria: a randomized, double-blind, placebo-controlled study. *International Journal of Dermatology* 2001;**40**(1):72–6. [MEDLINE: 11277962]

Salo 1989 *{published data only}*
Salo OP, Harvey SG, Calthrop JG, Gibson JR. A comparison of acrivastine versus hydroxyzine and placebo in the treatment of chronic idiopathic urticaria. *Journal of International Medical Research* 1989;**17**(Suppl 2):18B–21B. [MEDLINE: 2569996]

Sener 1999 *{published data only}*
Sener O, Taskapan O, Kalelioglu C, Ozanguc N. Efficacy of fluoxetine versus ketotifen in the treatment of chronic idiopathic urticaria. *Annals of Allergy, Asthma & Immunology* 1999;**82**:119. [CENTRAL: CN–00284498]

Staevska 2014 *{published data only}*
Staevska MT, Gugutkova MD, Lazarova TC, Kralimarkova TZ, Dimitrov VD, Popov TA. Effect of two different drug regimens containing higher than conventional doses of levocetirizine in weaning urticaria patients from systemic corticosteroid treatment. Conference: European Academy of Allergy and Clinical Immunology and World Allergy Organization World Allergy and Asthma Congress 2013 Milan Italy. Conference Start: 20130622 Conference End: 20130622. Conference Publication:. *Allergy: European Journal of Allergy and Clinical Immunology* 2013;**68**(Suppl 97):189–336.
* Staevska, M, Gugutkova M, Lazarova C, Kralimarkova T Dimitrov V, Zuberbier T, et al. Night-time sedating H1-antihistamine increases daytime somnolence but not treatment efficacy in chronic spontaneous urticaria: a randomized controlled trial. *British Journal of Dermatology* 2014;**171**(1):148–54. [MEDLINE: 24472058]

Thompson 2000 Study 1 *{published data only}*
Thompson A, Finn A, Schoenwetter W. Effect of 60 mg BID fexofenadine HCL on quality of life, work productivity, and regular activity in patients with chronic idiopathic urticaria. *Annals of Allergy, Asthma & Immunology* 1999;**82**:122. [CENTRAL: CN–00285038]
* Thompson AK, Finn AF, Schoenwetter WF. Effect of 60 mg twice-daily fexofenadine HCl on quality of life, work and classroom productivity, and regular activity in patients with chronic idiopathic urticaria. *Journal of the American Academy of Dermatology* 2000;**43**(1 Pt 1):24–30. [MEDLINE: 10863219]

Thompson 2000 Study 2 *{published data only}*
Thompson A, Finn A, Schoenwetter W. Effect of 60 mg BID fexofenadine HCL on quality of life, work productivity, and regular activity in patients with chronic idiopathic urticaria. Annals of Allergy, Asthma & Immunology 1999; Vol. 82:122. [CENTRAL: CN–00285038]
* Thompson AK, Finn AF, Schoenwetter WF. Effect of 60 mg twice-daily fexofenadine HCl on quality of life, work and classroom productivity, and regular activity in patients with chronic idiopathic urticaria. *Journal of the American Academy of Dermatology* 2000;**43**(1 Pt 1):24–30. [MEDLINE: 10863219]

Wan 2009 *{published data only}*
Wan KS. Efficacy of leukotriene receptor antagonist with an anti-H1 receptor antagonist for treatment of chronic idiopathic urticaria. Journal of Dermatological Treatment 2009; Vol. 20, issue 4:194–7. [MEDLINE: 19085267]

Wang 2012 *{published data only}*
Wang HJ, Zhang JA, Yu JB. Clinical observation of long-term decrement mizolastine therapy in the treatment of chronic urticaria. Journal of Clinical Dermatology 2012; Vol. 41, issue 7:440–2. [EMBASE: 2012596086]

Weller 2013 *{published data only}*
Weller K, Ardelean E, Scholz E, Martus P, Zuberbier T, Maurer M. Can on-demand non-sedating antihistamines improve urticaria symptoms? A double-blind, randomized, single-dose study. Acta Dermato-Venereologica 2013; Vol. 93, issue 2:168–74. [MEDLINE: 23053062]

Wu 2008 *{published data only}*
Wu S-X, Guo N-R, Chen J, Sun J-F. Different dosages of azelastine and in combination of cimetidine in the treatment of chronic urticaria. *Journal of Clinical Dermatology* 2008; **37**(3):194–6. [EMBASE: 2008197256]

Yin 2003a *{published data only}*
Yin R, Hao F, Xiang MM, Shun RS, Deng J. A clinical trial of levocetirizine in the treatment of chronic idiopathic urticaria. *Journal of Clinical Dermatology* 2003;**32**(8): 477–8.

Yin 2003b *{published data only}*
Yin R, Diao QC, Ye QY. Clinical research of three antihistamines in the treatment of chronic idiopathic urticaria. *Journal of Clinical Dermatology* 2003b;**32**(11): 675–77.

Zou 2002 *{published data only}*
Zou Y, Chen XP. Curative effect of desloratadine in the treatment of chronic idiopathic urticaria. *Central China Medical Journal* 2002;**27**(2):75–6.

Zuberbier 2010 *{published data only}*
Zuberbier T, Oanta A, Bogacka E, Medina I, Wesel F, Uhl P, et al. Comparison of the efficacy and safety of bilastine 20 mg vs levocetirizine 5 mg for the treatment of chronic idiopathic urticaria: a multi-centre, double-blind, randomized, placebo-controlled study. Allergy 2010; Vol. 65, issue 4:516–28. [MEDLINE: 19860762]

References to studies excluded from this review

Aberer 2001 *{published data only}*
Aberer W, Kränke B. One-year treatment of chronic urticaria with mizolastine: efficacy and safety. Journal of the European Academy of Dermatology & Venereology 2001; Vol. 15, issue 1:77–9. [MEDLINE: 11451333]

Abushareeah 1997 *{published data only}*
Abushareeah AM, Yousuf M, Decker LA, de Mahieu C. Double blind comparative study of cetirizine, mequitazine

and placebo in the treatment of chronic idiopathic urticaria [Abstract 3211]. The 19th World Congress of Dermatology 15-20 June, 1997 Sydney, Australia. *Australasian Journal of Dermatology* 1997;**38**(Suppl 2):211.

Alomar 1990b *{published data only}*
Alomar A, De La Cuadra, Fernandez J. Cetirizine vs astemizole in the treatment of chronic idiopathic urticaria. *Journal of International Medical Research* 1990;**18**(5): 358–65. [MEDLINE: 2147912]

Andri 1993 *{published data only}*
Andri L, Senna GE, Betteli C, Givanni S, Andri G, Lombardi C, et al. A comparison of the efficacy of cetirizine and terfenadine. A double-blind, controlled study of chronic idiopathic urticaria. *Allergy* 1993;**48**(5):358–65. [MEDLINE: 8368464]

Anon 1992 *{published data only}*
Anon. The steroid-sparing effect of astemizole in chronic urticaria [Chronische Urtikaria. Unter Astemizol–Therapie kann die Kortikosteroid–Dosis reduziert werden]. *H+G Zeitschrift fur Hautkrankheiten* 1992;**67**(9):820. [EMBASE: 1992296793]

Anonymous 1989 *{published data only}*
Anonymous. Terfenadine once daily in chronic urticaria. A multi-centre double-blind comparison of terfenadine once daily versus twice daily. *Allergy* 1989;**44**(7):447–52. [MEDLINE: 2573286]

Anonymous 1990 *{published data only}*
Anonymous (Wan-Qing L). A double-blind clinical trial of astemizole in the treatment of chronic urticaria (Chinese). *Chinese Journal of Dermatology* 1990;**26**(3):120–1.

Anonymous 1992 *{published data only}*
Anonymous. Acid casein and cyproheptadine in the treatment of 150 cases of chronic urticaria (Chinese). *Chinese Journal of Dermatology* 1992;**25**(4):263.

Arendt 1989 *{published data only}*
Arendt C, Bernheim J. Double-blind comparison of maintenance treatment of chronic idiopathic urticaria by cetirizine and terfenadine. *Current Therapeutic Research Clinical and Experimental* 1989;**46**(4):724–34. [EMBASE: 1989253098]

Atsushi 1985 *{published data only}*
Atsushi K, Shotaro H, Yusho M, Akira S, Hachiro T, Shoji O, et al. Evaluation of therapeutic effects of terfenadine on chronic urticaria: double blind comparative study with clemastine [Terfenadine no Mansei Jimmashin ni Taisuru Yuyosei no Kenrto: Clemastine o Taisho to Shita Niju Moken Gunkan Hikaku Shiken]. *Rinsho Iyaku (Journal of Clinical Therapeutics and Medicines)* 1985;**1**(9):1297–310. [CENTRAL: CN–00475854]

Bakos 1985 *{published data only}*
Bakos L. Comparative trial between terfenadine and dexchlorpheniramine in chronic urticaria [Estudo comparativo do terfenadine versus dextroclorofeniramina em urticaria cronica]. *Revista Brasileira de Clinica e Terapeutica* 1985;**14**(1-2):47–9. [EMBASE: 1985124642]

Baraf 1976 *{published data only}*
Baraf CS. Treatment of pruritus in allergic dermatoses: an evaluation of the relative efficacy of cyproheptadine and hydroxyzine. *Current Therapeutic Research Clinical and Experimental* 1976;**19**(1):32–8. [MEDLINE: 812662]

Bernd 1989 *{published data only}*
Bernd LAG. Astemizol and terfenadine: double-blind study in the treatment of chronic urticaria [Estudo duplo–cego entre astemizol e terfenadina no tratamento da urticaria cronica]. *Folha Medica* 1989;**99**(5-6):295–300. [EMBASE: 1990061508]

Bernstein 1986 *{published data only}*
Bernstein IL, Bernstein DI. Efficacy and safety of astemizole, a long-acting and non-sedating H1 antagonist for the treatment of chronic idiopathic urticaria. *Journal of Allergy & Clinical Immunology* 1986;**77**(1 Pt 1):37–42. [MEDLINE: 3080510]

Bernstein 2002 *{published data only}*
Bernstein JA, Levin L, Zhong W. Combination treatment with cetirizine and zafirlukast improves urticaria in patients with autoantibody to FcE1 receptors [Abstract 476]. American Academy of Allergy Asthma and Immunology 58th Annual Meeting. New York, New York, USA. March 1-6, 2002. Journal of Allergy, Asthma & Immunology. 2002; Vol. 109 (Suppl 1).

Bian 1996 *{published data only}*
Bian ZP, Qian ML, Mao NE, Luo BG. A randomised controlled trial of loratadine versus astemizole in the treatment of chronic urticaria (Chinese). *Journal of Clinical Dermatology* 1996;**25**(3):165–6.

Bleehen 1987 *{published data only}*
Bleehen SS, Thomas SE, Greaves MW, Newton J, Kennedy CT, Hindley F, et al. Cimetidine and chlorpheniramine in the treatment of chronic idiopathic urticaria: a multi-centre randomized double-blind study. *British Journal of Dermatology* 1987;**117**(1):81–8. [MEDLINE: 3307890]

Bloom 2004 *{published data only}*
Bloom M, Staudinger H, Herron J. Safety of desloratadine syrup in children. *Current Medical Research & Opinion* 2004;**20**(12):1959–65. [MEDLINE: 15701213]

Brunet 1990 *{published data only}*
Brunet C, Bedard PM, Hebert J. Effects of H1-antihistamine drug regimen on histamine release by non-lesional skin mast cells of patients with chronic urticaria. *Journal of Allergy & Clinical Immunology* 1990;**86**(5):787–93. [MEDLINE: 1699989]

Cainelli 1986 *{published data only}*
Cainelli T, Seidenari S, Valsecchi R, Mosca M. Double-blind comparison of astemizole and terfenadine in the treatment of chronic urticaria. *Pharmatherapeutica* 1986;**4** (10):679–86. [MEDLINE: 2885854]

Camarasa 2001 *{published data only}*
Camarasa JM, Aliaga A, Fernandez-Vozmediano JM, Fonseca E, Iglesias L, Tagarro I. Azelastine tablets in the treatment of chronic idiopathic urticaria. Phase III,

randomised, double-blind, placebo and active controlled multicentric clinical trial. *Skin Pharmacology & Applied Skin Physiology* 2001;**14**(2):77–86. [MEDLINE: 11316966]

Cassano 2007 ***{published data only}***
Cassano N, Cesare G, Tsapoga V, Vena GA. Cyclosporin in chronic urticaria: state of the art [Ciclosporina nell'orticaria cronica: stato dell'arte]. *Annali Italiani di Dermatologia Allergologica Clinica e Sperimentale* 2007;**61**(1):6–11. [EMBASE: 2007300249]

Cerio 1984 ***{published data only}***
Cerio R, Lessof MH. Treatment of chronic idiopathic urticaria with terfenadine. Clinical Allergy 1984; Vol. 14, issue 2:139–41. [MEDLINE: 6423314]

Chatterjee 1996 ***{published data only}***
Chatterjee G, Banerjee PK. A comparison of the efficacy of cetirizine and terfenadine in chronic idiopathic urticaria. *Indian Journal of Dermatology* 1996;**41**(3):82–6. [CENTRAL: CN–00663322]

Chen 2005 ***{published data only}***
Chen LY, Guo YQ. Observation on short-term therapeutic effect of Bo's abdominal acupuncture on chronic urticaria [Chinese]. *Zhongguo Zhenjiu* 2005;**25**(11):768–70. [MEDLINE: Chinese translation OBTAINED]

Church 2009 ***{published data only}***
Church D, Baiardini I, Staevska M, Popov T, Kralimarkova T, Dimitrov V, et al. The effectiveness of antihistamines in up to four-times conventional doses on urticarial discomfort and quality of life in difficult-to-treat urticaria [Abstract]. 28th Congress of the European Academy of Allergy and Clinical Immunology Abstract Book Warszawa Poland. Conference Start: 20090606 Conference End: 20090610. *Allergy: European Journal of Allergy & Clinical Immunology* 2009;**64**:571. [EMBASE: 70021424]

Cook 1983 ***{published data only}***
Cook LJ, Shuster S. Lack of effect of cimetidine in chronic-idiopathic urticaria. *Acta Dermato-Venereologica* 1983;**63**(3):265–7. [MEDLINE: 6192652]

Demaubeuge 1982 ***{published data only}***
Demaubeuge J, Tennstedt D, Broux R. Does mast cell protection plus mediator antagonism surpass the effect of a classic antihistaminic in the treatment of chronic urticaria? A double-blind comparison of oxatomide and mequitazine. Dermatologica 1982; Vol. 164, issue 6: 386–94. [MEDLINE: 6126399]

Devillier 2007 ***{published data only}***
Devillier P, Bousquet J. Inhibition of the histamine-induced weal and flare response: a valid surrogate measure for antihistamine clinical efficacy?. *Clinical & Experimental Allergy* 2007;**37**(3):400–14. [MEDLINE: 17359390]

Devillier 2008 ***{published data only}***
Devillier P, Roche N, Faisy C. Clinical pharmacokinetics and pharmacodynamics of desloratadine, fexofenadine and levocetirizine: a comparative review. *Clinical Pharmacokinetics* 2008;**47**(4):217–30. [MEDLINE: 18336052]

Dhurandhar 1987 ***{published data only}***
Dhurandhar MW, Sharma SD. Azatadine versus pheniramine in chronic urticaria. *Medicine and Surgery* 1987;**27**(9):15–7. [EMBASE: 1988189679]

Diller 1983 ***{published data only}***
Diller G, Orfanos CE. Management of idiopathic urticaria with H1 + H2 antagonists. A crossover double blind long-term study [Behandlung der idiopathischen urticaria mit H1+H2 antagonisten. Ergebnisse einer crossover–doppelblind–langzeitstudie]. *H+G Zeitschrift für Hautkrankheiten* 1983;**58**(11):785–93. [EMBASE: 1983171814]

Dockx 1981 ***{published data only}***
Dockx P, Vertommen J, Van Daele R. Oxatomide effective in chronic urticaria: a double-blind comparison with a placebo. *Current Therapeutic Research Clinical and Experimental* 1981;**29**(3 II):510–6. [EMBASE: 1981227927]

Farshchain 2002 ***{published data only}***
Farshchain M. Comparison of ketotifen effectiveness with hydroxyzine in the treatment of pruritus and chronic idiopathic urticaria [Abstract]. 20th World Congress of Dermatology Paris, 1st to 5th July 2002. *Annales de Dermatologie et de Venereologie* 2002;**129**:P1667.

Ferguson 1985 ***{published data only}***
Ferguson J, MacDonald KJ, Kenicer KJ. Terfenadine and placebo compared in the treatment of chronic idiopathic urticaria: a randomised double-blind study. *British Journal of Clinical Pharmacology* 1985;**20**(6):639–41. [MEDLINE: 3937549]

Fox 1986 ***{published data only}***
Fox RW, Lockey RF, Bukantz SC, Serbousek D. The treatment of mild to severe chronic idiopathic urticaria with astemizole: double-blind and open trials. *Journal of Allergy & Clinical Immunology* 1986;**78**(6):1159–66. [MEDLINE: 3097109]

Fredriksson 1986 ***{published data only}***
Fredriksson T, Hersle K, Hjorth N, Mobacken H, Persson T, Salde L, et al. Terfenadine in chronic urticaria: a comparison with clemastine and placebo. Cutis 1986; Vol. 38, issue 2:128–30. [MEDLINE: 2874958]

Gao 2009 ***{published data only}***
Gao H, Li XZ, Ye WW, Zhou BY, Jin YJ, Qiu Y, et al. [Influence of penetrative needling of Shendao (GV 11) on the symptom score and serum IgE content in chronic urticaria patients]. Zhen Ci Yan Jiu = Acupuncture Research/[Zhongguo Yi Xue Ke Xue Yuan Yi Xue Qing Bao Yan Jiu Suo Bian Ji] 2009; Vol. 34, issue 4:272–5. [MEDLINE: CHINESE TRANSLATION OBTAINED]

Ge 1987 ***{published data only}***
Ge ZP, Luo CH. The efficacy contrast between doxepin and cyproheptadine for chronic urticaria (Chinese). *Journal of Clinical Dermatology* 1987;**16**(5):242–3.

Giannetti 1991 ***{published data only}***
Giannetti A, Motolese A. Controlled clinical study of cetirizine versus astemizole in patients with idiopathic

chronic urticaria [Studio clinico controllato ceririzina verso astemizolo in pazienti con orticaria cronica idiopatica]. *Chronica Dermatologica* 1991;**1**(3):321–35. [EMBASE: 1991245329]

Gibson 1984 ***{published data only}***
Gibson JR, Harvey SG, Barth JH, Moss MY, Burke CA. An assessment of the novel antihistamine BW 825C in the treatment of chronic idiopathic urticaria. A placebo-controlled study. Dermatologica 1984; Vol. 169, issue 4: 179–83. [MEDLINE: 6149965]

Godse 2006 ***{published data only}***
Godse KV. Oral montelukast monotherapy is ineffective in chronic idiopathic urticaria: a comparison with oral cetirizine. *Indian Journal of Dermatology, Venereology & Leprology* 2006;**72**(4):312–4. [MEDLINE: 16880585]

Gong 1995 ***{published data only}***
Gong J, Gao GB, Zhang W. Combined treatment with cetirizine, cimetidine and dipyridamole in 57 patients with chronic urticaria (Chinese). *Journal of Clinical Dermatology* 1995;**24**(3):163–4.

Gonzalez-Morales 1985 ***{published data only}***
Gonzalez-Morales JE, Leal De Hernandez L, Welsh O. Tolerance and efficacy of terfenadine compared with placebo in idiopathic chronic urticaria [Tolerancia y eficacia de la tefernadina contra placebo en el tratamiento de la urticaria cronica idiopatica. Estudio comparativo doble ciego.]. *Dermatologia Revista Mexicana* 1985;**29**(3):100–4. [EMBASE: 1987098302]

Greaves 1981 ***{published data only}***
Greaves MW. Antihistamine treatment: a patient self-assessment method in chronic urticaria. *British Medical Journal (Clinical Research Edition)* 1981;**283**(6304):1435–6. [MEDLINE: 6119130]

Greene 1985 ***{published data only}***
Greene SL, Reed CE, Schroeter AL. Double-blind crossover study comparing doxepin with diphenhydramine for the treatment of chronic urticaria. *Journal of the American Academy of Dermatology* 1985;**12**(4):669–75. [MEDLINE: 3886724]

Grob 2009 ***{published data only}***
Grob JJ, Auquier P, Dreyfus I, Ortonne JP. How to prescribe antihistamines for chronic idiopathic urticaria: desloratadine daily vs PRN and quality of life. *Allergy* 2009; **64**(4):605–12. [PUBMED: 19133920]

Guaglianone 1988 ***{published data only}***
Guaglianone MH, Vergallo G, Iudice A, Henauer S. Once a day dosage of terfenadine in chronic urticaria: a double-blind comparison with the standard dosage. *Arerugi [Allergy]* 1988;**43**(Suppl 7):94.

Guerra 1994 ***{published data only}***
Guerra L, Vincenzi C, Marchesi E, Tosti A, Pretto E, Bassi R, et al. Loratadine and cetirizine in the treatment of chronic urticaria. *Journal of the European Academy of Dermatology & Venereology* 1994;**3**(2):148–52. [EMBASE: 1994126862]

Hair 2006 ***{published data only}***
Hair PI, Scott LJ. Levocetirizine: a review of its use in the management of allergic rhinitis and skin allergies. *Drugs* 2006;**66**(7):973–96. [MEDLINE: 16740020]

Hamerlinck 1994 ***{published data only}***
Hamerlinck FFV, Boyden B, Oei HD, Niordson AM, Avrach W, Ottevanger V, et al. A double-blind comparative study of loratadine and astemizole in chronic idiopathic urticaria. *Journal of Dermatological Treatment* 1994;**5**(4): 199–202. [EMBASE: 1995029316]

Hampel 2010 ***{published data only}***
Hampel F, Nayak A, Texter M. The safety and tolerability of levocetirizine dihydrochloride in children 1-5 years with allergic rhinitis or chronic idiopathic urticaria. Conference: Southwest Allergy Forum Puerto Vallarta Mexico. Conference Start: 20090114 Conference End: 20090118. *Allergy & Asthma Proceedings* 2009;**30**(2):209. [EMBASE: 70148899]
* Hampel F, Ratner P, Haeusler JMC. Safety and tolerability of levocetirizine dihydrochloride in infants and children with allergic rhinitis or chronic urticaria. *Allergy & Asthma Proceedings* 2010;**31**(4):290–5. [EMBASE: 2010482204]
NCT00619801. A multi-center, randomized, double blind, placebo controlled parallel group study of the safety of levocetirizine dihydrochloride oral liquid formulation b.i.d dosing in children aged 1 to < 6 years suffering from allergic rhinitis or chronic urticaria of unknown origin [completed]. clinicaltrials.gov/show/NCT00619801 (accessed 31 Jul 2008).

Han 1992 ***{published data only}***
Han G, Ran LH. The curative effect observation of terfenadine for 116 cases hives (Chinese). *Journal of Clinical Dermatology* 1992;**21**(3):159.

Hong 2010 ***{published data only}***
Hong JB, Lee HC, Hu FC, Chu CY. A randomized, double-blind, active-controlled, parallel-group pilot study to compare the efficacy and sedative effects of desloratadine 5 mg with levocetirizine 5 mg in the treatment of chronic idiopathic urticaria. Journal of the American Academy of Dermatology 2010; Vol. 63, issue 5:e100–2. [MEDLINE: 20950731]

Honsinger 1990 ***{published data only}***
Honsinger RW Jr, Thomsen RJ. Prolonged benefit in the treatment of chronic idiopathic urticaria with astemizole. *Annals of Allergy* 1990;**65**(3):194–200. [MEDLINE: 1976298]

Huo 2014 ***{published data only}***
Huo HM. Efficacy observation on acupuncture combined with bloodletting for chronic urticaria. Zhongguo Zhenjiu = Chinese Acupuncture & Moxibustion 2014; Vol. 34, issue 1:41–3. [MEDLINE: 24673054]

Ishibashi 1989 ***{published data only}***
Ishibashi Y, Yoshida H, Kukita A, Harada S, Nishikawa T, Okawara A, et al. Dose finding study of astemizole (MJD-30) on chronic urticaria [Astemizole (MJD–30) no Mansei Jimmashin ni Okeru Shiteki Yoryo no Kento]. *Rinsho Iyaku*

(Journal of Clinical Therapeutics and Medicines) 1989;**5**(12): 2531–43. [CENTRAL: CN–00547587]

Ishibashi 1990 ***{published data only}***
Ishibashi Y, Harada S, Niimura M, Ueda H, Imamura S, Yamamoto S, et al. Clinical evaluation of KG-2413 (emedastine difumarate) on chronic urticaria by multicenter double-blind study: comparative study between 2mg/day, 4mg/day, and ketotifen fumarate [Tashisetsu Niju Mokenho ni Yoru Mansei Jimmashin ni Taisuru Ko Arerugi Zai KG–2413 (Fumarusan Emedasuchin) no Rinsho Hyoka: 2mg/Nichi, 4mg/Nichi Oyobi Fumarusan Ketoshifen ni Yoru 3 Gunkan Hikaku Seiseki]. *Rinsho Iyaku (Journal of Clinical Therapeutics and Medicines)* 1990;**6**(1):141–59. [CENTRAL: CN–00547345]

Ishibashi 1990a ***{published data only}***
Ishibashi Y, Harada S, Kukita A, Nishikawa T, Yoshida H, Okawara A, et al. A clinical study of astemizole (MJD-30) in treating chronic urticaria: a double blind, comparative study using ketotifen fumarate as a control drug [Astemizole (MJD–30) no Mansei Jimmashin ni Taisuru Rinsho Shiken: Ketotifen Fumarate o Taishoyaku to Shita Niju Moken Hikaku Shiken]. *Rinsho Iyaku (Journal of Clinical Therapeutics and Medicines)* 1990;**6**(8):1623–38. [CENTRAL: CN–00547150]

Ishibashi 1990b ***{published data only}***
Ishibashi Y, Harada S, Kukita A, Nishikawa T, Yoshida H, Okawara A, et al. A clinical study of astemizole (MJD-30) in treating chronic urticaria: a double blind, comparative study using ketotifen fumarate as a control drug [Astemizole (MJD–30) no Mansei Jimmashin ni Taisuru Rinsho Shiken: Ketotifen Fumarate o Taishoyaku to Shita Niju Moken Hikaku Shiken]. *Rinsho Iyaku (Journal of Clinical Therapeutics and Medicines)* 1990;**6**(8):1623–38. [CENTRAL: CN–00547150]

Ishibashi 1997 ***{published data only}***
Ishibashi Y, Harada S, Niimura M, Kawashima M, Yamamoto S, Yoshida H, et al. A multicenter double-blind comparative study: clinical evaluation of TAU-284 (betotastine besilate) on chronic urticaria using terfenadine as a control drug [TAU–284 (Beshirusan Betotasuchin) no Mansei Jimmashin ni Taisuru Rinsho Hyoka: Terufenajin o Taishoyaku to Shita Tashisetsu Niju Moken Hikaku Shiken]. *Rinsho Iyaku (Journal of Clinical Therapeutics and Medicines)* 1997;**13**(5):1287–306. [CENTRAL: CN–00547332]

Ishibashi 1997a ***{published data only}***
Ishibashi, Y, Harada, S, Niimura, M. Early phase II study of TAU-284 (betotastine besilate) on chronic urticaria [in Japanese]. *Rinsho Iyaku* 1997;**13**(5):1199–215.

Ishibashi 1997b ***{published data only}***
Ishibashi, Y, Harada, S, Niimura, M. Late phase II study of TAU-284 (betotastine besilate) on chronic urticaria: optimal dose finding study by double-blind technique [in Japanese]. Rinsho Iyaku 1997; Vol. 13, issue 5:1237–57.

Isola 1985 ***{published data only}***
Isola E, Rosengarten S, Torre F. Comparative multicenter study of the tolerance and efficacy of terfenadine vs placebo in chronic urticaria [Estudio multicentrico comparativo sobre tolerancia y eficacia de terfenadina vs. placebo en urticaria cronica]. *Investigación Médica Internacional* 1985; **12**(1):40–8. [EMBASE: 1985205432]

Jauregui 2006 ***{published data only}***
Jauregui I, Mullol J, Bartra J, del Cuvillo A, Davila I, Montoro J, et al. H1antihistamines: psychomotor performance and driving. *Journal of Investigational Allergology & Clinical Immunology* 2006;**16**(Suppl 1): 37–44. [MEDLINE: 17357376]

Jia 1998 ***{published data only}***
Jia H, Liu XQ, Li HZ, Lin L, Cao YH, Cui PG, et al. Clinical observation on the efficacy of domestic cetirizine in the treatment of urticaria (Chinese). *Chinese Journal of Dermatology* 1998;**31**(5):339.

Jolliffe 1985 ***{published data only}***
Jolliffe DS, Sim-Davis D, Templeton JS. A placebo-controlled comparative study of sustained-release brompheniramine maleate against clemastine fumarate in the treatment of chronic urticaria. *Current Medical Research & Opinion* 1985;**9**(6):394–9. [MEDLINE: 3886304]

Juhlin 1988 ***{published data only}***
Juhlin L, Arendt C. Treatment of chronic urticaria with cetirizine dihydrochloride, a non-sedating antihistamine. *British Journal of Dermatology* 1988;**119**(1):67–71. [MEDLINE: 2900648]

Jyothi 2011 ***{published data only}***
Jyothi CH, Kiran LJ, Shashikala GH, Ravindra K, Santhosh R. Comparative study on safety and efficacy of loratadine, prednisolone & their combination in the treatment of chronic urticaria. *Pharmacologyonline* 2011;**3**:988–96. [EMBASE: 2012087113]

Kailasam 1987 ***{published data only}***
Kailasam V, Mathews KP. Controlled clinical assessment of astemizole in the treatment of chronic idiopathic urticaria and angioedema. Journal of the American Academy of Dermatology 1987; Vol. 16, issue 4:797–804. [MEDLINE: 2883202]

Kalimo 1980 ***{published data only}***
Kalimo K, Jansen CT. Treatment of chronic urticaria with an inhibitor of complement activation (cinnarizine). *Annals of Allergy* 1980;**44**(1):34–7. [MEDLINE: 7352689]

Kalis 1985 ***{published data only}***
Kalis B, Morel P, Prigent F. Chronic and cholinergic urticarias. Double blind comparison of mequitazine and hydroxyzine [Urticaires chroniques et cholinergiques. Etude comparative en double aveugle de la mequitazine et de l'hydroxyzine]. *Medecine et Hygiene* 1985;**43**(1604): 1133–6. [EMBASE: 1985098611]

Kalis 1996 ***{published data only}***
Kalis B. Double-blind multicentre comparative study of ebastine, terfenadine and placebo in the treatment of

chronic idiopathic urticaria in adults. *Drugs* 1996;**52**(Suppl 1):30–4. [MEDLINE: 8828024]

Kameyoshi 2007 ***{published data only}***
Kameyoshi Y, Tanaka T, Mihara S, Takahagi S, Niimi N, Hide M. Increasing the dose of cetirizine may lead to better control of chronic idiopathic urticaria: an open study of 21 patients. *British Journal of Dermatology* 2007;**157**(4): 803–4. [MEDLINE: 17627798]

Kamide 1989 ***{published data only}***
Kamide R, Niimura M, Ueda H, Imamura S, Yamamoto S, Yoshida H, et al. Clinical evaluation of ketotifen for chronic urticaria: multicenter double-blind comparative study with clemastine. *Annals of Allergy* 1989;**62**(4):322–5. [MEDLINE: 2650586]

Kaplan 2008 ***{published data only}***
Kaplan AP, Joseph K, Maykut RJ, Geba GP, Zeldin RK. Treatment of chronic autoimmune urticaria with omalizumab. *Journal of Allergy & Clinical Immunology* 2008;**122**(3):569–73. [MEDLINE: 18774392]

Kapp 2004 ***{published data only}***
Kapp A, Wedi B. Chronic urticaria: clinical aspects and focus on a new anti-histamine, levocetirizine. *Journal of Drugs in Dermatology* 2004;**3**(6):502–8.

Kapp 2006 ***{published data only}***
Kapp A, Demarteau N. Cost effectiveness of levocetirizine in chronic idiopathic urticaria: a pooled analysis of two randomised controlled trials. Clinical Drug Investigation 2006; Vol. 26, issue 1:1–11. [MEDLINE: 17163229]

Kapp 2006a ***{published data only}***
Kapp A, Pichler WJ. Levocetirizine is an effective treatment in patients suffering from chronic idiopathic urticaria: a randomized, double-blind, placebo-controlled, parallel, multicenter study. International Journal of Dermatology 2006; Vol. 45, issue 4:469–74. [MEDLINE: 16650180]

Kawada 2011 ***{published data only}***
Kawada A, Furukawa F, Hide M. Comparative efficacy of continuous and intermittent use of epinastine for chronic urticaria in an 8-week randomized, multicenter, parallel-group study [Abstract]. 69th Annual Meeting of the American Academy of Dermatology New Orleans, LA United States. Conference Start: 20110204. *Journal of the American Academy of Dermatology* 2011;**64**(2 Suppl 1): AB32. [EMBASE: 70331444]

Kawashima 2002 ***{published data only}***
Kawashima M, Harada S, Nakashima M. Phase III study of TAU-284 (bepotastine besilate) on chronic urticaria, a multicenter double blind comparative study with placebo. *Rinsho Iyaku* 2002;**18**:501–18.

Khalaf 2008 ***{published data only}***
Khalaf AT, Liu XM, Sheng WX, Tan JQ, Abdalla AN. Efficacy and safety of desloratadine combined with dipyridamole in the treatment of chronic urticaria. *Journal of the European Academy of Dermatology & Venereology* 2008; **22**(4):487–92. [MEDLINE: 18081747]

Kietzmann 1990 ***{published data only}***
Kietzmann H, Macher E, Rihoux JP, Ghys L. Comparison of cetirizine and terfenadine in the treatment of chronic idiopathic urticaria. *Annals of Allergy* 1990;**65**(6):498–500. [MEDLINE: 1979471]

Kim 2013 ***{published data only}***
Kim S, Baek S, Shin B, Yoon S-Y, Park SY, Lee T, et al. Influence of initial treatment modality on long-term control of chronic idiopathic urticaria. Plos ONE. 7. Public Library of Science. US, 2013; Vol. 8, issue 7:e69345.

Kukita 1985 ***{published data only}***
Kukita A, Harada S, Miura Y, Ishihara M, Takahashi H, Nonami E, et al. Investigation on the optimal dose of terfenadine: result by double blind study, double dummy method, for chronic urticaria [Terfenadine no Shiteki Toyoryo no Kento: Mansei Jimmashin o Taisho to Shita Niju Moken Genkan Hikaku Shiken Seiseki]. *Rinsho Iyaku (Journal of Clinical Therapeutics and Medicines)* 1985;**1**(9): 1283–95. [CENTRAL: CN–00475853]

Kukita1985a ***{published data only}***
Kukita A, Harada S, Miura Y, Shirato A, Tagami H, Okamoto S, et al. Evaluation of therapeutic effects of terfenadine on chronic urticaria: double blind comparative study with clemastine [Terfenadine no Mansei Jimmashin ni Taisuru Yuyosei no Kenrto: Clemastine o Taisho to Shita Niju Moken Gunkan Hikaku Shiken]. *Rinsho Iyaku (Journal of Clinical Therapeutics and Medicines)* 1985;**1**(9): 1297–310. [CENTRAL: CN–00475854]

Kukita 1990 ***{published data only}***
Kukita A, Harada S, Okawara A, Takahashi M, Tagami H, Ishibashi Y, et al. Clinical usefulness of loratadine on chronic urticaria: multicenter double blind study in comparison with mequitazine [Loratadine no Mansei Jimmashin ni Taisuru Yuyosei no Kento: Mequitazine o Taishoyaku to Shita Tashisetsu Niju Moken Hikaku Shiken]. *Rinsho Iyaku (Journal of Clinical Therapeutics and Medicines)* 1990;**6**(12): 2689–705. [CENTRAL: CN–00542666]

Kukita 1990a ***{published data only}***
Kukita A, Harada S, Okawara A, Takahashi M, Tagami H, Ishibashi Y, et al. Dose-finding clinical trial of loratadine on chronic urticaria: double blind controlled study [Loratadine no Shiteki Toyoryo Oyobi Toyo Hoho no Kento: Mansei Jimmashin o Taisho to Shita Niju Moken Hikaku Shiken]. *Rinsho Iyaku (Journal of Clinical Therapeutics and Medicines)* 1990;**6**(10):2037–50. [CENTRAL: CN–00542675]

Kukita 1991 ***{published data only}***
Kukita A, Harada S, Okawara A, Takahashi M, Tagami H, Ishikawa H, et al. Phase III study of WAL801CL (Epinastine) on chronic urticaria: a double blind study in comparison with ketotifen fumarate [WAL801CL (Epinastine) Jo no Mansei Jimmashin ni Taisuru Rinsho Dai III So Shiken: Ketotifen Fumarate o Taishoyaku to Shita Niju Moken Hikaku Shiken]. *Rinsho Iyaku (Journal of Clinical Therapeutics and Medicines)* 1991;**7**(10):2303–20. [CENTRAL: CN–00542689]

Kukita 1994 *{published data only}*
Kukita A, Harada S, Yoshida H, Ishibashi Y, Niimura M, Yamamoto S, et al. Phase III study of LAS-90 on chronic urticaria: double blind comparative study with ketotifen fumarate [LAS–90 no Mansei Jimmashin ni Taisuru Rinsho Dai III So Shiken: Ketotifen Fumarate o Taishoyaku to Shita Niju Moken Hikaku Shiken]. *Rinsho Iyaku (Journal of Clinical Therapeutics and Medicines)* 1994;**10**(4):895–912. [CENTRAL: CN–00542704]

Kukita 1994a *{published data only}*
Kukita A, Harada S, Yoshida H, Ishibashi Y, Niimura M, Yamamoto S, et al. Late phase II study of LAS-90 on chronic urticaria: optimal dose finding study by double-blind technique [LAS–90 no Mansei Jimmashin ni Taisuru Koki Rinsho Dai II So Shiken: Niju Mokenho ni Yoru Yoryo Settei Shiken]. *Rinsho Iyaku (Journal of Clinical Therapeutics and Medicines)* 1994;**10**:55–72. [CENTRAL: CN–00542708]

Kuokkanen 1971 *{published data only}*
Kuokkanen K, Paavilainen O. Evaluation of slow-releasing diphenylpyraline in chronic urticaria and various kinds of dermatites. *Acta Allergologica* 1971;**26**(6):454–62. [MEDLINE: 4401352]

Kuokkanen 1975 *{published data only}*
Kuokkanen K. A new antihistamine hc20-511 compared with dimetinden (fenistil retard) in the treatment of chronic urticaria and other pruritic dermatoses. *Acta Allergologica* 1975;**30**(2-3):73–9. [MEDLINE: 239517]

Kuokkanen 1977 *{published data only}*
Kuokkanen K. Comparison of a new antihistamine HC 20-511 with cyproheptadine (Periactin) in chronic urticaria. *Acta Allergologica* 1977;**32**(5):316–20. [MEDLINE: 21504]

Lambert 1990 *{published data only}*
Lambert D, Bloom M, Danglas P. Comparative double blind study of the delay of activity, efficacy and tolerance of terfenadine versus astemizole in the treatment of idiopathic chronic urticaria [Etude comparative en double aveugle du delai d'action, de l'efficacite et de la tolerance de la terfenadine versus astemizole dans l'urticaire chronique idiopathique]. *Comptes Rendus de Therapeutique et de Pharmacologie Clinique* 1990;**8**(88):21–7. [EMBASE: 1991294093]

Lambert 1993 *{published data only}*
Lambert D, Hantzperg M, Danglas P, Bloom M. Double-blind comparative study of terfenadine and cetirizine in chronic idiopathic urticaria [Etude comparative en double–aveugle de la terfenadine et de la cetirizine dans l'urticaire chronique idiopathique]. Allergie et Immunologie 1993; Vol. 25, issue 6:235–40. [MEDLINE: 8357472]

Lambert 1993a *{published data only}*
Lambert D, Hantzperg M, Danglas P, Bloom M. Chronic idiopathic urticaria: multicentre, double-blind comparison of terfenadine and cetirizine [Etude comparative en double–aveugle de la terfenadine et de la cetirizine dans l'urticaire chronique idiopathique]. *Allergie et Immunologie* 1993;**25**(6):235-236, 238-240. [EMBASE: 1993223997]

Lan 2002 *{published data only}*
Lan CG, Li H, Lin YK, Wu JJ, Wang XL, Ni ZZ. Efficacy and safety of desloratadine in the treatment of acute and chronic idiopathic urticaria. *Chinese Journal of New Drugs* 2002;**11**(8):631–3.

La Rosa 2001 *{published data only}*
La Rosa M, Leonardi S, Marchese G, Corrias A, Barberio G, Oggiano N, et al. Double-blind multicenter study on the efficacy and tolerability of cetirizine compared with oxatomide in chronic idiopathic urticaria in preschool children. *Annals of Allergy, Asthma, & Immunology* 2001;**87**(1):48–53. [MEDLINE: 11476462]

Lennox 2004a *{published data only}*
Lennox RD, Leahy MJ. Validation of the Dermatology Life Quality Index as an outcome measure for urticaria-related quality of life. Annals of Allergy, Asthma, & Immunology 2004; Vol. 93, issue 2:142–6. [MEDLINE: 15328673]

Li 2004 *{published data only}*
Li H, Yin J, Wen L, Yue F, Fang Q, Wang R, et al. Mizolastine provides effective symptom relief in patients suffering from chronic idiopathic urticaria: a randomized comparative study versus loratadine in China [Abstract]. American Academy of Allergy Asthma and Immunology, San Francisco, California, March 19-23 2004. *Journal of Allergy & Clinical Immunology* 2004;**113**(2 Suppl):S136. [CENTRAL: CN–00475902]

Liu 2002 *{published data only}*
Liu LL, Zhu XJ. A study on the efficacy and safety of astemizole versus loratadine in the treatment of chronic idiopathic urticaria. *Chinese Journal of Dermatovenereology* 2002;**16**(1):14–6. [CENTRAL: CN–00401668]

Magerl 2009 *{published data only}*
Magerl M, Schmolke J, Metz M, Zuberbier T, Siebenhaar F, Maurer M. Prevention of signs and symptoms of dermographic urticaria by single-dose ebastine 20 mg. *Clinical & Experimental Dermatology* 2009;**34**(5):e137–40. [MEDLINE: 19323664]

Magerl 2013 *{published data only}*
Magerl M, Rother M, Bieber T, Biedermann T, Brasch J, Dominicus R, et al. Randomized, double-blind, placebo-controlled study of safety and efficacy of miltefosine in antihistamine-resistant chronic spontaneous urticaria. *Journal of the European Academy of Dermatology & Venereology* 2013;**27**(3):e363–9. [EMBASE: 2013118378]

Maurer 2013a *{published data only}*
Maurer M, Rosen K, Hsieh HJ, Saini S, Grattan C, Gimenez-Arnau A, et al. Omalizumab for the treatment of chronic idiopathic or spontaneous urticaria. *New England Journal of Medicine* 2013;**368**(10):924–35. [MEDLINE: 23432142]

Meloy 2009 *{published data only}*
Meloy LD, Ratner PH, Texter MJ. The safety and tolerability of levocetirizine dihydrochloride in infants 6-11 months with allergic rhinitis or chronic idiopathic

urticaria [Abstract]. Western Society of Allergy, Asthma, and Immunology Meeting Wailea, HI United States. Conference Start: 20090125 Conference End: 20090129. *Allergy & Asthma Proceedings* 2009;**30**(2):210. [EMBASE: 70148903]

Monroe 1981 ***{published data only}***
Monroe EW, Cohen SH, Kalbfleisch J, Schulz CI. Combined H1 and H2 antihistamine therapy in chronic urticaria. *Archives of Dermatology* 1981;**117**(7):404–7. [MEDLINE: 6114712]

Monroe 2005 ***{published data only}***
Monroe EW, Gross G, Meeves S, Liao Y, Varghese ST, Georges G. Once-daily fexofenadine HCl 180 mg is effective for the treatment of CIU [Abstract]. American Academy of Allergy, Asthma and Immunology (AAAAI) 61st annual meeting. San Antonio, Texas, USA, March 18-22, 2005. *Journal of Allergy & Clinical Immunology* 2005; **115**(2 Suppl):S106. [CENTRAL: CN–00518315]

Monteseirin 1992 ***{published data only}***
Monteseirin Mateo J, Bobadilla Gonzalez P, Galindo Bonilla PA, Conde Hernandez J. Cinnarizine: a double-blind study in patients with chronic urticaria [Estudio a doble ciego con cinarizina de pacientes con urticaria crónica]. *Revista Española de Alergología e Inmunología Clínica* 1992;**7**(2): 71–4. [EMBASE: 1992171673]

Mora 2005 ***{published data only}***
Mora PM, Gonzalez Perez Mdel C, Jimenez Villarruel M, Rodriguez Castro E, Fogelbach GG. Therapeutic options in idiopathic chronic urticaria [Opciones terapeuticas en urticaria cronica idiopatica]. *Revista Alergia México* 2005;**52** (2):77–82. [MEDLINE: 16158780]

Nakayama 1980 ***{published data only}***
Nakayama Y, Akasaka T, Baba M, Iwasaki E, Funahashi S, Nishimuta T, et al. A double blind controlled trial of azatadine maleate syrup (idulamine syrup) in children with urticaria or atopic dermatitis. Comparison of effectiveness and side effect with d chlorpheniramine maleate syrup. *Rinsho Hyoka: Clinical Evaluation* 1980;**8**(1):235–78. [CENTRAL: CN–00268192]

Neumann 1984 ***{published data only}***
Neumann Y. Antihistaminic therapy of chronic urticaria. Results of a multicenter study with azatadine and terfenadine [Antihistaminika–Behandlung bei chronischer Urtikaria. Ergebnisse einer Multicenter–Studie mit Azatadin und Terfenadin]. *Fortschritte der Medizin* 1984; **102**(38):967–70. [MEDLINE: 6209194]

Nishiyama 1996 ***{published data only}***
Nishiyama S, Okamoto S, Ishibashi Y, Nishikawa T, Nishioka K, Nagai T. Phase III Study of KW-4679 (Olopatadine Hydrochloride) on Chronic Urticaria: A Double Blind Study in Comparison with Ketotifen Fumarate [KW–4679 (Ensan Oropatajin) Jo no Mansei Jimmashin ni Taisuru Dai III So Hikaku Shiken: Fumarusan Ketochifen o Taishoyaku to Shita Niju Moken Hikaku Shiken]. *Rinsho Iyaku (Journal of Clinical Therapeutics and Medicines)* 1996;**12**(9):1855–82. [CENTRAL: CN–00542941]

Nsouli 2013 ***{published data only}***
Nsouli SM. Efficacy of omalizumab, an anti-IgE recombinant humanized, monoclonal antibody, for the treatment of severe chronic idiopathic urticaria patients not controlled on oral antihistamines. Conference: 2013 Annual Meeting of the American College of Allergy, Asthma and Immunology Baltimore, MD United States. Conference Start: 20131107 Conference End: 2013. *Annals of Allergy, Asthma & Immunology* 2013;**111**(5 Suppl 1):A117. [EMBASE: 71307206]

Ormerod 1986 ***{published data only}***
Ormerod AD, Baker R, Watt J, White MI. Terfenadine and brompheniramine maleate in urticaria and dermographism. *Dermatologica* 1986;**173**(1):5–8. [MEDLINE: 2875904]

Ortonne 1998 ***{published data only}***
Ortonne J. Fexofenadine hydrochloride: a new anti-H1 in the treatment of chronic idiopathic urticaria. Study comparing the efficacy and safety of four dosage regimes [Abstract ST7-5]. The 7th Congress of the European Academy of Dermatology and Venereology, Nice, 7-11 Ocober 1998. *Journal of the European Academy of Dermatology & Venereology* 1998;**11**(Suppl 2):S103.

Paul 1984 ***{published data only}***
Paul E, Bödecker RH. Treatment of chronic urticaria with terfenadine and ranitidine. A randomized double-blind study [Therapie der chronischen Urticaria mit Terfenadin und Ranitidin. Eine randomisierte Doppelblind–Studie]. *Allergologie* 1984;**7**(4):159. [CENTRAL: CN–00252061]

Paul 1985 ***{published data only}***
Paul E, Bodeker RH. Comparison between astemizole and terfenadine in the treatment of chronic urticaria: a randomised double blind study of 40 patients. *Zeitschrift fur Hautkrankheiten* 1985;**60**(Suppl 1):50–5. [MEDLINE: 2859714]

Paul 1988 ***{published data only}***
Paul E, Reinel D, Ulrich R, Köhler ME. Comparison of efficacy and tolerability of terfenadine administered once daily versus twice daily in patients with chronic idiopathic urticaria. *Arerugi [Allergy]* 1988;**43**(Suppl 7):94. [CENTRAL: CN–00267227]

Paul 1988a ***{published data only}***
Paul E. Loratadine and terfenadine in the treatment of chronic urticaria. Results of a multicentre study. *Arerugi [Allergy]* 1988;**43**(Suppl 7):122. [CENTRAL: CN–00267241]

Paul 1988b ***{published data only}***
Paul E. Loratadine and terfenadine in the treatment of chronic urticaria. *Arerugi [Allergy]* 1988;**43**(Suppl 7):92. [CENTRAL: CN–00267223]

Paul 1989 ***{published data only}***
Paul E, Reinel D, Ulrich R, Kohler ME. Comparison of efficacy and tolerability of terfenadine administered once daily versus twice daily in patients with chronic idiopathic

urticaria. *Annals of Allergy* 1989;**63**(4):340–2. [MEDLINE: 2572189]

Paul 1989a *{published data only}*
Paul E, Bodeker RH. Comparative study of astemizole and terfenadine in the treatment of chronic idiopathic urticaria. A randomized double-blind study of 40 patients. *Annals of Allergy* 1989;**62**(4):318–20. [MEDLINE: 2565098]

Paul 1989b *{published data only}*
Paul E. Comparsion of loratadine and terfenadine in the treatment of chronic idiopathic urticaria. Results of an international multi-centre-study [Vergleich von Loratadin und Terfenadin in der Behandlung der chronischen idiopathischen Urticaria. Ergebnisse einer International Multi–Center–Studie]. *Allergologie* 1989;**11**(5):198. [CENTRAL: CN–00661504]

Pavic 2012 *{published data only}*
Pavic I, Hojsak I, Cepin-Bogovic J. Evidence-based management of chronic urticaria in children. *Pediatric, Allergy, Immunology, & Pulmonology* 2012;**25**(4):198–207. [EMBASE: 2012732053]

Peremans 1981 *{published data only}*
Peremans W, Mertens RL, Morias J, Campaert H. Oxatomide in the treatment of chronic urticaria. A double-blind placebo-controlled trial. Dermatologica 1981; Vol. 162, issue 1:42–50. [MEDLINE: 7014277]

Presch 1996 *{published data only}*
Presch A, Gorlich HD, Paul E. Terfenadine 120 mg vs. cetirizine 10 mg in patients with chronic idiopathic urticaria [Vergleich zwischen terfenadin 120 mg und cetirizin 10 mg bei chronischer idiopathischer urtikaria. Eine kontrollierte randomisierte doppelblinde multizentrische studie]. *Allergo Journal* 1996;**5**(1):31–5. [EMBASE: 1996071782]

Saihan 1983 *{published data only}*
Saihan EM, Littlewood SN. Ketotifen and terbutaline in chronic urticaria [Abstract]. *British Journal of Dermatology* 1983;**109**(Suppl 24):31. [EMBASE: 1983200922]

Salisbury 1987 *{published data only}*
Salisbury J, Bor S, Blair C. A double-blind placebo controlled study of terfenadine in the treatment of chronic idiopathic urticaria. *British Journal of Clinical Practice* 1987; **41**(8):859–61. [MEDLINE: 2896512]

Salmun 2000 *{published data only}*
Salmun LM, Herron JM, Banfield C, Padhi D, Lorber R, Affrime MB. The pharmacokinetics, electrocardiographic effects, and tolerability of loratadine syrup in children aged 2 to 5 years. *Clinical Therapeutics* 2000;**22**(5):613–21. [MEDLINE: 10868558]

Sanchez-Borges 2013a *{published data only}*
Sanchez-Borges M, Caballero-Fonseca F, Capriles-Hulett A. Aspirin-exacerbated cutaneous disease. *Immunology & Allergy Clinics of North America* 2013;**33**(2):251–62. [MEDLINE: 23639712]

Sanchez-Borges 2013b *{published data only}*
Sanchez-Borges M, Caballero-Fonseca F, Capriles-Hulett A. Treatment of recalcitrant chronic urticaria with nonsedating antihistamines: is there evidence for updosing?. *Journal of Investigational Allergology & Clinical Immunology* 2013;**23** (3):141–4. [MEDLINE: 23967751]

Shah 1986 *{published data only}*
Shah BH, Sharma SD. Comparative clinical study of azatadine and pheniramine in chronic urticaria. *Current Therapeutic Research Clinical and Experimental* 1986;**39**(3): 383–7. [EMBASE: 1987093636]

Shareeah 1998 *{published data only}*
Shareeah A, Youssuf M, Deckers I, De MC. Double-blind, parallel, randomized pilot study comparing the efficacy and tolerance of cetirizine 10 mg, mequitazine 2 x 5 mg and placebo in the treatment of patients suffering from chronic urticaria: comparison of suppressive effects on histamine-induced weals and flares. *Drug Development Research* 1998; **43**(4):185–92.

Shereff 1984 *{published data only}*
Shereff PH, Shah JK, Rawal RC, Shah BH. Comparative study of various therapeutic regimens in chronic urticaria. *Indian Journal of Dermatology, Venerology & Leprology* 1984; **50**(2):45–7. [CENTRAL: CN–00692723]

Sim-Davis 1983 *{published data only}*
Sim-Davis D, Templeton JS. A placebo-controlled comparative study of Dimotane LA against Optimine in the treatment of chronic urticaria with or without dermographism. *British Journal of Clinical Practice* 1983;**37** (7-8):253–8. [MEDLINE: 6136296]

Simons 1995 *{published data only}*
Simons FE, Sussman GL, Simons KJ. Effect of the H2-antagonist cimetidine on the pharmacokinetics and pharmacodynamics of H1-antagonists hydroxyzine and cetirizine in patients with chronic urticaria [Abstract no:1]. *Indian Journal of Dermatology, Venerology & Leprology* 1995; **61**:250. [CENTRAL: CN–00692606]

Singh 1987 *{published data only}*
Singh M, Kaur S. Relative efficacy of seven common H1 receptor antagonist antihistamines in chronic idiopathic urticaria. *Indian Journal of Dermatology, Venereology & Leprology* 1987;**53**(3):158–61. [EMBASE: 1988089884]

Sobye 1968 *{published data only}*
Sobye P, Ulrich J. Dimethpyrindene and a new antihistamine HS 592 (Sandoz) in the treatment of severe chronic urticaria. *Acta Allergologica* 1968;**23**(1):24–34. [MEDLINE: 4385407]

Staevska 2010 *{unpublished data only}*
Staevska M, Popov T, Kralimarkova T, Lazarova C, Kraeva S, Popova D, et al. The effectiveness of levocetirizine and desloratadine in up to 4 times conventional doses in difficult to treat urticaria. *Journal of Allergy & Clinical Immunology* 2010;**125**(3):676–82. [MEDLINE: 20226302]
Staevska, M, Kralimarkova T, Kraeva S, Lazarova C, Church, M, Dimitrov V, Popov T. Determinants of the success of treatment of subjects with chronic urticaria on higher than conventional doses of levocetirizine and desloratadine. Poster presentation. 2008.

Sussman 1991 *{published data only}*
Sussman G, Jancelewicz Z. Controlled trial of H1 antagonists in the treatment of chronic idiopathic urticaria. *Annals of Allergy* 1991;**67**(4):433–9. [MEDLINE: 1683191]

Taskapan 2000a *{published data only}*
Taskapan O, Sener O, Ozangue N. Cetirizine versus ketotifen in chronic idiopathic urticaria CIU: a single-blind, placebo-controlled study. *Annals of Allergy, Asthma & Immunology* 2000;**84**:138. [CENTRAL: CN–00385423]

Tilles 2005 *{published data only}*
Tilles SA. Approach to therapy in chronic urticaria: when benadryl is not enough. *Allergy & Asthma Proceedings* 2005; **26**(1):9–12. [MEDLINE: 15813282]

Valsecchi 1984 *{published data only}*
Valsecchi R, Tribbia G, Frigeni A. Oxatomide in treatment of chronic urticaria [IMPIEGO DELL'OXATOMIDE NELLA TERAPIA DELL'ORTICARIA CRONICA]. *Annali Italiani di Dermatologia Clinica e Sperimentale* 1984; **38**(3):323–8. [EMBASE: 1985054439]

Van Cauwenberge 2004 *{published data only}*
Van Cauwenberge P, De Belder T, Sys L. A review of the second-generation antihistamine ebastine for the treatment of allergic disorders. *Expert Opinion on Pharmacotherapy* 2004;**5**(8):1807–13. [MEDLINE: 15264995]

van Joost 1989 *{published data only}*
van Joost T, Blog FB, Westerhof W, Jansen FC, Starink TM, den Boer MS, et al. A comparison of acrivastine versus terfenadine and placebo in the treatment of chronic idiopathic urticaria. *Journal of International Medical Research* 1989;**17**(Suppl 2):14B–7B. [MEDLINE: 2569995]

Vena 2002 *{published data only}*
Vena GA, Cassano N, Filieri M, Filotico R, D'Argento V, Coviello C. Fexofenadine in chronic idiopathic urticaria: a clinical and immunohistochemical evaluation. International Journal of Immunopathology & Pharmacology 2002; Vol. 15, issue 3:217–24. [EMBASE: 2002402529]

Verhaegen 1980 *{published data only}*
Verhaegen H, De Cree J. Oxatomide in the treatment of idiopathic chronic urticaria. A placebo-controlled study [Behandlung der Chronisch–Idiopathischen Urtikaria mit Oxatomid. Ein Plazebo–Kontrollierter Versuch]. Allergologie 1980; Vol. 3, issue 1:30–3. [EMBASE: 1980131639]

Vijay 1994 *{published data only}*
Vijay M, Rawal RC, Billimoria FE. A comparative study of efficacy of cetirizine versus astemizole in chronic idiopathic urticaria. *Indian Journal of Dermatology, Venerology & Leprology* 1994;**60**(4):203–5. [EMBASE: 1995045872]

Wang 1998 *{published data only}*
Wang BZ, Wang X. A randomised controlled trial of cetirizine versus chlorpheniramine maleate in the treatment of urticaria of children (Chinese). *Journal of Clinical Dermatology* 1998;**27**(3):174–5.

Wang 2000 *{published data only}*
Wang KY, Li CY, Yu YJ, Sun XX, Gao HR. Cetirizine in treating chronic urticaria in 113 patients. *Chinese Journal of New Drugs & Clinical Remedies* 2000;**19**(1):19–20.

Warin 1966 *{published data only}*
Warin RP, Moore-Robinson M. A clinical trial of brompheniramine maleate in chronic urticaria. *Practitioner* 1966;**197**(178):212–4. [MEDLINE: 4380315]

Watson 2000 *{published data only}*
Watson NT, Weiss EL, Harter PM. Famotidine in the treatment of acute urticaria. Clinical & Experimental Dermatology 2000; Vol. 25, issue 3:186–9. [MEDLINE: 10844490]

Weitgasser 1967 *{published data only}*
Weitgasser H. Ambulatory testing of a new antihistaminic. Experience with Tavegil [Ambulante Prufung eines neuen Antihistaminikums. Erfahrungen mit Tavegil]. *Münchener Medizinische Wochenschrift* 1967;**109**(20): 1134–6. [MEDLINE: 4384702]

Weller 2010 *{published data only}*
Weller K, Ardelean E, Martus P, Zuberbier T, Maurer M. Improved reduction of symptoms by 20 versus 5 mg desloratadine in patients with chronic spontaneous urticaria: first results of a randomised, double-blind trial [Abstract]. 29th Congress of the European Academy of Allergy and Clinical Immunology, EAACI London United Kingdom. Conference Start: 20100605 Conference End: 20100609. *Allergy: European Journal of Allergy & Clinical Immunology* 2010;**65**:205–6. [EMBASE: 70177849]

Witte 2006 *{published data only}*
Witte F. Chronic urticaria: levocetirizine improves symptoms and quality of life [Chronische urtikaria: levocetirizin bessert symptome und lebensqualitat]. *Aktuelle Dermatologie* 2006;**32**(11):454. [EMBASE: 2006599161]

Wolfram 1967 *{published data only}*
Wolfram S. Clinical experience with a new antihistaminic [Klinische Erfahrungen mit einem neuen Antihistaminikum]. *Wiener Medizinische Wochenschrift* 1967;**117**(38):868–70. [MEDLINE: 4385553]

Wozel 1990 *{published data only}*
Wozel G, Sahre EM, Barth J. Effectiveness of combination treatment with H1-(Tavegyl) and H2-antagonists (Altramet) in chronic/chronically-recurrent urticaria [Effektivitat der Kombinationsbehandlung von H1–(Tavegyl) und H2–Antagonisten (Altramet) bei chronischer/chronisch rezidivierender Urtikaria]. *Dermatologische Monatschrift* 1990;**176**(11):653–9. [MEDLINE: 2083605]

Wu 1992 *{published data only}*
Wu GX, Yang DQ. Ranitidine and cyproheptadine use together for 52 chronic hives (Chinese). *Chinese Journal of Dermatovenereology* 1992;**6**(3):166–7.

Yamada 1968 *{published data only}*
Yamada M, Ogino S, Horio T, Ikeda T. Effect of a new antihistamine 8599RP on chronic urticaria, with special reference to its comparison with d-chlorpheniramine

maleate. *Acta Dermatologica-Kyoto English Edition* 1968;**63** (1):107–11. [MEDLINE: 4878092]

Youngchaiyud 1988 ***{published data only}***

Youngchaiyud U. Comparison of the efficacy of four antihistamines in chronic urticaria. *Journal of the Medical Association of Thailand* 1988;**71**(10):548–52. [MEDLINE: 2907911]

Zabel 1984 ***{published data only}***

Zabel M, Lindscheid KR. Treatment of chronic recidivating urticaria with H1-antagonist oxatomide and terfenadine [Die Behandlung der Chronisch–Rezidivierenden Urtikaria mit den H1–Antagonisten Oxatomid und Terfenadin. Ergebnisse einer Doppelblindstudie]. *Therapiewoche* 1984; **34**(30):4454–8. [EMBASE: 1984169236]

Zhang 1990 ***{published data only}***

Zhang CS, Shi XH, Zhang JZ. The efficacy observation of astemizole for 38 cases of chronic hives (Chinese). *Journal of Clinical Dermatology* 1990;**19**(1):38.

Zhang 1991 ***{published data only}***

Zhang HY, Zhang R, Ye ST. Multicenter, double-blind trial of terfenadine in treatment of urticaria and allergic rhinitis in 384 patients. *Chinese Journal of New Drugs & Clinical Remedies* 1991;**10**(3):023. [CENTRAL: CN–00715298]

Zhang 2001 ***{published data only}***

Zhang HY, Li H, Yue FM, Wang LL. A multicenter, randomized, comparative study on the safety and efficacy of mizolastine versus loratadine for the treatment of chronic idiopathic urticaria. *Chinese Journal of Microbiology & Immunology* 2001;**21**(S:S):56–9. [CENTRAL: CN–00366969]

Zhao 1994 ***{published data only}***

Zhao G, Zhang ZC. Clinical observation of the short-term efficacy of loratadine in the treatment of chronic urticaria (Chinese). *Chinese Journal of Dermatology* 1994;**27**(1):65.

Zhi 2004 ***{published data only}***

Zhi Y, Zhang H, Bi Z. A multicenter, double-blind, randomized, parallel-controlled study on the safety and efficacy of ebastine for the treatment of chronic idiopathic urticaria and allergic rhinitis. *Jiangsu Medical Journal* 2004; **30**(3):166–8. [CENTRAL: CN–00497534]

Zhou 2003 ***{published data only}***

Zhou X, Li H, Wang J. Observation of clinical efficacy on treating urticaria with desloratadine and loratadine. *Journal of Chongqing Medical University* 2003;**28**(1):78–9. [CENTRAL: CN–00476755]

Zuberbier 1995 ***{published data only}***

Zuberbier T, Aberer W, Burtin B, Rihoux JP, Czarnetzki BM. Efficacy of cetirizine in cholinergic urticaria. *Acta Dermato-Venereologica* 1995;**75**(2):147–9. [MEDLINE: 7604646]

References to studies awaiting assessment

Audi'cana 2007 ***{published data only}***

Audi´cana MTLM, Marquina A, Bressieux, JMLF, Valiente R. A double-blind, randomized, dose-ranging trial in four parallel groups of 10, 20 and 30 mg bilastine once daily vs placebo in the symptomatic treatment of chronic idiopathic urticaria (CIU). *Journal of Investigational Allergology & Clinical Immunology* 2007;**17**(Suppl 3):77.

Blanca Gomez 1984 ***{published data only}***

Blanca Gomez M, Lopez Perez-Lanzac JC. Chronic idiopathic urticaria: double blind study with H1 plus H2 blockers [Urticaria cronica idiopatica: estudio a doble ciego con bloqueantes H1 mas H2]. *Farmacia Clinica* 1984;**1**(7): 43–6. [EMBASE: 1984238444]

Boggs 1989 ***{published data only}***

Boggs PB, Ellis CN, Grossman J, Washburne WF, Gupta AK, Ball R, et al. Double-blind, placebo-controlled study of terfenadine and hydroxyzine in patients with chronic idiopathic urticaria. *Annals of Allergy* 1989;**63**(6 Pt 2): 616–20. [MEDLINE: 2574555]

Fan 2000 ***{published data only}***

Fan XZ, Zhou Y, Liu JX. Efficacy of loratadine in the treatment of chronic urticaria. *Shanghai Medical Journal* 2000;**21**(10):25–6. [CENTRAL: CN–00352746]

Feng 2001 ***{published data only}***

Feng J, Wang J, Yu B, Jia Q, Jin Z, Zhu W, et al. Observation of the efficacy of cetirizine in treatment of chronic and acute urticaria. *Chinese Journal of New Drugs* 2001;**10**(8):613–4. [CENTRAL: CN–00382803]

Guo 2013 ***{published data only}***

Guo YY, Qian JX, Tang Q, Sun ZH. Observation of the therapeutic effect on chronic urticaria treated with compound Fructus Kochiae Scopariae decoction combined with mizolastine. *Journal of Clinical Dermatology* 2013;**42** (4):254–6. [EMBASE: 2013380077]

Guo 2014 ***{published data only}***

Guo XL, Yang WB, Huang FY, Ouyang ZB. Clinical observation on the efficacy of mizolastine and ketotifen for treating chronic urticaria [Chinese]. *Journal of Clinical Dermatology* 2014;**42**(11):697–9. [EMBASE: 2014075041]

Hatano 1981 ***{published data only}***

Hatano H, Harada T, Naka W, Hada S, Ishikawa K, Nagashima M, et al. A Double-blind Controlled Study of Azatadine Maleate Tablet (Idulamine) on Urticaria and Pruritus Cutaneus. *Rinsho Hyoka (Clinical Evaluation)* 1981;**9**(2):461–99. [CENTRAL: CN–00268275]

Monroe 1992a ***{published data only}***

Monroe EW, Bernstein DI, Fox RW, Grabiec SV, Honsinger RW, Kalivas JT, et al. Relative efficacy and safety of loratadine, hydroxyzine, and placebo in chronic idiopathic urticaria. *Arzneimittel-Forschung* 1992;**42**(9):1119–21. [MEDLINE: 1445478]

Okubo 2013 ***{published data only}***

Okubo Y, Shigoka Y, Yamazaki M, Tsuboi R. Double dose of cetirizine hydrochloride is effective for patients with urticaria resistant: a prospective, randomized, non-blinded, comparative clinical study and assessment of quality of life. Journal of Dermatological Treatment 2013; Vol. 24, issue 2:153–60. [MEDLINE: 21810005]

Sil 2013 *{published data only}*
Sil A, Tripathi SK, Chaudhuri A, Das NK, Hazra A, Bagchi C, et al. Olopatadine versus levocetirizine in chronic urticaria: an observer-blind, randomized, controlled trial of effectiveness and safety. Journal of Dermatological Treatment 2013; Vol. 24, issue 6:466–72. [EMBASE: 2013726800]

Tanizaki 2013 *{published data only}*
Tanizaki H, Nakahigashi K, Miyachi Y, Kabashima K. Comparison of the efficacy of fexofenadine 120 and 240 mg/day on chronic idiopathic urticaria and histamine-induced skin responses in Japanese populations. *Journal of Dermatological Treatment* 2013;**24**(6):477–80. [EMBASE: 2013726806]

Wang 2002 *{published data only}*
Wang AH. Effects of mizolastine vs cyproheptadine in treating chronic urticaria. *Journal of Chinese Clinical Medicine* 2002;**3**(17):33–4. [CENTRAL: CN–00451399]

Zhang 2012 *{published data only}*
Zhang Y, Shang T. Observation of therapeutic effect of mizolastine combined with compound glycyrrhizin in chronic idiopathic urticaria. *Journal of Clinical Dermatology* 2012;**41**(11):695–8. [EMBASE: 2013056366]

Zhang 2013 *{published data only}*
Zhang W, Xu XY, Wang N, Wu SY, Shi Y. Montelukast combined with cetirizine in the treatment of refractory urticaria: a clinical observation [Chinese]. *Journal of Clinical Dermatology* 2013;**42**(5):317–8. [EMBASE: 2013442383]

Zhu 2012 *{published data only}*
Zhu Y. Therapeutic effect and safety of mizolastine in the treatment of urticaria and allergic rhinitis. *Journal of Clinical Dermatology* 2012;**41**(11):699–701. [EMBASE: 2013056367]

References to ongoing studies

CTRI/2014/04/004545 *{unpublished data only}*
CTRI/2014/04/004545. Comparison of efficacy, safety and cost effectiveness of rupatadine and olopatadine, anti-histaminics, in patient of urticaria. www.ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=8753 (accessed 2 June 2014).

EudraCT: 2004-000771-34 *{unpublished data only}*
EudraCT: 2004-000771-34. A 6-week multicentre, double-blind, randomised, placebo-controlled, parallel-group study to assess the efficacy and safety of rupatadine 10 and 20 mg in the treatment of chronic idiopathic urticaria (CIU): a phase III clinical trial. clinicaltrialsregister.eu/ctr-search/search?query=eudract˙number:2004-000771-34 (accessed 3 July 2013).

EudraCT: 2005-002749-38 *{unpublished data only}*
EudraCT: 2005-002749-38. A randomized, double-blind, placebo-controlled exploratory trial to evaluate a one-week oral treatment with R129160 (60 mg o.d.) in patients with chronic idiopathic urticaria. clinicaltrialsregister.eu/ctr-search/search?query=eudract˙number:2005-002749-38 (accessed 3 July 2013).

JPRN-UMIN000001163 *{unpublished data only}*
JPRN-UMIN000001163. Study of optimal treatment duration with antihistamine in idiopathic urticaria patients. www.umin.ac.jp/ctr/index.htm (accessed 24 June 2014).

JPRN-UMIN000003290 *{unpublished data only}*
JPRN-UMIN000003290. Study of the antipruritic effect and onset of sleepiness with oral antihistamines. // www.umin.ac.jp/ctr/index.htm (accessed 24 June 2014).

JPRN-UMIN000008062 *{unpublished data only}*
JPRN-UMIN000008062. A study evaluating efficacy of non-sedative antihistamine up-titration in patients with chronic urticaria who did not respond to standard therapy. www.umin.ac.jp/ctr/index.htm (accessed 24 June 2014).

JPRN-UMIN000008461 *{published data only}*
JPRN-UMIN000008461. A study on the optimal treatment for chronic idiopathic urticaria insufficient for the second-generation antihistamines. www.umin.ac.jp/ctr/index.htm (accessed 24 June 2014).

JPRN-UMIN000010265 *{unpublished data only}*
JPRN-UMIN000010265. Preliminary trial of the increase of antihistamines in dose and a combination of different antihistamine on refractory spontaneous urticaria. www.umin.ac.jp/ctr/index.htm (accessed 24 June 2014).

NCT00199238 *{unpublished data only}*
NCT00199238. A 4-week dose-finding, multicentre, double-blind, randomised, placebo-controlled, parallel-group trial to assess the efficacy and safety of different doses of rupatadine compared to placebo in the treatment of chronic idiopathic urticaria [Efficacy of rupatadine 5, 10 and 20 mg in chronic idiopathic urticaria]. ClinicalTrials.gov/show/NCT00199238 (accessed 3 July 2013).

NCT00199251 *{unpublished data only}*
NCT00199251. Efficacy and safety of rupatadine 10 and 20 mg in chronic idiopathic urticaria. ClinicalTrials.gov/show/NCT00199251 (accessed 3 July 2013).

NCT00421109 *{unpublished data only}*
EudraCT: 2006-001245-33. Double-blind, randomised, placebo-controlled, phase III study comparing the efficacy and safety of bilastine 20 mg once daily and levocetirizine 5 mg for the treatment of chronic idiopathic urticaria [Estudio en fase III, doble ciego, randomizado, controlado con placebo, comparativo de la eficacia y seguridad de bilastina 20 mg una vez al día y levocetirizina 5 mg para el tratamiento de la urticaria crónica idiopática"]. clinicaltrialsregister.eu/ctr-search/search?query=eudract˙number:2006-001245-33 (accessed 3 July 2013).
NCT00421109. Efficacy study for the symptomatic treatment of chronic idiopathic urticaria. ClinicalTrials.gov/show/NCT00421109 (accessed 3 July 2013).

NCT00751166 *{unpublished data only}*
NCT00751166. A comparative double-blind, double-dummy study of desloratadine (dl) 5 mg once daily, cetirizine 10 mg once daily, and placebo once daily in

patients with chronic idiopathic urticaria (study p03736) (terminated). ClinicalTrials.gov/show/NCT00751166 (accessed 3 July 2013).

NCT00751218 ***{unpublished data only}***

NCT00751218. A comparative double-blind, double-dummy study of desloratadine (dl) 5 mg once daily, cetirizine 10 mg once daily, and placebo once daily in patients with chronic idiopathic urticaria (study p03735) (completed). ClinicalTrials.gov/show/NCT00751218 (accessed 3 July 2013).

NCT00783354 ***{unpublished data only}***

NCT00783354. A comparison of Aerius continuous treatment versus Aerius prn for chronic idiopathic urticaria (study p03147)(completed). ClinicalTrials.gov/show/NCT00783354 (accessed 3 July 2013).

Additional references

Champion 1969

Champion RH, Roberts SO, Carpenter RG, Roger JH. Urticaria and angio-oedema: a review of 554 patients. *British Journal of Dermatology* 1969;**81**(8):588–97. [MEDLINE: 5801331]

Charlesworth 2002

Charlesworth EN. Urticaria and angioedema. *Allergy & Asthma Proceedings* 2002;**23**(5):341–5. [MEDLINE: 12476545]

Church 2012

Church MK, Maurer M. H(1)-antihistamines and urticaria: how can we predict the best drug for our patient?. *Clinical & Experimental Allergy* 2012;**42**(10):1423–9. [PUBMED: 22994340]

Demera 2001

Demera RS, Ryhal B, Gershwin ME. Chronic idiopathic urticaria. *Comprehensive Therapy* 2001;**27**(3):213–7. [PUBMED: 11569322]

DuBuske 1999

DuBuske LM. Second-generation antihistamines: the risk of ventricular arrhythmias. *Clinical Therapeutics* 1999;**21**(2):281–95. [PUBMED: 10211532]

Fedorowicz 2012

Fedorowicz Z, van Zuuren EJ, Hu N. Histamine H2-receptor antagonists for urticaria. *Cochrane Database of Systematic Reviews* 2012, Issue 3. [DOI: 10.1002/14651858.CD008596.pub2]

Gaig 2004

Gaig P, Olona M, Munoz Lejarazu D, Caballero MT, Dominguez FJ, Echechipia S, et al. Epidemiology of Urticaria in Spain. *Journal of Investigational Allergology & Clinical Immunology* 2004;**14**(3):214–20. [PUBMED: 15552715]

Grattan 2001

Grattan C, Powell S, Humphreys F, British Association of Dermatologists. Management and diagnostic guidelines for urticaria and angio-oedema. *British Journal of Dermatology* 2001;**144**(4):708–14. [MEDLINE: 11298527]

Grattan 2007

Grattan CE, Humphreys F, British Association of Dermatologists Therapy Guidelines and Audit Subcommittee. Guidelines for evaluation and management of urticaria in adults and children. *British Journal of Dermatology* 2007;**157**(6):1116–23. [MEDLINE: 18021095]

Hauser 2003

Hauser C. Chronic urticaria. Evidence-Based Dermatology. http://www.blackwellpublishing.com/medicine/bmj/dermatology/pdfs/chronic˙urticaria.pdf 2003 (accessed December 2004).

Hellgren 1972

Hellgren L. The prevalence of urticaria in the total population. *Acta Allergologica* 1972;**27**(3):236–40. [MEDLINE: 4678809]

Higgins 2011

Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. www.cochrane-handbook.org 2011.

Holgate 2003

Holgate ST, Canonica GW, Simons E, Taglialatela M, Tharp M, Timmerman H, et al. Consensus Group on New-Generation Antihistamines (CONGA): present status and recommendations. *Clinical & Experimental Allergy* 2003;**33**(9):1305–24. [EMBASE: 2003372691]

Humphreys 1998

Humphreys F, Hunter JA. The characteristics of urticaria in 390 patients. *British Journal of Dermatology* 1998;**138**(4):635–8. [MEDLINE: 9640369]

James 2011

James WD, Berger TG, Elston DM. *Andrews' Diseases of the Skin: Clinical Dermatology*. 11th Edition. St Louis: Saunders Elsevier, 2011. [: ISBN 1437703143]

Kavosh 2011

Kavosh ER, Khan DA. Second-generation H1-antihistimines in chronic urticaria: an evidence-based review. *American Journal of Clinical Dermatology* 2011;**12**(6):361–76. [MEDLINE: 21967114]

Kozel 2001

Kozel MMA, Mekkes JR, Bossuyt PMM, Bos JD. Natural course of physical and chronic urticaria and angioedema in 220 patients. Journal of the American Academy of Dermatology. Mosby, 2001; Vol. 45, issue 3:387–91. [EMBASE: 2001306464]

Maurer 2011

Maurer M, Weller K, Bindslev-Jensen C, Gimenez-Arnau A, Bousquet PJ, Bousquet J, et al. Unmet clinical needs in chronic spontaneous urticaria. A GA(2)LEN task force report. *Allergy: European Journal of Allergy and Clinical Immunology* 2011;**66**(3):317–30. [EMBASE: 2011077490]

Maurer 2013

Maurer M, Bindslev-Jensen C, Gimenez-Arnau A, Godse K, Grattan CEM, Hide M, et al. Chronic idiopathic urticaria

(CIU) is no longer idiopathic: time for an update. *British Journal of Dermatology* 2013;**168**(2):455–6. [EMBASE: 2013077748]

NCT00264303

NCT00264303. CUTE (Chronic Urticaria Treatment Evaluation). //clinicaltrials.gov/show/NCT00264303 (accessed 3 July 2013).

Nolen 1997

Nolen TM. Sedative effects of antihistamines: safety, performance, learning, and quality of life. *Clinical Therapeutics* 1997;**19**(1):39–55. [EMBASE: 1997130608]

RevMan 2014

The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Sarbijt 2014

Sarbijt S. Chronic urticaria: clinical manifestations, diagnosis, pathogenesis, and natural history. www.uptodate.com/contents/chronic-urticaria-clinical-manifestations-diagnosis-pathogenesis-and-natural-history?source=see˙link&anchor=H23#H25) (accessed 13 March 2014).

Spector 2007

Spector SL, Shikiar R, Harding G, Meeves S, Leahy MJ. The effect of fexofenadine hydrochloride on productivity and quality of life in patients with chronic idiopathic urticaria. *Cutis* 2007;**79**(2):157–62. [MEDLINE: 17388220]

Zuberbier 2012

Zuberbier T. A Summary of the New International EAACI/GA2LEN/EDF/WAO Guidelines in Urticaria. *World Allergy Organization Journal* 2012;**5**(Suppl 1):S1–5. [DOI: 10.1097/WOX.0b013e3181f13432]

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Alomar 1990a

Methods	Design: randomised double-blind 2-arm parallel-group study of cetirizine hydrochloride vs placebo Duration: 15 days
Participants	Number randomly assigned: 30 participants Sex: 44% male, 56% female Age of participants, years: 21 to 64 Unit of allocation: participant Country and setting: Spain; secondary care, hospital clinic **Inclusion criteria of the trial** • Chronic idiopathic urticaria; none of the participants had been receiving systemic corticosteroids, and all stopped all medications for at least 48 hours before starting the study (15 days for other allergy medications) **Exclusion criteria of the trial** • Not stated • Previous unresponsiveness to antihistamine: not stated
Interventions	**Interventions, dose, duration** • 10 mg/d cetirizine hydrochloride • Placebo Duration of intervention: intermediate-term (15 days) Length of follow-up: 15 days
Outcomes	Timing of outcome assessment: baseline and 15 days **Primary outcomes of the trial** • Daily presence of itching and weals, rated on a scale between 0 and 4: 0 = absent, 1 = mild, 2 = moderate, 3 = severe, 4 = very severe. Participants also evaluated response to treatment using a visual analogue scale 100 mm in length, graduated from 0 (very poor) to 700 (excellent response) • Quality of life measures: none **Secondary outcomes of the trial** • Laboratory values including blood electrolytes, cholesterol, triglycerides, kidney and liver function • Adverse events: somnolence, epigastric nausea, itching Clinician or participant report: participant and clinician
Notes	In Spanish with English abstract Investigators concluded that cetirizine was more active than placebo in terms of clinician reports of efficacy; findings were not statistically significantly different

Risk of bias

Bias	Authors' judgement	Support for judgement

Alomar 1990a (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Described as random allocation, no details given
Allocation concealment (selection bias)	Unclear risk	Not described in published report
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Stated to be double-blind, details of blinding not stated
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	30 randomly assigned: 15 intervention, 15 control. 13/15 completed intervention, 12/15 control. 5 from each group experienced adverse effects, but it is unclear whether they withdrew from the study. Reasons for dropout not stated
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were reported
Other bias	Low risk	None detected. Funder: not stated

Anuradha 2010

Methods	Design: randomised open comparative clinical study of loratadine vs levocetirizine Duration: 4 weeks
Participants	Number randomly assigned: 60 (loratadine n = 30; levocetirizine n = 30) Sex: 40% male, 60% female; in loratadine group, 43.3% male; in levocetirizine group, 56.7% female Age of participants, years: 12 to 60 (mean age 33.4 and 34.8 in loratadine and levocetirizine groups, respectively) Unit of allocation: participant Country and setting: India; secondary, outpatient **Inclusion criteria of the trial** • Diagnosed with CSU **Exclusion criteria of the trial** • Other forms of urticaria with significant concomitant illness (e.g. malignancies; hepatic, psychiatric, endocrine or other major systemic diseases); pregnant women, lactating mothers, females on oral contraceptive pills; individuals taking antihistaminic therapy for 72 hours or steroids for 1 month • Previous unresponsiveness to antihistamine: not stated
Interventions	**Interventions, dose, duration** • Loratadine 10 mg/d • Levocetirizine 5 mg/d

	Duration of intervention: intermediate-term (4 weeks) Length of follow-up: 4 weeks
Outcomes	Timing of outcome assessment: 4 weeks **Primary outcomes of the trial** • Efficacy measures: All participants were evaluated for degree of pruritus, size of weals, number of weals and number of separate urticarial episodes • Efficacy measures were scored according to the following scales: pruritus: 0 = none, 1 = mild, 2 = moderate and 3 = severe; number of weals: 0 (none), 1 (1-10), 2 (11-20) and 3 (> 20); size of weals (mean diameter): 0 (no lesions), 1 (< 1.27 cm), 2 (1. 27-2.54 cm) and 3 (> 2.54 cm); number of separate urticarial episodes: 0 (none), 1 (1), 2 (2-3) and 3 (> 3). Maximum value of total symptoms score (TSS) was 12 • Quality of life measures: none **Secondary outcomes of the trial** • Adverse events: Safety and tolerability were assessed on the basis of adverse events reported, or through comparison of baseline symptoms with postdrug symptoms, or changes in vital signs and physical examination findings recorded before and at the end of treatment Clinician or participant report: clinician and participant
Notes	Study authors conclude that this safety and efficacy study proves the superiority of levocetirizine over loratadine for CSU

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Unclear (described as quote from 'Subjects' section of report of study as 'systematic randomisation')
Allocation concealment (selection bias)	High risk	Not stated, but trial described as 'open'
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding in this open study
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding in this open study
Incomplete outcome data (attrition bias) All outcomes	Low risk	51/60 completed. Six participants did not report for follow-up (no reasons given), and 3 participants were non-compliant with treatment
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were reported

Other bias	Low risk	None detected. Funder: none (drugs free of charge from hospital pharmacy)

Beck 1985

Methods	Design: randomised double-blind 2-arm parallel-group trial of oxatomide vs clemastine Duration: 6 weeks
Participants	Number randomly assigned: 30 participants (15 in each group) Sex: 43% (13) male, 57% (17) female Age of participants, years: between 15 and 67 Unit of allocation: participant Country and setting: Denmark; setting unclear **Inclusion criteria of the trial** • With chronic urticaria for 3 months or longer **Exclusion criteria of the trial** • Not stated • Previous unresponsiveness to antihistamine: not stated
Interventions	**Interventions, dose, duration** • Oxatomide 30 mg twice daily for 6 weeks • Clemastine 1 mg twice daily for 6 weeks Doses could be increased to 4 capsules daily. Cinnarizine 5 mg every 4 hours could be added if insufficient efficacy in either group Duration of intervention: intermediate-term (6 weeks) Length of follow-up: 6 weeks (duration of study)
Outcomes	Timing of outcome assessment: 1, 3 and 6 weeks **Primary outcomes of the trial** • Efficacy (severity of weals, erythema and itching; 24-hour urine samples for determination of 1,4 MIAA) • Quality of life measures: none **Secondary outcomes of the trial** • Adverse events: Any occurring were reported Clinician or participant report: participants and clinician
Notes	Study investigators concluded that the effect of oxatomide was equal to that of clemastine

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote (page 50): "the 30 patients were randomly assigned to a 6 weeks double-blind treatment..." Unclear which method of randomisation was used
Allocation concealment (selection bias)	Unclear risk	Not stated

Beck 1985 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote (page 50): "double-blind treatment" Method used not described, no further information available
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote (page 50): "double-blind treatment" Method used not described, no further information available
Incomplete outcome data (attrition bias) All outcomes	High risk	0/30 dropped out
Selective reporting (reporting bias)	High risk	No participant numbers given in results, only statistical differences (and percentages for adverse events). No figures given (graph only) Severity of weals, erythema and itching noted but not mentioned in the results. No figures given, graph only. No further information available
Other bias	Unclear risk	No clear definition of disease given; washout period not specified; concomitant treatment permitted Funder: not stated

Belaich 1990

Methods	Design: randomised double-blind 3-arm parallel-group multi-centre study of loratadine vs terfenadine vs placebo Duration: 28 days
Participants	Number of participants randomly assigned: 187 (61 in loratadine group; 64 in terfenadine group; 62 in placebo group) Sex: 46% male, 53% female. Number of male/female: 32/27 loratadine; 36/24 terfenadine; 20/32 placebo Age of participants, years: average 37 Unit of allocation: participant Country and setting: France, Belgium, Germany; setting unclear, included private practice and dermatology clinics **Inclusion criteria of the trial** • Chronic idiopathic urticaria, duration of disease 3 to 4 years **Exclusion criteria of the trial** • Not stated • Previous unresponsiveness to antihistamine: not stated
Interventions	**Interventions, dose, duration** • Loratadine 10 mg once daily • Terfenadine 60 mg twice daily • Placebo

	Loratadine 10 mg (active drug in the morning and placebo in the evening), 60 mg terfenadine twice daily or placebo twice daily for 28 days Duration of intervention: intermediate-term (28 days) Length of follow-up: 28 days
Outcomes	Timing of outcome assessment: participants seen at baseline (day 1), then at days 7, 14 and 28 **Primary outcomes of the trial** • Numerical ratings of itching and erythema: 0 = none, 1 = mild, 2 = moderate, 3 = severe. Count of weals: 0 (none), 1 (1-6), 2 (7-12), 3 (> 12) • Size of largest weal: 0 (none), 1 (< 1.5 cm), 2 (1.5-2.5 cm), 3 (> 2.5 cm) • Overall assessment: 0 = none, 1 = mild, 2 = moderate, 3 = severe • Complete suppression of urticaria • Proportion with good/excellent response • Quality of life measures: none **Secondary outcomes of the trial** • Adverse events, including sedation, dry mouth Clinician or participant report: investigator report
Notes	Study investigators concluded that loratadine 10 mg once daily is safe and effective

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Qualified patients were randomly assigned..." Method of randomisation not stated
Allocation concealment (selection bias)	Unclear risk	Not stated, unclear whether allocation was concealed
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Stated to be a double-blind study, method of blinding not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Stated to be a double-blind study, method of blinding not described
Incomplete outcome data (attrition bias) All outcomes	High risk	No ITT. 15/187 dropouts due to protocol violation (no details given): 1/61 loratadine; 4/64 terfenadine; 52/62 placebo dropped out
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were reported
Other bias	Low risk	Groups were comparable at baseline Funder: not stated

Breneman 1995

Methods	Design: double-blind multi-centre 3-arm randomised trial of cetirizine vs astemizole vs placebo Duration: 4 weeks
Participants	Number randomly assigned: 187 (62 patients in cetirizine group; 62 in astemizole group; 63 in placebo group) Sex: 27% male, 73% female Age of participants, years: > 12, average 37.7 Unit of allocation: participant Country and setting: USA; university medical centres • Chronic idiopathic urticaria **Exclusion criteria of the trial** • Not stated • Previous unresponsiveness to antihistamine: not stated
Interventions	**Interventions, dose, duration** • Cetirizine 10 mg once daily • Astemizole 10 mg once daily • Placebo once daily for 4 weeks Duration of intervention: intermediate-term (4 weeks) Length of follow-up: 4 weeks
Outcomes	Timing of outcome assessment: 1, 2, 3 and 4 weeks **Primary outcomes of the trial** • Complete suppression • Good/excellent response rated by investigator on a 4-point scale as follows: total number of lesions: 0 (0), 1 to 10 (1), 11 to 20 (2), > 20 (3). Number of episodes: 0 (0), 1 (1), 2 or 3 (2), > 3 (3). Average lesion size (inches): 0 (0), < 1/2 (1), 1/2 to 1 (2), > 1 (3). Average duration of lesions (hours): none (0), up to 4 (1), > 4 to 12 (2), > 12 (3). Pruritus: none = 0, mild = 1, moderate = 2, severe = 3 • Quality of life measures: none **Secondary outcomes of the trial** • Adverse events (requiring drug withdrawal): headache, vasovagal/vomiting/palpitations, dizziness, nausea, lethargy, syncope • Minor adverse events: headache, somnolence, fatigue, dry mouth Clinician or participant report: participant and investigator
Notes	Study investigators concluded that cetirizine provides effective relief of symptoms

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 192): "...patients were randomly assigned to receive either 10 mg cetirizine, 10 mg astemizole, or placebo once each night for 4 weeks." No further details given

Breneman 1995 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unclear; stated to be "double-blind trial" (page 192) but no details given
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear; stated to be "double-blind trial" (page 192) but no details given
Incomplete outcome data (attrition bias) All outcomes	High risk	51/187 randomly assigned participants dropped out/lost to follow-up; lost to follow-up were 51 participants (27.3%). 43 participants were withdrawn before trial completion; 1 failed to take astemizole; 7 were lost to follow-up Serious adverse events (requiring drug withdrawal): cetirizine: n = 2 (headache n = 1; vasovagal/vomiting/palpitations n = 1); astemizole: n = 1 (dizziness, nausea, lethargy, syncope). Evaluable participants: n = 136 Comment: high loss to follow-up
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were reported
Other bias	Unclear risk	Severity of urticaria comparable at baseline, but statistical differences between other demographic details (age and race) Funder: Pfizer Labs

Breneman 1996

Methods	Design: randomised double-blind placebo-controlled multi-centred 3-arm study of cetirizine vs hydroxyzine vs placebo Duration: 4 weeks
Participants	Number randomly assigned: 188 (60 in cetirizine group; 63 in hydroxyzine group; 65 in placebo group) Sex: 32% male, 68% female Age of participants, years: > 12; mean: cetirizine: 36.8; hydroxyzine: 34.5; placebo: 38.8 Unit of allocation: participant Country and setting: USA; allergy practice settings **Inclusion criteria of the trial** • Symptomatic chronic idiopathic urticaria of at least 6 weeks' duration **Exclusion criteria of the trial** • Within 36 hours of start of study, tranquillisers, hypnotics, antiepileptics, antidepressants, agents acting on the CNS; within 1 week of start of study, astemizole;

	within 6 weeks of start of study, any participants with asthma using therapies other than inhaled bronchodilator • Previous unresponsiveness to antihistamine: not stated
Interventions	**Interventions, dose duration** • Cetirizine 10 mg once daily plus placebo twice daily • Hydroxyzine 25 mg 3 times daily • Placebo 3 times daily Duration of intervention: intermediate-term (4 weeks) Length of follow-up: 4 weeks
Outcomes	Timing of outcome assessment: 4 weeks **Primary outcomes of the trial** • Efficacy (definite or complete improvement) on a 4-point scale as follows: total number of lesions: 0 (0), 1 to 10 (1), 11 to 20 (2), > 20 (3) • Number of episodes longer than 1 hour apart: 0 (0), 1 (1), 2 or 3 (2), > 3 (3) • Average lesion size (cm): 0 (0), ≤ 1.25 (1), > 1.25 to ≤ 2.5 (2), > 2.5 (3) • Average duration of lesion (hours): none (0), up to 4 (1), > 4 to 12 (2), > 12 (3) • Pruritus: none = 0, mild = 1, moderate = 2, severe = 3 • Normal blood and urine values • Quality of life measures: none **Secondary outcomes of the trial** • Serious adverse events (requiring withdrawal of drug): cetirizine: somnolence, sweating, vertigo and vomiting, lethargy, headache; hydroxyzine: somnolence; placebo: somnolence • Minor adverse events: cetirizine: somnolence; hydroxyzine: somnolence; placebo: somnolence Clinician or participant report: participant and investigator
Notes	Study investigators concluded that cetirizine 10 mg was equivalent to hydroxyzine 25 mg in symptom control

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote (page 1076) "randomised, parallel-group..." but no further details
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-dummy used, but blinding not fully described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear how blinding of outcome assessors was achieved

Breneman 1996 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	9/188 dropouts were recorded for each group as the result of serious adverse events requiring withdrawal of drug (1/60 in cetirizine group; 4/63 in hydroxyzine group; 4/65 in placebo group) Cetirizine: somnolence (n = 1) Hydroxyzine: somnolence (n = 4) Placebo: (n = 4) consisted of somnolence n = 1; sweating, vertigo and vomiting (n = 1) ; lethargy n = 1; headache n = 1 Dropouts balanced between groups
Selective reporting (reporting bias)	High risk	Reporting of results in graph form (means with statistical significance) only
Other bias	Unclear risk	No power calculation-may have missed significant differences between groups if underpowered Definition of disease partially defined, with physical urticaria not explicitly excluded Funder: Pfizer Laboratories

Bronsky 2001

Methods	Design: multi-centre double-blind randomised parallel-group study comparing desloratadine 5 mg vs placebo Duration: 6 weeks
Participants	Number of participants randomly assigned: 225 (115 in desloratadine group and 110 in placebo group) Sex: not stated Age of participants: not stated Unit of allocation: participant Country and setting: USA; setting unclear **Inclusion criteria of the trial** • CSU 6 weeks **Exclusion criteria of the trial** • Not stated
Interventions	**Interventions, dose duration** • Desloratadine 5 mg • Placebo for 6 weeks Duration of intervention: intermediate-term (6 weeks) Length of follow-up: 6 weeks
Outcomes	Timing of outcome assessment: twice daily for 6 weeks **Primary outcomes of the trial** • Change in symptom score TSS (number of hives, pruritus and size of largest weals)

Bronsky 2001 (*Continued*)

	• Quality of life outcomes not reported **Secondary outcomes of the trial** • Adverse events Clinician or participant report: unclear
Notes	Study investigators concluded that desloratadine produced substantial efficacy after just 1 dose, which was maintained throughout study. All measures were statistically significant in favour of desloratadine vs placebo and were sustained at all time points

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Stated to be double-blind, unclear how this was done
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Stated to be double-blind, unclear how this was done
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No mention of dropouts/adverse events
Selective reporting (reporting bias)	High risk	Pruritus score given for days 1 to 8, then total symptoms score given for days 2 to 8
Other bias	Unclear risk	None detected. Short report (abstract). Funder: not stated

Brostoff 1996

Methods	Design: randomised double-blind multi-centre 2-arm trial of mizolastine vs placebo Duration: 28 days
Participants	Number of participants randomly assigned: 56; 28 in each group Sex: 55% male, 45% female Age of participants, years: 18; mean 38 ± 15 Unit of allocation: participant Country and setting: UK; setting research clinics **Inclusion criteria of the trial** • Urticaria of at least 6 weeks' duration with at least 2 episodes per week **Exclusion criteria of the trial**

	• Pregnant, women not using contraception, driving, dangerous machinery, inability to comply, concomitant disease or abnormal laboratory value • Previous unresponsiveness to antihistamine: not stated
Interventions	**Interventions, dose, duration** After single-blind placebo run-in period of 4 to 10 days: • Mizolastine 10 mg a day • Placebo once daily for 28 days Duration of intervention: intermediate-term (28 days)
Outcomes	Timing of outcome assessment: days 7 and 28 **Primary outcomes of the trial** • Symptoms, including itch, sleep, daily activities, weals, erythema and discomfort rated on a 4-point visual analogue scale • Percentage of "responders" at 28 weeks • Quality of life measures: none **Secondary outcomes of the trial** • Dropouts due to inefficacy • Adverse events and dropouts reported Clinician or participant report: clinician and participant
Notes	Study authors concluded that mizolastine controlled symptoms of urticaria

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote (page 321): "a two-centre, double-blind randomised, placebo-controlled parallel group study... allocated according to the randomisation"
Allocation concealment (selection bias)	Unclear risk	No details given about allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote (page 321): "Patients received single blind placebo medication for a variable period of 4-10 days (initially, then were allocated to one of two treatment groups)" Quote (page 321): "All tablets were identical in appearance, ensuring double blind nature of trial." Unclear how investigators were blinded to treatment
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear how investigators were blinded to treatment Comment: participants probably blind, as all tablets were identical

Brostoff 1996 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	High risk	29/56, 51% losses to follow-up (29/56 with 10/28 in mizolastine arm and 19/28 in placebo arm). A large proportion of participants dropped out; this is unbalanced across trial arms 1 participant in mizolastine group did not take treatment Lack of efficacy in 5 in mizolastine group and in 17 in placebo group Drowsiness in 1 in mizolastine group Loss to follow-up at day 7 in 2 mizolastine group 1 participant in each group "unco-operative" 1 in each group discontinued for reasons unrelated to study Analysis in the paper is presented as ITT
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were reported
Other bias	Unclear risk	Funder: Synthelabo Key outcome based on physician VAS estimate of urticaria severity (i.e. totally subjective); no indication of how many participants were cleared on treatment

Commens 1978

Methods	Design: double-blind cross-over 3-arm randomised controlled trial of cimetidine and chlorpheniramine vs placebo Duration: 2 weeks
Participants	Number of participants randomly assigned: 25 entered study. Numbers in each group not stated Sex: 32% male, 68% female Age of participants, years: 18 to 66 Unit of allocation: cross-over, without washout (consecutive 2-week treatments) Country and setting: UK; outpatient clinic **Inclusion criteria of the trial** • Urticaria of unknown cause **Exclusion criteria of the trial** • Pregnant or lactating women • Previous unresponsiveness to antihistamine: not stated
Interventions	**Interventions, dose, duration** • Cimetidine 200 mg twice daily and chlorpheniramine 4 mg once daily • Chlorphenamine 4 mg once daily and placebo for 2 weeks • Placebo

Commens 1978 (*Continued*)

	Duration of intervention: short-term (2 weeks)
Outcomes	Timing of outcome assessment: 2 weeks **Primary outcomes of the trial** • Estimation of number of weals present in clinic after each 2 weeks of treatment (none/a few/many) • Severity of itching • Impression of participant (improvement/no change/deterioration) • Quality of life measures: none **Secondary outcomes of the trial** • Laboratory values (blood, biochemistry) • Adverse events: drowsiness, vomiting and dizziness, dry mouth, intestinal colic Clinician or participant report: clinician and participant
Notes	Study investigators concluded that chlorpheniramine is effective in controlling symptoms in some patients with urticaria

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not stated. Quote: "On entry to the trial patients were allocated, on a random double blind basis, to the consecutive 2-week treatment" Cross-over study with no apparent washout
Allocation concealment (selection bias)	Unclear risk	No allocation concealment stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Study stated double-blinding; method unclear, no indication whether identical tablets/capsules given, no details about methods of blinding. Dosages were different for each intervention, so blinding incomplete (intervention group could potentially be guessed by number of tablets)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Study stated double-blinding; method unclear
Incomplete outcome data (attrition bias) All outcomes	High risk	6/25 participants recruited (24%) were lost to follow-up (non-compliance 5; spontaneous remission 1) and were not included in the analysis. Unclear which group drop-outs belonged to. No ITT

Commens 1978 (*Continued*)

Selective reporting (reporting bias)	High risk	Results not clearly reported. Results for numbers of participants in each group not stated, only mean scores (no SD) provided
Other bias	Unclear risk	Unclear schedule of assignment, unclear whether each phase was given consecutively, as results reported only for intervention and control-not by phase of the study Funder: Smith Kline and French Laboratories Ltd

Dakhale 2014

Methods	Design: double-blind 2-arm randomised controlled trial of cetirizine vs rupatadine Duration: 6 weeks
Participants	Number of participants randomly assigned: 70 Sex: cetirizine females 64.5%, rupatadine females 61.2% Age of participants, years: cetirizine 41.5 (SD 11.49); rupatadine 43.81 (SD 12.30) Unit of allocation: participant Country and setting: India; secondary care **Inclusion criteria of the trial** • 18 to 65 years of age; men or women with a history of urticarial weal and/or angio-oedema for ≥ 3 days per week for 6 consecutive weeks for which no obvious cause had been established • Patients using any antihistamines other than rupatadine and cetirizine were included in the trial only after a washout period of 7 days, irrespective of doses of their previous drugs **Exclusion criteria of the trial** • Acute and physical urticaria and all physical and other subtypes of urticaria, such as aquagenic, cholinergic, contact and exercise-induced urticaria • History of asthma or any other disease requiring long-term use of inhaled or systemic corticosteroids • Use of corticosteroids (inhaled or systemic) • History of allergy to study medication or intolerance to antihistamines • Use of study drug or topical steroid in previous 7 days • Use of oral steroid in previous 8 weeks • Parenteral steroids in previous 3 months • Use of any other immunomodulatory therapy • Systemic co-morbidities • Pregnant and nursing mothers Previous unresponsiveness to antihistamine: excluded any with previous failure to respond to antihistamine
Interventions	**Interventions, dose, duration** • Cetirizine 10 mg daily, rupatadine 10 mg daily Duration of intervention: intermediate Length of follow-up: 6 weeks

Outcomes	Timing of outcome assessment: 6 weeks Study outcomes **Primary outcomes of the trial** Trial was undertaken to test whether treatment with rupatadine was more successful than treatment with cetirizine in resolving symptoms as follows: • Mean number of weals (scored as 0 (none), 1 (1-5), 2 (6-15), 3 (16-25), or 4 (> 25)) • Pruritus: 0 = none, 1 = mild, 2 = moderate, 3 = severe, 4 = very severe • Mean total symptoms score (MTSS) calculated by adding mean number of weals (MNW) and mean pruritus score (MPS) • Size of weal scored as 0 (no weal), 1 (< 0.5 cm), 2 (0.6-2.0 cm), 3 (2.1-4.0 cm) or 4 (> 4.0 cm); interference of weals with sleep (SIWS) (0 = none, 1 = mild, 2 = moderate, 3 = severe) • Sedation: visual analogue scale (VAS) for sedation (scored on a scale of 0-100, where 0 = alert and 100 = very sleepy) **Secondary outcomes of the trial** • None Adverse events: general clinical follow-up and monitoring of adverse events, no serious adverse events requiring withdrawal of treatment; cetirizine group: total affected 12, 38.71% (headache n = 2, gastric irritation n = 1, dry mouth n = 1, sedation n = 8). Rupatadine group: total affected 7, 21.21% (headache n = 2, dry mouth n = 1, sedation n = 4) Quality of life measures: none Clinician or participant report: participant and clinician
Notes	Study investigators concluded that rupatadine led to improvement in all outcomes by the end of the trial, and that rupatadine is a particularly attractive therapeutic modality compared with cetirizine for the treatment of CSU

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Block randomisation, with block sizes of 4 in equal proportions to ensure a uniform allocation ratio. Randomised treatment allocation sequence was generated by a statistician using a random numbers table
Allocation concealment (selection bias)	Low risk	Quote (page 644): "The codes used in this random allocation sequence were retained in a sealed envelope, which was opened only after the completion of the study"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Both participants and investigators were unaware of the treatment administered. Drugs (21 tablets of cetirizine or rupatadine) were handed over in identical plastic

Dakhale 2014 (*Continued*)

		containers to a third person, who was not directly involved in this study. Drugs were presented in identical format in terms of shape, size, texture and packing
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Both participants and investigators were unaware of the treatment administered
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	64/70 completed. 5 participants were lost to follow-up at end of first week of the study (3 in cetirizine group and 2 in rupatadine group). One from cetirizine group was dropped from the study and was shifted to another drug because of non-response. Data for these 6 participants were not integrated into the analysis
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were reported
Other bias	Low risk	None detected. Funder: none

Degonda 2002

Methods	Design: double-blind 2-arm randomised controlled trial of fexofenadine vs placebo Duration: 21 days
Participants	Number of participants randomly assigned: 21 (further information obtained from trial investigator); 13 evaluable participants with 6 in fexofenadine group and 7 in placebo group Sex: 38% female Age of participants, years: 38 Unit of allocation: participant Country and setting: Switzerland; hospital allergy clinics **Inclusion criteria of the trial** • Chronic urticaria of unknown aetiology, normal ECG, informed consent **Exclusion criteria of the trial** • Pregnancy • Previous unresponsiveness to antihistamine: not stated
Interventions	**Interventions, dose, duration** • Fexofenadine 180 mg once daily for 21 days • Placebo once daily for 21 days (1-week washout period, then 3-week run-in, with all participants taking fexofenadine; then participants were randomly assigned to fexofenadine or placebo) Duration of intervention: intermediate-term (21 days) Length of follow-up: 21 days

Degonda 2002 (*Continued*)

Outcomes	Timing of outcome assessment: 21 days **Primary outcomes of the trial** Assessment scores used were as follows: • Global assessment score: better/unchanged to better/unchanged/worse • Tiredness: none/mild/moderate/severe • Itching: none/mild/moderate/severe • Quality of life measures: none **Secondary outcomes of the trial** • Adverse events: fexofenadine: headache, sleep disturbance, diarrhoea; placebo: headache and dizziness, anxiety, dry mouth. Unclear whether or not adverse events led to dropout. Further information from trial investigator: Of adverse effects reported, only in 1 case could headache be correlated with fexofenadine intake (reported in 3/21 on fexofenadine and in 1 on placebo); diarrhoea 1/21, 0 in placebo arm Clinician or participant report: clinician and participant
Notes	Study investigators concluded that fexofenadine had a beneficial effect on urticaria Main report language is German

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Performed by pharmacist who was not involved in the study Comment: Although randomisation sequence was generated offsite, adequacy of sequence generation is unclear, as no further information was provided by trial investigator
Allocation concealment (selection bias)	Unclear risk	No details about allocation concealment available Comment: Although only allocation number was visible on sealed medication boxes, allocation concealment up to the point of assignment of the intervention is unclear
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study drugs and placebo were identical in appearance Comment: Further information from trial investigators stated that identical small and white tablet boxes were sealed with a plastic band (only allocation number could identify the participant)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Study drugs and placebo were identical in appearance Comment: Further information from trial

Degonda 2002 (*Continued*)

		investigators states that identical small and white tablet boxes were sealed with a plastic band (only allocation number could identify the participant). Outcome assessors were unaware of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	18 commenced active study (Phase II): 3 dropped out from the fexofenadine group (1 lack of efficacy, 1 worsening of condition, 1 moved house and lost contact). No participants dropped out from the placebo group (i.e. 15/18 completed) (further information supplied by trial investigator)
Selective reporting (reporting bias)	Unclear risk	All prespecified outcomes were reported, but results were presented in graph format or as percentages; number of once-daily treated participants in each group is unclear, therefore calculations may be prone to error
Other bias	Unclear risk	Funder: Aventis Odd and unclear trial design by which all participants were given active drug as run-in, then were randomly assigned again to fexofenadine or placebo

Di Lorenzo 2004

Methods	Design: randomised parallel-group 4-arm study conducted to compare desloratadine vs montelukast vs desloratadine plus montelukast vs placebo Duration: 6 weeks
Participants	Number of participants randomly assigned: 160 with 40 in each group Sex: 31% male, 69% female Age of participants, years: 18 to 69; mean 43.9 (SD 13.4) Unit of allocation: participant Country and setting: Italy; outpatient clinics of university hospitals **Inclusion criteria of the trial** • Chronic idiopathic urticaria **Exclusion criteria of the trial** • Physical, allergic or urticaria vasculitis, NSAID-induced urticaria, positive skin test to autologous serum or food additive challenge. Pregnancy, breast feeding, concomitant disease; corticosteroids or LT-RAs for 2 months before start of study (or 1 month oral corticosteroids before start of study) • Previous unresponsiveness to antihistamine: not stated

Interventions	**Interventions, dose, duration** • 5 mg desloratadine every morning plus placebo at night • 5 mg desloratadine every morning plus 10 mg montelukast at night • Placebo every morning plus montelukast 10 mg at night; placebo every morning plus placebo at night Rescue therapy: loratadine 10 mg allowed (frequency and duration unclear) Duration of intervention: intermediate-term (6 weeks) Length of follow-up: 8 weeks i.e. follow-up extended after cessation of treatment
Outcomes	Timing of outcome assessment: baseline, after 3 weeks of treatment, after 6 weeks, follow-up at 8 weeks **Primary outcomes of the trial** • 4-point scale of pruritus, number of hives, size of largest hive (cm), interference with sleep, interference with daily activities, remission of urticaria, excellent response, no variation, worse data (some of which were supplied as additional data by study investigator) • Clinical efficacy of desloratadine alone or combined with montelukast • Quality of life measures: none **Secondary outcomes of the trial** • Efficacy of montelukast as monotherapy, number of days when rescue therapy not required • Adverse events: incidence of emergency discontinuations due to adverse events, changes in vital signs, laboratory values and ECG Clinician or participant report: clinician and participant
Notes	Study investigators concluded that on average, desloratadine and desloratadine plus montelukast appear to be more effective than placebo or montelukast alone

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Method of randomisation not stated in publication. Further information from trial investigator: "We used the StatsDirect software for the list of randomised patients"
Allocation concealment (selection bias)	Unclear risk	No details given about allocation concealment; sealed envelopes were used and were opened after the study had ended. Further details supplied by study investigator
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (page 620): "The pharmacist of the University Hospital of Verona prepared a specific set with the treatments to be used for the study"; "The investigators and patients were blinded with respect to the contents of each set"

		Comment: unclear whether tablets were of identical appearance but probably adequate
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear whether or how outcome assessors were blinded Participants assessed some outcomes and were blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	62/160 initially randomly assigned participants dropped out, but this is unclear. Study investigator states that dropouts resulted from inefficacy and from requests from participants to discontinue therapy Dropouts from the study were included in the analysis Losses to follow-up: 68% (27/40)in montelukast plus placebo group; 88% (35/40) in placebo only group. Assumed no dropouts in desloratadine monotherapy or in combined therapy dropped out Comment: high dropout rates unevenly distributed between groups Results presented in graph format or as statistical significance; raw data not given
Selective reporting (reporting bias)	Unclear risk	Results obscure; expressed as numbers of participants not given (mean plus 95% CI or graphs) Adverse events: not stated ("low incidence… mild")
Other bias	Unclear risk	Funder: Ministero Italiano Universita e Ricerca; no pharmaceutical industry support All data potentially confounded by allowance of rescue medication. Our interpretation suggests that of a possible 1680 patient-days per group in the active study, Group 1 took rescue medication on average (median) on all but 90.6 days; Group 2 on all but 91 days; Group 3 on all but 45. 2 days; Group 4 on all but 54 days

Dubertret 1999

Methods	Design: multi-centre double-blind 3-arm placebo-controlled parallel-group study of mizolastine vs loratadine vs placebo Duration: 1-week placebo run- in period, then participants received therapy for 4 weeks
Participants	Number of participants randomly assigned: 247 enrolled: 88 to mizolastine; 79 to loratadine; 80 to placebo Sex: 36.8% male, 63.2% female Age of participants, years: 42 ± 15 Unit of allocation: participant Country and setting: France, Spain, Italy; secondary care, hospital clinics **Inclusion criteria of the trial** • At least 18 years of age, documented history of CSU (with or without angio-oedema), at least 2 episodes per week in the absence of treatment **Exclusion criteria of the trial** • Pregnancy, lactation, not using contraception, operating dangerous machinery or driving as occupation, hereditary angio-oedema or isolated dermographism and or major systemic disease • Previous unresponsiveness to antihistamine: not stated
Interventions	**Interventions, dose, duration** After 1-week placebo run-in period, participants received 4 weeks: • Mizolastine 10 mg/d • Loratadine 10 mg/d • Placebo Duration of intervention: intermediate-term (4 weeks) Length of follow-up: 4 weeks
Outcomes	Timing of outcome assessment: 2 weeks and 4 weeks **Primary outcomes of the trial** • Pruritus severity on visual analogue scale (0 = no discomfort, 100 = extreme discomfort) related to 7 days preceding the visit • Weekly number of episodes of urticaria, total urticaria score (severity of itching/size of lesion/number of lesions), intensity of angio-oedema • Quality of life measures: none **Secondary outcomes of the trial** • Adverse events: serious leading to study withdrawal: vasculitis (mizolastine group) , preexisting; appendicitis (loratadine group); other 5 not stated; minor: drowsiness, headache, fatigue, 'flu-like' symptoms, nausea Clinician or participant report: participant and clinician
Notes	Study acronym: 'MILOR' Study investigators concluded that mizolastine 10 mg daily is an effective and well-tolerated agent

Risk of bias

Bias	Authors' judgement	Support for judgement

Dubertret 1999 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Described as randomised, but method of randomisation not stated
Allocation concealment (selection bias)	Unclear risk	No methods of allocation concealment given in the study report, no further information available
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "Patients were randomised to a 4-week double-blind treatment..." but no methods of blinding given
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described in the study report
Incomplete outcome data (attrition bias) All outcomes	Low risk	205/247 completed Losses to follow-up: total 17%; mizolastine: 13/88 (14.8%); loratadine: 10/79 (12.9%); placebo: 19/80 (23.7%), with reasons given Mizolastine: lack of efficacy 3; adverse events 4; non-compliance 2; "other" 2; loss to follow-up 2 Loratadine: lack of efficacy 5; adverse events 3; non-compliance 0; "other" 2; loss to follow-up 0 Placebo: lack of efficacy 11; non-compliance 4; "other" 2; loss to follow-up 2
Selective reporting (reporting bias)	Unclear risk	All prespecified outcomes were reported, but data were given as mean scores plus SD; no participant numbers were given
Other bias	Unclear risk	Funder: Synthelabo research

Dubertret 2007

Methods	Design: randomised double-blind placebo-controlled 4-arm dose-ranging study of rupatadine (3 doses) vs placebo Duration: 28 days
Participants	Number of participants randomly assigned: 283 (rupatadine 5 mg n = 68, rupatadine 10 mg n = 73, rupatadine 20 mg n = 67, placebo n = 69) Sex: 28% male, 72% female Age of participants, years: range between 12 and 65; average 38.1 ± 13.0 Unit of allocation: participant Country and setting: France, Romania, Argentina, Hungary; secondary care, hospital clinics and skin research clinics

	Inclusion criteria of the trial • CSU at least 3 days per week for 6 weeks **Exclusion criteria of the trial** • Physical urticaria, cholinergic urticaria, urticaria of known aetiology, medications that are inhibitors of cytochrome P450 isozyme CYP3A4 • Previous unresponsiveness to antihistamine: not stated
Interventions	**Interventions, dose, duration** • Rupatadine 5 mg, 10 mg, 20 mg • Placebo (as a single once-daily tablet) Duration of intervention: intermediate-term (28 days) Length of follow-up: 28 days
Outcomes	Timing of outcome assessment: 14 days and 28 days **Primary outcomes of the trial** • Efficacy assessed by change from baseline in mean pruritus score, mean number of weals, mean total symptoms score calculated as sum of mean pruritus score and mean number of weals; mean interference in daily activity score; mean interference with sleep score over 4-week period • Quality of life measures not reported **Secondary outcomes of the trial** "All remaining variables," that is: • Physician's global assessment of efficacy at 14 days and 28 days on basis of symptom severity; change from baseline scored as 0 = worse than at prestudy, 1 = no change, 2 = slight improvement, 3 = good improvement • Participants recorded symptoms on daily diary card twice daily. Pruritus: 0 = none; 1 = mild, not annoying or troublesome; 2 = moderate, annoying/troublesome; 3 = severe, very annoying, substantially interfering with sleep/daily activities; 4 = very severe, warranting physician visit. For number of weals, scored as follows: 0 (none), 1 (1-5), 2 (6-15), 3 (16-25), 4 (> 25) • Participants also scored extent of interference with daily activities and sleep: 0 = none, 1 = mild, 2 = moderate, 3 = severe • Adverse events: minor only at 4 weeks: somnolence, headache, transient rise in serum creatine phosphokinase (CPK) Clinician or participant report: clinician and participant
Notes	Study investigators concluded that over the 4-week period, rupatadine 10 mg and 20 mg significantly reduced mean pruritus score compared with placebo

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not stated
Allocation concealment (selection bias)	Unclear risk	No methods of allocation concealment given in study report

Dubertret 2007 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote (page 224): "This was a phase II dose-ranging, randomised, double-blind, placebo-controlled..." No details given about method of blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote (page 224): "This was a phase II dose-ranging, randomised, double-blind, placebo-controlled..." No details given about method of blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	244/283 completed study according to protocol 39 participants (14%); 25 (10 given placebo, 9 given 5 mg, 3 given 10 mg, 3 given 20 mg) withdrew because of lack of efficacy: 1 for adverse event, 2 for incorrect treatment allocation, 11 for other or personal reasons However, 6 participants were excluded from analysis without explanation (i.e. 283 randomly assigned); 277 were included in study ITT analysis
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were reported
Other bias	Unclear risk	Funder: Uriach y Compania (Barcelona, Spain); National Scientific Research Program of the Spanish Minister of Science and Technology Unclear clinical meaning of primary outcome (0.5-point drop in mean pruritus severity score)

Finn 1999

Methods	Design: double-blind multi-centre placebo-controlled 5-arm trial to evaluate efficacy and safety of 4 different doses of fexofenadine vs placebo Duration: 4 weeks
Participants	Number of participants randomly assigned: 476 from 35 centres Number in each group: placebo 78; 20 mg twice daily 81; 60 mg twice daily 79; 120 mg twice daily 86; 240 mg twice daily 80 Sex: 30% male, 70% female Ethnicity: 90% white, 4% black, 4% "Asian" and 2% multi-racial Age of participants, years: 12 to 65 Unit of allocation: participants Country and setting: USA; setting research clinics **Inclusion criteria of the trial**

	• Presence of urticarial weals for at least 3 days per week for 6 consecutive weeks before entry; minimum of 1 to 5 weals, confirmed by investigator; moderate to severe itching during the previous 12 hours; informed consent **Exclusion criteria of the trial** • Urticaria associated with underlying disease (e.g. Hodgkin's disease, vasculitis, hyperthyroidism, lupus erythematosus, hepatitis); physical urticaria; urticaria due to medications, insect bites, food or other known aetiology. Dermographism; those unresponsive to prior antihistamine treatment; malnutrition; drug abuse or alcoholism; blood dyscrasia; malignancy; renal or hepatic insufficiency; malabsorption; chronic infection; psychiatric, cardiovascular, hepatic, neurological, endocrine or other major systemic disease. Not pregnant or lactating • Previous unresponsiveness to antihistamine: excluded if unresponsive to prior antihistamine treatment
Interventions	**Interventions, dose, duration** Single-blind placebo run-in for 24 hours • Placebo • 20 mg fexofenadine HCl • 60 mg fexofenadine HCl • 120 mg fexofenadine HCl • 240 mg fexofenadine HCl Twice a day for 4 weeks Duration of intervention: intermediate-term (4 weeks) Length of follow-up: 4 weeks
Outcomes	Timing of outcome assessments: unclear. Results based on at least 1 postbaseline 12-hour reflective mean pruritus score (MPS) assessment **Primary outcomes of the trial** • Change in mean pruritus score over 4-week period • Quality of life measures: none **Secondary outcomes of the trial** • Change events: any adverse events, changes in laboratory values, physical examination at first and last visits Clinician or participant report: participant and investigator
Notes	Study investigators concluded that fexofenadine HCl was well tolerated and statistically superior to placebo in treating CSU and in ameliorating interference with sleep and daily activities. They concluded that doses of 60 mg twice daily or greater were most effective

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not described
Allocation concealment (selection bias)	Unclear risk	No methods of allocation concealment given in the study report

Finn 1999 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "...4 week double blind treatment period." Methods of blinding not described in the study report
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "...4 week double blind treatment period." Methods of blinding not described in the study report
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	439/476 available for analyses (baseline scores and 1 postbaseline reflective MPS assessment). 103 (21.6%) lost to follow-up. Issues with losses to follow-up with participants involved in total discontinuation of treatment accounting for 21.6% Reasons for withdrawal: • Adverse event 19 • Treatment failure 44 • Elected to discontinue 11 • Defaulted from follow-up 3 • Required disallowed medication 7 • Other (not stated) 19 Comment: Table 1 in the study report gives a full description of reasons for dropout by group; however as the level of dropout is high at 21.6%, it is unclear whether dropout was a significant source of bias in this study
Selective reporting (reporting bias)	High risk	Only participants with baseline *and* at least 1 postbaseline mean pruritus score were included in analysis
Other bias	Unclear risk	Groups comparable at baseline except significant differences in interference with daily activities at baseline Funder: Hoechst Marion Roussel

Gale 1989

Methods	Design: randomised double-blind cross-over 2-arm study comparing the efficacy of acrivastine vs chlorpheniramine Duration: 24 days
Participants	Number of participants randomly assigned: 20 Sex: 55% male, 45% female Age of participants, years: mean 39.2 (range 18-27) Unit of allocation: cross-over (24 days) Country and setting: Australia; setting unclear

	Inclusion criteria of the trial • Urticaria of 4 weeks' duration, daily attacks (or alternate days) **Exclusion criteria of the trial** • No concomitant therapy with tranquillisers or sedatives, other antihistamines, systemic corticosteroids for at least 4 weeks before entry into the study • Previous unresponsiveness to antihistamine: not stated
Interventions	**Interventions, dose, duration** • 8 mg acrivastine • 4 mg chlorpheniramine maleate Three times daily for 24 days in this cross-over study. No wash out period reported, but no participant self-assessments reported in the first 3 days after cross-over to eliminate carryover effects from previous therapies Duration of intervention: intermediate-term (24 days) Length of follow-up: 24 days
Outcomes	Timing of outcome assessment: after each 24-day treatment period **Primary outcomes of the trial** • Weals 0-4: 0 (none), 1 (1-5), 2 (6-10), 3 (11-20), 4 (> 20); itching 0-4 (0 = none, 1 = minimal, 2 = mild, 3 = moderate, 4 = severe) • Quality of life measures: none **Secondary outcomes of the trial** • Adverse events: no information given Clinician or participant report: participant and investigator. Participants self-assessed daily. Participant reviewed by physician after each 24-day treatment period-physician recorded opinion on which treatment worked best and suited participant best overall
Notes	Study investigators concluded that both active drugs were effective, with no significant differences noted between them

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not stated
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Study states that this is a double-blind study; no methods of blinding given
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Method of blinding of outcome assessors not stated

Gale 1989 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	4/20 participants excluded from analysis because of protocol violations (20% lost to follow-up), with no ITT
Selective reporting (reporting bias)	High risk	Incomplete reporting of data (only means given); no comment on adverse events
Other bias	Unclear risk	Definition of disease given but CSU defined as > 4 weeks; however, no included participants had urticaria < 2 months Underpowered Funder: Wellcome Research Laboratories

Garavaglia 1995

Methods	Design: randomised double-blind 6-week study of cetirizine vs terfenadine vs placebo in CSU; parallel 3-arm trial Duration: 6 weeks
Participants	Number of participants randomly assigned: n = 63 took part in the study; however as participants dropped out, they were replaced, so 47 are presented (number given cetirizine n = 17; terfenadine n = 16; placebo n = 14) Sex: cetirizine: 29.41% male, 70.59% female; terfenadine: 18.75% male, 69.23% female; placebo: 69.23% male, 30.77% female Age of participants, years: cetirizine 33.8 ± 13.8; terfenadine 35.88 ± 17.3; placebo 37.8 ± 16.45 Unit of allocation: participant Country and setting: Argentina; outpatient research clinic **Inclusion criteria of the trial** • Participant's written consent to study conditions. 6-week history of regular attacks of idiopathic urticaria: minimum frequency of 3 episodes per week **Exclusion criteria of the trial** • Younger than 18 years of age, pregnant women or women with potential for pregnancy, serious renal or hepatic dysfunction, dependent on corticosteroids, taking drugs that interfere with cutaneous reactions unless they had stopped these before entry into the study; urticaria of known causes (contact, pressure, cold, heat, cholinergic, dermographism) • Previous unresponsiveness to antihistamine: not stated
Interventions	**Interventions, dose, duration** • Placebo, cetirizine 10 mg per day, 1 tablet • Terfenadine 120 mg per day, 2 tablets Duration of intervention: intermediate-term (6 weeks) Length of follow-up: 6 weeks
Outcomes	Timing of outcome assessment: 3 visits in total, initial at 3 weeks and final at 6 weeks from start of study **Primary outcomes of the trial**

	• Routine physical examination, including heart rate, blood pressure, height, weight • Clinician assessed the following: giant papules present or absent, papules present or absent; if papules present, fewer, or more than 20, erythema present or absent, oedema present or absent; objective description of lesions including distribution, size, location. • Participant report: visits 1 and 2: Participants were asked to complete daily diary cards to record their assessments of intensity of itching, redness and papules. Symptom report of mild, moderate or intense based on a visual analogue scale • Quality of life measures: none **Secondary outcomes of the trial** • Overall efficacy and tolerance assessed at end of study by participant and clinician • Adverse events: types of adverse events reported. Total adverse events: 2/17 in cetirizine, 2/16 in terfenadine. Types of adverse events reported: cetirizine: gastritis, dyspepsia, dry mouth, bitter taste, somnolence; terfenadine: morning sickness, menstrual alteration (delay, pain), shortening of cycle. No participant abandoned the study because of intolerable adverse effects • Participants were withdrawn if they had adverse reactions, interruption of medication for up to 3 days on more than one occasion, concomitant use of other active medication, withdrew consent, did not co-operate, violated study protocol, did not attend follow-up sessions, or there were other reasons (not specified) at the researcher's discretion. Clinician or participant report: clinician and participant
Notes	Study report written in Spanish Study investigators concluded that cetirizine is superior to terfenadine in terms of efficacy and tolerability; for symptom control, both active drugs were significantly better than placebo

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quote (page 180): "Randomly divided (in threes) into three equal groups" However, if participants dropped out, they were replaced with new participants (14 did not take the medication, 35 did not return for assessment, 37 did not take the correct medication. All of these participants were replaced). As participants who dropped out were replaced with new participants, it is unclear whether the trial design is truly randomised; it is not clear whether new participants were randomly assigned de novo or were assigned to the group of the most recent dropout. The trial report states: "since the randomisation was performed on groups of 3, it was actually necessary for each loss of a patient [to result in

		resumed] treatment of three patients" (page 182) (page 186) "9 patients were replaced as three were withdrawn due to protocol violations (lost medication, did not attend tests, did not take correct medication). Therefore 9 new [participants] were recruited, as randomisation was [done] in threes"
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Tablets and dosages prepared to be identical (boxes of white round tablets), presented so that each drug or placebo was administered in a uniform way. A scratch-off label would reveal the drug type in case of emergency
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Outcome assessors (clinicians and participants) would not have had indications of treatment group because of uniform packaging, but methods of blinding are not explicitly stated
Incomplete outcome data (attrition bias) All outcomes	High risk	47/63 completed. Dropped out: 3/17 in cetirizine; 3/16 in terfenadine; 9/14 placebo. 15 left the study because of inefficacy and were not replaced; they were "statistically computable" (page 186). It is unclear how results were computed for participants who dropped out because of inefficacy. Note: This may have introduced bias, as the study was possibly biased towards positive results Other reasons for dropout: adverse events: 2/17 in cetirizine; 2/16 in terfenadine due to adverse events No participant left the study because of intolerable adverse reactions
Selective reporting (reporting bias)	High risk	Only results for the cetirizine and terfenadine arms of the study were included in the published report. No results were presented for the placebo arm The researcher was able to withdraw participants on the basis of his opinion
Other bias	Unclear risk	Funder: not stated Analyses were not statistically significantly different and placebo results were not pre-

		sented; therefore conclusions of the study as stated in the study report are unreliable

Ghosh 1990

Methods	Design: randomised controlled trial of doxepin 10 mg thrice daily vs pheniramine maleate 22.5 mg thrice daily Duration: 3 weeks
Participants	Number of participants randomly assigned: 56 Sex: 67% female in doxepin group, 60% female in pheniramine group Age of participants, years: 18 to 59 Unit of allocation: participant Duration of urticaria: 8 weeks to 4 years Country and setting: India; secondary care **Inclusion criteria of the trial** • CSU; participants refractory to previous treatment **Exclusion criteria of the trial** • < 18 years of age, pregnant and lactating mothers • Previous unresponsiveness to antihistamine; all participants refractory to previous treatment
Interventions	**Interventions, dose, duration** • Doxepin 10 mg thrice daily • Pheniramine 22.5 mg thrice daily Length of follow-up: 4 weeks (follow up extended 1 week after cessation of therapy)
Outcomes	Timing of outcome assessment: 3 weeks and 4 weeks **Primary outcomes of the trial** • Complete remission; partial remission; no improvement after 3 weeks; recurrence 7 days after cessation of treatment • Quality of life measures: none **Secondary outcomes of the trial** • Laboratory investigations, blood counts, blood biochemistry • Adverse events: drowsiness, dry mouth, serum creatinine higher in 1 participant in doxepin group Clinician or participant report: both
Notes	Study investigators concluded that after 3 weeks of therapy, 8 (28.6%) participants in doxepin group and 3 (10.7%) in pheniramine group were symptom free (complete suppression)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Participants non-responsive to other antihistamine treatment excluded

Ghosh 1990 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Unclear allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Does not appear to be blinded: "twenty eight subjects were given doxepin 10 mg thrice weekly for 3 weeks"..."Another 28 subjects...were treated with pheniramine maleate 22.5 mg thrice weekly for 3 weeks"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Does not appear to be blinded: "twenty eight subjects were given doxepin 10 mg thrice weekly for 3 weeks"..."Another 28 subjects...were treated with pheniramine maleate 22.5 mg thrice weekly for 3 weeks
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No dropouts apparent
Selective reporting (reporting bias)	Unclear risk	Partial remission/improvement amongst participants is not defined or specific
Other bias	Low risk	None detected. Funder: none

Gimenez-Arnau 2007

Methods	Design: a randomised multi-centre multi-country double-blind parallel-group placebo-controlled 3-arm study of rupatadine at 2 different doses Duration: 6 weeks
Participants	Number of participants randomly assigned: 334 Sex: placebo: male 37.8%, female 62.2%; rupatadine 10 mg: 30% male, 70% female; rupatadine 20 mg: 26.9% male, 73.1% female Age of participants, years: mean (SD): placebo: 35.8 (13.4); rupatadine 10 mg: 40.2 (3.6); rupatadine 20 mg: 37.6 (14.6) Unit of allocation: participant Country and setting: Spain, Romania, Argentina, Poland, Germany, Italy; multi-centre, research clinics **Inclusion criteria of the trial** • ECG within normal limits • Women of child-bearing potential who tested negative for pregnancy **Exclusion criteria of the trial** • Other medication, including specific H1-receptor antagonists for at least 7 days, and inhibitors cytochrome P450 and isozyme CYP3A4. Acute urticaria, physical urticaria (cholinergic, cold/heat pressure, etc.) and chronic urticaria associated with some underlying disease (e.g. Hodgkin's disease, vasculitis, lupus erythematosus, hepatitis) • Previous unresponsiveness to antihistamine: not stated

Interventions	**Interventions, dose, duration** • Rupatadine 10 mg • Rupatadine 20 mg • Placebo Once daily for 6 weeks Duration of intervention: intermediate-term (6 weeks) Length of follow-up: up to 6 weeks
Outcomes	Timing of outcome assessment: after 2, 4 and 6 weeks of treatment **Primary outcomes of the trial** • Change from baseline in mean pruritus score (MPS) over 4-week treatment period • Quality of life measures: none **Secondary outcomes of the trial** • Change from baseline in mean number of weal score (MNW), mean total symptoms score (MTSS = MPS + MNW); DLQI; visual analogue scale over 4 and 6 periods (VAS 0: no discomfort; to 100: extreme discomfort) • Pruritus was assessed by scoring on a 5-point scale of 0 to 4 (0 = none; 1 = mild, not annoying or troublesome; 2 = moderate, annoying or troublesome; 3 = severe, very annoying, substantially interfering with sleep/daily activities; 4 = very severe, warranting doctor visit). Similarly, the number of weals was scored on a 5-point scale: 0 (0), 1 (1-5), 2 (6-15), 3 (16-25), 4 (> 25) • Overall efficacy was assessed after 2, 4 and 6 weeks of treatment; investigator-assessed global efficacy 0 to 4 (0 = worse, 1 = no change, 2 = slight improvement, 3 = good improvement, 4 = excellent improvement) • Adverse events: any adverse events recorded (no serious adverse events recorded) Clinician or participant report: participant and investigator (patient daily diary cards) Adverse events: any adverse events; headache; somnolence; hypertension; "metrorrhagia"
Notes	Investigators conclude that rupatadine 10 mg is a fast long-acting treatment with a better safety profile than rupatadine 20 mg

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "...according to a centralized computer-generated randomisation code provided by the sponsor of the study" Further information from the study investigator "The randomisation procedures were carried out at J. Uriach y Compañía, S.A. The Production Quality Management Department of J. Uriach y Compañía, S.A. drew up a randomisation list for the treatments. Afterwards, the Quality Assurance Unit of J. Uriach y Compañía S.A. randomly assigned a treatment to each code. Two copies

		of the randomisation code and two of the randomised list of patients were obtained"
Allocation concealment (selection bias)	Low risk	Quote: "A duly closed and sealed copy of each document was kept in the Quality Assurance Unit and in the Production Quality Management Department of J. Uriach y Compañía S.A. A third closed and sealed copy randomised list was prepared for the CRO MDS PS Pharma Services. In addition, once the study was concluded, all the individual envelopes were returned to the monitor, who checked that none of them had been opened for an unjustified reason. After the lock of study database, the copy kept by the Quality Assurance Unit was opened and filed in the master file of the study" (further information obtained from study investigator)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote from study: "... double-blind, placebo-controlled... study.." Further information from study investigator: "This was a double-blind study so that neither the investigator nor the patient knew treatment assignation. To preserve double blinding, medication was packaged identically for both types of treatments, with identical outside appearance of the strips and boxes. Individual envelopes identified with the patient assignation number were prepared. Each one included the identity of the treatment assigned to each patient. These envelopes, duly closed and sealed, were submitted to the investigator" "All medication was given in a two tablets scheme, that is, the 10 mg dose was given in two (10 mg plus placebo) tablets, the 20 mg dose was given in two (10 mg plus 10 mg) tablets, and the placebo was given in two (placebo plus placebo) tablets" Further information from study investigator
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"... double-blind, placebo-controlled... study.." Comment: as above

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No ITT; no actual scores given for DLQI, even at baseline 41/334 lost to follow-up (12.2%) with 293 evaluable participants Reasons for withdrawal: rupatadine 10 mg: participant decision n = 4; loss to follow-up n = 1; exclusion criteria n = 2; treatment failure n = 7; non-attendance at scheduled visits n = 2; other n = 1 Rupatadine 20 mg: loss to follow up n = 1; exclusion criteria n = 3; treatment failure n = 4; lack of compliance n = 1 Placebo: participant decision n = 2; loss to follow-up n = 1; serious adverse event n = 1; treatment failure n = 11
Selective reporting (reporting bias)	Low risk	SAF population stands for safety population (i.e. all randomly assigned participants who received any study drug). Figure 2 in the study report is done with the ITT population, as 5 patients did not present the efficacy variables; this is why the intention-to-treat analysis was performed in 329 participants In Figure 1, the number of participants completing the trial from the placebo group is 98, not 88 (as confirmed by study investigator) DLQI scores not stated in published report (percentages only)
Other bias	Unclear risk	Funder: J Uriach y Compania, Spain

Go 1989

Methods	Design: double-blind randomised 3-arm RCT comparing cetirizine, terfenadine and placebo in a cross-over study Duration: cross-over study lasting for 6 weeks, subdivided into 3 periods of 2 weeks
Participants	Number of participants randomly assigned: 30 Sex: not stated Age of participants, years: 15 to 69 (mean 48.8), but included at least 1 participant ineligible by age according to exclusion criteria Unit of allocation: cross-over Country and setting: Netherlands, Belgium; setting not stated **Inclusion criteria of the trial** • Chronic CSU of at least 6 weeks' duration with at least 1 daily episode of weals and pruritus

Go 1989 (*Continued*)

	Exclusion criteria of the trial • Younger than 16 years, pregnancy, lactation, impaired renal or hepatic function, angioneurotic oedema, glaucoma pressure or aspirin-sensitive urticaria. Washout of up to 14 days if other medication taken before study commenced • Previous unresponsiveness to antihistamine: not stated
Interventions	**Interventions, dose, duration** • Cetirizine 10 mg at night for 2 weeks plus placebo every morning • Terfenadine 60 mg twice daily • Placebo twice daily for 2 weeks No washout between treatments Participants could elect to finish particular treatment before 2 weeks was up and to move to next treatment in sequence Duration of intervention: short-term (2 weeks per intervention) Length of follow-up: 6 weeks (i.e. follow-up extended beyond cessation of therapy)
Outcomes	Timing of outcome assessment: at 2 weeks **Primary outcomes of the trial** • Investigator-recorded presence/absence of "giant" (undefined) or other weals: 0 (0), 1 (< 20), 2 (> 20), erythema and oedema (baseline, plus at end of each treatment) • Participant daily diaries-itching, erythema and weals (0 = none, 1 = mild, 2 = moderate, 3 = severe) • Also VAS for overall condition **Secondary outcomes of the trial** • Reasons for discontinuation • Adverse events: incidence of side effects. Serious adverse events unclear for all 3 treatments. Minor adverse events: cetirizine: sedation; headache; dizziness; nausea. Terfenadine: sedation; headache; malaise. Placebo: sedation; headache; dizziness; nausea; other GI disturbance. Quality of life measures: none • Serious adverse events unclear for all 3 treatments • Minor adverse events: cetirizine: sedation; headache; dizziness; nausea; terfenadine: sedation; headache; malaise; placebo: sedation; headache; dizziness; nausea; other GI disturbance. Clinician or participant report: both
Notes	Study investigators concluded as follows: By investigator measures, cetirizine significantly was better than placebo in all outcomes; terfenadine findings were only borderline or were not significant By participant measures, both drugs were equally (and statistically) superior to placebo

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not stated

Go 1989 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	No allocation concealment methods described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study states that it was double-blind Quote: 'products were given as identical capsules bid, with placebo as the morning intake in the cetirizine sequence'
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Study states that it was double-blind. Unclear how outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	2/30 were excluded after placebo sequence (refusal to participate) (6%) Serious adverse events were unclear for all 3 treatments 10/30 early withdrawals from treatment: inefficacy in placebo group n = 3; adverse events: cetirizine n = 1; placebo n = 1; terfenadine n = 3; unspecified reason: placebo: n = 2. No ITT (although low dropout rate)
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were reported. Mixed dichotomous and continuous outcome reporting
Other bias	Unclear risk	Funder: UCB (makers of cetirizine)

Godse 2007

Methods	Design: randomised double-blind placebo-controlled parallel multi-centre study comparing efficacy of fexofenadine and levocetirizine Duration: up to 1 month
Participants	Number of participants: 40 (20 in each group) Sex: 50% male, 50% female Age of participants, years: 14 to 70 Unit of allocation: participant Country and setting: India; setting hospital clinic **Inclusion criteria of the trial** • Described as having CSU; criteria for diagnosis not described. No infection or underlying cause of diagnosis. Blood count, urine and sugar analysed before treatment began • Informed consent **Exclusion criteria of the trial** • Other than pregnancy or lactation, not stated • Previous unresponsiveness to antihistamine: not stated

Godse 2007 (*Continued*)

Interventions	**Interventions, dose, duration** • Fexofenadine HCl 180 mg once daily • Levocetirizine 5 mg daily For relief of symptoms up to 1 month Duration of intervention: intermediate-term (up to 1 month) Length of follow-up: up to 4 weeks
Outcomes	Timing of outcome assessment: 2 week and 4 weeks **Primary outcomes of the trial** • Mean change in Urticaria Activity Score (defined in paper) at 2 weeks and 4 weeks (compared with baseline) **Secondary outcomes of the trial** • Adverse events: fexofenadine: headache; levocetirizine: drowsiness • Quality of life measures: none Clinician or participant report: clinician
Notes	Study investigators concluded that fexofenadine was superior to levocetirizine

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "All participants were divided into two groups," described as randomised but no details given
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not stated
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	High risk	2/20 participants in levocetirizine group were lost to follow-up (no reasons given) and were replaced by 2 new participants. No ITT
Selective reporting (reporting bias)	High risk	Small study; no raw data; means and SDs of scores only; results not expressed as participant numbers. States placebo controlled, but no placebo results reported
Other bias	Unclear risk	Sponsor: Sanofi-Aventis and Systopic Laboratories (provided drugs)

Goh 1991

Methods	Design: cross-over study comparing cetirizine with placebo Duration: 1 week
Participants	Number of participants randomly assigned: 32 Sex: 50% female Age of participants, years: range 18 to 46 (mean 30.4 ± 8.2) Unit of allocation: cross-over Country and setting: Singapore; secondary care **Inclusion criteria of the trial** • Chronic idiopathic urticaria **Exclusion criteria of the trial** • Angio-oedema, liver or renal disease, steroids in last 28 days • Previous unresponsiveness to antihistamine: not stated
Interventions	**Interventions, dose, duration** • Cetirizine 10 mg at night for 1 week • Placebo at night for 1 week and crossed over Length of follow-up: 1 week Duration of intervention: short-term (1 week per intervention)
Outcomes	Timing of outcome assessment: 1 week **Primary outcomes of the trial** • Visual analogue scale of baseline urticaria severity (unclear over what period this related to): 0 = very bad, 100 = excellent • Daily diary for itching and weals: 0 = none, 1 = mild, 2 = moderate, 3 = severe • Initial mean severity on VAS by investigators: 45.5 out of 100 (range 21-94) • Cetirizine yielded significantly better scores than placebo on physician and participant VAS and on participant diaries for itch and weals • Quality of life measures: none **Secondary outcomes of the trial** • Adverse events: minor adverse events: cetirizine: drowsiness; placebo: drowsiness Clinician or participant report: both
Notes	Study investigators concluded that cetirizine yielded significantly better scores than placebo on physician and participant VAS and in participant diaries for itch and weals

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not stated
Allocation concealment (selection bias)	High risk	No allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Probably done

Goh 1991 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Investigators' assessment of severity on VAS
Incomplete outcome data (attrition bias) All outcomes	High risk	No ITT. No mention of serious adverse events or dropouts due to them. 4 participants (12.5%) lost to follow-up
Selective reporting (reporting bias)	High risk	Results derived from visual analogue scales; not stated whether groups were comparable at baseline
Other bias	Unclear risk	Funder: none No washout between treatments, but no sequential effect shown

Grant 1988

Methods	Design: double-blind multi-centre 3-arm trial of terfenadine, chlorpheniramine and placebo Duration: 6 weeks
Participants	Number of participants randomly assigned: 136 Age group and gender: not stated Unit of allocation: participant Country and setting: USA; setting recruited from medical practices of principal investigators at 10 university research clinics (assumed that the practices were the settings) **Inclusion criteria of the trial** • Pruritic weals of unknown cause for 3 days per week for 6 consecutive weeks **Exclusion criteria of the trial** • Participants previously unresponsive to antihistamines were excluded: pregnant, lactating or not using effective contraception, concomitant medications, abnormality in laboratory values, medical history or physical examination findings
Interventions	**Interventions, dose, duration** Participants entered a single-blind placebo period for a week, and if hives of moderate severity were present for 3 days during the week, participants were assigned to • Terfenadine 60 mg twice daily • Chlorpheniramine 4 mg 3 times a day • Placebo for 6 weeks (frequency of placebo not stated) Duration of intervention: intermediate-term (6 weeks) Length of follow-up: up to 6 weeks
Outcomes	Timing of outcome assessment: weekly for 6 weeks **Primary outcomes of the trial** • Mean symptom scores recorded by participants during baseline single-blind phase and double-blind 6-week period • Number of hives: none, 1 to 5, 6 to 15, 16 to 25, > 25

	• Redness: absent, slight, definite, extreme • Itching: absent, mild, moderate, severe • Waking with hives: none, < 1 hour, 1 to 6 hours, > 6 hours • Quality of life measures: none **Secondary outcomes of the trial** • Adverse events: including drowsiness, fatigue/tiredness, headache, nausea Clinician or participant report: investigators and participants
Notes	Study investigators concluded that chlorpheniramine was not statistically significantly different from placebo

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation: Quote (page 575): "participants were randomly assigned to one of three groups of equal size..."
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Method of blinding unclear: Quote (page 575): "Acceptable participants entered the first phase of the study and were administered placebo in a single-blind fashion for a week. Those who developed moderately severe hives for at least 3 days that were actually observed by the investigators were then enrolled in the double-blind phase" Also, unclear if blinding adequate: quote: "In order to limit the number of drop-outs, diphenhydramine 25mg capsules were offered as relief medication"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear method of blinding outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	122/136 who were randomly assigned completed the study (of an undisclosed number, 'more than half' were initially screened but excluded) 14 (10.2%) were lost to follow-up Withdrawals due only to treatment failure: terfenadine n = 1; chlorpheniramine n = 4; placebo n = 9. Unbalanced between groups but unlikely to introduce bias

Grant 1988 (*Continued*)

Selective reporting (reporting bias)	High risk	Results presented graphically only, no participant numbers or means with SD
Other bias	Unclear risk	Participants allowed a different antihistamine if uncontrolled: 22/42 (52%) of placebo group took diphenhydramine; 12/46 (26%) of chlorpheniramine group and 4/46 (9%) of terfenadine group already a subgroup, as participants unresponsive to antihistamines were excluded Funder: none stated

Gu 2002

Methods	Design: multi-centre (4 centres) randomised double-blind parallel 2-arm study of desloratadine vs loratadine Duration: 28 days
Participants	Number of participants randomly assigned: 158 Sex: male 45%, female 64% Age of participants, years: 18 to 65, desloratadine mean 38.6; loratadine mean 39.1 Unit of allocation: participant Country and setting: China; secondary care **Inclusion criteria of the trial** • Mean age 16 to 65 male or female • Known CSU • Classical weal (not longer than 24 hours) • Chronic idiopathic urticaria > 6 weeks • Weal seen on day of assessment • Participants able to consent to study **Exclusion criteria of the trial** • Other form of urticaria due to insect-, food- and drug-induced urticaria, cold urticaria, pressure urticaria, solar urticaria, cholinergic, etc., urticaria vasculitis, SLE, thyroid-induced urticaria • Occupation pilot, driver • Cardiac disease and cardiac arrhythmia, liver disease, peptic ulcer and other chronic disease • Pregnant women, breast feeding and any women who plan to have pregnancy • Known allergies to desloratadine and loratadine, multi-drug allergies • Participated in another clinical trial within last 3 months • Using cardiac medications, morphine and sedatives • Non-compliant with medications, unable to attend follow-up, unforeseen circumstances (e.g. accident), not willing to consent • Previous unresponsiveness to antihistamine: not mentioned Duration of disease in desloratadine group 26.9 weeks; loratadine group 26.1 weeks Groups comparable at baseline with t value and P value in Chart 2

Gu 2002 (*Continued*)

Interventions	**Interventions, dose, duration** • Desloratadine 5 mg/d by mouth once daily, 28 days • Loratadine 10 mg/d once daily by mouth, 28 days Duration of intervention: 28 days (intermediate) Length of follow-up: seen before treatment, at 14 days, at 28 days Concomitant/rescue treatment: not mentioned
Outcomes	Timing of outcome assessment: 14 days and 28 days **Primary outcomes of the trial** • Total symptoms scores, number and size of weals • Symptom improvements, weal number, weal size, redness, itching intensity • Quality of life measures: none **Secondary outcomes of the trial** • Adverse events: including severity of adverse events ○ Mild: not requiring intervention ○ moderate: obvious but can continue with the trial ○ Severe: symptoms needing medication ○ Adverse events that may be/may not be/obviously related to trial drugs Timing of outcome assessment: seen before treatment, at 14 days and at 28 days Clinician or participant report: clinician and participant
Notes	Study investigators concluded that desloratadine is safe and effective in the treatment of CSU. No significant differences between the 2 groups, no serious adverse events. Desloratadine safe and effective Main study report in Chinese

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Stated to be randomised
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Participants and personnel were blinded to treatment group Not mentioned clearly
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Outcome assessors were blinded to treatment group Not mentioned clearly
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear, no details about dropout in translation of published report. ITT analysis carried out: unclear

Gu 2002 (*Continued*)

Selective reporting (reporting bias)	Unclear risk	All prespecified outcomes were reported, but reporting of adverse events is unclear. Severity of adverse advents and whether or not these were likely to have been caused by trial medication were specified as an outcome, but reported results are unclear and state only that no serious adverse events occurred
Other bias	Unclear risk	Funder: not stated Assessment of compliance undertaken but not clearly stated, apart from exclusion criteria

Guo 2003

Methods	Design: randomised double-blind parallel-group comparison of mizolastine vs loratadine Duration: 4 weeks
Participants	Number of participants randomly assigned: 47; n = 24 mizolastine, n = 23 loratadine Sex: 36% male, 55% female Age of participants, years: 17 to 53, mizolastine mean 34.9; loratadine mean 33.0 Unit of allocation: participant Country and setting: China; secondary care **Inclusion criteria of the trial** • CSU over 16 years of age • Fulfilled criteria for chronic Idiopathic urticaria; mean duration 1.5 month to 144 months • Symptoms within 24 hours before entry into the study **Exclusion criteria of the trial** • On medications, pregnant or lactating women; other types of urticaria, other skin diseases (not specified); patients with severe liver, kidney and haematological diseases; known allergies to H1-antagonists and allergic to mizolastine; taking astemizole < 8 weeks or another antihistamine fewer than 7 days; known to have heart disease, cardiac arrhythmia, prolonged QT interval; known to have cancer; in high-intensity profession • Previous unresponsiveness to antihistamine: not stated
Interventions	**Interventions, dose, duration** • Mizolastine 10 mg • Loratadine 10 mg once daily for 4 weeks Duration of intervention: intermediate-term (4 weeks) Length of follow-up: 4 weeks
Outcomes	Timing of outcome assessment: 7, 14 and 28 days **Primary outcomes of the trial** • Symptoms: itching severity (VAS score), diameter of largest weal, number of weals per day, duration of weals (hours) • Clinical improvements: complete suppression/significant improvements/

Guo 2003 (*Continued*)

	improvements/no changes using SSRI score (symptom scores reduction index) • Quality of life measures: not stated **Secondary outcomes of the trial** • Adverse events: dry mouth, sleepiness, lethargy, no differences in side effects between the 2 groups Clinician or participant report: clinician and participant
Notes	Study investigators concluded that no difference in side effects was found between the 2 groups. Findings indicated that the effect of mizolastine was much better than that of loratadine, and it could be selected as the priority treatment for CSU Main study reported in Chinese

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Double-blind randomisation stated. Quote (page 482): "divided into two groups by randomised method"
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote (page 482): "double-blind," but no further details given
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote (page 482): "double-blind," but no further details given
Incomplete outcome data (attrition bias) All outcomes	High risk	Stated 47 cases, but analyses include 23 in each group; data analysis was based on 46 cases; no reason given for this dropout
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were reported
Other bias	Low risk	None detected Funder: not stated

Handa 2004

Methods	Design: randomised 2-arm double-blind study of cetirizine vs fexofenadine Duration: 28 days
Participants	Number of participants randomly assigned: 116; n = 59 cetirizine; n = 57 fexofenadine Sex: not stated Age of participants, years: range of 17 to 65 Unit of allocation: participant Country and setting: India; dermatology institute clinic

	Inclusion criteria of the trial • CSU (weals for at least 2 days per week for consecutive weeks before study) **Exclusion criteria of the trial** • Other forms of urticaria, dermatographism, pregnant, lactating • Previous unresponsiveness to antihistamine: not stated
Interventions	**Interventions, dose, duration** • Cetirizine 10 mg/d • Fexofenadine 180 mg/d Duration of intervention: intermediate-term (28 days) Length of follow-up: 28 days
Outcomes	Timing of outcome assessment: days 14 and 28 **Primary outcomes of the trial** • Final response: symptom-free: no signs or symptoms; partial improvement, no improvement (judged by physician) • Participant evaluation by "analogue scale": itching: 0 = none; 1 = mild, not annoying; 2 = moderate, annoying and troublesome; 3 = severe, interfering with sleep and daily activities • Quality of life measures: none **Secondary outcomes of the trial** • Adverse events: minor adverse events (not requiring treatment withdrawal): included drowsiness, constipation, epigastric pain, cough, headache plus swollen feet Clinician or participant report: participant and investigator
Notes	Study investigators concluded that cetirizine seemed to have therapeutic advantage over fexofenadine

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Method of randomisation not stated, described as randomised. Further information from study investigator states: "For the study we generated a randomisation list using a random number table"
Allocation concealment (selection bias)	Low risk	Study investigator states: "The code was kept with the central authority-not directly involved with the study and assessment of endpoints. Both the investigators and patients were blinded since the central authority provided the patients with similar looking sealed envelopes containing the medication and labelled only as A or B"

Handa 2004 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study investigator states: "Both the investigators and patients were blinded since the central authority provided the patients with similar looking sealed envelopes containing the medication and labelled only as A or B. The blinding was opened after assessing the results and the statistical analysis of the two groups A and B. It was done by inquiring from the central authority which was dispensing the drugs to the patient"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Study investigator states: "Both the investigators and patients were blinded since the central authority provided the patients with similar looking sealed envelopes containing the medication and labelled only as A or B. The blinding was opened after assessing the results and the statistical analysis of the two groups A and B. It was done by inquiring from the central authority which was dispensing the drugs to the patient"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	High dropout rate, no ITT (no ITT confirmed by study investigator); 19/116 lost to follow-up in total (13%): 7 in cetirizine group and 12 in fexofenadine group within 2 weeks, "the most common reason being treatment failure." Unclear if this contributes to bias
Selective reporting (reporting bias)	Unclear risk	All prespecified outcomes were reported, but other outcomes were reported as well (e.g. duration of weals, diurnal variation, intensity of itching, presence of weals). Symptoms during the day were not reported by groups
Other bias	Low risk	Funder: not stated. No indication of comparability of groups at baseline

Hao 2003

Methods	Design: randomised multi-centre double-blind 2-arm parallel-group comparison of desloratadine vs loratadine Duration: 28 days

Participants	Number of participants randomly assigned: 217; desloratadine n = 108; loratadine n = 109 Sex: male 43.8%, female 56.2% Age of participants, years: 18 to 65 Unit of allocation: participant Country and setting: China, secondary care, Southern Hospital, 3rd Military Medical University. Chongqing, China **Inclusion criteria of the trial** • CSU by clinical signs, chronic Idiopathic urticaria > 6 weeks, urticaria not due to other causes • Consented, agreed for clinical study, not on antibiotics or other agents **Exclusion criteria of the trial** • Known allergies to desloratadine and loratadine • Taking immunosuppressants (and other medications, type not stated), taking desloratadine or loratadine within 4 weeks of start of study • Previous unresponsiveness to antihistamine: unclear, washout period-treatment commenced after 4-week washout period from previous antihistamines or immunosuppressants (type not stated) • Taking medication that prolonged QT interval; high-intensity profession • Previous unresponsiveness to antihistamines not stated
Interventions	**Interventions, dose, duration** • Desloratadine 5 mg per day • Loratadine 10 mg per day in once-daily doses Duration of intervention: intermediate-term (28 days) Length of follow-up: 28 days
Outcomes	Timing of outcome assessment: 7, 14 and 28 days **Primary outcomes of the trial** • Effectiveness and safety. Symptoms: itching severity; diameter of largest weal; number of weals per day; degree of weal swelling; duration of weals (hours) • Clinical improvements: complete suppression/significant improvement/ improvement/no change • Quality of life measures: none **Secondary outcomes of the trial** • Safety of medications (blood pressure, heart rate/FBC/U/E LFT) • Adverse events: dry mouth, sleepiness, lethargy, no details were given about why participants with severe adverse effects required withdrawal Clinician or participant report: clinician and participant
Notes	Main study report in Chinese Study investigators concluded that desloratadine is an effective and safe agent for CSU

Risk of bias

Bias	Authors' judgement	Support for judgement

Hao 2003 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Stated to be randomised
Allocation concealment (selection bias)	Unclear risk	No details given
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Stated to be double-blind, no further details given about blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Stated to be double-blind, no further details given about blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	3/105 dropped out or were lost from the desloratadine group; 3/106 dropped out or were lost from the loratadine group; no reasons given
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were reported
Other bias	Low risk	None detected. Funder: not stated

Harvey 1981

Methods	Design: double-blind randomised cross-over study in which participants were treated sequentially (5-arm comparison of hydroxyzine plus placebo, hydroxyzine plus terbutaline, hydroxyzine plus chlorpheniramine, hydroxyzine plus cimetidine) Duration: 7 to 10 days
Participants	Number of participants randomly assigned: 23 Sex: 79% female Age of participants, years: mean 37 (range 24-64) Unit of allocation: cross-over participants Country and setting: USA; setting University of Colorado Health Sciences Center **Inclusion criteria of the trial** • Chronic urticaria refractory to treatment, normal physical examination findings and laboratory values **Exclusion criteria of the trial** • Not stated • Previous unresponsiveness to antihistamine: population was selected as refractory to treatment
Interventions	**Interventions, dose, duration** Cross-over study in which participants were treated sequentially with 5 regimens in double-blind random sequence • Hydroxyzine plus terbutaline (beta agonist) = 25 mg 4 times a day plus 2.5 mg 4 times a day for 7 to 10 days • Hydroxyzine plus cyproheptadine = 25 mg 4 times a day plus 4 mg 4 times a day

Harvey 1981 (*Continued*)

	for 7 to 10 days • Hydroxyzine plus chlorpheniramine = 25 mg 4 times a day plus 4 mg 4 times a day for 7 to 10 days • Hydroxyzine plus cimetidine (H2-antihistamine) = 25 mg 4 times a day plus 300 mg 4 times a day for 7 to 10 days • Hydroxyzine plus placebo = 25 mg 4 times a day for 7 to 10 days (details of placebo not stated) Duration of intervention: short-term (7-10 days each intervention) Length of follow-up: unclear
Outcomes	Timing of outcome assessment: 7 to 10 days **Primary outcomes of the trial** • Participants selected which regimen they believed was most effective; symptom diary recorded twice daily (for final 5 days of each treatment regime)-hive count: 0 (none), 1 (1-6), 2 (7-12), 3 (> 12); itching: 0 = none, 1 = mild, 2 = moderate, 3 = severe • Suppression of skin weals following intradermal histamine • Quality of life measures: none **Secondary outcomes of the trial** • Adverse events: extreme tremulousness (n = 2) in terbutaline necessitated abbreviated treatment course Clinician or participant report: participant and investigator
Notes	Study investigators concluded that hydroxyzine plus cimetidine was significantly better than other combinations. Hydroxyzine had transient soporific effects but was well tolerated. Unclear whether soporific effects were due to hydroxyzine and not to one of the other sedating antihistamines

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not stated: "participants were treated orally in a double-blind randomised serial fashion..."
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"participants were treated orally in a double-blind randomised serial fashion..." Method of blinding unclear
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"participants were treated orally in a double-blind randomised serial fashion..." Method of blinding unclear
Incomplete outcome data (attrition bias) All outcomes	High risk	19/23 completed. 4 removed because of non-compliance (17% lost to follow-up). One participant not accounted for Extreme tremulousness (n = 2) in terbu-

Harvey 1981 (*Continued*)

		taline necessitated "abbreviated treatment course" ITT unclear (some terbutaline participants did not complete the course, but non-compliant participants were excluded from analysis)
Selective reporting (reporting bias)	High risk	Adverse events not clearly reported
Other bias	Unclear risk	Funder: NIH Allergic Disease Center Grants Study duration not clearly defined ("7-10 days") No stated exclusions, and physical urticaria may have been included. Two groups were given a combination of 2 first-generation antihistamines; concomitant treatment with hydroxyzine allowed in all groups

Hjorth 1988

Methods	Design: double-blind randomised 2-arm cross-over study of terfenadine vs clemastine Study 1: clemastine vs placebo Study 2: terfenadine vs placebo Duration: 2 weeks
Participants	Number of participants randomly assigned: 60; 30 per group in each cross-over phase Sex: 33% male, 67% female Age of participants, years: 18-72 (mean 37) Unit of allocation: cross-over, no washout period described Country and setting: Denmark; setting unclear **Inclusion criteria of the trial** • CSU (no definition stated), may include participants with atopic dermatitis **Exclusion criteria of the trial** • None stated • Previous unresponsiveness to antihistamine: not stated
Interventions	**Interventions, dose, duration** • Clemastine 1 mg twice daily for 2 weeks • Placebo twice daily for 2 weeks • Followed by cross-over to terfenadine 60 mg twice daily for 2 weeks Duration of intervention: short-term (2 weeks per intervention) Length of follow-up: 14 days
Outcomes	Timing of outcome assessment: 14 days **Primary outcomes of the trial** • Participants kept written record of number of weals, itch severity and side effects

	• Physicians' overall rating: none, moderate, excellent • Efficacy rated according to number of weals, as symptom score used in results was not defined • Quality of life measures: none **Secondary outcomes of the trial** • Adverse events: only drowsiness reported Clinician or participant report: participant and clinician
Notes	Study author concluded that terfenadine was more efficacious than clemastine or placebo No review outcomes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"in random order, participants were assigned..."; no further details given
Allocation concealment (selection bias)	Unclear risk	Unclear, no details given
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Study is stated to be double-blind; unclear how this was achieved
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Study is stated to be double-blind; unclear how this was achieved, as only 1 study author/single investigator was involved
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Number of participants who dropped out from each group not stated. Withdrawals not mentioned
Selective reporting (reporting bias)	High risk	Results incompletely reported, no numerical data (graphs only); able to rate efficacy only according to number of weals, as symptom score used in results was not defined
Other bias	Unclear risk	Funder: not stated Diagnosis of CSU not clearly defined; unclear whether concomitant medications allowed; single study author

Hoxha 2011

Methods	Design: double-blind randomised controlled 3-arm study comparing levocetirizine vs desloratadine vs placebo Duration: not stated
Participants	Number of participants randomly assigned: 107; levocetirizine group: 37; desloratadine group: 34; placebo: 36 Sex: not stated Age of participants, years: 18 to 60 Unit of allocation: participant Country and setting: Albania; tertiary centre **Inclusion criteria of the trial** • CSU symptoms at least 6 weeks **Exclusion criteria of the trial** • Not specified
Interventions	**Interventions, dose, duration** • 5 mg levocetirizine and • 5 mg desloratadine (each increasing weekly to 10 mg, then 20 mg) Duration of intervention: unclear Length of follow-up: not stated
Outcomes	**Primary outcomes of the trial** • Timing of outcome assessment: not stated • Number of participants symptom free • Adverse events: no serious adverse events with either drug • Quality of life measures: Increasing doses improved quality of life
Notes	Study investigators concluded that Increasing the dosage of levocetirizine and desloratadine up to 4-fold improved chronic urticaria symptoms without compromising safety

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study states randomly assigned, but not clear how done
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Study says double-blind but no other details
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated

Hoxha 2011 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	All participants accounted for, but 9 from active arms left the study (reason not stated) , and all participants from placebo arm (36) dropped out from the study
Selective reporting (reporting bias)	Unclear risk	No timing of assessment stated
Other bias	Unclear risk	Funder: not specified This study was available as a short conference abstract only; we were unable to identify a published report or to obtain further information from the study investigator

Juhlin 1987

Methods	Design: randomised double-blind 3-arm cross-over placebo-controlled study of acrivastine and clemastine Duration: 5 days each cross-over period
Participants	Number of participants randomly assigned: 18 Sex: 33% male, 67% female Age of participants, years: 14 to 75 (mean 43.2) Unit of allocation: cross-over Country and setting: UK; setting unclear **Inclusion criteria of the trial** • Informed consenting adults, with CSU **Exclusion criteria of the trial** • Not stated • Previous unresponsiveness to antihistamine: not stated
Interventions	**Interventions, dose, duration** • Cross-over: All participants had acrivastine 8 mg 3 times daily for 5 days, then • Clemastine 1 mg 3 times daily for 5 days, then • Placebo 3 times daily for 5 days Cycle through each regimen with 2-day breaks in between with no relevant treatment Duration of intervention: short-term (5 days per intervention) Length of follow-up: unclear (at end of each 5-day treatment period?)
Outcomes	Timing of outcome assessment: 5 days **Primary outcomes of the trial** • Questionnaire: itching/wealing/caused drowsiness/suited participant/best overall • Quality of life measures: none **Secondary outcomes of the trial** • Adverse events: no withdrawals/serious adverse events. Minor adverse events: drowsiness Clinician or participant report: investigator and participant questionnaire

Juhlin 1987 (*Continued*)

Notes	Study investigators concluded no significant differences in efficacy were noted between acrivastine and clemastine; both were significantly preferred by participants over placebo

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised, but randomisation method was unclear
Allocation concealment (selection bias)	Unclear risk	No allocation concealment described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"A double-blind, placebo-controlled study." Mentioned only in title; no other details given
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"A double-blind, placebo-controlled study." Mentioned only in title; no other details given
Incomplete outcome data (attrition bias) All outcomes	Low risk	18/18 completed. None lost to follow-up
Selective reporting (reporting bias)	High risk	Although both doctor questionnaire and participant self-assessment were carried out, only simple participant perceptions reported; no objective data provided
Other bias	Unclear risk	Funder: Sponsorship: Wellcome Foundation Ltd No mention of whether concomitant treatments were permitted Underpowered

Juhlin 1991

Methods	Design: randomised double-blind cross-over 3-arm trial comparing 10 or 20 mg cetirizine vs placebo Duration: 15 days
Participants	Number of participants randomly assigned: 30 Sex: 27% male, 63% female Age of participants, years: range 15 to 70 (mean 43) Unit of allocation: cross-over Country and setting: Sweden; setting unclear **Inclusion criteria of the trial** • In the first study, participants had severe CSU (daily eruptions of weal) for mean

Juhlin 1991 (*Continued*)

	of 4 years' duration **Exclusion criteria of the trial** • Not stated • Previous unresponsiveness to antihistamine: reported as 'variably effective,' but non-responders were not excluded from this study
Interventions	**Interventions, dose, duration** • Cetirizine 10 mg/d for 15 days • Placebo once daily for 15 days After 15 days, participants were allowed to cross over with no washout period. Non-responders were allowed to increase to twice-daily dosing Duration of intervention: short-term (15 days) Length of follow-up: end of each 15-day treatment period
Outcomes	Timing of outcome assessment: 15 days. Visits at baseline and at end of each treatment phase **Primary outcomes of the trial** • Participant daily diary for weals, erythema, pruritus and oedema: 0 = absent, 1 = mild, 2 = moderate, 3 = severe • VAS by participants for evaluation of condition: 0 to 100 mm • Global evaluation of improvement judged on % basis: 91% to 100% = excellent; 30% or less = poor • Quality of life measures: none **Secondary outcomes of the trial** • Adverse events: minor adverse events: dry mouth, diarrhoea, heaviness of the head, sedation. No serious side effects noted Clinician or participant report: participant
Notes	Study investigators concluded that cetirizine was significantly more effective than placebo in reducing incidence of erythema, weals and pruritus Study 2 in the published report was a laboratory study on the effects of certain agonists; the results were not included in this analysis

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Unclear method of randomisation. Participants 'randomly assigned'
Allocation concealment (selection bias)	Unclear risk	Unclear. Not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind study. Unclear how this was done
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Double-blind study. Unclear how this was done

Juhlin 1991 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Number of participants who dropped out from the study (if any) unclear
Selective reporting (reporting bias)	High risk	Extensive laboratory tests were carried out (for adverse effects) but were not reported. Measures of incidence and severity of weals were reported
Other bias	Low risk	None detected. Funder: not stated

Kalivas 1990

Methods	Design: randomised multi-centre parallel-group 3-arm double-blind placebo-controlled study of cetirizine vs hydroxyzine vs placebo Duration: 4 weeks
Participants	Number of participants randomly assigned: 219; cetirizine: 69, hydroxyzine: 69, placebo: 73 Sex: not stated Age of participants, years: 12+, no further details Unit of allocation: participant Country and setting: USA; centres included medical and science centres and private practice **Inclusion criteria of the trial** • Clinically documented CSU **Exclusion criteria of the trial** • Not stated • Previous unresponsiveness to antihistamine: not stated
Interventions	**Interventions, dose, duration** • Cetirizine 5 mg once daily (increasing to max 20 mg once daily in 2 steps "as necessary") for 4 weeks • Hydroxyzine 25 mg once daily (increasing to twice daily, then 3 times daily "as necessary") for 4 weeks Intermediate dose of cetirizine not stated Duration of intervention: intermediate-term (4 weeks) Length of follow-up: 4 weeks
Outcomes	Timing of outcome assessment: baseline, 3 days, 1 week, 2 weeks, 3 weeks, 4 weeks **Primary outcomes of the trial** • Daily diary with 4-point scale: measured number, size, duration of lesions and number of urticarial episodes, degree of pruritus; same scale used by investigator at baseline, after 3 days' treatment, 1 week, 2 weeks, 4 weeks. Scale as follows: number of lesions: 0 (0), 1 (1-10), 2 (11-20), 3 (> 20); number of episodes: 0 (0), 1 (1), 2 (2-3), 3 (> 3); average lesion size in inches: 0 (0), 1 (< 0.5), 2 (0.5-1), 3 (> 1); duration of lesions in hours: 0 (0), 1 (1-4), 2 (4-12), 3 (12-24); pruritus: none/mild/moderate/severe • Adverse events (serious adverse events requiring treatment withdrawal): minor adverse events (not requiring treatment withdrawal): headache, somnolence, nausea,

	dizziness, fatigue, dry mouth, dyspepsia • Quality of life measures: none **Secondary outcomes of the trial** • Global evaluation of treatment efficacy, sedation. After 4 weeks, investigator made global assessment on 5-point scale: 0 = no improvement/worse, 1 = slight improvement, 2 = definite improvement, 3 = highly effective, 4 = complete disappearance of symptoms Clinician or participant report: participant
Notes	Investigator concludes that cetirizine and hydroxyzine have equivalent efficacy, and both are superior to placebo; no significant differences in adverse effects were noted, except for somnolence and nausea; no significant differences between cetirizine and placebo were observed in terms of somnolence

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Participants "randomly assigned"; quote (page 1015), no further information
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	High risk	Stated to be double-blinded but unclear how this was achieved; in addition, participants and personnel do not appear blinded Quote (page 1015): "All patients receiving active drugs began by taking the lowest daily dose... The dose was titrated up as necessary in two steps to respective allowable maximums..."
Blinding of outcome assessment (detection bias) All outcomes	High risk	Stated to be double-blinded but unclear how this was achieved; in addition, participants and personnel do not appear blinded Quote (page 1015): "All patients receiving active drugs began by taking the lowest daily dose... The dose was titrated up as necessary in two steps to respective allowable maximums..."
Incomplete outcome data (attrition bias) All outcomes	High risk	Losses to follow-up not clearly described 31/219 randomly assigned lost to follow-up (14%) Each table provides different numbers of included participants; not clear why and when participants were lost to follow-up; study authors note in discussion that 10% of cetirizine group, 7% of hydroxyzine

Kalivas 1990 (*Continued*)

		group and 24% of placebo group withdrew because of lack of efficacy Adverse events (serious adverse events requiring treatment withdrawal): • Cetirizine group: 1 withdrawal due to adverse effects (ns) • Hydrozyzine group: 3 withdrawals due to adverse effects (ns) • Placebo group: 1 withdrawal due to adverse effects (ns)
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were reported
Other bias	Low risk	None detected. Funder: not stated

Kaplan 2005

Methods	Design: multi-centre randomised double-blind parallel-group placebo-controlled 2-arm study of fexofenadine vs placebo Duration: 4 weeks
Participants	Number of participants randomly assigned: 259 Sex: 26% male, 74% female Age of participants, years: 247 younger than 65; 8 older than 65 Unit of allocation: participant Country and setting: US; setting secondary care **Inclusion criteria of the trial** • Chronic idiopathic urticaria **Exclusion criteria of the trial** • < 12 years, inactive urticaria at baseline, less than moderate severity of pruritus, pregnancy or lactation, mental illness, malnutrition, blood dyscrasia, renal/hepatic insufficiency, chronic infection, drug abuse, alcoholism, cancer, malabsorption, previous hypersensitivity to fexofenadine, other major systemic disease • Previous unresponsiveness to antihistamine: excluded those unresponsive to antihistamine treatment
Interventions	**Interventions, dose, duration** • Fexofenadine 180 mg once daily for 28 days • Placebo once daily for 28 days Single-blind placebo run-in phase for 2 to 5 days At next visit, participants had to qualify for entry into randomised portion of study, then were randomly assigned 2:1 to fexofenadine:placebo Duration of intervention: intermediate-term (28 days) Length of follow-up: 4 weeks
Outcomes	Timing of outcome assessment: seen weekly for 4 weeks **Primary outcomes of the trial** • Efficacy assessment: change from baseline scores, participants' mean daily number of weals, pruritus severity scale (0 = none, 1 = mild, 2 = moderate, 3 = severe, 4 =

	warrants physician) • Complete suppression of urticaria (from patient global assessment scores) • Proportion with good/excellent response (decreased mean daily number of weals and pruritus severity; mean pruritus severity) • Secondary efficacy assessment: number, frequency, size, duration of lesions; severity of pruritus according to modified total symptoms score: 0 (0 weals), 1 (1-10 weals), 2 (11-20 weals), 3 (> 20 weals); number of total weal episodes longer than 1 hour apart, average size of lesions, pruritus severity • Participant and investigator global evaluation of overall efficacy at final visit or early termination visit (0 = no improvement/worsening, 1 = slight but insufficient improvement, 2 = definite improvement, 3 = substantial improvement, 4 = complete disappearance of symptoms) • Quality of life measures (from Spector 2007): mean total DLQI score from baseline to 4 weeks compared with placebo in 2 individual domains (symptoms and feelings; personal relationships) **Secondary outcomes of the trial** • Adverse events: asthma requiring hospitalisation, headache. Not stated whether these required treatment withdrawal • WPAI (work productivity and activity impairment) • Pharmokinetic variables were reported elsewhere
Notes	Same study as Spector 2007 Study investigators concluded that fexofenadine at 180 mg once daily offered effective well-tolerated relief of the symptoms of urticaria

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote (page 662): "Randomisation in a 2: 1 manner to receive either fexofenadine hydrochloride,180mg, or placebo once daily"
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study stated as double-blind. Initial single-blind run-in with placebo for 2 to 5 days Quote (page 663): "Patients received double blind study medications packaged in bottles with 40 tablets" (enough for course of treatment) Comment: probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Study stated as double-blind. Initial single-blind run-in with placebo for 2 to 5 days. Participants received study medication in bottles with 40 tablets (enough for course of treatment) Comment: probably done, but unclear how

Kaplan 2005 (*Continued*)

		outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Did not include participants lacking post-baseline result. Unclear how many dropped out at each time point along with reasons for dropout Losses to follow-up of 259 randomly assigned: fexofenadine 12/167 (7%); 13/92 (14%): 7% dropped out of fexofenadine group, 14% from placebo group (lack of efficacy) Adverse events: Most common reason for loss to follow-up was lack of efficacy (6 of 13 from placebo group, and 1 of 12 from fexofenadine group). Other reasons not stated Asthma requiring hospitalisation: n = 1 in fexofenadine group; headache occurred in 5% of fexofenadine group and 3% of placebo group; not stated whether any of these required treatment withdrawal Numbers of participants in each study were very unclear at each time point
Selective reporting (reporting bias)	High risk	Study authors combined unadjusted mean DLQI scores from 2 weeks and 4 weeks
Other bias	Unclear risk	Funder: Aventis Inc (Sanofi-Aventis Group)

Kint 1989

Methods	Design: double-blind randomised multiple (3)-arm cross-over study comparing cetirizine, terfenadine and placebo Duration: 6 weeks
Participants	Number of participants randomly assigned: 30 in sequence Sex: 44% male, 56% female Age of participants, years: 41.2 ± 14.7 (range 21-74) Country and setting: Belgium; secondary care Unit of allocation: cross-over **Inclusion criteria of the trial** • Not stated **Exclusion criteria of the trial** • 16 years; pregnancy/lactation; renal/hepatic dysfunction; glaucoma; angio-oedema • Previous unresponsiveness to antihistamine: not stated

Interventions	**Interventions, dose, duration** • Cetirizine 10 mg at night plus placebo every morning for 2 weeks • Terfenadine 60 mg twice daily for 2 weeks • Placebo twice daily for 2 weeks in random order (multiple cross-over using Latin square design) Unclear which treatments were compared at each phase Duration of intervention: short-term (2 weeks) Length of follow-up: 2 weeks (for each phase) No washout between treatments; if intolerable, symptoms due to lack of response could progress early to next in sequence (after clinic visit). Seen at each change in treatment 5 instances of rescue medications used in placebo group only (antihistamines n = 4, dexamethasone n = 1) (against protocol)
Outcomes	Timing of outcome assessment: end of weeks 1 and 3 at each phase **Primary outcomes of the trial** • At each visit, investigator noted presence or absence of weals or giant weals, erythema, oedema; also VAS for overall assessment 0 to 100 (extremely poor to excellent) • Daily diary cards to record itching, erythema and weals; VAS weekly • At last visit, participant and investigator stated which treatment they preferred **Secondary outcomes of the trial** • Compliance and protocol violations • Quality of life measures: none • Adverse events: minor sedation, headache, dry mouth, malaise, dizziness, GI symptoms
Notes	Study investigators concluded that no significant differences in efficacy were found between the 2 active treatments; both were better than placebo

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Random sequence"; multiple sequence defined by Latin square design
Allocation concealment (selection bias)	Unclear risk	Unclear, no apparent allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical capsules
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear how outcome assessors were blinded to treatment allocation

Kint 1989 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	3/30 participants lost to follow-up (10%) . 2 dropouts due to lack of efficacy during first sequence (cetirizine n = 1 and terfenadine n = 1); 1 dropout in second sequence for same (cetirizine)
Selective reporting (reporting bias)	High risk	Results not clearly reported; placebo sequence had rescue medication. Study investigators conclude... "thus only for wheals were borderline or significant differences from placebo recorded by investigator" 5 instances of rescue medication used in placebo group only (antihistamines n = 4, dexamethasone n = 1) (against protocol)
Other bias	Unclear risk	Funder: UCB Braine-L'Alleud

Leyh 1989

Methods	Design: randomised double-blind 4-arm cross-over study to investigate efficacy of acrivastine at 2 doses vs clemastine and placebo Duration: 5 days in each arm
Participants	Number of participants randomly assigned: 20 Sex: 60% female Age of participants, years: 18 to 72 (mean 41.3) Country and setting: Lubeck; secondary care Unit of allocation: cross-over **Inclusion criteria of the trial** • Allowed participants with acute urticaria (longer than 2 weeks), although none included with urticaria < 2 months **Exclusion criteria of the trial** • Systemic steroids in last 2 weeks, concurrent sedatives/antihistamines • Previous unresponsiveness to antihistamine: not stated
Interventions	**Interventions, dose, duration** • Acrivastine 4 mg 3 times daily for 5 days • Cross-over acrivastine 8 mg 3 times daily for 5 days • Clemastine 1 mg 3 times daily for 5 days • Placebo 3 times daily for 5 days in random order Unclear which treatments were compared at each phase 3-day washout initially, then 2-day break between treatments Duration of intervention: short-term (5 days per intervention) Length of follow-up: 5 days
Outcomes	Timing of outcome assessment: 5 days **Primary outcomes of the trial** • Participants self-assessed daily: weals 0 to 4 (0 (0), 1 (1-5), 2 (6-10), 3 (11-20), 4

	(> 20)); itching 0 to 4 (0 = none, 1 = minimal, 2 = mild, 3 = moderate, 4 = severe) • Investigator at end of study recorded *in his opinion* which treatment worked best and suited participant best overall • Quality of life measures: none **Secondary outcomes of the trial** • Minor adverse events (not requiring treatment withdrawal): drowsiness Clinician or participant report: investigator and participant (self-assessment form)
Notes	Study investigators concluded that assessment showed all 3 active drugs were better than placebo; no statistically significantly difference was noted between them

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not stated
Allocation concealment (selection bias)	Unclear risk	Unclear
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Study stated to be double-blind, but no details given
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear if blinded. As investigators appear to have made subjective decision on best treatment, it is possible that they were not blinded to treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Only 20 participants; no dropouts; no serious adverse events noted. Raw figures not shown (means only)
Selective reporting (reporting bias)	Unclear risk	Incomplete reporting of data (mean scores only, without SD of self-assessment for wealing, itching and overall discomfort). Percentage scores of physician assessment and overall improvement
Other bias	Unclear risk	Funder: Wellcome Research Laboratories

Leynadier 2000

Methods	Design: randomised double-blind parallel-group 2-arm study of mizolastine vs loratadine Duration: 28 days

Participants	Number of participants randomly assigned: 61 Sex: 64% male, 46% female Age of participants, years: 40 ± 13 Country and setting: France; secondary care Unit of allocation: participant **Inclusion criteria of the trial** • Chronic idiopathic urticaria, < 2 episodes of urticaria during 3- to 7-day run-in with symptom score < 2; age < 18 years **Exclusion criteria of the trial** • No exclusions stated • Previous unresponsiveness to antihistamine: not stated
Interventions	**Interventions, dose, duration** • Mizolastine 10 mg once daily for 4 weeks • Loratadine 10 mg once daily for 4 weeks; 3 to 7 single-blind run-in Not stated whether this was with placebo (although placebo seems likely) Duration of intervention: short-term (28 days) Length of follow-up: 4 weeks
Outcomes	Timing of outcome assessment: 4 visits in total: at screening (day 3 or 7), at inclusion (day 10), after 14 and 28 days of treatment **Primary outcomes of the trial** • Principal criteria included number of episodes of urticaria per week as evaluated by investigator and evaluation by participant of the discomfort caused by urticaria during the week before the visit. Investigator evaluated symptoms at baseline and at 2 and 4 weeks; number of urticaria episodes during the week before the visit, as recorded in the participant's self-evaluation notebook (SEN); whether the participant had an urticaria episode at the time of the visit; number and size of weals; number of weals and/or plaques: 0 (absent), 1 (10), 2 (> 10), 3 (body covered in plaques and/or weals); size of plaques: 1 (1.5 cm), 2 (> 1.5 cm and ≤ 2.5 cm), 3 (> 2.5 cm); severity of itching: 0 (absent), 1 (present, but mild), 2 (moderate), 3 (severe); and severity of any associated angio-oedema. The severity of each symptom was scored using a 4-point scale from 0 (symptom absent) to 3 (severe symptom), as was the clinical global impression for angio-oedema (0 = absent; 1 = mild; 2 = moderate with tight feeling; 3 = severe, disfiguring) • Participants used the same scale to complete a daily diary; at baseline and at weeks 2 and 4, participants used a visual analogue scale (0 = no discomfort to 100 = extreme discomfort) (related to that day). Overall mean daily score defined as sum of scores evaluating severity of itching and number and size of weals was recorded daily by the participant • Quality of life measures: none **Secondary outcomes of the trial** • Signs and symptoms of urticaria episodes at time of visit, as evaluated by investigator, tolerance to pharmacological effect, participant's evaluation of signs and symptoms of urticaria (mean overall daily score) and mean total duration of episodes • Adverse events: serious leading to withdrawal: mizolastine: painful erythema of hands • Minor events: fatigue, drowsiness, dizziness, rhinitis Clinician or participant report: investigator and participant

Notes	Study investigators concluded that no statistically significant differences in efficacy were found between drugs, as measured by number of urticarial episodes and discomfort from symptoms; duration of episodes shorter with mizolastine (not statistically significant)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Patients were randomly allocated..."; no details given about method of randomisation
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind study. Unclear how blinding was achieved
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Double-blind study. Unclear how blinding was achieved
Incomplete outcome data (attrition bias) All outcomes	High risk	Number of participants completing the study and evaluable does not match corresponding information given about non-completers 7/61 lost to follow-up (11%): mizolastine group: 3/26, loratadine group: 4/35 Withdrawals: adverse events: serious leading to withdrawal: mizolastine: painful erythema of hands n = 1 Minor events: mizolastine: fatigue n = 2; drowsiness n = 1; loratadine: drowsiness n = 1; dizziness n = 1; rhinitis n = 1 A figure of n = 56 is given as the number of evaluable participants in the published report, but after withdrawals and losses to follow-up, the number of participants remaining in the trial is 54
Selective reporting (reporting bias)	Unclear risk	All outcomes reported but presented only as number of participants free of symptoms, which decreased significantly in both groups (numbers not given; results expressed graphically and related to number of participants free of individual symptom (e.g. pruritus), but not possible to tell how many participants were symptom-free overall

Leynadier 2000 (*Continued*)

Other bias	Unclear risk	Number of participants free of symptoms decreased significantly in both groups, but numbers not given; figures given relate to numbers of participants free of individual symptom (e.g. pruritus), but not possible to tell how many participants were symptom-free overall Funder: none

Liu 2003

Methods	Design: 5-centre double-blind parallel-group randomised trial of mizolastine vs loratadine
Participants	Number of participants randomly assigned: 213 enrolled: 104 mizolastine, 102 loratadine, 206 completed the trial Sex: mizolastine: male 46 (42.6%), female 62 (57.4%); loratadine: male 50 (47.6%), female 55 (52.4%) Age of participants, years: mizolastine 39.32; loratadine 37.9 Unit of allocation: participant Country and setting: Beijing, China; multi-centre secondary care **Inclusion criteria of the trial** • CSU confirmed, age > 16 years, duration of disease > 6 weeks, frequency at least twice/wk or occurrence 2 days/wk, symptoms less than 24 hours, urticaria within 24 hours before randomisation, signed and consented **Exclusion criteria of the trial** • Pregnant and lactating women, other types of urticaria (not chronic idiopathic urticaria), hypersensitivity to H1-antagonist or known mizolastine allergies, known serious liver dysfunction, kidney failure, ischaemic heart disease, endocrine dysfunction, taking steroid/immunosuppressant (stopping medication within 4 weeks), stopping astemizole less than 8 weeks before; reference is made in the study report to participants stopping antibiotics within 7 days, but this is unclear • Previous unresponsiveness to antihistamine: not stated • Astemizole previously used; at least 8 weeks washout
Interventions	**Interventions, dose, duration** • Mizolastine 10 mg • Loratadine 10 mg, once daily at night for 28 days Duration of intervention: intermediate-term (28 days) Length of follow-up: 28 days
Outcomes	Timing of outcome assessment: 7, 14, 28 days **Primary outcomes of the trial** • Efficacy assessment based on symptom score reducing index (SSRI) • Score of diameter of largest weal, weekly urticarial episodes • Visual analogue score • Quality of life measures: none **Secondary outcomes of the trial**

	• Itching score, number of weals, diameter of largest weal, duration of urticaria (weals), frequency of attacks per week, VAS score (participants rated severity of itch by visual analogue scale) • Adverse events: no serious adverse event. Other adverse events included sleepiness, lethargy, dry mouth, headache, abdominal pain, constipation, nausea, diarrhoea, anxiety and palpitations. One participant from the mizolastine group withdrew because of severe diarrhoea Clinician or participant report: participant and clinician. Outcomes reported by clinician apart from VAS score (participant rated severity of itch by visual analogue scale)
Notes	Study investigators concluded that mizolastine is quicker in action than loratadine, with similar efficacy. The incidence of adverse effects is similar in the 2 groups Main study report is written in Chinese

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote (page 306): "randomly divided"
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote (page 306): "double blind"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote (page 306): "double blind"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	206/213 completed, but study stated that 12 participants dropped out; it is unclear if they dropped out from the number enrolled or the number completing
Selective reporting (reporting bias)	Unclear risk	All prespecified outcomes were reported
Other bias	Low risk	None detected. Funder: not stated

Liu H-N 1990

Methods	Design: double-blind 2-arm cross-over trial comparing nifedipine (calcium channel blocker) with chlorpheniramine Duration: 4 weeks
Participants	Number of participants randomly assigned: 22 Sex: 13% male, 27% female Age of participants, years: 36 (range 21-54)

Liu H-N 1990 (*Continued*)

	Unit of allocation: cross-over Country and setting: Taiwan; secondary care **Inclusion criteria of the trial** • CSU for at least 6 weeks, with no underlying cause **Exclusion criteria of the trial** • > 18 years of age, pregnant or lactating • Previous unresponsiveness to antihistamine: not stated
Interventions	**Interventions, dose, duration** Washout of at least 12 hours, then randomised: • Group 1: nifedipine 10 mg 4 times a day for 4 weeks, placebo for 2 days and chlorpheniramine 4 mg 4 times a day for 4 weeks • Group 2: chlorpheniramine 4 mg 4 times a day for 4 weeks, placebo for 2 days and nifedipine 10 mg 4 times a day for 4 weeks Participants had one or another active drug, then 2 days of placebo, then the other active drug; all capsules identical in appearance Duration of intervention: intermediate-term (4 weeks) Length of follow-up: 4 weeks
Outcomes	Timing of outcome assessment: unclear (daily scores) **Primary outcomes of the trial** • Degree of itching (scale 0-3); frequency of episodes (scale 0-4); number of hives per episode (scale 0-4, where 0 = 0 hives; 1 = 1 to 6 hives; 2 = 7 to 12 hives; 3 = 13 to 18 hives; and 4 = ≥ 19 hives); size of the hives (scale 0-4, where 0 = 0 mm, 1 = 0 to 10 mm, 2 = 11 to 20 mm, 3 = 21 to 30 mm, 4 = > 30 mm) and duration of the hives (hours) (scale 0-4, where 0 = 0 hours, 1 = 0 to 6 hours, 2 = 7 to 12 hours, 3 = 13 to 24 hours, 4 = > 24 hours) • Quality of life measures: none **Secondary outcomes of the trial** • Blood pressure • Adverse events: nausea, dizziness, drowsy, mild hypotension • No minor adverse effects stated for chlorpheniramine Clinician or participant report: investigator and participant
Notes	Study investigators concluded that nifedipine not a first-line drug for chronic urticaria, and that it is helpful for only some selected patients

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomisation method unclear
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind study. All medication in capsules and identical in appearance; participants blinded. Probably done but no de-

Liu H-N 1990 (*Continued*)

		tails given
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Double-blind study. All medication in capsules and identical in appearance; participants blinded. Probably done but no details given
Incomplete outcome data (attrition bias) All outcomes	Low risk	18/22 participants completed the study (18% lost to follow-up): n = 3 military personnel posted elsewhere, n = 1 severe nausea on nifedipine ×1 Minor adverse events: nifedipine: n = 3 dizziness, n = 1 drowsiness, n = 2 mild hypotension Comment: Substantial losses to follow-up may have introduced a source of bias to the study. No ITT
Selective reporting (reporting bias)	High risk	Duration of follow-up not clearly defined Unclear whether concomitant medications were permitted or whether participants were compliant Blood pressure results not reported in full, only in terms of adverse events
Other bias	Unclear risk	Underpowered Funder: none

Locci 1991

Methods	Design: topical treatment of urticaria; randomised controlled 2-arm study of oxatomide gel vs dechlorpheniramine cream Duration:15 days
Participants	Number of participants randomly assigned: 27; 12 in oxatomide group and 15 in dechlorpheniramine group Sex: 50% female oxatomide group, 33% female dechlorpheniramine group Age of participants, years: oxatomide group: mean 39.6 ± 5.2; dechlorpheniramine group: mean 38.3 ± 2.6 Country and setting: Italy; secondary care Unit of allocation: participant **Inclusion criteria of the trial** • CSU (not clearly defined) **Exclusion criteria of the trial** • Eczema, skin infection or infestation; pregnancy/lactation; children • Previous unresponsiveness to antihistamine: not stated

Locci 1991 (*Continued*)

Interventions	**Interventions, dose, duration** • Oxatomide gel 5% twice daily • Dechlorpheniramine cream twice daily to affected sites Duration of intervention: short-term (15 days) Length of follow-up: 15 days
Outcomes	Timing of outcome assessment: 15 days **Primary outcomes of the trial** • Progress of itching (severity, site, duration), appearance of lesions with reference to presence of erythema (intensity, site), weals (size, site, number), lesions due to scratching • Severity 0 to 4 scale on participant daily diary • Quality of life measures: not stated **Secondary outcomes of the trial** • Adverse events: transitory erythema after application Clinician or participant report: clinician and participant
Notes	Study investigators concluded that similar statistically significant improvements were observed in erythema and number of weals. Study authors concluded that both treatments worked

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "According to a controlled experimental design completely randomised between patients, half were treated with oxatomide (O) and half with dechlorpheniramine (D)"; no details about method of randomisation
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding described Comment: open to bias as 2 different formulations (gel and cream preparations)
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding described Comment: open to bias as 2 different formulations (gel and cream preparations)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No ITT; 2/27 (13%) lost to follow-up (did not attend) in dechlorpheniramine group (2/15). No reasons given Comment: unclear whether this degree of loss to follow-up in a small study introduced a source of bias

Locci 1991 (*Continued*)

Selective reporting (reporting bias)	Unclear risk	All outcomes reported but presented graphically; improvement in symptoms expressed as percentage (change in mean score and SD), not by participant number Included some participants with localised urticaria. No measurement of actual dose applied Comment: unclear
Other bias	Low risk	None detected. Funder: not stated

Maiti 2011

Methods	Design: randomised single-blinded single-centred parallel-group 2-arm trial comparing rupatadine with levocetirizine Duration: 4 weeks
Participants	Number of participants randomly assigned: 70 (rupatadine n = 35; levocetirizine n = 35) Sex: rupatadine group: male 15 (43%), female 20 (57%); levocetirizine group: male 16 (45%), female 19 (60%) Age of participants, years: 12 to 60 Unit of allocation: participant Country and setting: India; secondary care **Inclusion criteria of the trial** • Unclear **Exclusion criteria of the trial** • Significant concomitant illness, pregnancy or lactation, oral contraceptive pills, antihistamines within 72 hours, oral steroids within a month, physical urticaria, cold urticaria, cholinergic urticaria • Previous unresponsiveness to antihistamine: unclear
Interventions	**Interventions, dose, duration** • Rupatadine 10 mg once daily or • Levocetirizine 5 mg once daily Duration of intervention: intermediate-term (4 weeks) Length of follow-up: 4 weeks
Outcomes	Timing of outcome assessment: 4 weeks **Primary outcomes of the trial** • Pruritus, size of weals, number of weals and number of separate urticarial episodes • Differential and absolute eosinophil count, serum IgE • Aerius Quality of Life Questionnaire (AEQLQ), based on DLQI (not validated) • Physician or investigator assessment of global efficacy based only on participant symptom scores **Secondary outcomes of the trial** • Adverse events: drowsiness, headache, dry mouth, gastric irritation Clinician or participant report: both

Notes	Study investigators concluded that the incidence of adverse drug reactions was found to be less in the rupatadine group. Rupatadine is a better choice in CSU in comparison with levocetirizine because of a better efficacy and safety profile

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unclear which group was blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear which group was blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	54/70 completed (10 did not report for follow-up, 6 were non-compliant). No participant stopped treatment because of adverse effects
Selective reporting (reporting bias)	Unclear risk	All prespecified outcomes were reported
Other bias	Low risk	None detected. Funder: not stated

Makino 2012

Methods	Design: randomised 3-arm open study Duration**:** 4 weeks
Participants	Number of participants randomly assigned: 97 (olopatadine 10 mg group 35; olopatadine 5 mg group 30; no medication group 32) Sex: olopatadine 10 mg group: male 31.4%, female 68.6%; olopatadine 5 mg group: male 16.7%, female 83.3%; no medication group: male 28.1%, female 71.9% Age of participants, years (mean): olopatadine 10 mg group 55.2 ± 14.9; olopatadine 5 mg group 55.0 ± 13.5; no medication group 59.1 ± 15.1 Unit of allocation: participant Washout period: none, but run-in phase of 4 to 6 weeks with all participants receiving 10 mg olopatadine; no cross-over Country and setting: Japan; secondary care **Inclusion criteria of the trial** • Chronic urticaria > 6 weeks with no causes **Exclusion criteria of the trial**

	• Patients with physical urticaria, pregnant females and lactating mothers; urticaria with VAS score less than 50 out of maximum 100 At least moderate to severe disease Duration of disease greater than 6 weeks
Interventions	**Interventions, dose, duration** All participants with CSU with a VAS itch score higher than 50 were treated with 10 mg olopatadine hydrochloride daily for 4 to 6 weeks. Of these, participants having a VAS itch score less than 20 were randomly allocated to 1 of 2 groups: • Group 1: 10 mg olopatadine hydrochloride daily • Group 2: 5 mg olopatadine hydrochloride daily • Group 3: stopped taking medication Duration of intervention: intermediate-term (4 weeks) Length of follow-up: 4 weeks Concomitant/rescue treatment not permitted
Outcomes	Timing of outcome assessment: Efficacy end point was defined as length of time the VAS itch score remained less than 50 with no additional treatment and ongoing up to 4 weeks **Primary outcomes of the trial** • Number of participants whose VAS score went above 50 • Quality of life measures: none **Secondary outcomes of the trial** • Adverse events: No participants reported adverse effects Clinician or participant report: clinician
Notes	Study investigators concluded that both 10 mg olopatadine and 5 mg olopatadine were effective and were better than no treatment but were not significantly different from each other

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomised, but no details
Allocation concealment (selection bias)	High risk	Allocation not apparently concealed, as the trial was open
Blinding of participants and personnel (performance bias) All outcomes	High risk	No
Blinding of outcome assessment (detection bias) All outcomes	High risk	No

Makino 2012 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Withdrawals noted were 12 out of 35 in 10 mg group, 6 out of 30 in 5 mg group and 22 out of 32 in no medication group. Reasons for all withdrawals were unclear. ITT analysis was carried out
Selective reporting (reporting bias)	Low risk	Outcomes reported
Other bias	Unclear risk	Funder: not stated

Marks 1980

Methods	Design: randomised double-blind 3-arm cross-over study of chlorpheniramine vs placebo Duration: not stated
Participants	Number of participants randomly assigned: 24. Numbers in each group not stated Sex: not stated Age of participants: not stated Unit of allocation: cross-over, chlorpheniramine vs placebo arm data used in this review Country and setting: Australia; secondary care **Inclusion criteria of the trial** • CSU **Exclusion criteria of the trial** • Not stated • Previous unresponsiveness to antihistamine: not stated
Interventions	**Interventions, dose, duration** • Chlorphenamine 4 mg 4 times a day • Chlorphenamine plus cimetidine • Chlorphenamine 4 mg 4 times a day plus cimetidine 400 mg 4 times a day (H1 + H2 antagonist) • Placebo: frequency not clear Duration of intervention: for all 3 interventions, duration of treatment was not stated Length of follow-up: not stated
Outcomes	Timing of outcome assessment: not stated **Primary outcomes of the trial** • Improvement in urticaria • Quality of life measures: none **Secondary outcomes of the trial** • Adverse events: not stated Clinician or participant report: investigator
Notes	Study investigators concluded that significant improvement in urticaria was seen with chlorpheniramine and with chlorpheniramine plus cimetidine compared with placebo; no difference was noted between efficacy of active treatments
Risk of bias	

Marks 1980 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation method not stated
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unclear, no details given
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear, no details given
Incomplete outcome data (attrition bias) All outcomes	High risk	Numbers in each group not stated. No adverse events described; 2/24 randomly assigned (8%) lost to follow-up because of irregular tablet intake
Selective reporting (reporting bias)	Unclear risk	Write-up published as item of correspondence, unclear whether all prespecified outcomes were reported
Other bias	Unclear risk	Funder: none Very short report, no further information available

Monroe 1988

Methods	Design: double-blind randomised multi-centre 2-arm trial of loratadine vs placebo Duration: 4 weeks
Participants	Number of participants randomly assigned: unclear; 169 evaluated for safety, 153 evaluated for efficacy, numbers randomly assigned to each group unclear Sex: not stated Unit of allocation: participant Age of participants: not stated Country and setting: USA (primary and secondary) **Inclusion criteria of the trial** • CSU (not specified) **Exclusion criteria of the trial** • Not stated • Previous unresponsiveness to antihistamine: not stated
Interventions	**Interventions, dose, duration** • Loratadine 10 mg daily for 4 weeks

	• Placebo daily for 4 weeks Duration of intervention: intermediate-term (4 weeks) Length of follow-up: 4 weeks
Outcomes	Timing of outcome assessment: at baseline, then weekly for 4 weeks **Primary outcomes of the trial** • Proportion with good/excellent response (itching erythema and number and size of hives), overall condition and therapeutic response • Quality of life measures: none **Secondary outcomes of the trial** • Adverse events (minor): loratadine: sedation and dry mouth Clinician or participant report: investigator
Notes	Study investigators concluded that loratadine is efficacious and safe

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomisation method unclear
Allocation concealment (selection bias)	Unclear risk	No allocation concealment described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No details given about blinding, described as double-blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details given about blinding, described as double-blind
Incomplete outcome data (attrition bias) All outcomes	High risk	Numbers randomly assigned and number in each group unclear (not stated). 169 evaluated for safety, 153 for efficacy. Treatment failure: loratadine group n = 1; placebo group n = 10; other numbers of and reasons for withdrawal not stated
Selective reporting (reporting bias)	High risk	Raw figures not given-only percentages and P values. Outcome measures unclear; statistics not specified. Raw figures not stated; origin of P values not stated (i.e. appropriateness of statistical methods unclear)
Other bias	Unclear risk	Funder: none Very short report

Monroe 1992

Methods	Design: randomised double-blind 3-arm trial of loratadine vs hydroxyzine vs placebo Duration: 1 week
Participants	Number of participants randomly assigned: 59 total, 18 for urticaria (disaggregated data obtained from study authors for CSU and atopic dermatitis participants) Sex: 29% male, 71% female Age of participants, years: 18 to 63 Unit of allocation: participant Country and setting: USA; secondary care **Inclusion criteria of the trial** • CSU in an active state for at least 3 weeks before study commencement **Exclusion criteria of the trial** • Steroids in previous 10 days (or depot steroid in last 28 days) • Pregnant (pregnancy test administered before start of study) • Previously unresponsive to antihistamine excluded
Interventions	**Interventions, dose, duration** • Loratadine 10 mg every morning plus placebo twice daily for 1 week • Hydroxyzine 25 mg 3 times daily for 1 week • Placebo 3 times daily for 1 week Duration of intervention: short-term (1 week) Length of follow-up: 1 week
Outcomes	Timing of outcome assessment: 1 week **Primary outcomes of the trial** • Proportion with good/excellent response ("marked or complete relief"): pruritus, erythema, hives • Quality of life measures: none **Secondary outcomes of the trial** • Adverse events: included with dermatitis group in same study: somnolence, hydroxyzine more sedative than loratadine Clinician or participant report: investigator and participant (diary). Diary cards including size and number of weals, erythema and pruritus; scored between 0 and 3; summed for total symptoms score plus global estimation of effect at end
Notes	Study investigators concluded that loratadine is as effective as hydroxyzine in the treatment of urticaria

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not clear; "randomly assigned"
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias)	Low risk	No details about blinding given, described as double-blind

Monroe 1992 (*Continued*)

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No details about blinding given, described as double-blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Number of dropouts from 18 randomly assigned with urticaria not stated. Results expressed as percentages with P values. No outcomes expressed as participant numbers; no baseline values. Unclear how many withdrew with reasons Comment: The report does not contain sufficient information to allow a judgement about whether incomplete outcome data introduced a source of bias
Selective reporting (reporting bias)	Unclear risk	Laboratory tests conducted at start, unclear whether these were monitored as an outcome. Erythema not reported as an outcome (but included in overall symptom score) Comment: unclear whether outcomes were fully reported. No further information was available from investigators
Other bias	Unclear risk	Funder: none. Short report with insufficient information to allow a judgement about risk of other bias

Monroe 2003

Methods	Design: randomised double-blind multi-centre parallel 2-arm placebo-controlled study of desloratadine 5 mg vs placebo Duration: 6 weeks
Participants	Number of participants randomly assigned: 226 (116 desloratadine; 110 placebo) Sex: 27% male, 73% female desloratadine group; 24% male, 76% female placebo Age of participants, years: desloratadine 41.8 (range 13-80); placebo 39.2 (range 13-84) Unit of allocation: participant Country and setting: US, Chile, Canada, Venezuela, Germany, Norway, Sweden, Belgium; setting unclear **Inclusion criteria of the trial** • CSU for at least 6 weeks before entry into study with at least 1 flare in previous 3 weeks • Normal physiological and laboratory values • Informed consent • Use of adequate contraception method is appropriate **Exclusion criteria of the trial** • < 12 years old, patients with urticaria < 3 days/wk in preceding 3 weeks, <

	moderate severity, no weals at time of screening, pruritus score < 14 over last 3 days and on morning of baseline visit • Pregnancy/lactation • Concomitant illness • Other urticaria medication • Previous intolerance of antihistamines • Participants deemed unable to keep accurate symptom diary • Excluded if previously non-responsive to antihistamines
Interventions	**Interventions, dose, duration** • Desloratadine 5 mg for 6 weeks • Placebo daily Duration of intervention: intermediate-term (6 weeks) Length of follow-up: 6 weeks
Outcomes	Timing of outcome assessment: 1, 2, 4 and 6 weeks (visits at screening, at baseline (day 1), on day 4, at weeks 1, 2, 4 and 6. Efficacy and safety assessments made at visit day 4 and weeks 1, 2, 4 and 6) **Primary outcomes of the trial** • Proportion with good/excellent response ("marked or complete relief"): pruritus, erythema, hives • Global assessment at visits agreed by participant and physician: 0 = none, 1 = mild (signs/symptoms minimally aware and easily tolerated), 2 = moderate (definite awareness of signs/symptoms but tolerable), 3 = severe (signs/symptoms difficult to tolerate and interfering with daily activities or sleep) • Therapeutic response agreed on by participant and physician (visit day 4 and weeks 1, 2, 4 and 6): 1 = complete relief, virtually no signs/symptoms; 2 = marked relief, signs/symptoms greatly improved, causing little trouble; 3 = moderate relief, signs/symptoms present and troublesome but noticeably improved; 4 = slight relief, minimal improvement in signs/symptoms; 5 = treatment failure, signs/symptoms unchanged or worse than baseline • Quality of life measures: none **Secondary outcomes of the trial** • Participants given diary cards, completed twice daily. Symptom score in diary on 4-point scale: pruritus, number of hives, size of largest hive, interference with sleep, interference with daily activities • Compliance assessed by study diary, tablet count, questioning • Adverse events: serious (requiring withdrawal): bronchitis/sinusitis URTI, nausea) ; vomiting, sedation; minor adverse events: headache, nausea, dry mouth Clinician or participant report: investigator and participant
Notes	Study investigators concluded that at week 1: mean improvement from baseline in reflective pruritus score significantly greater in desloratadine group; overall more effective than placebo; significant improvement in total symptoms score and interference in sleep and daily activities in desloratadine group; reduction in number and size of largest hive significantly better in desloratadine group Statistically significant improvements noted by day 2 of study Week 6: statistically significant improvement in pruritus from baseline in desloratadine group compared with placebo; desloratadine-treated participants had significantly greater

	control of morning instantaneous total symptoms score compared with placebo patients. Overall, desloratadine was statistically significantly better than placebo

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 536): "1:1 ratio according to computer generated schedule" "Blocks of 4 using random numbers generated by SAS function UNIFORM with seed based on clock-time" Comment: adequate randomisation
Allocation concealment (selection bias)	Low risk	Quote (page 537): "A set of sealed envelopes containing the identification of test drug corresponding to each subject was provided to each center. This enabled the investigator to identify the treatment assignment of individual subjects in the event of an emergency without compromising the blinding of other subjects. The randomisation schedule for blinding of treatments was disclosed only after study completion" Comment: Sealed envelopes indicate that this was probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (page 537): "Desloratadine, in 5 mg tablets, and placebo were identical in appearance and packaged identically in sealed coded envelopes. All study personnel were blinded to the identity of medication. A set of sealed envelopes containing the identification of test drug corresponding to each subject was provided to each center. This enabled the investigator to identify the treatment assignment of individual subjects in the event of an emergency without compromising the blinding of other subjects. The randomisation schedule for blinding of treatments was disclosed only after study completion"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (page 537): "Desloratadine, in 5 mg tablets, and placebo were identical in appearance and packaged identically in sealed coded envelopes. All study personnel were blinded to the identity of medication. A

		set of sealed envelopes containing the identification of test drug corresponding to each subject was provided to each center. This enabled the investigator to identify the treatment assignment of individual subjects in the event of an emergency without compromising the blinding of other subjects. The randomisation schedule for blinding of treatments was disclosed only after study completion"
Incomplete outcome data (attrition bias) All outcomes	High risk	Lost to follow-up: desloratadine 19/116 (19%); placebo 35/110 (31%) Treatment failure: desloratadine n = 14, placebo n = 29; other adverse events: desloratadine n = 3, placebo n = 2, non-compliance each group n = 1, loss to follow-up: desloratadine n = 1, placebo n = 2, lack of desire to continue placebo n = 1 Adverse events: serious (requiring withdrawal): desloratadine: 3 (1 bronchitis/sinusitis, 1 URTI, 1 nausea); placebo: 2 (1 vomiting, 1 sedation); minor adverse events: desloratadine: headache n = 18, nausea n = 7, dry mouth n = 6; placebo: headache n = 11, nausea n = 2, dry mouth n = 5 Actual participant numbers missing from results (percentages of improvement in scores and statistical significance only given); ITT stated by authors but unclear because of lack of provided data Comment: judged as high risk because of high dropout rate
Selective reporting (reporting bias)	Unclear risk	Prespecified outcomes were reported, other than compliance Excluded participants previously non-responsive to antihistamines; may involve selective reporting of positive results
Other bias	Unclear risk	Funder: Schering-Plough Research Institute

NCT00536380

Methods	Design: randomised double-blind parallel-group study; desloratadine 5 mg, 10 mg, 20 mg Duration: 4 weeks
Participants	Number of participants randomly assigned: 314 Country and setting: Germany; setting unclear **Inclusion criteria of the trial** • Males and females with CSU 18 to 75 years of age • Willingness to participate in the study. Participant must be 18 to 75 years of age, of either gender and of any race. Participant must have had this episode of chronic idiopathic urticaria for at least 6 weeks and must have been dosing with a second-generation antihistamine for 2 weeks or longer • Current episode of urticaria is sufficiently symptomatic at the screening visit to qualify for this study • Baseline week (entry period) UAS between 10 and 30 inclusive. Participants must understand and be willing to assess and record symptom scores; must have voluntarily signed a written informed consent • Must confirm that all prior medication washout times have been observed • Female volunteers of childbearing potential (including women who are less than 1 year postmenopausal and women who will be sexually active during the study) must agree to use a medically accepted method of contraception or must be surgically sterilised before screening • Must be free of any clinically relevant disease other than chronic idiopathic urticaria (CIU) that would, in the principal investigator's and/or sponsor's opinion, interfere with conduct of the study or study evaluations. Participants must be able to adhere to dosing and visit schedules and must agree to record symptom severity scores, medication times, concomitant medications and adverse events (AEs) accurately and consistently in a daily diary **Exclusion criteria of the trial** • Female who is pregnant or intends to become pregnant during the study, is nursing or intends to be nursing during the study or within 90 days after study completion • Has not observed designated washout periods for any of the prohibited medications. Has used any investigational product within 30 days before enrolment • Symptomatic seasonal or perennial allergic rhinitis • Asthma not controlled by short-acting beta-2 agonists used as necessary • Severe diseases, especially those affecting the immune system, except urticaria. Presence of a permanent gastrointestinal condition that may influence oral therapy (chronic diarrhoea diseases, congenital malformations or surgical mutilations of gastrointestinal tract) • History of/or presence of epilepsy, significant neurological disorders, cerebrovascular attacks or ischaemia. History of/or presence of myocardial infarction or cardiac arrhythmia that requires drug therapy. Evidence/history of significant renal disease • Significant hepatic disease. Presence of cancer, which requires chemotherapy or radiation therapy • Glaucoma • Urinary bladder neck obstruction with emptying difficulties • Acute urticaria

	• Body mass index (BMI) > 35. Has any clinically significant deviation from appropriate reference range in the physical examination, or another clinical evaluation that, in the investigator's judgement, may interfere with the study evaluation or may affect participant safety. Is in a situation or condition that, in the opinion of the investigator, may interfere with optimal participation in the study • Participating in any other clinical study • Is on the staff or is affiliated with or a family member of staff personnel directly involved with this study. Is allergic to or has a history of hypersensitivity to the study drug (desloratadine), to any of its excipients or to loratadine • Galactose intolerance, lactase deficiency or glucose-galactose malabsorption
Interventions	**Interventions, dose, duration** • Desloratadine 5, 10, 20 mg • 20 mg for 4 weeks Intermediate duration of intervention (4 weeks)
Outcomes	Timing of outcome assessment: 4 weeks **Primary outcomes of the trial** • Change in Urticaria Activity Score (UAS) from baseline to final week for desloratadine 5 mg versus desloratadine 20 mg (time frame: baseline and 4 treatment weeks) • UAS is a composite diary-recorded score. Diary-recorded scores included weal score and pruritus score, with numerical severity intensity ratings of 0 = none to 3 = intense. Scoring was to be done twice daily within 1 hour of arising and in the evening, approximately 12 hours later. Scoring was reflective, covering the 12-hour period since the previous recording. Daily UAS is the average of morning and evening scores. Final week by definition was the terminal week. It was the last week that participants stayed for the treatment period • Quality of life measures: none Clinician or participant report: UAS participant reported
Notes	Study investigators provided no conclusions Study number P04849; also indexed as EudraCT: 2006-001449-33. Results available online

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomised, no details given
Allocation concealment (selection bias)	Unclear risk	No details given
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants and personnel were blinded to treatment group

NCT00536380 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors were blinded to treatment group
Incomplete outcome data (attrition bias) All outcomes	Low risk	Group 5 mg 12/106 • 2 withdrawals unrelated to study drug • 7 withdrawals related to study drug • 3 non-compliance with protocol Group 10 mg: 9/104 • 2 adverse events • 5 withdrawals related to study drug • 2 non-compliance with protocol Group 20 mg: 10/104 • 2 adverse events • 1 loss to follow-up • 1 withdrawal unrelated to study drug • 2 withdrawals related to study drug • 2 non-compliance with protocol • 1 did not meet eligibility • 1 administrative Withdrawal and losses accounted for and balanced between groups ITT analysis carried out
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	Unclear risk	Underpowered because of poor recruitment; thus study is inconclusive Funder: Schering-Plough

Nelson 2000

Methods	Design: multi-centre double-blind randomised placebo-controlled 5-arm parallel study with 4 different doses of fexofenadine vs placebo Duration: 4 weeks
Participants	Number of participants randomly assigned: 468 Sex: 30% male, 70% female placebo; 31% male, 69% female 20 mg; 29% male, 71% female 60 mg; 33% male, 68% female 120 mg; 27% male, 73% female 240 mg Age of participants, years: range 12 to 65 Country and setting: USA; secondary care Unit of allocation: participant **Inclusion criteria of the trial** • CSU of at least 6 weeks' duration for at least 3 days per week **Exclusion criteria of the trial** • Urticaria associated with underlying disease (e.g. Hodgkin's, vasculitis, hyperthyroid, lupus, hepatitis, malnutrition, drug abuse, alcoholism, blood dyscrasia,

	malignancy, renal/hepatic insufficiency, malabsorption, chronic infection; psychological, heart, neurological or other systemic diseases) excluded if previously non-responsive to antihistamines
Interventions	**Interventions, dose, duration** • Placebo • 20 mg, 60 mg,120 mg or • 240 mg fexofenadine HCl twice daily Duration of intervention: intermediate-term (4 weeks) Length of follow-up: 4 weeks
Outcomes	Timing of outcome assessment: 1, 2, 3, 4 weeks **Primary outcomes of the trial** • Participants' twice-daily diaries recording pruritus severity (0-4; 0 = none; 1 = mild; 2 = moderate, may interfere with sleep/activities; 3 = severe, very annoying, substantially interfering with sleep/activities; 4 = needs physician) • Number of weals over previous 12 hours; also assessed interference with sleep and daily activities • Efficacy measures reported as average daily means. • Quality of life measures: none **Secondary outcomes of the trial** • Efficacy measures: change in average mean pruritus score from baseline to 4 weeks • Weals: change from baseline; 0 to 4 (0 = none, 1 = 1-5, 2 = 6-15, 3 = 16-25, 4 = > 25) • Interference with sleep/daily activities (0 = none, 1 = mild, 2 = moderate, 3 = severe) • Participants recorded scores for pruritus severity and number of weals (over the previous 12 hours) in a daily diary. Efficacy variables included mean daily changes from baseline in pruritus severity, number of weals and interference with sleep and daily activities due to urticaria • Adverse events: withdrawals: 4 in 20 mg group, 5 in 60 mg group, 4 in 120 mg group, 1 in 240 mg group and 2 in placebo group Clinician or participant report: investigator and participant
Notes	Study investigators concluded that all fexofenadine groups were significantly better than placebo groups re pruritus, reduction in weal score and reduced interference with sleep/ activities

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation unclear, no details given; described as randomised
Allocation concealment (selection bias)	Unclear risk	No details given

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Described as 24-hour single-blind lead-in, followed by 4-week double-blind treatment, but no details given
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Described as 24-hour single-blind lead in, followed by 4-week double-blind treatment, but no details given about blinding of outcome assessors
Incomplete outcome data (attrition bias) All outcomes	High risk	186/468 randomly assigned lost to follow-up as follows: 437 had at least 1 postbaseline adverse event assessment; 418 had at least 1 postbaseline 12-hour mean pruritus score assessment (i.e. for safety analysis, losses of n = 31 (6%); for efficacy assessments, losses of n = 50 (10.6%)) In text, study authors state that only 282 participants completed the study (losses n = 186 (40%)) Serious adverse events present in all groups but not specified. Most common adverse events reported (not specified which led to withdrawal of treatment) were as follows: headache ~ 25%, URTI ~ 8%, nausea 5%, dyspepsia 5%, diarrhoea 2%, gastroenteritis 2%, "pain" 4%, abdominal pain 2%, myalgia 4% Frequencies similar across all groups including placebo Incorrectly stated ITT; large number of withdrawals not accounted for Table implies that figures states 325 were evaluated at end of study (4 weeks). This is not resolved in text Study authors state ITT analysis but did not include all participants randomly assigned at the beginning of the study (31 with no data and not included in the analysis) Comment: Discrepancies in number of dropouts and large number of withdrawals suggest that attrition bias could have been introduced
Selective reporting (reporting bias)	Unclear risk	All prespecified outcomes were reported but excluded persons known to be unresponsive to antihistamines; serious adverse events present in all groups but not specified

		Comment: unclear whether selective reporting and participant selection introduced a source of bias
Other bias	Unclear risk	Funder: Hoechst Marion Roussel

Nettis 2004

Methods	Design: randomised double-blind placebo-controlled 3-arm study of desloratadine alone vs desloratadine with montelukast (H1- and H2-antagonists) vs placebo Duration: 6 weeks
Participants	Number of participants randomly assigned: 81 (27 in each group) Sex: 24% male, 76% female desloratadine; 15.4% male, 84.6% female desloratadine plus montelukast; 40% male, 60% female placebo Age of participants, years: 37.5 ± 10.9 (desloratadine plus placebo); 35.6 ± 12.8 (desloratadine plus montelukast); 36.8 ± 10.7 (placebo) Country and setting: Italy; secondary care Unit of allocation: participant **Inclusion criteria of the trial** • CSU **Exclusion criteria of the trial** • Atopic disease; concomitant illness including hepatic, endocrine, psychological disorder; cancer; other major symptoms; delayed pressure urticaria excluded by test • Previous unresponsiveness to antihistamine: not stated
Interventions	**Interventions, dose, duration** • Desloratadine 5 mg once daily and placebo for 6 weeks, desloratadine 5 mg once daily and montelukast 10 mg for 6 weeks • Placebo daily for 6 weeks 1-week single-blind placebo run-in ended with 1-week single-blind placebo washout. Concomitant medications not allowed during course of trial Duration of intervention: intermediate-term (6 weeks) Length of follow-up: 6 weeks
Outcomes	Timing of outcome assessment: baseline, 3 weeks and 6 weeks (participants examined by physician 4 times over 8-week period: first after 1-week placebo run-in, second after 3 weeks' active treatment, third at end of treatment, final at end of placebo washout week) **Primary outcomes of the trial** • Complete suppression of urticaria. Efficacy measures were scored according to the following scales: pruritus: 0 (none), 1 (mild), 2 (moderate) and 3 (severe); number of weals: 0 (none), 1 (1-10 weals), 2 (11-20 weals) and 3 (> 20 weals); average size of weals: 0 (no lesion), 1 (< 1.27 cm), 2 (1.27-2.54 cm) and 3 (> 2.54 cm); number of separate urticarial episodes: 0 (no episodes), 1 (1 episode), 2 (2-3 episodes) and 3 (> 3 episodes). The maximum value of the total symptoms score (TSS) was 12. At each clinical visit, participants also completed a 10-cm visual analogue scale (VAS) indicating overall severity of their urticaria over the previous days from 0 (none) to 10 (worst) • Quality of life measures: 5-item questionnaire administered (using part of DLQI) at each visit (0-3, no problems to severe problems)

	Secondary outcomes of the trial • Adverse events: no major or minor events in all 3 groups Clinician or participant report: investigator and participant
Notes	Study investigators concluded that both treatments were significantly more effective than placebo

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation unclear
Allocation concealment (selection bias)	Unclear risk	Methods of allocation concealment not stated. Sealed envelopes in pharmacy Comment: Not entirely clear whether sealed envelopes related to blinding of medication or allocation concealment, judged as unclear
Blinding of participants and personnel (performance bias) All outcomes	Low risk	1-week single-blind placebo run-in and run-out. Double-blind study, adequately blinded Quote (page 1402): "Patients were not informed that the treatment would be divided into specific periods" "The tablets were encapsulated in double blind fashion and sealed in envelopes by a pharmacist along with the instruction sheets at the beginning of the trial. All treatments were dispensed by a third party"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors were blinded as above Comment: probably done, inferred from text
Incomplete outcome data (attrition bias) All outcomes	Low risk	5/81; 5 lost to follow-up (6%) Number and reasons for withdrawal: • Desloratadine plus placebo n = 2 • Desloratadine plus montelukast n = 1 • Placebo n = 2 • Non-compliance n = 3, lack of desire to continue n = 1, need to take steroids for acute angio-oedema n = 1 Comment judged as low risk, as withdrawals with reasons were given and were balanced between the 2 groups No ITT; most results reported as number

		of participants showing any improvement, with no indication of effect size
Selective reporting (reporting bias)	Unclear risk	Attempt at QoL measurement, but DLQI into non-validated scale; HRQoL results unclear-presented only graphically; y-axis (if consistent with other graphs) indicates only % participants showing any improvement (no indication of effect size) Baseline data unclear: Symptom severity scale appears to be out of 12, yet at baseline, mean is stated as about 60 in each group
Other bias	Unclear risk	Funder: none

Nettis 2006

Methods	Design: randomised double-blind 2-arm placebo-controlled study of levocetirizine 5 mg vs placebo Duration: 6 weeks
Participants	Number of participants randomly assigned:106, n = 53 levocetirizine, n = 53 placebo Sex: 33% male, 67% female levocetirizine; 41% male, 59% female placebo Age of participants, age: mean 41.1 (SD 22-71) levocetirizine; mean 39 (SD 22-69) placebo Country and setting: Italy; secondary care Unit of allocation: participant **Inclusion criteria of the trial** • CSU **Exclusion criteria of the trial** • Atopics, concurrent disease (malignancies or hepatic, psychiatric, endocrine or other major systemic diseases) • Previous unresponsiveness to antihistamine: not stated
Interventions	**Interventions, dose, duration** • Levocetirizine 5 mg once daily for 6 weeks • Placebo once daily for 6 weeks 1-week placebo run-in (single-blind), then treatment for 6 weeks, then 1-week placebo washout at end of study Duration of intervention: intermediate-term (6 weeks) Length of follow-up: 8 weeks i.e. follow-up extended after cessation of therapy
Outcomes	Timing of outcome assessment: screening, after placebo run-in, after 3 weeks of active treatment, after 1 week of washout (at 6 weeks) Examined by physician 4 times over 8-week period: first after placebo run-in (1 week); second after 3 weeks' active treatment; third after 6 weeks' active treatment; fourth after final week of placebo-participants complete visual analogue scale for overall severity of urticaria since last visit (0 = none, 10 = worst) **Primary outcomes of the trial**

	• Complete suppression of urticaria • Quality of life measures: a 5-question urticaria quality of life questionnaire administered, evaluating cutaneous symptoms, emotions, practical problems: "over the last week, how itchy, sore, painful or stinging has your skin been? How embarrassed or self-conscious have you been because of your skin? How much has your skin influenced the choice of clothes that you wear? How much has your skin affected any social or leisure activities? Has your skin prevented you from working or studying? If no, how much of a problem has your skin been at work or studies?" Answered on 4-point scale (0 = no problems to 3 = severe). Participants used daily diary: pruritus (0 = none, 1 = mild, 2 = moderate, 3 = severe); number of weals (0 = none, 1 = 1-10, 2 = 11-20, 3 = > 20); size of weal (mean diameter) (0 = none, 1 = < 1.27 cm, 2 = 1.27-2.54 cm, 3 = > 2. 54 cm); number of separate urticarial episodes (0 = none, 1 = 1 episode, 2 = 2-3 episodes, 3 = > 3 episodes) **Secondary outcomes of the trial** • Adverse events: no serious or minor adverse events in either group • Proportion relapsing within 1 month of cessation of drug Clinician or participant report: both
Notes	Study investigators concluded that mean total symptoms score decreased by 81% vs 1% by end of study period in levocetirizine vs placebo group, respectively Treatment group had statistically significant decrease in number of weals at all visits (overall 79% reduction in score); also statistically significant decrease in urticarial episodes and size of weals (75% reduction); pruritus also (85% reduction)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation unclear ("randomly assigned")
Allocation concealment (selection bias)	Unclear risk	Sealed envelopes in pharmacy. Comment: not entirely clear whether sealed envelopes related to blinding of medication or allocation concealment, judged as unclear
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study; participants not informed that treatments would be divided up into specific periods: 1-week placebo run-in (single-blind), then treatment for 6 weeks, then 1-week placebo washout at end of study. Double-blind study: "tablets were encapsulated in a double blind fashion and sealed in envelopes by a pharmacist together with instruction sheets." 1-week placebo run-in (single-blind), then treatment for 6 weeks, then 1 week placebo washout at end of study. Medications dis-

		pensed by third party
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors were blinded as above Comment: probably done, inferred from text
Incomplete outcome data (attrition bias) All outcomes	Low risk	100/106 randomly assigned participants completed Withdrawals: levocetirizine n = 2, n = 4 in placebo group, dropped out in placebo run-in phase because of non-compliance n = 2, heart attack n = 1, needed to take oral steroids for aggravated urticaria n = 3 (2 in placebo group and 1 in levocetirizine group) No ITT Comment: low number of dropouts, evenly balanced between groups, not thought to contribute bias
Selective reporting (reporting bias)	Unclear risk	Results not clearly reported. Attempt at measuring quality of life, but not with validated scale; results of this inadequately reported. Quality of life scores statistically significantly improved from baseline in levocetirizine group but not in placebo group (no scores given)
Other bias	Low risk	Funder: none

Ollert 1999

Methods	Design: randomised 2-arm multi-centre (10 centres) parallel-group comparison of mizolastine vs placebo Duration: 4 weeks
Participants	Number of participants randomly assigned: 78 (39 each in mizolastine and placebo) Sex: 40% male, 60% female Age of participants, years: 40 ± 13 Unit of allocation: participant Country and setting: Germany; research clinic **Inclusion criteria of the trial** • CSU with or without angio-oedema for at least 6 weeks, with at least 2 urticarial episodes per week **Exclusion criteria of the trial** • Pregnant, not using effective contraception (in women of childbearing age), use of machinery at work, abnormal physiological values, serious concomitant illness including psychiatric illness and alcoholism, taking other medications concomitantly with mizolastine

	• Previous unresponsiveness to antihistamine: not stated
Interventions	**Interventions, dose, duration** Placebo run-in periods (i.e. variable washout period of any other medications (depending on previous medication type) before study commenced) • 10 mg mizolastine a day • Identical placebo Duration of intervention: intermediate-term (4 weeks) Length of follow-up: 4 weeks
Outcomes	Timing of outcome assessment: at days 0, 14 and 28 **Primary outcomes of the trial:** • Mean total symptoms score (participant report); number of urticarial episodes per week • Visual analogue scale parameters ranged from no reduction in symptoms (0%) to very strong reduction in symptoms (100%) • Response to treatment (responder) was defined by a score decrease > or = 50% between day 0 and day 28, and by reduced frequency of urticaria episodes/wk • Evaluation was done with reference to the study protocol and to participant diaries of all symptoms the week before • VAS: 4-point scale for itching (0 = absent, 1 = mild, 2 = moderate, 3 = severe) and weal and erythema (0 = none, 1 = < 10, 2 = > 10, 3 = generalised outbreak) • Quality of life measures: none **Secondary outcomes of the trial** • Cardiovascular measures and body weight • Adverse events: reported, 14 adverse events in 13 participants in the mizolastine group; asthenia, fatigue, headache and influenza-like symptoms were reported, whereas rhinitis and bronchitis were reported more frequently in the placebo group. Drowsiness or sedation not reported in either group Clinician or participant report: clinician and participant
Notes	Study report written in German Study investigators concluded that mizolastine demonstrates clinical and statistical superiority over placebo in the treatment of CSU, and showed a good safety profile

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Stated to be randomised, unclear as method not stated
Allocation concealment (selection bias)	Unclear risk	Unclear, no details given
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Stated to be double-blind, identical placebos given

Ollert 1999 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Stated to be double-blind, but no details given
Incomplete outcome data (attrition bias) All outcomes	Low risk	Stated to be ITT analysis. 19 participants dropped out: 11/39 mizolastine, 8/39 placebo. Reasons given: 2 in total for undesirable effects, 12 in total for lack of effect, 5 in total for other reasons (page S26, table 2)
Selective reporting (reporting bias)	Unclear risk	Unclear; not all physiological measures were reported in full in the study report
Other bias	Low risk	None detected. Funder: not stated

Ortonne 2004

Methods	Design: randomised parallel-group 2-arm study of desloratadine vs placebo Duration: 42 days
Participants	Number of participants randomly assigned: 137 (desloratadine n = 65, placebo n = 72) Sex: gender not stated Age of participants, years: 18, mean age not stated Unit of allocation: participant Country and setting: France (multicentre), research clinics **Inclusion criteria of the trial** • CSU history for ≥ 6 weeks and active disease at enrolment (pruritus score ≥ 2 (screening); AM/PM pruritus sum score (days -3 to 1) ≥ 14; global CSU severity ≥ 2 (screening/randomisation)) **Exclusion criteria of the trial** • Not stated • Previous unresponsiveness to antihistamine: unclear
Interventions	**Interventions, dose, duration** • Desloratadine 5 mg • Placebo once daily Duration of intervention: intermediate-term (6 weeks) Length of follow-up: 42 days
Outcomes	Timing of outcome assessment: 14 days and 42 days **Primary outcomes of the trial** • Change from baseline in mean reflective pruritus score at day 14 **Secondary outcomes of the trial** • Therapeutic response and changes in individual CSU signs/symptoms scores • Adverse events were rated according to severity/relation to treatment • Therapeutic response and changes in individual CSU signs/symptoms scores Clinician or participant report: participant and clinician

Ortonne 2004 (*Continued*)

Notes	Study investigators concluded that desloratadine was effective from the first dose and throughout 6 weeks in CSU

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated, described as randomised
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not stated
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear how many out of 137 randomly assigned participants completed the study
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were reported
Other bias	Unclear risk	Funder: Schering-Plough. Short conference abstract

Ortonne 2007

Methods	Design: multi-centre 2-arm randomised double-blind trial of desloratadine vs placebo Duration: 42 days
Participants	Number of participants randomly assigned: 142 (desloratadine n = 65, placebo n = 77) Age, years: > 18; desloratadine 41.2 ± 15.4; placebo 41.5 ± 15.2 Gender: desloratadine 36.9% male, 63.1% female; placebo 40.3% male, 59.7% female Unit of allocation: participant Country and setting: France; set in 40 dermatology centres **Inclusion criteria of the trial** • Active moderate to severe CSU, pruritic weals of unknown cause for 3 days per week for 6 consecutive weeks and a flareup before visit 1 • > 18 years of age, good general health • Female participants using contraception • Other entry criteria included a pruritus score of 2 (at least moderate pruritus), a weal score of 1 (at least 1-6 weals) and a global CSU severity score of 2 (at least moderate severity) at screening and at baseline • Participants were also required to show an AM/PM reflective pruritus score of 14 for the 3 consecutive days before baseline and the morning of day 1

	Exclusion criteria of the trial • Pregnant or lactating, asthma requiring inhaled or systemic corticosteroids, had been injected with corticosteroids within 90 days of screening • Had been hospitalised for CSU for 3 months of screening, had antihistamine-resistant CSU • Skin reactions due to drug- or food-related allergies, hypersensitivity to desloratadine • Concomitant disease • Unable to give informed consent • Prior unresponsiveness to antihistamines, history of "poor motivation, non-compliance with medications or treatment protocols"
Interventions	**Interventions, dose, duration** • Desloratadine 5 mg daily • Placebo Duration of intervention: intermediate-term (6 weeks) Length of follow-up: up to 6 weeks
Outcomes	Timing of outcome assessment: days 7, 14, 42 (patient diaries collected at these times or at time of early termination, if applicable) **Primary outcomes of the trial** • Pruritus evaluated at visits and reflectively (last 12 hours) • Primary efficacy measure was variation in mean AM/PM reflective pruritus scores over first 2 weeks of treatment, expressed as change from baseline to day 14 and area under curve of reflective pruritus score vs time from baseline to day 14 • Quality of life measures: See primary outcomes above **Secondary outcomes of the trial** • Disruption of sleep and daily activities. Variation in mean AM/PM reflective pruritus scores after 1 and 6 weeks of treatment (0 = none; 1 = mild, noticeable but discreet, easy to tolerate; 2 = moderate, obvious, unpleasant presence but bearable; 3 = severe, hard to bear), instantaneous pruritus scores on days 1 to 4 and change in number of weals (0 = none, 1 = 1-6, 2 = 7-12, 3 = > 12) and maximum size of weals (0 = none, 1 = < 1 cm, 2 = 1-5 cm, 3 = > 5 cm) after 1, 2, 6 weeks' treatment; global response to treatment defined as % with complete response, marked or moderate (after 6 weeks); safety profile • Also global severity score (0 = no signs/symptoms; 1 = signs/symptoms clearly present but associated with minimal awareness, easily tolerated; 2 = definite awareness of signs/symptoms that are bothersome but tolerable; 3 = signs/symptoms hard to tolerate, causing interference with daily activities/sleep) appears to have been measured, but not stated to be a specific endpoint. Variation of the scores of 2 QoL dermatology-specific tools measured between baseline and day 42, the French translation version of the Dermatology Life Quality Index (DLQI) and the VQ-Dermato (a French language scoring instrument) • Adverse events: serious events requiring withdrawal: desloratadine group: pregnancy (not treatment-related) • Other adverse events: similar incidence in both groups, greater in placebo group. One participant in placebo group withdrew because of exacerbation of urticaria Clinician or participant report: participant diaries, general (non-directive) questions by investigators, or clinical examination

Notes	Study investigators concluded that desloratadine was shown to be significantly superior to placebo in improving severity of pruritus as measured by reflective pruritus scores measured between days 0 and 14

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote (page 39): "following screening (visit 1), a computer-generated allocation code was used to randomly assign patients"
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Described as double-blind, medication was provided to participants in a numbered container based on their randomisation code
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Described as double-blind but method of investigator blinding not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	85/142 randomly assigned participants completed the study Figure 1 of the study report provides an account of dropouts from each group. 142 randomly assigned (65 desloratadine, 77 placebo). 5 withdrawn as received no treatment or had no baseline data. Of remaining 137 (65 desloratadine, 72 placebo), 85 completed (49 desloratadine, 36 placebo) . 16 withdrew from desloratadine group (12 lack of efficacy, 1 adverse event (pregnancy, not treatment-related), 1 withdrew consent, 1 was lost to follow-up, 1 other reason). 36 withdrew from placebo group (34 lack of efficacy, 2 lost to follow-up described as 'loss of sight' in fact lost to follow-up)
Selective reporting (reporting bias)	Unclear risk	All prespecified outcomes were reported, but results are presented as percentages or as graphs with statistical significance Comment: endpoint at 6 weeks is not clear

Other bias	Unclear risk	Funder: Schering-Plough Research Institute

Patel 1997

Methods	Design: randomised double-blind 2-arm parallel-group study of loratadine vs cetirizine Duration: 2 weeks
Participants	Number of participants randomly assigned: 46 (22 loratadine, 18 cetirizine) Sex: not stated Age of participants: not stated Unit of allocation: participant Country and setting: not stated; investigators located in USA and Canada **Inclusion criteria of the trial** • CSU with moderate to severe pruritus and hives **Exclusion criteria of the trial** • Not stated • Previous unresponsiveness to antihistamine: not stated
Interventions	**Interventions, dose, duration** • 10 mg of loratadine • Cetirizine once daily (mornings for 2 weeks) Duration of intervention: short-term (2 weeks) Length of follow-up: 2 weeks
Outcomes	Timing of outcome assessment: baseline and days 7 and 14 **Primary outcomes of the trial** • Pruritus, number and size of hives and erythema. Primary efficacy parameter was physician-evaluated change in pruritus between baseline and day 7. Pruritus and erythema were rated as follows: 0 = none, 1 = mild, 2 = moderate, 3 = severe. Number of hives was evaluated on a 3-point scale (0 = none, 1 = 1 to 6, 2 = 7 to 12, 3 = > 12). Diameters of the largest hives were measured and rated as 0 = none, 1 = < 1.5 cm, 2 = 1.5 to 2.5 cm, 3 = > 2.5 cm. The overall condition of chronic idiopathic urticaria was graded as 0 = none, 1 = mild, 2 = moderate, 3 = severe. Ratings of therapeutic response to study drug were 1 = complete relief, 2 = marked relief, 3 = moderate relief, 4 = slight relief, 5 = treatment failure • Quote (page 319): "Histamine skin-prick challenge was performed before therapy was initiated and 2 hours after the last dose on the last study day after all clinical evaluations". Results were transferred onto clear tape; planimetry was used to measure areas • Quality of life measures: not stated **Secondary outcomes of the trial** • Adverse events: recorded by participants, sedation recorded by 2 in the cetirizine group Clinician or participant report: clinician and participant diary card
Notes	Study investigators concluded that loratadine and cetirizine were well tolerated with comparable efficacy

Patel 1997 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Stated to be randomised, methods not described
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Stated to be double-blind, no details given
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Stated to be double-blind, no details given
Incomplete outcome data (attrition bias) All outcomes	Low risk	40/46 complete (22 loratadine, 18 cetirizine). These non-completers had fewer than 7 days of therapy or lack of valid follow-up visit or both
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were reported
Other bias	Unclear risk	Funder: Schering-Plough, USA

Paul 1998

Methods	Design: multi-centre double-blind randomised parallel-group study comparing fexofenadine 60 mg, 120 mg, 180 mg, 240 mg or placebo, each once daily Duration: 6 weeks
Participants	Number of participants randomly assigned: 222 (details unclear) Age of participants, years: placebo 43 ± 13; fexofenadine 60 mg 44 ± 17; fexofenadine 120 mg 45 ± 12; fexofenadine 180 mg 43 ± 15; fexofenadine 240 mg 44 ± 14 Overall age, years: 44 ± 14 Sex (% female): placebo 54%, fexofenadine 60 mg 58%, fexofenadine 120 mg 47%, fexofenadine 180 mg 68%, fexofenadine 240 mg 59% Total female: 58% Duration of symptoms: 3 years ± 5 Severity of urticaria: unclear Unit of allocation: participant Country and setting: France, UK, Germany; secondary care **Inclusion criteria of the trial** • CSU symptoms at least once a week **Exclusion criteria of the trial** • "Predominantly" physical urticaria, urticarial vasculitis, hypersensitivity to terfenadine or not responsive to antihistamine treatment; topical and systemic

	treatment for CSU
Interventions	**Interventions, dose, duration** • Fexofenadine 60 mg • Fexofenadine 120 mg • Fexofenadine 180 mg • Fexofenadine 240 mg • Placebo (each once daily) Duration of intervention: intermediate-term (6 weeks) Length of follow-up: 6 weeks
Outcomes	Timing of outcome assessment: weekly assessment Total symptoms score (TSS) (0-4 for number of weals; 0-3 for itching intensity; 0-7 combined TSS) **Primary outcomes of the trial** • Mean daily TSS and weekly TSS • Quality of life measures: none **Secondary outcomes of the trial** • Sleep interference (0-3), daily activity (0-3), global participant score for effectiveness (0-4) • Physician assessments: intensity of erythema, lesion size, number and extent • Adverse events: headache 12% in active group, 14% in placebo group Clinician or participant report: both
Notes	Study investigators concluded that good or excellent response in 60 mg group = 63%, 120 mg group 50%, 180 mg group 64%, 240 mg group 55% and placebo group 41%; not clear whether timing for this result but may be 6 weeks Fexofenadine is effective at 120 mg and above from week 1 as compared with placebo

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Participants non-responsive to other anti-histamine treatment excluded Method of randomisation not stated
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not stated how
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated how

Paul 1998 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	No ITT. 76 participants withdrew before completion: 30 lost from placebo, 14 from 120 mg group, 16 from 180 mg group and 8 from 240 mg group Treatment group reason for withdrawal: lack of effect 13%, adverse events 7%, patient request 6% Placebo group: lack of effect 33% and adverse events 20%
Selective reporting (reporting bias)	Unclear risk	No ITT; study says weekly as well as fortnightly; all active drug groups put together and reported only selectively
Other bias	Unclear risk	Funder: Hoechst Marion Roussel

Peyri 1991

Methods	Design: randomised double-blind multi-centre placebo-controlled 2-arm study of ebastine 10 mg daily vs placebo Duration: 14 days
Participants	Number of participants randomly assigned: 204 (ebastine 100, placebo 104) Sex: not stated Age of participants: not stated Unit of allocation: participant Country and setting: Spain; secondary care (outpatient clinics) **Inclusion criteria of the trial** • CSU, of at least 3 months' duration, cutaneous eruptions, active disease **Exclusion criteria of the trial** • Angio-oedema, neoplasia, steroids in last 2 weeks (topical or systemic) • Previous unresponsiveness to antihistamine: not stated
Interventions	**Interventions, dose, duration** • Ebastine 10 mg once daily for 14 days • Placebo once daily for 14 days Duration of intervention: short-term (14 days) Length of follow-up: 14 days
Outcomes	Timing of outcome assessment: baseline, 7 days, 14 days **Primary outcomes of the trial** • Participants assessed itching severity and number/size of weals on 4-point scale: nil/mild/moderate/severe • Investigator recorded number of weals • Joint assessment of mean weekly duration of symptoms • Both scored overall treatment efficacy at end of trial period: no change/moderate improvement (improvement in approximately half of symptoms)/good (improvement in most or all of symptoms), but reported as 'cure, improvement, no change, or

	worsening' • Tolerability assessed by physician and participant as good/moderate/poor **Secondary outcomes of the trial** • Side effects rated as absent/mild/moderate/severe • Adverse events (serious, requiring withdrawal) Clinician or participant report: both
Notes	Study investigators concluded that a significantly greater reduction in weal size and weal number was seen in ebastine group over placebo. Pruritus significantly less in ebastine group

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not stated
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind study; matching placebo capsules; unclear whether blinding was adequate for both participants and personnel
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear, no details given
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses to follow-up: 27/204 (13%), ebastine 9/100 (9%), placebo 18/104 (17%) Withdrawals due to lack of efficacy: ebastine n = 3 and placebo n = 13; poor tolerability: ebastine n = 1; lack of efficacy plus poor tolerability: ebastine n = 1, placebo n = 3; other reasons not due to treatment: ebastine n = 4, placebo n = 2 Withdrawals with reasons stated and balanced between the 2 groups No ITT
Selective reporting (reporting bias)	Unclear risk	No clear definition of outcomes, unclear how outcome assessments were used to generate assessments of (Quote) (page 52): "cure, improvement, no change, worsening" Age and sex of participants not known
Other bias	Unclear risk	Funder: Almirall Note: Groups were well matched for age, sex, duration of urticaria, previous treat-

Peyri 1991 (*Continued*)

		ment and response to prior antihistamine therapy

Phanuphak 1987

Methods	Design: double-blind randomised placebo-controlled 2-arm study of ketotifen (mast cell stabiliser) vs placebo Duration: 2 weeks
Participants	Number of participants randomly assigned: 30 (16 ketotifen and 14 placebo) Sex: 25% male, 75% female ketotifen; 26% male, 64% female placebo Age of participants, years: mean 30.4 Unit of allocation: participant Country and setting: Thailand; secondary care **Inclusion criteria of the trial** • CSU for longer than 6 weeks **Exclusion criteria of the trial** • Pregnancy, lactation, < 15 years old • Previous unresponsiveness to antihistamine: not stated
Interventions	**Interventions, dose, duration** • Ketotifen 1 mg twice daily • Placebo twice daily 2-week run-in: participants allowed to take chlorpheniramine 4 mg prn up to 6-hourly; then randomly assigned to ketotifen or placebo and still allowed to take chlorpheniramine concomitantly; numbers of chlorpheniramine tablets taken recorded Duration of intervention: short-term (2 weeks) Length of follow-up: 2 weeks
Outcomes	Timing of outcome assessment: baseline and 2 weeks **Primary outcomes of the trial** • Proportion with good/excellent response: scored as 0 = no lesion or no symptoms, 1 = mild symptoms, 2 = moderate symptoms, 3 = severe symptoms • Quality of life measures: none **Secondary outcomes of the trial** • Adverse events: minor and serious Clinician or participant report: investigator and participant diaries
Notes	Study investigators concluded that ketotifen was significantly better than placebo. Chlorphenamine requirement was dropped in significantly more participants taking ketotifen than placebo (94% vs 7%)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Participants were randomly assigned to 2 groups, method not described

Phanuphak 1987 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Third party sealed envelopes with code number, containing active treatment or placebo prepared and sealed by a third person, but unclear if this refers to blinding or to concealment of allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study; identical white tablets provided to participants, blinded to participants, as supplied in sealed coded envelopes prepared by a third party
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear whether outcome assessors were blinded and how
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up: 30 (16 ketotifen and 14 placebo)
Selective reporting (reporting bias)	Unclear risk	All prespecified outcomes were reported Comment: The 'slightly effective' and 'ineffective' evaluation of patient score put together as ineffective
Other bias	Unclear risk	Funder: Sandoz Allowed concomitant treatment with chlorpheniramine such that positive results of ketotifen group might be due to this alone or to the combination of ketotifen plus chlorpheniramine; very small numbers; sponsored by manufacturer

Pons-Guiraud 2006

Methods	Design: randomised double-blind multi-centre 2-arm trial comparing emedastine and loratadine Duration: 4 weeks
Participants	Number of participants randomly assigned: 192 (emedastine n = 84, loratadine n = 77) Sex: loratadine: 34.5% male, 65.5% female; emedastine: 25% male, 75% female Age of participants, years: loratadine: 42.6 ± 14.7; emedastine:43.4 ± 13.3 Country and setting: Italy, France, Hungary, Czech Republic; secondary care Unit of allocation: participant **Inclusion criteria of the trial** • Other skin/systemic disease that could affect efficacy evaluation; concomitant antihistamines, sedatives, steroids • Hypersensitivity to loratadine or emedastine or excipient pregnancy or lactation • Premenopausal women not on contraceptive; profession requiring driving/ operation of machinery

	• Raised liver enzymes/creatinine; drug/alcohol abuse • < 75% compliance during placebo run-in • Lack of co-operation; "previous enrolment into the trial"; non-Caucasians < 18 or > 64 • Those with history of failure to respond to antihistamine • Included only if at least moderate itching for at least 3 days during 7-day run-in
Interventions	**Interventions, dose, duration** • Emedastine difumarate 2 mg twice daily • Loratadine 10 mg once daily (plus placebo once daily) Duration of intervention: intermediate-term (4 weeks) Length of follow-up: 4 weeks (plus optional visits 2 weeks after cessation of therapy)
Outcomes	Timing of outcome assessment: 1, 2 and 4 weeks (plus optional visits at week 2 and 2 weeks after discontinuation of treatment) • Complete suppression of urticaria, proportion with good/excellent response, good or excellent response but not completely suppressed • Primary endpoint (from daily symptom diary): total urticaria symptoms score: sum of itching intensity score + hive number score (measured twice daily) • Erythema intensity score, largest hive score, extension of involved skin score, final overall effectiveness scores (participant and investigator) • Itching: 0 = none; 1 = mild, symptom present but not annoying/troublesome; 2 = moderate, frequently troublesome, not interfering with sleep/activities; 3 = severe, sufficient to interfere with sleep/activities • Number of weals (0 = none, 1 = 1-6, 2 = 7-12, 3 = > 12) • Intensity of erythema (0 = absent, 1 = slight/pale, 2 = definite or red, 3 = extreme/bright red) • Extent of skin involved (0 = weals absent; 1 = 1%-10% body involved; 2 = moderate amount of body involved, 11%-30%; 3 = large amount of body involved, > 30%) • Overall effectiveness of medication (0 = no improvement/worse, 1 = slight improvement, 2 = moderate improvement, 3 = marked improvement, 4 = complete disappearance of symptoms) • Quality of life measures: none **Secondary outcomes of the trial** • Size of largest hive (0 none, 1 = < 1.5 cm, 2 = 1.5-2.5 cm, 3 = > 2.5 cm) • Adverse events: Safety analysis included all 192 randomly assigned participants (96 in each group) • Serious: loratadine: attempted suicide; emedastine: bilateral calcaneum fractures following fall • Minor adverse events: sleepiness, nausea, constipation, palpitations, dry mouth; emedastine: sleepiness, headache, fatigue, increased liver enzymes Clinician or participant report: both
Notes	Study investigators concluded that no significant differences between treatments were noted at 4 weeks according to investigator and participant scores; mean symptom scores improved significantly from baseline in both groups
Risk of bias	

Pons-Guiraud 2006 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer list prepared by sponsor
Allocation concealment (selection bias)	Low risk	Sealed envelopes containing code breaks were given to each centre
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, double-dummy study; 2 identical capsules; placebo run-in
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind, double-dummy study; 2 identical capsules; placebo run-in, but unclear whether outcome assessors were specifically blinded to allocation Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	152/192 completed 12 participants excluded after randomisation, as they took prohibited antihistamines. 19 more excluded after randomisation, as they failed to report scores for hives/itching during placebo run-in period. Only the remaining 161 participants were included in ITT. 31 lost to follow-up (16%). Per-protocol (PP) analysis included only 153 participants-8 had major protocol violations or dropped out Two were withdrawn because of serious adverse events: 1 suicide attempt, 1 fracture following a fall in emedastine group No ITT Comment: All dropouts accounted for but not clearly by group
Selective reporting (reporting bias)	Low risk	No selective reporting Comment: excluded participants unresponsive to antihistamines
Other bias	Unclear risk	Funder: Saluc-Pharma S.A. Study drug manufactured and packaged by sponsor; no power calculation

Potter 2009

Methods	Design: randomised multi-centre randomised parallel-group double-blind 2-arm study comparing levocetirizine 5 mg and desloratadine 5 mg Duration: 4 weeks
Participants	Number of participants randomly assigned: 886 (levocetirizine n = 438, desloratadine n = 448) Sex: levocetirizine 35.2% male, 64.8% female; desloratadine 36.2% male, 68.3% female Age of participants, years (range): levocetirizine 43.36 (18-79.2); desloratadine 42.85 (18.1-81.3) Unit of allocation: participant Country and setting: multi-centre Germany and UK; secondary **Inclusion criteria of the trial** • Male and female outpatients 18 years of age and older, with a clinical history of CSU (i.e. episodes of hives of characteristic weal and flare appearance, occurring regularly, at least 3 times a week) for a period of at least 6 weeks during last 3 months without an identifiable cause were recruited into the study • All participants were additionally required to have a pruritus severity score (over last 24 hours) $\geq$ 2 and number of weals score $\geq$1 for at least 3 days in the week before randomisation **Exclusion criteria of the trial** • Physical urticaria, drug-induced urticaria, vasculitis, senile pruritus, hereditary angio-oedema, other dermatological or clinically significant disease; steroids in last 4 weeks; desloratadine, loratadine, levocetirizine, cetirizine in last 10 days; astemizole in last 12 weeks; ketotifen in last 2 weeks; leukotriene antagonists in last 3 days; CNS acting agents • Pregnant/breastfeeding • Previous unresponsiveness to antihistamine: not stated
Interventions	**Interventions, dose, duration** • Levocetirizine 5 mg once daily • Desloratadine 5 mg once daily Duration of intervention: intermediate-term (4 weeks) Length of follow-up: 5 weeks i.e. follow up extended after cessation of therapy
Outcomes	Timing of outcome assessment: 4 scheduled visits over a period of 5 weeks: screening visit 1 (V1; week -1), randomisation visit (V2; week 0), control visit (V3; week 1) and final visit (V4; week 4) **Primary outcomes of the trial** • Mean pruritus severity score, mean pruritus duration, number and size of weals, mean CSU composite score (sum of pruritus severity score and score for number of weals) • Participants evaluated and recorded severity of pruritus and duration of pruritus over last 24 hours (reflective) and number and size of weals (at the time of evaluation) in DRCs on 4-point scales of 0 to 3, once a day in the evening over entire duration of the trial • Pruritus severity was scored (0 = none; 1 = mild (present but not disturbing); 2 = moderate (disturbing but not hampering daytime activities and/or sleep); and 3 = severe/intense (disturbing and hampering daytime activities and/or sleep)), and duration of pruritus was scored (0 = no pruritus; 1 = < 1 hour; 2 = 1-6 hours; and 3 = >

	6 hours) • Similarly, number of weals was scored (0 = none; 1 = mild (< 20 weals/24 h); 2 = moderate (21-50 weals/24 h); and 3 = severe/intense (> 50 weals/24 h)), as was size of weals (diameter of the greatest weal) (0 = no weal; 1 = 1-1.5 cm; 2 = 1.5-3.0 cm; and 3 = > 3.0 cm) • Quality of life measures: self-administered DLQI; QoL and participant's and investigator's global satisfaction with treatment were evaluated as secondary efficacy measures **Secondary outcomes of the trial** • Adverse events: "Safety and tolerability of treatment was evaluated according to the frequency, severity, nature and duration of adverse events reported by the patients during the entire study period. Any abnormalities noted during the physical examinations were also evaluated" Clinician or participant report: participant and clinician
Notes	Study investigators concluded that levocetirizine 5 mg was significantly more efficacious than desloratadine 5 mg in the treatment of CSU symptoms

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 597): "Randomization to the study drug was achieved by allocation of a unique study number to each subject and a computer-generated sequential randomisation number provided by the Biostatistics Department of the study sponsor (UCB S.A., Brussels, Belgium)"
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote (page 597): "capsules identical in shape, size and colour to allow a double-blind design"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear how outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	832/886 completed • Levocetirizine group: lack of efficacy n = 10; "other" n = 6; adverse events n = 4; loss to follow-up n = 3; withdrawal of consent n = 2 • Desloratadine group: lack of efficacy n = 13; "other" n = 7; adverse event n = 3; loss to follow-up n = 3; withdrawal of

Potter 2009 (*Continued*)

		consent n = 3 • Comment: numbers balanced between groups, reasons for losses stated In NCT00264303, reasons for withdrawal were given but do not correspond with the number of participants analysed-n = 25 levocetirizine and n = 29 desloratadine-because of adverse event, lack of efficacy, loss to follow-up, participant preference to withdraw, other reasons. However, number of participants analysed was n = 434 in levocetirizine group and n = 443 (877 total) in desloratadine group (only 9 losses out of 886 specified, reasons unclear). Judged as unclear risk
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were reported
Other bias	Unclear risk	Funder: UCB

Ring 2001

Methods	Design: randomised double-blind placebo-controlled parallel-group 2-arm study of desloratadine vs placebo Duration: 6 weeks
Participants	Number of participants randomly assigned: 190 (95 in each group) Sex: 29% male, 71% female desloratadine; 22% male, 78% female placebo Age of participants, years: 12 to 79 Country and setting: USA and Germany; secondary care Unit of allocation: participant **Inclusion criteria of the trial** • CSU, men and women > 12 years of age, minimum 6-week history of CSU and active flare • CSU for longer than 3 weeks before screening, with weals visible for > 3 days per week • Overall moderate disease severity at screening and baseline, moderate pruritus and presence of weals at screening • At baseline, participants also had to have a total reflective pruritus score > 14 (at least moderate) over the previous 3 days and on the morning of the baseline visit • Normal laboratory and physiological values **Exclusion criteria of the trial** • Significant concomitant illnesses (e.g. malignancy) or pharmacological agents that could interfere with study drug, asthma with leukotriene inhibitors or required long-term inhaled or systemic corticosteroid therapy • Previous unresponsiveness to antihistamine: not stated

Interventions	**Interventions, dose, duration** • Desloratadine 5 mg • Placebo Once daily for 6 weeks (sufficient time for washout of any medications before study was employed) Duration of intervention: intermediate-term (6 weeks) Length of follow-up: 6 weeks
Outcomes	Timing of outcome assessment: days 1 and 4, then weeks 1, 2, 4, 6 **Primary outcomes of the trial** • Participants used 4-point scale (reflective related to previous 12 hours-scored twice daily; instantaneous related to immediate time of assessment on all study days) for pruritus, number of weals, size of largest weal; summed to give total symptoms score • Recorded interference with sleep and interference with daily activities • Severity assessed by physician and participant at days 1 and 4, then at weeks 1, 2, 4 and 6 (0 = none, 1 = mild, 2 = moderate, 3 = severe) • Therapeutic response jointly assessed on 5-point scale (1 = complete relief to 5 = treatment failure) • Quality of life measures: none **Secondary outcomes of the trial** • Adverse events: serious adverse events (requiring treatment withdrawal): desloratadine n = 3, placebo n = 2 (not specified but not life threatening) • Minor adverse events: desloratadine: n = 53 headache, fatigue, pharyngitis, URTI, dizziness; placebo n = 41: headache, fatigue, pharyngitis, URTI, dizziness, viral infection Clinician or participant report: investigator and participant
Notes	Study investigators concluded that results from week 1 were maintained throughout study duration Desloratadine significantly superior to placebo in reducing average mean reflective pruritus score (56% vs 21%) and total symptoms score (51.6% vs 19.3%). Interference with sleep and daily activities, number of weals, size of largest weal all significantly reduced by desloratadine vs placebo

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated schedule, randomly assigned
Allocation concealment (selection bias)	Unclear risk	Unclear, no details given
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study; matched placebo

Ring 2001 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Double-blind study; unclear how outcome assessors were blinded to treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Losses to follow-up: desloratadine: 19/95 (20%); placebo: 32/95 (34%) Treatment failure: desloratadine n = 13, placebo n = 21; non-compliance: desloratadine n = 3, placebo n = 6; adverse events: desloratadine n = 3, placebo n = 2; other losses to follow-up: desloratadine n = 0, placebo n = 2; did not wish to continue: placebo n = 1 Adverse events: serious adverse events (requiring treatment withdrawal): desloratadine: 3 not specified (not life threatening); placebo: 2 not specified (not life threatening) Comment: high level of loss to follow-up; more losses in the placebo group; unclear whether this contributed to bias
Selective reporting (reporting bias)	Unclear risk	Desloratadine significantly superior to placebo in reducing average mean reflective pruritus score (74% vs 49%). Numbers for total symptoms score not given at 6 weeks, but said to be significant. Actual reductions in scores not stated, only percentages; unclear how clinically significant these reductions are
Other bias	Unclear risk	Funder: Schering-Plough Research Institute

Salo 1989

Methods	Design: randomised double-blind cross-over 3-arm study comparing acrivastine vs hydroxyzine vs placebo Duration: 5 days each treatment
Participants	Number of participants randomly assigned: 21 Sex: 47% female Age of participants, years: 18-70, mean 38.3 Country and setting: Finland and UK; secondary Unit of allocation: cross-over participants **Inclusion criteria of the trial** • Defined CSU as > 4 weeks; however, no participants included with urticaria < 2 months; adults over 18 years **Exclusion criteria of the trial**

	• Systemic steroids in last 4 weeks, concurrent sedatives, other antihistamines • Previous unresponsiveness to antihistamine: not stated
Interventions	**Interventions, dose, duration** • Acrivastine 8 mg 3 times daily • Hydroxyzine hydrochloride 20 mg 3 times daily • Placebo 3 times daily during three 5-day periods 3-day washout initially; then 2-day washout period between treatments Duration of intervention: short-term (5 days per intervention) Length of follow-up: 5 days for each treatment
Outcomes	Timing of outcome assessment: at 5 days for each treatment **Primary outcomes of the trial** • Participants self-assessed daily (weals 0-4; 0 = none, 1 = 1-5, 2 = 6-10, 3 = 11-20, 4 = > 20) (itching 0-4; 0 = none, 1 = minimal, 2 = mild, 3 = moderate, 4 = severe) • Investigator at end of study recorded in his opinion which treatment worked best and suited participant best overall • Quality of life measures: none **Secondary outcomes of the trial** • Adverse events: reasons for 3 withdrawals not stated. Minor events not stated Clinician or participant report: investigator and participant (daily diary)
Notes	Study investigators concluded that participant data showed no differences between active treatments; both better than placebo (P value < 0.05) Physician data showed active treatment better than placebo

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of randomisation unclear, described as randomised
Allocation concealment (selection bias)	Unclear risk	Unclear. Not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind study. Method of blinding not stated
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Double-blind study. Method of blinding not stated
Incomplete outcome data (attrition bias) All outcomes	High risk	Incomplete reporting of data; reasons for withdrawal not stated. No ITT 3/21 lost to follow-up (34%)

Salo 1989 (*Continued*)

Selective reporting (reporting bias)	High risk	Investigators appear to have made subjective decision on best treatment. No raw data-mean scores only. Adverse effects of drowsiness significantly more prevalent with hydroxyzine than with placebo, but numbers of participants experiencing this not stated
Other bias	Unclear risk	Funder: Wellcome Research Laboratories

Sener 1999

Methods	Design: randomised 2-arm parallel-group study comparing ketotifen and fluoxetine Duration: 6 weeks
Participants	Number of participants randomly assigned: 60 (30 in each group) Sex: 41% female, 59% male Unit of allocation: participant Age of participants, years (SD): 19-74 (42.08 ± 19.24) Country and setting: Turkey, research clinic **Inclusion criteria of the trial** • CSU **Exclusion criteria of the trial** • None • Previous unresponsiveness to antihistamine: not stated
Interventions	**Interventions, dose, duration** • Ketotifen (H1-antihistamine first generation) 1 mg twice daily for 6 weeks • Fluoxetine (SSRI) 20 mg 4 times a day for 6 weeks (not a cross-over) Duration of intervention: intermediate-term (6 weeks) Length of follow-up: 6 weeks
Outcomes	Timing of outcome assessment: baseline, weekly and at 6 weeks **Primary outcomes of the trial** • Number of lesions • Degree of itching and discomfort • Amount of angio-oedema graded 0 to 4 for each participant • Quality of life measures: not stated **Secondary outcomes of the trial** • Adverse events: not stated Clinician or participant report: unclear
Notes	Study investigators concluded that significantly greater improvement in symptom score was seen in the ketotifen group (P value < 0.001); fluoxetine led to significant improvement in number of lesions, degree of itch and angio-oedema

Risk of bias

Sener 1999 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation unclear ("randomly divided")
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding (1 treatment twice daily and the other treatment 4 times daily)
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding (1 treatment twice daily and the other treatment 4 times daily)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No raw data; adverse events not mentioned, nor withdrawals from study
Selective reporting (reporting bias)	Unclear risk	Limited report of outcomes, as reported only as abstract for poster presentation
Other bias	Unclear risk	Funder: not stated. Very short poster abstract

Staevska 2014

Methods	Design: prospective randomised double-blind cross-over trial Duration: 5 days
Participants	Number of participants randomly assigned: 24 Sex: 75% female Age of participants, years: mean 45, range 19 to 68 Unit of allocation: cross-over (first phase only considered) Country and setting: Bulgaria; tertiary care **Inclusion criteria of the trial** • ≥ 18 years of age • 6-week documented history of urticaria with intake of 15 to 30 mg prednisolone **Exclusion criteria of the trial** • Participants with physically induced urticaria • Pregnancy and lactation • Any chronic disease requiring daily other drug treatment including antihypertensives, antipsychotics and antidepressants • Other skin disease • Previous unresponsiveness to antihistamine: not stated
Interventions	**Interventions, dose, duration** Initial in-hospital treatment, assessment of effectiveness and tolerability of levocetirizine 10 and 20 mg vs hydroxyzine 100 and 200 mg. This was done in a double-blind fashion

	on alternate-day regimens • Levocetirizine 20 mg per day and levocetirizine 15 mg plus hydroxyzine 50 mg as evening dose for 5 days. After 5 days, participants from arm 1 and arm 2 were crossed over to the alternative treatment. No washout Length of follow-up: 5 days on each treatment Short duration of intervention (5 days) Length of follow-up: 5 days
Outcomes	Timing of outcome assessment: day 5 **Primary outcomes of the trial** • Urticaria-specific quality of life **Secondary outcomes of the trial** • Effect of the 2 regimens on urticaria symptoms • To compare the effects of the 2 regimens on urticaria symptoms (number of weals, pruritus severity) • Effect on nighttime sleep • To compare the effects of the 2 regimens on quality of nighttime sleep • Effects on daytime somnolence • To compare the effects of the 2 regimens on daytime somnolence • Effects on blood eosinophil numbers, Na^{2+}, K^{+}, ALAT, ASAT, ECG • To document the effects of treatment with higher doses of levocetirizine or hydroxyzine on blood eosinophil numbers, Na^{+}(sodium ion), K^{+}(potassium ion), ALAT (alanine transaminase), AST (aspartate transaminase), ECG (electrocardiogram) • To assess adverse events • To investigate safety by assessing the nature, incidence and severity of adverse events within treatment groups • Adverse events: not mentioned Quality of life measures: median CU-Q2oL scores Clinician or participant report: physicians calculated weal scores and severity of pruritus
Notes	Study investigators concluded that higher than standard doses of cetirizine can improve quality of life in participants discontinuing steroid treatment. Addition of hydroxyzine does not seem to provide benefit but causes increased daytime somnolence Study ID NCT01250652

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Stated to be randomised. Randomisation, ensuring balanced numbers of cases in the 2 treatment arms, was performed pair-wise at a specialised website (http://www.randomizer.org/) Comment: Exposure to study medication after randomisation to determine tolerability of medications on alternate-day regimens may have compromised randomisation through a potential carry-over ef-

Staevska 2014 (*Continued*)

		fect (insufficient washout period between phases)
Allocation concealment (selection bias)	Unclear risk	Unclear
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind: "Medication was given morning and evening in opaque gelatine capsules that were prepared by a technician who was not aware of the clinical work"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"The investigators, who were blinded to the treatment groups"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	25 participants were initially randomly assigned. 24 participants completed the study-1 withdrawal after randomisation (personal reasons)
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were reported
Other bias	Unclear risk	Funder: UCB Pharma. Short report, conference abstract

Thompson 2000 Study 1

Methods	Design: randomised multi-centre double-blind 2-arm placebo-controlled parallel study of fexofenadine vs placebo Duration: 4 weeks
Participants	Number of participants randomly assigned: 160 Sex, fexofenadine: 18% male, 72% female; placebo: 30% male, 70% female Age of participants, years: fexofenadine: 40 ± 11; placebo: 38 ± 13 Country and setting: US; secondary care Unit of allocation: participant **Inclusion criteria of the trial** • CSU, 1 to 5 weals confirmed by investigator and moderate to severe itching in last 12 hours **Exclusion criteria of the trial** • Drug/alcohol abuse, blood dyscrasia, malabsorption, malignancy, chronic infection, pregnancy/lactation, psychological disorder; cardiac, hepatic, immunological, endocrine, other major systemic disease; participants with less than moderate to severe itching in previous 12 hours, inactive urticaria • Previous unresponsiveness to antihistamine: not stated
Interventions	**Interventions, dose, duration** • Fexofenadine 60 mg twice daily for 4 weeks • Placebo twice daily for 4 weeks Duration of intervention: intermediate-term (4 weeks)

Thompson 2000 Study 1 (*Continued*)

	Length of follow-up: 4 to 6 weeks i.e. follow-up extended after the cessation of therapy
Outcomes	Timing of outcome assessment: 4 or 6 weeks **Primary outcomes of the trial** • Average change from baseline in overall DLQI score for 4- to 6-week study, percentage work or classroom productivity, percentage work/classroom time missed • Quality of life measures: significant improvement in DLQI in fexofenadine groups in both studies compared with placebo (over "4-6 week period"); in individual domains of DLQI (symptoms/feelings, daily activities, leisure, work or school, personal relations, treatment), significantly better improvement in fexofenadine achieved in both studies in symptoms/feelings, daily activities, work or school and personal relations for leisure and treatment **Secondary outcomes of the trial** • Adverse effects: not stated • Average change from baseline in individual DLQI domains, daily activity/ productivity, overall work/classroom productivity, percentage work/classroom productivity (i.e. 100%-percentage work/class time missed) • Pruritus severity scale (0 = none; 1 = mild, not annoying or troublesome; 2 = moderate, annoying/troublesome, may interfere with daily activities/sleep; 3 = severe, very annoying, substantially interfering with sleep/daily activities; 4 = very severe, warrants physician visit Clinician or participant report: Participants completed self-administered questionnaire, DLQI (score range 0-30), work productivity and activity impairment questionnaire (WPAI-0-100%, high = greater productivity) at entry, interim visit (15 ± 2 days' treatment), final visit (30 ± 4 days) or early termination
Notes	Study investigators concluded that significant differences were demonstrated in only 1 study out of 2. Increase in "work productivity," "overall work productivity," regular daily activities significantly higher in fexofenadine group compared with placebo group (both studies); no differences between groups re time missed from class/work

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomised to receive 60 mg fexofenadine HCl twice daily or placebo twice daily..."
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "24 hour single-blind placebo lead-in, and a subsequent 4-week double blind treatment period." Unclear how blinding was achieved
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "24 hour single-blind placebo lead-in, and a subsequent 4-week double blind treatment period." Unclear how blinding

Thompson 2000 Study 1 (*Continued*)

		was achieved
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No mention of whether there were drop-outs; therefore unable to corroborate ITT analyses as reported in Study 1
Selective reporting (reporting bias)	Unclear risk	Ambiguity re duration of trial, as reported methods say 4 weeks and results say 4 to 6 weeks. DLQI measures reported but not as proportions of participants with 50% or greater improvement in quality of life measurements whilst taking H1-antihistamines; therefore not possible to include DLQI data
Other bias	Unclear risk	Funder: Hoechst Marion Roussel. Study investigators report 2 identical studies in this paper; if studies identical, unclear why not combined as a single study

Thompson 2000 Study 2

Methods	Design: randomised multi-centre double-blind 2-arm placebo-controlled parallel study of fexofenadine vs placebo Duration: 4 weeks
Participants	Number of participants randomly assigned: 165 Sex: fexofenadine: 26% male, 74% female; placebo: 27% male, 77% female Age of participants, years: fexofenadine: 38 ± 13; placebo:40 ± 13 Country and setting: USA; secondary care Unit of allocation: participant **Inclusion criteria of the trial** • CSU, 1 to 5 weals confirmed by investigator and moderate to severe itching in last 12 hours **Exclusion criteria of the trial** • Drug/alcohol abuse, blood dyscrasia, malabsorption, malignancy, chronic infection, pregnancy/lactation, psychological disorder; cardiac, hepatic, immunological, endocrine, other major systemic disease; participants with less than moderate to severe itching in previous 12 hours, inactive urticaria • Previous unresponsiveness to antihistamine: not stated
Interventions	**Interventions, dose, duration** • Fexofenadine 60 mg twice daily for 4 weeks • Placebo twice daily for 4 weeks Duration of intervention: intermediate-term (4 weeks) Length of follow-up: 4 to 6 weeks i.e. follow-up extended after the cessation of therapy

Thompson 2000 Study 2 (*Continued*)

Outcomes	Timing of outcome assessment: 4 or 6 weeks **Primary outcomes of the trial** • Average change from baseline in overall DLQI score for the 4- to 6-week study, percentage work or classroom productivity, percentage work/classroom time missed • Quality of life measures: significant improvement in DLQI in fexofenadine groups in both studies compared with placebo (over "4-6 week period"); in individual domains of DLQI (symptoms/feelings, daily activities, leisure, work or school, personal relations, treatment) **Secondary outcomes of the trial** • Average change from baseline in individual DLQI domains, daily activity/ productivity, overall work/classroom productivity, percentage work/classroom productivity (i.e. 100%-percentage work/class time missed) • Pruritus severity scale (0 = none; 1 = mild, not annoying or troublesome; 2 = moderate, annoying/troublesome, may interfere with daily activities/sleep; 3 = severe, very annoying, substantially interfering with sleep/daily activities; 4 = very severe, warrants physician visit • Participants completed self-administered questionnaire, DLQI (0-30), work productivity and activity impairment questionnaire (WPAI-0-100%, high = greater productivity) at entry, interim visit (15 ± 2 days' treatment), final visit (30 ± 4 days) or early termination Clinician or participant report: participant (for QoL questionnaires) and clinician
Notes	Study investigators reported that significantly better improvement in fexofenadine was achieved in both studies in symptoms/feelings, daily activities, work or school and personal relations; for leisure and treatment, significant difference was demonstrated in 1 study out of 2 Increase in "work productivity," "overall work productivity," regular daily activities significantly higher in fexofenadine group compared with placebo group (both studies); no difference between groups re time missed from class/work

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomised to receive 60 mg fexofenadine HCl twice daily or placebo twice daily..."
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "24 hour single-blind placebo lead-in, and a subsequent 4-week double blind treatment period." Unclear how blinding was achieved
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "24 hour single-blind placebo lead-in, and a subsequent 4-week double blind treatment period." Unclear how blinding

Thompson 2000 Study 2 (*Continued*)

		was achieved
Incomplete outcome data (attrition bias) All outcomes	High risk	Study 2: number randomly assigned stated in text to be 165; in tables, total number adds up to 167; no mention of whether there were dropouts. Unable to confirm ITT numbers in study report for Study 2
Selective reporting (reporting bias)	Unclear risk	Ambiguity regarding duration of trial methods: says 4 weeks; results say 4 to 6 weeks. DLQI measures reported but not as proportions of participants with 50% or greater improvement in quality of life measurements whilst taking H1-antihistamines; therefore not possible to include DLQI data
Other bias	Unclear risk	Funder: Hoechst Marion Roussel Study authors report 2 identical studies in this paper; if studies identical, unclear why not combined as a single study

Wan 2009

Methods	Design: randomised single-blind 4-arm trial comparing a combination of sedating H1-antihistamine and non-sedating H1-antihistamine (hydroxyzine plus cetirizine); combination of H1-antihistamine and H2-antihistamine (hydroxyzine plus famotidine); and combination of H1-antihistamine and LRA (hydroxyzine plus montelukast) vs placebo Duration: 4 weeks
Participants	Number of participants randomly assigned: 120 Sex: 38% male, 62% female Age of participants, years: 31 (18-45); 36.4 (20-52); 34.8 (20-54); 33.2 (18-48) Unit of allocation: participant Country and setting: Taiwan; secondary care **Inclusion criteria of the trial** • Newly diagnosed CSU patients **Exclusion criteria of the trial** • Recent use of systemic corticosteroids or immunosuppressants • Previous unresponsiveness to antihistamine: unclear
Interventions	**Interventions, dose, duration** 1-week 'run-in' period to wash out previous antihistamine used for treatment. Randomly assigned to receive: • Oral hydroxyzine 25 mg plus cetirizine 5 mg twice a day • Oral hydroxyzine 25 mg plus famotidine 20 mg twice a day • Oral hydroxyzine 25 mg twice a day plus montelukast 5 mg twice a daily • Oral placebo twice a day Duration of intervention: intermediate-term (4 weeks)

	Length of follow-up: 4 weeks
Outcomes	Timing of outcome assessment: baseline and after 4 weeks of treatment **Primary outcomes of the trial** • Participant completed a daily record for the preceding 24 hours of the numbers of small (diameter < 3 cm) and large (> 3 cm) skin weals, according to a specific classification number, and with scoring as follows: 0 = < 10 weals; 1 = 10 to 15 small weals or < 10 large weals; and 3 = almost entirely covered with weals. Relative severity of itch was scored as follows: 0 = none; 1 = mild; 2 = moderate; 3 = severe. The possible weekly aggregate urticaria activity score (UAS) therefore ranged from 0 to 42 • Participants also provided a 10-cm visual analogue scale score from 0 (none) to 10 (worst) during each outpatient clinic visit, which indicated the overall severity of their urticaria over the previous 2 weeks. (A response to medication was defined as a reduction in weekly UAS to < 25% of baseline, and a relapse as a return to > 75% of baseline UAS) • Quality of life measures: none **Secondary outcomes of the trial** • Adverse events: serious adverse events (none reported), sedation Clinician or participant report: participant and clinician
Notes	Study investigators concluded that the combination of H1- and H2-receptor antagonists provided the greatest treatment efficacy according to the measures used in this small study

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Participants were not blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote (page 195): "The same investigating physician who was blinded to the treatment regimens saw the patient"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	107/120 randomly assigned completed the study (13 of 30 participants from placebo group dropped out after experiencing no real benefit following therapy for 1-2 weeks) Comment: All dropouts were from the placebo group, but as the reasons for this are given, we have judged the risk of bias as

Wan 2009 (*Continued*)

		low
Selective reporting (reporting bias)	Unclear risk	All prespecified outcomes were reported
Other bias	Unclear risk	Funder: Montelukast provided by manufacturer Merck Sharp Dohme

Wang 2012

Methods	Design: randomised controlled trial of mizolastine 10 mg daily for 4 weeks followed by 10 mg every other day for 4 weeks and followed by 10 mg per 3 days in the last 4 weeks for comparison with long-term mizolastine 10 mg daily for 12 weeks Duration: 12 weeks
Participants	Number of participants randomly assigned: 100 (experimental decremental dose group) ; control n = 50, long-term 10 mg mizolastine n = 50 Sex: intervention: men 27, women 23 (46% female); control group: men 28; women 22 (44% female) Age of participants, mean in years: experimental group 32.66; control group 30.86 Unit of allocation: single participants Country and setting: China; secondary care **Inclusion criteria of the trial** • Chronic Idiopathic urticaria > 6 weeks, urticaria not due to other causes, age 12 to 65 years; no history of ischaemic heart disease, liver, lung or renal dysfunction; no consumption of medication within 4 weeks or antihistamine within 1 week **Exclusion criteria of the trial** • Other type of urticaria, known to be allergic to mizolastine, pregnant or lactating women, taking other medications • Previous unresponsiveness to antihistamine: not mentioned
Interventions	**Interventions, dose, duration** • Mizolastine 10 mg daily for 4 weeks • 10 mg alternate days for 4 weeks • 10 mg every third day for 4 weeks Duration of intervention: intermediate-term (4 weeks) Length of follow-up: not mentioned Concomitant/rescue treatment permitted: not mentioned
Outcomes	Timing of outcome assessment: 4, 8, 12 weeks **Primary outcomes of the trial** • Measurement of plasma level of antihistamine (EIA), symptoms: itching severity, diameter of largest weal, number of weals per day, duration of weals (hours); clinical improvement: complete suppression, significant improvement, improvement, no change • Quality of life measures: none **Secondary outcomes of the trial** • Adverse events: dry mouth, sleepiness, lethargy Clinician or participant report: clinician

Wang 2012 (*Continued*)

Notes	Study investigators concluded that long-term decrement in mizolastine therapy is effective, safe and convenient in the treatment of chronic urticaria

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised, no details given
Allocation concealment (selection bias)	Unclear risk	No details given
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	3/50 participants in each group were lost to follow-up, no reasons given No ITT analysis carried out
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	Low risk	Funder: not stated

Weller 2013

Methods	Design: randomised double-blind parallel-group single-dose study of desloratadine 5 mg vs 20 mg desloratadine Duration: 5 hours (short-term)
Participants	Number or participants randomly assigned: n = 29 (5 mg desloratadine n = 13, 20 mg desloratadine n = 16) Sex: 5 mg desloratadine group: 9 women/4 men (64% female); 20 mg desloratadine group: 7 women/9 men (43% female) Age of participants, mean years: 5 mg desloratadine group 43.5 ± 12.9; 20 mg desloratadine group: 41.7 ± 11.3 Unit of allocation: selected body area in single participants Country and setting: Germany; Allergie-Centrum-Charité, a tertiary referral centre for allergies and urticaria **Inclusion criteria of the trial** • Chronic idiopathic urticaria > 6 weeks, outpatients, age 18 to 75 years; eligible for the study if they had moderate to severe CSU according to their clinical history, if they exhibited spontaneous urticaria lesions at the second visit for a baseline assessment (as explained below) and if they had a history of beneficial effect derived from

	antihistamine treatment **Exclusion criteria of the trial** • Presence of acute urticaria/acute angio-oedema, intake of corticosteroids or other immunosuppressive therapy within 14 days before the beginning of the study, use of depot corticosteroids or long-term systemic corticosteroids within 21 days before the beginning of the study, presence of permanent severe disease (especially disease affecting the immune system); presence of galactose intolerance, lactase deficiency or glucose galactose malabsorption; history of adverse reactions including hypersensitivity to desloratadine or loratadine • Intake of medication that could cause changes in QT interval (drugs listed on www.qtdrugs.org) • Met any criteria from a typical list of exclusion criteria for pharmacological studies: presence of a permanent gastrointestinal condition that may influence oral therapy, history or presence of epilepsy; significant neurological disorders, cerebrovascular attacks or ischaemia; history or presence of myocardial infarction or cardiac arrhythmia that requires drug therapy, evidence of severe renal dysfunction, evidence of significant hepatic disease, presence of active cancer that requires chemotherapy, presence of alcohol abuse or drug addiction, participation in any clinical trial within 4 weeks before enrolment, pregnancy or breastfeeding and existing or planned placement in an institution after ruling according to §40AMG (Arzneimittelgesetz) Mild to severe disease, duration of disease longer than 6 weeks
Interventions	**Interventions, dose, duration** • 5 mg vs • 20 mg desloratadine short-term (5 hours) Length of follow-up: after 5 hours
Outcomes	Timing of outcome assessment (state which time points): 5 hours **Primary outcomes of the trial** • Primary efficacy parameter of the study was assessment of the reduction in size of spontaneous urticaria lesions by thermography (hyperthermic skin area) before and during treatment with study medication • Quality of life measures: none **Secondary outcomes of the trial** • Additional parameters of efficacy included assessment of the reduction in size of spontaneous urticarial lesions by planimetric analysis of digital time-lapse photography, volumetric analysis of selected weals and evaluation of weal numbers • Adverse events: no serious adverse events reported Clinician or participant report: clinician
Notes	Study investigators concluded that a direct comparison between 5 mg and 20 mg of desloratadine showed no difference in weal area, weal volume or number of weals. "In contrast, a comparison of the reduction in the total weal number after 5 hours during treatment with 5 mg desloratadine minus no treatment versus treatment with 20 mg minus no treatment showed significant differences ($p < 0.01$)"
Risk of bias	

Weller 2013 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation scheme
Allocation concealment (selection bias)	Unclear risk	Unclear
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All participants and clinical staff, for example, study nurses and study physicians involved in the study, were blinded until the end of the trial
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All participants and clinical staff, for example, study nurses and study physicians involved in the study, were blinded until the end of the trial
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear whether any were lost to follow-up and any reasons No ITT analysis carried out
Selective reporting (reporting bias)	Low risk	No selective outcome reporting
Other bias	Unclear risk	Funder: This study was financially supported by Schering-Plough (Essex Pharma GmbH, Germany). In addition, the study medication was provided by Schering-Plough

Wu 2008

Methods	Design: randomised 3-arm trial of azelastine 2 mg/d; azelastine 4 mg/d vs combined azelastine and cimetidine 2 mg/d Duration: 4 weeks
Participants	Number of participants randomly assigned: 103 Sex: male 52%, female 48% (from 100 participants who were available for analysis) Unit of allocation: participant Country and setting: China; secondary care Age between 16-81 years, mean age 39.16 years **Inclusion criteria of the trial** • Chronic idiopathic urticaria > 6 weeks (duration of disease between 6 weeks and 560 weeks (mean 29 weeks), urticaria not due to other causes, no antihistamine within 4 weeks, no immunosuppressant or other medications, consented) **Exclusion criteria of the trial** • Known allergies to azelastine and cimetidine; taking medications including anticholinergic agent, beta-agonists, tranquilliser and medications that prolong QT period in less than 4 weeks; other types of urticaria and angio-oedema; taking

	medication that prolonged QT interval; high-intensity profession; other organ dysfunction diseases • Previous unresponsiveness to antihistamine: not stated
Interventions	**Interventions, dose, duration** • Azelastine 4 mg/d (n = 33) • Azelastine 2 mg/d (n = 34) • Azelastine plus cimetidine 2 mg/d (n = 33) Duration of intervention: intermediate-term (4 weeks) Length of follow-up: not specified but assumed to be at endpoint (i.e. 4 weeks)
Outcomes	**Primary outcomes of the trial** • Side effects of treatment, diameter of largest weal, number of weals per day, duration of weals (hours) • Proportion with good/excellent response • Quality of life measures: none **Secondary outcomes of the trial** • Adverse events: dry mouth, sleepiness, lethargy Clinician or participant report: clinician
Notes	Main study report written in Chinese Study investigators concluded that all 3 groups have similar efficacy, but azelastine 4 mg/d and combined azelastine and cimetidine 2 mg had greater efficacy than azelastine 2 mg alone The difference in this comparison was statistically significant (P < 0.05)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Unclear, described as open randomisation
Allocation concealment (selection bias)	High risk	No concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	103 were randomly assigned; 100 are included in the analyses with no reasons given for dropout
Selective reporting (reporting bias)	High risk	No clear definition of outcomes; unclear whether assessment of compliance was carried out

Wu 2008 (*Continued*)

Other bias	Low risk	None detected. Funder: not stated

Yin 2003a

Methods	Design: randomised double-blind parallel-group comparing cetirizine and levocetirizine Duration: 28 days
Participants	Number of participants randomly assigned: 44 (22 in each group) Sex: levocetirizine: 54% (female); cetirizine: 63% (female) Age of participants (between 18 and 65), mean in years: levocetirizine 36.27; cetirizine 36.73 Unit of allocation: participant Country and setting: China; secondary care **Inclusion criteria of the trial** • Clinical diagnosis of CSU (> 6 weeks); not taking medications within 4 weeks, such as antibiotics, immunosuppression, etc. **Exclusion criteria of the trial** • Known to have allergic reaction to H1-antihistamine, levocetirizine and cetirizine; other forms of urticaria and angio-oedema; unable to stop antihistamines such as astemizole, loratadine < 4 weeks; taking medications that can prolong QT interval; high-demand concentration job • Previous unresponsiveness to antihistamine: unclear
Interventions	**Interventions, dose, duration** • Levocetirizine 5 mg • Cetirizine 10 mg once daily Duration of intervention: intermediate-term (28 days) Length of follow-up: 7, 14, 28 days
Outcomes	Timing of outcome assessment: 7, 14, 28 days **Primary outcomes of the trial** • Severity of itching, weal size, daily weal count, degree of weal swelling, duration of weal, symptom reduction in score index • Adverse events: reported sleepiness, dry mouth, headache • Quality of life measures: none **Secondary outcomes of the trial** • None Clinician or participant report: clinician
Notes	Study investigators concluded that no significant difference in curative effect was noted between the 2 groups. No serious adverse effects were found. Levocetirizine is effective and safe in the treatment of CSU

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Yin 2003a (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Quote (page 477): 'randomised, double blinded'
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: 'randomised, double blinded,' but no further details given
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: 'randomised, double blinded,' but no further details given
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear whether any dropped out; not stated
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were reported
Other bias	Low risk	None detected. Funder: not stated

Yin 2003b

Methods	Design: randomised open-label parallel-group 3-arm comparison of mizolastine vs cetirizine vs loratadine Duration: 28 days
Participants	Number of participants randomly assigned: 96; mizolastine n = 30, cetirizine n = 34, loratadine n = 32 Sex: 60% male, 40% female Age of participants (18 to 72), mean age in years: mizolastine 45, cetirizine 38, loratadine 36.5 Unit of allocation: participant Country and setting: China; secondary care **Inclusion criteria of the trial** • CSU, but no further definitions given **Exclusion criteria of the trial** • Not stated • Previous unresponsiveness to antihistamine: unclear
Interventions	**Interventions, dose, duration** • Mizolastine 10 mg • Cetirizine 10 mg vs loratadine 10 mg, once daily each medication, for 28 days Duration of intervention: intermediate-term (28 days) Length of follow-up: 5 weeks i.e. follow-up extended after the cessation of therapy
Outcomes	Timing of outcome assessment: 14, 28 and a further follow up at 7 days post intervention **Primary outcomes of the trial** • Efficacy and safety, itching severity VAS; diameter of largest weal; number of

Yin 2003b (*Continued*)

	weals per day; symptom score reduction index (SSRI) • Quality of life measures: none **Secondary outcomes of the trial** • Adverse events: no obvious and severe side effects, but dry mouth, sleepiness, headache, nausea reported Clinician or participant report: clinician
Notes	Study investigators concluded that all 3 antihistamines have high clinical efficacy and safety in the treatment of CSU. No statically significant difference was noted among the 3 groups

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Open-label. randomised
Allocation concealment (selection bias)	High risk	No concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label, no blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open label, no blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No dropouts reported
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	Low risk	None detected. Funder: not stated

Zou 2002

Methods	Design: randomised 2-arm parallel trial of desloratadine vs loratadine Duration: 4 weeks
Participants	Number of participants randomly assigned: 41 (desloratadine n = 21, loratadine n = 20) Sex: 49% female, 51% male: desloratadine 42% female (12 men/9 women); loratadine 55% female (9 men/11 women) Age of participants, mean in years: desloratadine 32.7; loratadine 31.8 Unit of allocation: participant Country and setting: China; secondary care **Inclusion criteria of the trial** • Clinical diagnosis of CSU > 6 weeks, not taking medication within 4 weeks such as antibiotics, immunosuppression, etc.

	Exclusion criteria of the trial • Known to have allergic reaction to H1-antihistamine, loratadine and desloratadine; taking medication that is known to prolong QT interval; known chronic stomach ulcer; known ischaemic heart disease, liver disease and renal failure; occupation that requires high concentration such as driver, pilot; pregnant women and breastfeeding women
Interventions	**Interventions, dose, duration** • Desloratadine 5 mg once daily • Loratadine 10 mg once daily Duration of intervention: intermediate-term (4 weeks) Length of follow-up: not mentioned Concomitant rescue treatment not permitted
Outcomes	Timing of outcome assessment: assumed to be at end of intervention period-4 weeks **Primary outcomes of the trial** • Study of curative effects and safety of desloratadine in the treatment of CSU • Comparison of symptoms of itching severity, size of weal, weal number, weal swelling severity, frequency, duration of weal • Quality of life measures: not stated **Secondary outcomes of the trial** • Adverse events: desloratadine: severe headache, mouth dryness, sleepiness; loratadine: mouth dryness, sleepiness Clinician or participant report: participant
Notes	Study investigators concluded that no significant difference in curative effect was noted between the 2 groups. No serious adverse effects were found. Desloratadine was found to be effective and safe in treating patients with CSU

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Double-blind randomised controlled trial
Allocation concealment (selection bias)	Unclear risk	Not mentioned in this study
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Participants and personnel were blinded to treatment group Not clear about this, as it was not mentioned clearly in the method of assessment
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Outcome assessors were blinded to treatment group Not clear, as it was not mentioned in the method of assessment

Zou 2002 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No dropouts reported
Selective reporting (reporting bias)	Low risk	None, all prespecified outcomes were reported
Other bias	Unclear risk	Funder: not stated. Severity of disease was not clear. Duration of disease with desloratadine ranged from 6 weeks to 6 years, and with loratadine from 6 weeks to 6.5 years

Zuberbier 2010

Methods	Design: international multi-centre double-blind randomised placebo and active treatment-controlled parallel-group 2-arm study comparing bilastine 20 mg vs levocetirizine 5 mg once daily and placebo Duration: 28 days
Participants	Number of participants randomly assigned: 525 (bilastine n = 173, levocetirizine n = 166, placebo n = 184, unclear numbers) Sex: bilastine: 63% male, 27% female; levocetirizine: 54% male, 46% female; placebo: 40% male, 60% female Age of participants, years: bilastine 41.7, levocetirizine 39.8, placebo 39.4 Unit of allocation: participants Country and setting: Argentina, Belgium, France, Germany, Poland, Romania, Spain (46 centres); secondary care **Inclusion criteria of the trial** • "documented history of CU; characterized by erythematous skin weals accompanied by itching attributable to no identifiable cause and occurring regularly at least three times per week for 6 weeks prior to entry in the study; were recruited. Eligible patients were additionally required to demonstrate a symptoms score of ‡2 (i.e. moderate-to-severe intensity scores) for any two of the three features of pruritus, number of weals, or minimum size of weals (rated on predefined scales of 0-3) for at least 3 days during the screening period (day)7) and at randomisation visit (day 0)" **Exclusion criteria of the trial** • "contact urticaria, urticaria caused by vasculitis and/or collagenosis, paraneoplastic urticaria, parasitic urticaria, urticaria related with thyroid pathology, eczema or atopic dermatitis); autoimmune disorders, Hodgkin's disease and any clinically significant condition (cardiovascular, neurological, hepatic, renal or malignant diseases); systemic or topical corticosteroids within 4 weeks, astemizole within 6 weeks, ketotifen within 2 weeks, any other systemic antihistamine (including loratadine, desloratadine, ebastine, rupatadine, mizolastine, cetirizine or levocetirizine) within 3 days, anti-leukotrienes within 3 days, sodium cromoglycate or nedocromil within 2 weeks, and tricyclic antidepressants within 1 week of randomisation • pregnant or breast-feeding women and patients with hypersensitivity to H1-antihistamines, benzimidazoles or lactose" • Previous unresponsiveness to antihistamine: not stated

Interventions	**Interventions, dose, duration** • Bilastine 20 mg • Levocetirizine 5 mg • Placebo (once daily) Duration of intervention: intermediate-term (28 days) Length of follow-up: 28 days
Outcomes	Timing of outcome assessment: 0, 14 and 28 days (or at early discontinuation visit in cases of withdrawal from the study) **Primary outcomes of the trial** • Reflective daily total symptoms score (TSS), DLQI scores; participants' VAS scores; impact of urticaria on participant sleep scores and evaluation of symptom scores • Severity of pruritus, number of weals and maximum size of weals were assessed daily in the morning and in the evening over the last 12-hour period (reflective) and at the time of clinic visit (instantaneous), using 4-point scales of 0 to 3 (modified scale) • Pruritus severity was scored as follows: 0 = absent; 1 = mild (not annoying); 2 = moderate (causing little disruption of activity); and 3 = severe (intense itching causing disruption of activity), whereas the number of weals was scored as 0 = absent, 1 = some (≤ 10), 2 = numerous (> 10) and 3 = extensive areas of the body covered • Similarly, size of weals (diameter of the greatest weal) was scored as follows: 0 = absent, 1 = > 1.5 cm, 2 = > 1.5 to < 2.5 cm and 3 = > 2.5 cm • Quality of life measures: Dermatology Life Quality Index (DLQI) questionnaire **Secondary outcomes of the trial** • Investigator's assessment of treatment was evaluated as secondary efficacy measures • Adverse events: Safety was assessed according to adverse events, laboratory tests and electrocardiograms. No serious adverse events were noted in any of the groups • Minor adverse events: bilastine: headache, somnolence, "drug-related adverse events," fatigue; levocetirizine: headache, somnolence, "drug-related adverse events," fatigue: placebo: headache, somnolence, "drug-related adverse events," fatigue Clinician or participant report: both
Notes	Study investigators concluded that no significant difference in efficacy was noted between the 2 active groups; both were better than placebo

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Probably done; quote (page 517): "Randomization to treatment was achieved according to a computer-generated randomisation code provided by the study sponsor (FAES FARMA, SA, Spain)"
Allocation concealment (selection bias)	Unclear risk	Quote (page 518): "treatments were allocated to each patient in their chronological order of entry into the study"

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (page 518): "The study medications were supplied as identical over-encapsulated tablets in individually coded aluminium blister packs to ensure blinding of both the investigators and the patients to treatment"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	As above Comment: unclear whether investigators had access to the randomisation list, but this is unlikely given that randomisation was carried out offsite, so we have judged this as low risk
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	457/525 completed. Withdrawals as follows: placebo (n = 35): lack of efficacy 24, adverse event 1, participant decision 3, poor compliance with protocol 3, loss to follow-up 2, "other" 2; bilastine (n = 15): lack of efficacy 5, adverse event 3, participant decision 4, loss to follow-up 1, "other" 1; levocetirizine (n = 15): lack of efficacy 7; participant decision 4, poor compliance with protocol 1, loss to follow-up 2, "other" 1 Comment: Although the study report states ITT, the analysis did not include 3 participants who were randomly assigned but did not receive any medication; another 6 participants were not included in the analysis
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	Unclear risk	Funder: FAES Farma (bilastine makers). MDS Pharma Services Inc for technical assistance for development of study, data management and statistical analysis

AE: adverse event.
AEQLQ: Aerius Quality of Life Questionnaire.
ALAT: alanine transaminase.
ASAT: aspartate transaminase.
BMI: body mass index.
CIU: chronic idiopathic urticaria.
CPK: creatine phosphokinase.
CSU: chronic spontaneous urticaria.
DLQI: Dermatology Life Quality Index.

ECG: electrocardiogram.
FBC: full blood count.
ITT: intention-to-treat.
K^+: potassium ion.
LFT: liver function test.
MNW: mean number of weals.
MPS: mean pruritus score.
MTSS: mean total symptoms score.
Na^{2+}: sodium ion.
NSAID: non-steroidal anti-inflammatory drug.
QoL: quality of life.
RCT: randomised controlled trial.
SAF: safety population.
SIWS: scale for interference of wheals with sleep
SD: standard deviation.
SSRI: symptom scores reduction index.
TSS: total symptoms score.
UAS: Urticaria Activity Score.
U/E: upper extremity.
URTI: upper respiratory tract infection.
VAS: visual analogue scale.

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

Study	Reason for exclusion
Aberer 2001	Letter to editor, no study results, not an RCT
Abushareeah 1997	CIU mentioned only in abstract, not defined further, no further information available
Alomar 1990b	RCT of astemizole vs cetirizine with no placebo group, astemizole excluded as withdrawn
Andri 1993	Quote: "...randomly divided into two 15 participant groups" Unclear if this is true randomisation. Terfenadine vs cetirizine, terfenadine no longer in use
Anon 1992	RCT on astemizole
Anonymous 1989	No chronic ordinary urticaria; does not meet inclusion criteria. Only terfenadine: not in use
Anonymous 1990	CIU not defined
Anonymous 1992	CIU not defined, described only as urticaria
Arendt 1989	Included acute urticaria (less than 1 month's duration)
Atsushi 1985	Acute urticaria, not CIU
Bakos 1985	Not proper randomisation ('divididos em 2 grupos de 10')

(*Continued*)

Baraf 1976	Chronic urticaria unspecified; other causes of pruritus included
Bernd 1989	Included physical urticaria
Bernstein 1986	Astemizole (not in use)
Bernstein 2002	All participants given same combination of antihistamines
Bian 1996	Not CSU by our definition
Bleehen 1987	All participants given same H1-antihistamine
Bloom 2004	Included participants with allergic rhinitis ('All patients had allergic rhinitis or CSU')
Brunet 1990	Chronic urticaria unspecified; did not exclude physical urticaria/vasculitis
Cainelli 1986	Astemizole and terfenadine: not in use
Camarasa 2001	No definition of chronic idiopathic urticaria; methods do not state any diagnosis
Cassano 2007	Study of ciclosporin
Cerio 1984	RCT on terfenadine
Chatterjee 1996	RCT on terfenadine
Chen 2005	RCT, included other forms of urticaria
Church 2009	Chronic urticaria, not further specified
Cook 1983	No relevant data, described participants allocated to double-blind treatment in random order. Not randomised. Compared chlorpheniramine plus cimetidine (no other active treatment). No information about dose
Demaubeuge 1982	Chronic urticaria, not CSU
Devillier 2007	No clinical trials; not relevant to study
Devillier 2008	No clinical trials; review on pharmacokinetics and pharmacodynamics-not relevant to study
Dhurandhar 1987	Chronic urticaria treatment described, CSU not defined (duration of urticaria history not stated)
Diller 1983	No P values; outcome measures not meaningful
Dockx 1981	Included acute urticaria
Farshchain 2002	Quote: "Patients were divided into two 75 person-groups." Not an RCT

(*Continued*)

Ferguson 1985	Terfenadine only (not in use)
Fox 1986	Astemizole only (not in use)
Fredriksson 1986	Included conditions other than CSU
Gao 2009	RCT, included other forms of urticaria
Ge 1987	Not a comparison of H1-antihistamines
Giannetti 1991	Included acute urticaria (1 month's duration)
Gibson 1984	Included conditions other than CSU
Godse 2006	Montelukast vs cetirizine. Chronic urticaria not fully defined in terms of duration
Gong 1995	Chronic urticaria, not CSU
Gonzalez-Morales 1985	Terfenadine vs placebo
Greaves 1981	Chronic urticaria unspecified, random order administration, unclear whether randomised, self-assessment questionnaire
Greene 1985	Included other causes of urticaria (e.g. vasculitis)
Grob 2009	Compared regular vs prn desloratadine in participants known to be responsive to the drug. All participants given desloratadine, no comparison
Guaglianone 1988	Terfenadine only (not in use)
Guerra 1994	CSU not defined
Hair 2006	Review article
Hamerlinck 1994	RCT. Multi-centre parallel-group 2-arm double-blind study of loratadine vs astemizole. Astemizole no longer in use, excluded
Hampel 2010	Rhinitis and urticaria put together, no separate data
Han 1992	Terfenadine only (not in use); looking at hives, not chronic ordinary urticaria
Hong 2010	CSU not defined, no efficacy data
Honsinger 1990	Astemizole only (not in use)
Huo 2014	Acupuncture combined with bloodletting and regular Western medication (loratadine), loratadine arm not compared with active pharmacological intervention

(*Continued*)

Ishibashi 1989	Included acute urticaria
Ishibashi 1990	Included acute urticaria
Ishibashi 1990a	Included acute urticaria
Ishibashi 1990b	Included acute urticaria
Ishibashi 1997	Included acute urticaria
Ishibashi 1997a	Included acute urticaria
Ishibashi 1997b	Included acute urticaria
Isola 1985	Terfenadine only (not in use); did not use proper randomisation
Jauregui 2006	Review article specific to effects of interventions on driving
Jia 1998	Included participants with acute and chronic urticaria with no separate data (CSU not defined)
Jolliffe 1985	Included physical urticaria ('1 had cold urticaria')
Juhlin 1988	Not randomised
Jyothi 2011	Included acute urticaria
Kailasam 1987	Astemizole
Kalimo 1980	Included physical urticaria
Kalis 1985	Included physical urticaria
Kalis 1996	Included physical, cholinergic urticaria; urticaria less than 6 weeks' duration
Kameyoshi 2007	Included acute urticaria (less than 1 month's duration)
Kamide 1989	Included urticaria less than 6 weeks' duration
Kaplan 2008	Included autoimmune urticaria
Kapp 2004	Included physical urticaria
Kapp 2006	Cost-effectiveness study
Kapp 2006a	Included physical urticaria
Kawada 2011	Chronic urticaria not further specified

(*Continued*)

Kawashima 2002	Phase III study of TAU-284 (bepotastine besilate) on chronic urticaria: a multi-centre double-blind comparative study with placebo. Included urticaria of less than 1 month's duration
Khalaf 2008	Both groups received same antihistamine
Kietzmann 1990	RCT, compared only cetirizine vs terfenadine with no placebo group; therefore excluded, as terfenadine not in use
Kim 2013	Retrospective observational single-centre study of participants with CSU in Korea; 'divided patients into two study groups'
Kukita 1985	Terfenadine only (not in use)
Kukita 1990	Duration of disease less than 4 weeks (acute urticaria)
Kukita 1990a	Duration of disease less than 4 weeks (acute urticaria)
Kukita 1991	Included acute urticaria
Kukita 1994	Included acute urticaria
Kukita 1994a	Included acute urticaria
Kukita1985a	Terfenadine only (not in use)
Kuokkanen 1971	Included physical urticaria
Kuokkanen 1975	Included physical urticaria
Kuokkanen 1977	Included physical urticaria
La Rosa 2001	Included acute urticaria
Lambert 1990	Astemizole vs terfenadine (not in use)
Lambert 1993	Included acute urticaria
Lambert 1993a	Included acute urticaria
Lan 2002	Included acute urticaria with CSU, separate data not available
Lennox 2004a	Validation study of DLQI
Li 2004	CSU not defined (abstract only)
Liu 2002	RCT of astemizole vs loratadine, no placebo group. Excluded, as astemizole now withdrawn
Magerl 2009	Included physical urticaria

(*Continued*)

Magerl 2013	Randomised double-blind placebo-controlled study of safety and efficacy of miltefosine (not an H1-antihistamine) in antihistamine-resistant chronic spontaneous urticaria
Maurer 2013a	Randomised, omalizumab, not an H1-antihistamine
Meloy 2009	CSU not defined, rhinitis and urticaria combined, no separate data
Monroe 1981	Combined H1 and H2 therapy
Monroe 2005	CSU not defined, abstract only, no other details available
Monteseirin 1992	States randomly divided, but not randomised
Mora 2005	Abstract states 'randomly divided,' but translation of methods indicates that participants were 'put into groups numbered 1 to 4,' without mention of randomisation
Nakayama 1980	Included acute urticaria
Neumann 1984	Included acute urticaria (4 weeks' duration)
Nishiyama 1996	Included acute urticaria
Nsouli 2013	All participants taking same antihistamine, cetirizine
Ormerod 1986	RCT, but compared terfenadine with brompheniramine; terfenadine no longer in use, therefore excluded
Ortonne 1998	CSU not defined, mentions only chronic urticaria
Paul 1984	Chronic urticaria unspecified; no useful data
Paul 1985	Chronic urticaria unspecified
Paul 1988	Terfenadine only (not in use)
Paul 1988a	Terfenadine only (not in use)
Paul 1988b	Terfenadine only (not in use)
Paul 1989	Terfenadine only (not in use)
Paul 1989a	Included acute urticaria
Paul 1989b	RCT terfenadine
Pavic 2012	Review article: treatment in children
Peremans 1981	Included physical urticaria, excluded on that basis

(*Continued*)

Presch 1996	RCT, compared only terfenadine with cetirizine, no placebo group, terfenadine no longer in use, therefore excluded
Saihan 1983	Lack of data; study authors contacted; data not available
Salisbury 1987	Included acute urticaria
Salmun 2000	Included participants with allergic rhinitis
Sanchez-Borges 2013a	Management of aspirin-exacerbated urticaria
Sanchez-Borges 2013b	Review article on updosing
Shah 1986	Chronic urticaria unspecified
Shareeah 1998	Chronic urticaria, not CSU
Shereff 1984	CCT, not RCT
Sim-Davis 1983	Included acute urticaria (4 weeks' duration)
Simons 1995	Randomised, but pharmacology study only, no clinical outcomes
Singh 1987	Not properly randomised: medications dispensed "in random order," but unclear whether this was true randomisation. No details on number of participants in each group
Sobye 1968	Included acute urticaria (less than 1 month)
Staevska 2010	Included delayed pressure urticaria
Sussman 1991	Included physical urticaria
Taskapan 2000a	Participants were divided, not randomly assigned
Tilles 2005	Chronic urticaria, not CSU
Valsecchi 1984	Chronic urticaria, CSU not defined
Van Cauwenberge 2004	Allergic disorders; not chronic ordinary urticaria
van Joost 1989	Included acute urticaria (4 weeks' duration or less)
Vena 2002	Outcomes are histochemical only
Verhaegen 1980	Double-blind but not an RCT
Vijay 1994	RCT on astemizole

(*Continued*)

Wang 1998	Included acute urticaria
Wang 2000	Test of domestic vs imported cetirizine, randomised, but no control or placebo group. No CSU, chronic urticaria only
Warin 1966	CCT and included cholinergic urticaria
Watson 2000	Included acute urticaria
Weitgasser 1967	Other dermatoses included; not an RCT; clinical observation study
Weller 2010	Included chronic spontaneous urticaria; CSU not defined
Witte 2006	Inadequate data and reporting
Wolfram 1967	Not an RCT; included other dermatoses
Wozel 1990	Combination therapy H1 and H2; all participants took same combination
Wu 1992	Combined H1- and H2-antihistamines
Yamada 1968	Included physical urticaria, duration not specified
Youngchaiyud 1988	Chronic urticaria unspecified
Zabel 1984	Included acute urticaria (4 weeks' duration)
Zhang 1990	Chronic urticaria unspecified
Zhang 1991	RCT taking terfenadine
Zhang 2001	Included acute urticaria, no separate data
Zhao 1994	RCT of loratadine vs astemizole (not in use), no placebo group
Zhi 2004	CSU duration of less than 4 weeks included (i.e. acute urticaria included)
Zhou 2003	Described as 'chronic urticaria' but CIU not defined; also included acute urticaria with no separate data
Zuberbier 1995	Cholinergic urticaria

CCT: controlled clinical trial.
CIU: chronic idiopathic urticaria.
DLQI: Dermatology Life Quality Index.
RCT: randomised controlled trial.

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

Audi'cana 2007

Methods	Double-blind randomised dose-ranging trial in 4 parallel groups
Participants	CSU, number randomly assigned unclear
Interventions	10, 20 and 30 mg bilastine once daily vs placebo
Outcomes	Unclear
Notes	Unable to locate a copy at this time for further assessment

Blanca Gomez 1984

Methods	Double-blind (CCT?)
Participants	Unclear
Interventions	H1- plus H2-blockers
Outcomes	Unclear, included pruritus
Notes	Unable to locate a copy at this time for further assessment

Boggs 1989

Methods	RCT (double-blind randomised placebo-controlled parallel study)
Participants	37 participants
Interventions	Terfenadine, 60 mg twice daily, vs placebo vs hydroxyzine, 25 mg four times daily
Outcomes	Adverse effects including somnolence, therapeutic use
Notes	Unable to locate a copy at this time for further assessment

Fan 2000

Methods	RCT
Participants	Urticaria
Interventions	Astemizole and loratadine
Outcomes	Unclear

Fan 2000 (*Continued*)

Notes	Unable to locate a copy at this time for further assessment

Feng 2001

Methods	Design: unclear, states 'random allocation'
Participants	Unclear, no abstract available
Interventions	Unclear, includes cetirizine but no details about comparator arms
Outcomes	Unclear
Notes	Unable to locate a copy at this time for further assessment

Guo 2013

Methods	RCT (randomly divided into 3 groups)
Participants	One hundred and twenty cases of chronic urticaria
Interventions	38 participants in the combination therapy group orally received half pack of compound FKS decocted in water twice daily and mizolastine tablet 10 mg once daily; 39 participants orally received mizolastine tablet 10 mg once daily; 38 patients in the combination therapy group orally received half pack of compound FKS decocted in water twice daily and mizolastine tablet 10 mg once daily; 39 participants orally received mizolastine tablet 10 mg once daily for 4 weeks
Outcomes	Efficacy, scores of symptoms and signs, improvement.
Notes	Chinese language study; awaiting copy of paper and translation

Guo 2014

Methods	RCT (randomly divided)
Participants	209 participants were randomly divided into 2 groups: experimental group (106 cases) and control group (103 cases)
Interventions	One arm given mizolastine and ketotifen with gradual dose reduction for 10 weeks, while the other participants were given mizolastine alone with gradual dose reduction for 10 weeks
Outcomes	Total effective rates for experimental group and control group were 76.1% and 43.5%, respectively (P value < 0. 05). 4 weeks after treatment, recurrence rates for experimental group and control group were 10.4% and 22.8%, respectively (P value < 0.05). Adverse effects included dry mouth and drowsiness
Notes	Chinese language study awaiting copy of paper and translation

Hatano 1981

Methods	RCT or CCT, double-blind
Participants	121 participants with chronic urticaria
Interventions	Azatadine maleate 2 mg/d (1 mg/tablet) was administered for 5 days to 61 participants with chronic urticaria, and clemastine fumarate 2.68 mg/d (1.34 mg/tablet) was given to a matched control group of 60 participants
Outcomes	Efficacy, itching, adverse effects
Notes	Unable to locate a copy at this time for further assessment

Monroe 1992a

Methods	RCT
Participants	203 participants with chronic idiopathic urticaria
Interventions	Loratadine, hydroxyzine and placebo
Outcomes	Efficacy and safety
Notes	Unable to locate a copy at this time for further assessment

Okubo 2013

Methods	Prospective randomised non-blinded comparative clinical study and assessment of quality of life
Participants	n = 51
Interventions	Cetirizine 10 mg once daily to 51 participants with urticaria. Participants with inadequate symptom control were randomly assigned to cetirizine 20 mg once daily (dose-increase group) or olopatadine 5 mg twice daily (drug-change group)
Outcomes	Severity of weal and itching and quality of life (QoL) were measured by Skindex-16 were evaluated
Notes	Awaiting interlibrary loan and, if available, full translation

Sil 2013

Methods	Observer-blind RCT, single centre
Participants	Chronic urticaria, characterised by frequent appearance of weals for > 6 weeks
Interventions	Olopatadine (5 mg twice daily) or levocetirizine (5 mg/d) for 9 weeks, continuously for first 4 weeks and then on demand basis for last 5 weeks

Sil 2013 (*Continued*)

Outcomes	Primary outcome measures were Urticaria Activity Score (UAS) and urticaria total severity score (TSS). Routine haematological and biochemical tests and treatment-emergent adverse events were monitored for safety
Notes	Awaiting interlibrary loan

Tanizaki 2013

Methods	Unclear
Participants	CSU and healthy participants
Interventions	Conventional and double doses of fexofenadine HCl on CSU (and on histamine-induced skin responses by iontophoresis using visual and laser Doppler imaging scales in healthy donors)
Outcomes	Cutaneous manifestations in CSU (and histamine-induced flare and itch in healthy donors)
Notes	Awaiting interlibrary loan

Wang 2002

Methods	RCT
Participants	Urticaria
Interventions	Mizolastine vs cyproheptadine
Outcomes	Unclear
Notes	Unable to locate a copy at this time for further assessment

Zhang 2012

Methods	RCT
Participants	136 participants with chronic idiopathic urticaria
Interventions	Randomly assigned to 3 groups: mizolastine 10 mg daily; loratadine 10 mg daily; mizolastine 10 mg daily combined with compound glycyrrhizin 75 mg 3 times a day
Outcomes	Symptom score reduction index (SSRI)
Notes	Awaiting interlibrary loan and, if available, full translation

Zhang 2013

Methods	RCT
Participants	92 participants with refractory urticaria
Interventions	Montelukast combined with cetirizine, and control group with *Tripterygium* glycoside combined with cetirizine
Outcomes	Total symptoms scores were calculated for participants at baseline and at week 2 and week 4 during treatment based on individual scores for weal and pruritus; incidence of adverse events was recorded
Notes	Chinese language study awaiting translation

Zhu 2012

Methods	RCT
Participants	120 mixed group of acute/chronic urticaria with allergic rhinitis
Interventions	Mizolastine vs cetirizine
Outcomes	Therapeutic effect and adverse reactions
Notes	Awaiting interlibrary loan and, if available, full translation

CCT: controlled clinical trial.
CSU: chronic spontaneous urticaria.
QoL: quality of life.
RCT: randomised controlled trial.
SSRI: symptom score reduction index.
TSS: total severity score.
UAS: Urticaria Activity Score.

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

CTRI/2014/04/004545

Trial name or title	Comparison of efficacy, safety and cost-effectiveness of rupatadine and olopatadine, antihistaminics, in study participants with urticaria
Methods	To compare efficacy, safety and cost-effectiveness of rupatadine and olopatadine in participants with chronic idiopathic urticaria: a randomised double-blind comparative parallel-group study Method of generating randomisation sequence: random numbers table Method of allocation concealment: prenumbered or coded identical containers Blinding and masking: participant and Investigator blinded

CTRI/2014/04/004545 (*Continued*)

Participants	Target sample size 60, with CSU **Inclusion criteria** • Those who were willing to participate in the study and comply with its procedures by signing a written informed consent • Participant from Out-patient Department (OPD) of dermatology between ages of 18 and 65 years, of either sex • History of urticarial weal and/or angio-oedema for at least 3 days a week for 6 consecutive weeks with no obvious cause before inclusion in study • Mean total symptoms score (24 hours reflective) at screening. This includes 1 to 5 weals; at least moderate severity of pruritus • Participants who were taking any antihistamines except rupatadine and olopatadine were also included in the trial only after a washout period of 7 days, irrespective of doses of previous drugs • Those who understood and agreed to adhere to dosing and visit schedules, and agreed to assess and record their symptom severity scores, medication times, concomitant medications and adverse events accurately and consistently in a daily diary **Exclusion criteria** • History of asthma or any other disease requiring long-term use of inhaled or systemic corticosteroids • Participants with acute spontaneous urticaria or all physical and other subtypes of urticaria such as aquagenic, cholinergic, contact and exercise-induced urticaria • Had been unresponsive to antihistamine treatment in the past • History of allergies to study medication or unable to tolerate antihistamines • Use of study drug in the last 7 days before baseline and not willing to take washout period • Pregnant female, nursing mothers • Participants with significant hematopoietic, cardiovascular, hepatic, renal, neurological, psychiatric or autoimmune disease
Interventions	• Olopatadine 5 mg once a day at night for 6 weeks • Rupatadine 10 mg once a day at night for 6 weeks
Outcomes	**Primary outcomes assessed at 1, 3 and 6 weeks** • Efficacy of rupatadine and olopatadine in participants with CSU • Difference in mean total symptoms score (MTSS) at baseline and at 6 weeks • Observed difference in average mean number of weals (MNW), mean pruritus scale (MPS) and MTSS from baseline to end of 1, 3 and 6 weeks **Secondary outcomes assessed at 1, 3 and 6 weeks** • Average change from baseline to end of 6-week treatment period • 12-hour reflective MNW • 2-hour reflective MPS • Interference of weals with sleep • Observed difference in scale for interference of skin condition with sleep (SIWS) between baseline and 6 weeks
Starting date	17 April 2014
Contact information	Dr Ganesh N Dakhale Department of Pharmacology, Government Medical College, Nagpur. 440003 Nagpur, MAHARASHTRA India 8308833593 gndakhle@rediffmail.com

CTRI/2014/04/004545 (*Continued*)

	Government Medical College Nagpur, India
Notes	Other study ID CTRI/2014/04/004545, ongoing, sponsored by Indira Gandhi Government Medical College, India

EudraCT: 2004-000771-34

Trial name or title	A 6-week multi-centre double-blind randomised placebo-controlled parallel-group study to assess the efficacy and safety of rupatadine 10 and 20 mg in the treatment of chronic idiopathic urticaria (CIU): a phase III clinical trial
Methods	RCT
Participants	Male or female 12 to 65 years of age
Interventions	• Rupatadine 10 and 20 mg for the treatment of CSU symptoms over 4-week treatment period • Placebo
Outcomes	**Primary outcomes:** Primary endpoint will be based on daily subjective assessment of the severity of each symptom of CSU, as recorded by participants in their diaries: • Change in mean pruritus score (MPS) over 4-week treatment period **Secondary outcomes** • Efficacy and safety of rupatadine 10 and 20 mg for the treatment of CSU symptoms over 6-week treatment period in comparison with placebo • Safety of rupatadine 10 and 20 mg for the treatment of CSU symptoms over 4-week treatment period in comparison with placebo • Participant discomfort assessed by using a VAS • Participant QoL assessed by a specific questionnaire, the DLQI
Starting date	2004-10-28
Contact information	J Uriach y Compañía, S.A.
Notes	Ongoing

EudraCT: 2005-002749-38

Trial name or title	A randomised double-blind placebo-controlled exploratory trial to evaluate 1-week oral treatment with R129160 (60 mg twice daily) in participants with chronic idiopathic urticaria-oral treatment with R129160 (60 mg twice daily) in participants with chronic idiopathic urticaria
Methods	RCT
Participants	Male and female 18 to 64 years of age with CSU, Czech Republic, Belgium, Netherlands
Interventions	• 60 mg R129160 (vapitidine) • Placebo

EudraCT: 2005-002749-38 (*Continued*)

Outcomes	**Primary outcomes** • Effect on itch associated with CSU
Starting date	18 July 2007
Contact information	Barrier Therapeutics nv
Notes	Not recruiting, no results posted

JPRN-UMIN000001163

Trial name or title	Study of optimal treatment duration with antihistamine in idiopathic urticaria patients
Methods	Parallel cluster-randomised by institution, open. Allocation concealment by centralised registration
Participants	120 (target sample size). Male or female 20 years of age or older **Inclusion criteria** • Participants with idiopathic urticaria • Symptoms/signs free of urticaria for at least 48 hours at randomisation • Symptom/signs resolved in the period of 2 to 6 weeks from onset of urticaria • Not younger than 20 years old (no upper limit) • Written informed consent **Exclusion criteria** • Pregnant or lactating women or women of childbearing potential not using contraception • Participants with a history of hypersensitivity to fexofenadine hydrochloride • Participants who use medications that interfere with efficacy evaluation (e.g. other antihistamines, drugs with antiallergy action, systemic steroids) • Others whom the physician judges are not suitable
Interventions	4 week treatment with fexofenadine (120 mg/d) vs no treatment
Outcomes	**Primary outcomes** • Cumulative recurrence rate at 3 months after relief of urticaria symptoms (signs) **Secondary outcomes** • Cumulative recurrence rate at 4 and 8 weeks after relief of urticaria symptoms (signs) • Safety
Starting date	23 May 2008
Contact information	Motoaki Inoue Clinical Research Support Center Kyusyu Secretariat 3-1-1 Umade, Higashi-ku Fukuoka, 812-8582 +81-92-631-2920 http://www.cres-kyusyu.or.jp inoue@cres-kyushu.or.jp

JPRN-UMIN000001163 (*Continued*)

Notes	Also known as SOLIDARITIE. Closed, no results posted Sponsored by West Japan Urticaria Therapy Study Group, Clinical Research Support Center Kyusyu

JPRN-UMIN000003290

Trial name or title	A study of the antipruritic effect and onset of sleepiness with oral antihistamines. Comparison of sedative and non-sedative antihistamine
Methods	Randomised cross-over open allocation concealment by numbered containers
Participants	Male and female 16 years of age and older **Inclusion criteria** • Diagnosed with atopic dermatitis, chronic urticaria and pruritus • Participants who were scored NRS 3 and over for pruritus • Participants who gave their written informed consent **Exclusion criteria** • Participants who have history of hypersensitivity to any of the study drugs • Participants who had been taking an antihistamine drug within 7 days before registration • Participants who are pregnant, might be pregnant, are lactating or are wishing a pregnancy during the study period • Participants who are complaining of sleepiness due to the influence of a regularly used drug that is not an antihistamine • Participants who are commonly complaining of intense sleepiness • Participants who are considered unsuitable for this study by the investigator
Interventions	• Bepotastine besilate (14 days), washout (7 days) and d-chlorpheniramine maleate or ketotifen (14 days) • d-chlorpheniramine maleate or ketotifen (14 days), washout (7 days) and bepotastine besilate (14 days).
Outcomes	**Primary outcomes** • Incidence and severity of sleepiness (JESS score, a Japanese version of the Epworth Sleepiness Scale) **Secondary outcomes** • NRS scoring for pruritus • NRS scoring for sleepiness • QoL with relation to skin diseases (Skindex-16) • Evaluation of severity of atopic dermatitis and evaluation of severity of pruritus in other skin diseases • Safety
Starting date	3 May 2005
Contact information	Hiramatsu Yusunari Future Medical Research Institute LLC Japan hiramatsu@ebms.co.jp Telephone: 03-5777-1001 EBMs Co, Ltd Clinical Business Division

JPRN-UMIN000003290 (*Continued*)

Notes	Sponsored by Non-Profit Organization Health Institute Research of Skin Closed, no results posted

JPRN-UMIN000008062

Trial name or title	A study evaluating efficacy of non-sedative antihistamine up-titration in patients with chronic urticaria who did not respond to standard therapy
Methods	Parallel randomised
Participants	Male and female 16 years of age and older **Inclusion criteria** • Participants who have been diagnosed with chronic urticaria (unclear if meeting definition of CSU) • Participants with urticaria with a severity level of 3 or higher according to "Guidelines for the Diagnosis and Treatment of Urticaria and Angioedema" after treatment with oral bepotastine besilate for 2 weeks • Participants who received an explanation of the study details and signed a written consent form • Participants 16 years of age or older at the time of registration. For those younger than 20 years, their guardians must also have signed the consent form **Exclusion criteria** • Participants with a known allergy to any component of the study drug • Pregnant or possibly pregnant women, or breastfeeding women. Women who wish to become pregnant during study participation • Participants who are judged inappropriate to participate in the study by the investigator
Interventions	• 14 days of treatment with bepotastine besilate (20 mg twice daily) • 14 days of treatment with bepotastine besilate (10 mg twice daily)
Outcomes	**Primary outcomes** • Improvement in the degree of itching in the daytime and at nighttime **Secondary outcomes** • Improvement in the duration of rash • Improvement in the degree of skin eruption (erythema, weal, area/extent) • Change in QoL (Skindex-16) • Overall improvement rating (degree of skin eruption, degree of itching) • Degree of satisfaction regarding efficacy • Safety
Starting date	1 June 2012
Contact information	Sayumi Hasegawa World Trade Center Bldg 24F 2-4-1, Hamamatsu-cho, Minato-ku, Tokyo 105-6124 Japan, Japan hasegawa@ebms.co.jp EBMs Co, Ltd Business Strategy Division
Notes	Completed, no results posted Funder: non-profit organisation, Health Institute Research of Skin

JPRN-UMIN000008461

Trial name or title	A study on the optimal treatment for chronic idiopathic urticaria insufficient for the second-generation antihistamines
Methods	Parallel, randomised, open
Participants	Male and female 20 years of age or older. **Inclusion criteria** • Participants with idiopathic chronic urticaria > level 2 **Exclusion criteria** • Participants with cholinergic urticaria, pregnant women, etc.
Interventions	Antihistamines (details unclear)
Outcomes	**Primary outcomes** • Efficacy
Starting date	1 April 2011
Contact information	Tamotsu Ebihara 35 Shiannomachi Shinjuku-ku Tokyo, JAPAN, Japan ebitamo@yahoo.co.jp Keio University School of Medicine, Department of Dermatology
Notes	Ongoing, recruiting Sponsored by Keio University School of Medicine

JPRN-UMIN000010265

Trial name or title	Preliminary trial of the increase in antihistamines in dose and a combination of different antihistamines for refractory spontaneous urticaria
Methods	Open parallel-group randomised allocation concealed by numbered containers
Participants	Target of 32 participants with idiopathic urticaria (definition and duration not stated), male or female 20 years of age or older **Inclusion criteria** • Adult participant with spontaneous urticaria • Without reduction in daily urticaria scores of 4 or more over 3 days or longer, after 7 days of treatment with 5 mg/d levocetirizine. Or with reductions in daily urticaria score of 1 or more in 3 days or more, out of 7 days, by taking levocetirizine 5 mg/d, and with daily urticarial score 4 or more in the last 3 days of the subsequent 1 week of treatment • Granted permission with written informed consent • Able to score daily urticaria activities according to the formatted urticaria diary. • Agreed to revisit the clinic for evaluation **Exclusion criteria** • History of drug allergy • Pregnant or lactating • Glaucoma, hyper-intraocular pressure or inferior urinary tract obstruction

JPRN-UMIN000010265 (*Continued*)

	• Hyperthyroidism or any cardiovascular disease • Stegnotic gastrointestinal ulceration or pylorus stegnosis • Taking central nervous depressant, alcohol, MAO inhibitor or anticholine agent • Disease that discourages taking of anticholinergic drugs or antihistamines • High renal or liver damage • Decreased cognitive ability or comprehension. • History of taking antileukotriene or H2-blocker within 2 weeks before agreement • History of taking steroids by topical application or injection within 4 weeks before agreement • Occupation driving or operating machines • Any participants evaluated as inadequate by physicians.
Interventions	• Levocetirizine 10 mg once daily • Levocetirizine 5 mg/d and chlorpheniramine maleate 4 mg daily
Outcomes	**Primary outcomes** • Rate of complete response **Secondary outcomes** • Days symptom free • Change in symptom scores during treatments • Sleepiness
Starting date	1 April 2013
Contact information	Takuma Kohsaka Hiroshima University Hospital Department of Dermatology 1-2-3, Kasumi, Minami-ku, Hiroshima, 734-8551 +81-82-257-5237 takumuchi0116@yahoo.co.jp
Notes	Sponsored by Hiroshima Univeristy, and funded by GlaxoSmithKline, ongoing, completing 31 March 2015

NCT00199238

Trial name or title	A 4-week dose-finding multi-centre double-blind randomised placebo-controlled parallel-group trial to assess the efficacy and safety of different doses of rupatadine compared with placebo in the treatment of chronic idiopathic urticaria
Methods	RCT
Participants	Male and female 12 to 65 years of age with CSU
Interventions	• Rupatadine • Placebo
Outcomes	**Primary outcomes** • Efficacy measure of each treatment will compare the frequency and severity of symptoms of CSU as measured by the participant in terms of change in mean pruritus score (MPS) over the 4-week treatment

NCT00199238 (*Continued*)

	period **Secondary outcomes** • Change from baseline over 4-week treatment period in the mean number of weals (MNW) score • Mean total symptoms score (MTSS), calculated as sum of MPS (mean pruritus symptoms) • MNW scores and interference with sleep and daily activities due to urticaria symptoms • Criteria for evaluation (safety): adverse effects, laboratory tests and vital signs
Starting date	October 2002
Contact information	Eva Arnaiz, PhD, J Uriach y Compania
Notes	Terminated, no study results posted

NCT00199251

Trial name or title	A 6-week multi-centre double-blind randomised placebo-controlled parallel-group study to assess the efficacy and safety of rupatadine 10 and 20 mg in the treatment of chronic idiopathic urticaria (CIU): a phase III clinical trial
Methods	RCT
Participants	Male and female 12 to 65 years of age with CSU
Interventions	• Rupatadine 10 mg and 20 mg • Placebo
Outcomes	**Primary outcomes** • Frequency and severity of symptoms of CSU as measured by the participant in terms of change in mean pruritus score (MPS) over the 4-week treatment period **Secondary outcomes** • Change from baseline over the 4- and 6-week treatment period in mean number of weals (MNW) score • Mean total symptoms score (MTSS), calculated as the sum of the MPS (mean pruritus symptoms) and MNW (mean number of weals) scores • Severity of symptoms of CSU as measured by the participant in terms of change in MPS over the 6-week treatment period, using a visual analogue scale (VAS) • Quality of life (QoL), which will be assessed by the Dermatology Life Quality Index (DLQI) • Safety: ECGs baseline and final visit; clinical laboratory controls, physical examination, incidence of adverse events
Starting date	April 2004
Contact information	J Uriach and Company
Notes	Terminated, no study results posted Other study ID IC010RUP304

NCT00421109

Trial name or title	Double-blind, randomised, placebo-controlled, phase III study comparing the efficacy and safety of bilastine 20 mg once daily and levocetirizine 5 mg for the treatment of chronic idiopathic urticaria
Methods	RCT
Participants	Male and female 18 to 70 years of age with CSU
Interventions	• Bilastine 20 mg and levocetirizine 5 mg (once daily) • Placebo
Outcomes	**Primary outcomes** • Change from baseline in the AM/PM total symptoms score (TSS3) over 28 days of the treatment period according to participant's assessment on the diary card (reflective symptoms)
Starting date	July 2006
Contact information	Faes Farma, S.A. Principal Investigator: Olmos, MD Hosp Clinico San Carlos, Servicio Dermatologia (Madrid, Spain) Principal Investigator: De Weert, MD Uz Gent/De Pintelaan 185 (Belgium) Principal Investigator: Dubertret, MD Hopital St Louis/Sce Dermatologie/1 Av Claude Vellefaux (Paris, France) Principal Investigator: Simon, MD Univ Klinikum Leipzig/Klinik Für Dermatologie (Germany) Principal Investigator: Kapinska-Mrowiecka, MD Szpital Specjalistyczny Im S Zeromskiego/Oddzial Dermatologii/Os Mlodosci 11 (Krakow, Poland) Principal Investigator: Benea, MD Spit Clin Dermato-Venero, Prof Dr/Scarlat Longhin/alea Serban Voda 216, Sector4 (Bucharest, Romania) Principal Investigator: Herrero, MD Consultorio De Alergia 1° Piso/Hospital Juan A. Fernandez/Cervino 3355 (Buenos Aires, Argentina)
Notes	Completed July 2007 (final data collection date for primary outcome measure), no study results posted Other study IDs EudraCT 2006-001245-33, BILA 2006/UCI

NCT00751166

Trial name or title	A comparative double-blind double-dummy study of desloratadine (dl) 5 mg once daily, cetirizine 10 mg once daily and placebo once daily in patients with chronic idiopathic urticaria (CIU)
Methods	RCT
Participants	Male and female 12 to 70 years of age with CSU
Interventions	• Desloratadine 5 mg once daily • Cetirizine 10 mg once daily • Placebo
Outcomes	**Primary outcomes** • Efficacy of study treatments with respect to change from baseline in average AM/PM 12-hour reflective pruritus severity score (diary recordings)

NCT00751166 (*Continued*)

Starting date	March 2004
Contact information	Schering-Plough
Notes	Terminated May 2005, no study results posted. Study terminated, as could not be resupplied with study medication in a timely manner Other study ID P03736

NCT00751218

Trial name or title	A comparative double-blind double-dummy study of desloratadine (dl) 5 mg once daily, cetirizine 10 mg once daily and placebo once daily in patients with chronic idiopathic urticaria (CIU)
Methods	RCT
Participants	Male and female 12 to 70 years of age with CSU
Interventions	• Desloratadine 5 mg once daily • Cetirizine 10 mg once daily • Placebo
Outcomes	**Primary outcomes** • Efficacy of study treatments with respect to change from baseline in the average AM/PM 12-hour reflective pruritus severity score (diary recordings) after the first 7 days of treatment
Starting date	May 2004
Contact information	No contacts or locations posted, Schering-Plough
Notes	Terminated August 2005, no study results posted Other study ID P03735

NCT00783354

Trial name or title	A pilot multi-centre double-blind randomised study for comparison of Aerius® "Continuous Treatment" versus Aerius® "PRN Regimen" on chronic idiopathic urticaria patient quality of life
Methods	RCT
Participants	Male and female over 18 years of age with CSU
Interventions	• Desloratadine • Placebo
Outcomes	**Primary outcomes** • Changes from Visit 2 to Visit 4 in Vq-Derm Questionnaire score • DLQI quality of life score

NCT00783354 (*Continued*)

Starting date	April 2003
Contact information	Head, Clinical Trials Registry & Results Disclosure Group, Schering-Plough
Notes	Known as ATTITUD. Completed April 2004, no study results posted Other study ID P03147

CIU: chronic idiopathic urticaria.
CSU: chronic spontaneous urticaria.
DLQI: Dermatology Life Quality Index.
MAO: monoamine oxidase.
MNW: mean number of weals.
MPS: mean pruritus scale.
MTSS: mean total symptoms score.
NRS: numerical rating scale
OPD: Out-patient Department.
QoL: quality of life.
SIWS: scale for interference of wheals with sleep
VAS: visual analogue scale.

DATA AND ANALYSES

Comparison 1. Loratadine 10 mg versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Proportion of participants with 'good' or 'excellent' response whilst taking H1-antihistamines	2	124	Risk Ratio (M-H, Random, 95% CI)	1.86 [0.91, 3.79]
1.1 Short-term duration of intervention (10 mg)	1	12	Risk Ratio (M-H, Random, 95% CI)	3.0 [0.42, 21.30]
1.2 Intermediate-term duration of intervention (10 mg)	1	112	Risk Ratio (M-H, Random, 95% CI)	1.73 [0.81, 3.72]

Comparison 2. Loratadine 10 mg versus cetirizine 10 mg

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Proportion of participants with complete suppression of urticaria whilst taking H1-antihistamines	2	103	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.76, 1.43]
1.1 Short-term duration of intervention	1	37	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.64, 2.01]
1.2 Intermediate-term duration of intervention	1	66	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.69, 1.47]

Comparison 3. Loratadine 10 mg versus desloratadine 5 mg

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Proportion of participants with complete suppression of urticaria whilst taking H1-antihistamines	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Intermediate-term duration of intervention	2	369	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.78, 1.06]

2 Proportion of participants with 'good' or 'excellent' response whilst taking H1-antihistamines	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Intermediate-term duration of intervention	3	410	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.64, 1.71]

Comparison 4. Loratadine 10 mg versus mizolastine 10 mg

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Proportion of participants with complete suppression of urticaria whilst taking H1-antihistamines	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Intermediate-term duration of intervention	3	316	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.64, 1.16]
2 Proportion of participants with 'good' or 'excellent' response whilst taking H1-antihistamines	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Intermediate-term duration of intervention	3	314	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.55, 1.42]
3 Proportion of participants with at least 50% improvement in QoL whilst taking H1-antihistamines	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 Intermediate-term duration of intervention	2	252	Risk Ratio (M-H, Random, 95% CI)	3.21 [0.32, 32.33]
4 Serious adverse events (i.e. serious enough to require withdrawal of treatment)	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 Intermediate-term duration of intervention	2	267	Risk Ratio (M-H, Random, 95% CI)	0.38 [0.04, 3.60]

Comparison 5. Loratadine 10 mg versus emedastine 2 mg

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Proportion of participants with complete suppression of urticaria whilst taking H1-antihistamines	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.1 Intermediate-term duration of intervention	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

2 Proportion of participants with good or excellent response whilst taking H1-antihistamines	1	Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 Intermediate-term duration of intervention	1	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3 Serious adverse events (i.e. serious enough to require withdrawal of treatment)	1	Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3.1 Intermediate-term duration of intervention	1	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Comparison 6. Loratadine 10 mg versus hydroxyzine 25 mg

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Proportion of participants with complete suppression of urticaria whilst taking H1-antihistamines	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.1 Short-term duration of intervention	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Comparison 7. Cetirizine 10 to 20 mg versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Proportion of participants with complete suppression of urticaria whilst taking H1-antihistamines	2	178	Risk Ratio (M-H, Random, 95% CI)	2.72 [1.51, 4.91]
1.1 Short-term duration of intervention (cetirizine 10 mg)	1	56	Risk Ratio (M-H, Random, 95% CI)	2.8 [1.17, 6.73]
1.2 Intermediate-term duration of intervention (cetirizine 10 mg)	1	122	Risk Ratio (M-H, Random, 95% CI)	2.66 [1.20, 5.90]
2 Serious adverse events (i.e. serious enough to require withdrawal of treatment)	3	389	Risk Ratio (M-H, Random, 95% CI)	3.00 [0.68, 13.22]
2.1 Intermediate-term duration of intervention (cetirizine 10 mg)	2	247	Risk Ratio (M-H, Random, 95% CI)	4.60 [0.79, 26.67]

2.2 Intermediate-term duration of intervention (cetirizine 10 to 20 mg)	1	142	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.07, 16.59]

Comparison 8. Cetirizine 10 mg versus hydroxyzine 25 mg

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Serious adverse events (i.e. serious enough to require withdrawal of treatment)	2	261	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.25, 2.45]
1.1 Intermediate-term duration of intervention (cetirizine 10 mg)	1	123	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.27, 4.01]
1.2 Intermediate-term duration of intervention (cetirizine 5 to 25 mg)	1	138	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.04, 3.13]

Comparison 9. Desloratadine 5 to 20 mg versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Proportion of participants with complete suppression of urticaria whilst taking H1-antihistamines	2		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.1 Short-term duration of intervention (desloratadine 5 mg)	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 Short-term duration of intervention (desloratadine 10 mg)	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.3 Short-term duration of intervention (desloratadine 20 mg)	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.4 Intermediate-term duration of intervention (desloratadine 5 mg)	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 Serious adverse events (i.e. serious enough to require withdrawal of treatment)	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Intermediate-term duration of 5 mg of intervention	3	466	Risk Ratio (M-H, Random, 95% CI)	1.46 [0.42, 5.10]

Comparison 10. Hydroxyzine 25 mg versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Serious adverse events (i.e. serious enough to require withdrawal of treatment to withdrawal)	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Intermediate-term duration of intervention	2	270	Risk Ratio (M-H, Random, 95% CI)	3.64 [0.77, 17.23]

Comparison 11. Levocetirizine 5 to 20 mg versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Proportion of participants with complete suppression of urticaria whilst taking H1-antihistamines	2		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.1 Short-term duration of intervention (levocetirizine 5 mg)	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 Short-term duration of intervention (levocetirizine 10 mg)	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.3 Short-term duration of intervention (levocetirizine 20 mg)	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.4 Intermediate-term duration of intervention (levocetirizine 5 mg)	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Comparison 12. Rupatadine 10 to 20 mg versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Proportion of participants with 'good' or 'excellent' response whilst taking H1-antihistamines	1	245	Risk Ratio (M-H, Random, 95% CI)	1.35 [1.03, 1.77]
1.1 Intermediate-term duration of intervention (rupatadine 10 mg)	1	122	Risk Ratio (M-H, Random, 95% CI)	1.28 [0.86, 1.91]

1.2 Intermediate-term duration of intervention (rupatadine 20 mg)	1	123	Risk Ratio (M-H, Random, 95% CI)	1.42 [0.98, 2.06]

Analysis 1.1. Comparison 1 Loratadine 10 mg versus placebo, Outcome 1 Proportion of participants with 'good' or 'excellent' response whilst taking H1-antihistamines.

Review: H1-antihistamines for chronic spontaneous urticaria

Comparison: 1 Loratadine 10 mg versus placebo

Outcome: 1 Proportion of participants with 'good' or 'excellent' response whilst taking H1-antihistamines

Study or subgroup	Loratadine n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Short-term duration of intervention (10 mg)					
Monroe 1992	3/6	1/6		13.2 %	3.00 [0.42, 21.30]
Subtotal (95% CI)	**6**	**6**		**13.2 %**	**3.00 [0.42, 21.30]**
Total events: 3 (Loratadine), 1 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.10 (P = 0.27)					
2 Intermediate-term duration of intervention (10 mg)					
Belaich 1990	16/60	8/52		86.8 %	1.73 [0.81, 3.72]
Subtotal (95% CI)	**60**	**52**		**86.8 %**	**1.73 [0.81, 3.72]**
Total events: 16 (Loratadine), 8 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.41 (P = 0.16)					
Total (95% CI)	**66**	**58**		**100.0 %**	**1.86 [0.91, 3.79]**
Total events: 19 (Loratadine), 9 (Placebo)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.26, df = 1 (P = 0.61); I^2 =0.0%					
Test for overall effect: Z = 1.72 (P = 0.086)					
Test for subgroup differences: Chi^2 = 0.26, df = 1 (P = 0.61), I^2 =0.0%					

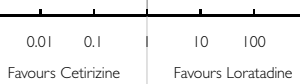
Analysis 2.1. Comparison 2 Loratadine 10 mg versus cetirizine 10 mg, Outcome 1 Proportion of participants with complete suppression of urticaria whilst taking H1-antihistamines.

Review: H1-antihistamines for chronic spontaneous urticaria

Comparison: 2 Loratadine 10 mg versus cetirizine 10 mg

Outcome: 1 Proportion of participants with complete suppression of urticaria whilst taking H1-antihistamines

Study or subgroup	Loratadine n/N	Cetirizine n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Short-term duration of intervention					
Patel 1997	12/20	9/17		30.1 %	1.13 [0.64, 2.01]
Subtotal (95% CI)	**20**	**17**		**30.1 %**	**1.13 [0.64, 2.01]**
Total events: 12 (Loratadine), 9 (Cetirizine)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.43 (P = 0.67)					
2 Intermediate-term duration of intervention					
Yin 2003b	20/32	21/34		69.9 %	1.01 [0.69, 1.47]
Subtotal (95% CI)	**32**	**34**		**69.9 %**	**1.01 [0.69, 1.47]**
Total events: 20 (Loratadine), 21 (Cetirizine)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.06 (P = 0.95)					
Total (95% CI)	**52**	**51**		**100.0 %**	**1.05 [0.76, 1.43]**
Total events: 32 (Loratadine), 30 (Cetirizine)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.11, df = 1 (P = 0.75); I^2 =0.0%					
Test for overall effect: Z = 0.29 (P = 0.77)					
Test for subgroup differences: Chi^2 = 0.10, df = 1 (P = 0.75), I^2 =0.0%					



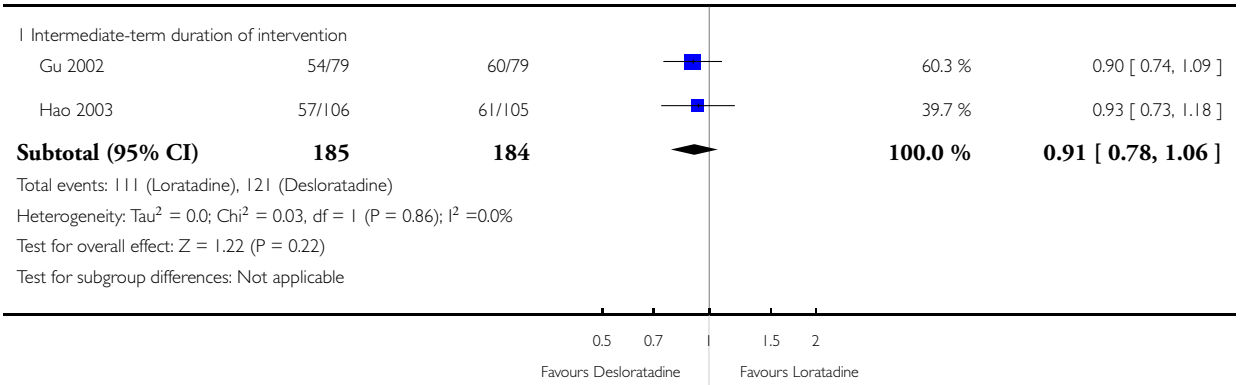
Analysis 3.1. Comparison 3 Loratadine 10 mg versus desloratadine 5 mg, Outcome 1 Proportion of participants with complete suppression of urticaria whilst taking H1-antihistamines.

Review: H1-antihistamines for chronic spontaneous urticaria

Comparison: 3 Loratadine 10 mg versus desloratadine 5 mg

Outcome: 1 Proportion of participants with complete suppression of urticaria whilst taking H1-antihistamines

Study or subgroup	Loratadine n/N	Desloratadine n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Intermediate-term duration of intervention					
Gu 2002	54/79	60/79		60.3 %	0.90 [0.74, 1.09]
Hao 2003	57/106	61/105		39.7 %	0.93 [0.73, 1.18]
Subtotal (95% CI)	**185**	**184**		**100.0 %**	**0.91 [0.78, 1.06]**
Total events: 111 (Loratadine), 121 (Desloratadine)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.03$, df = 1 (P = 0.86); $I^2 = 0.0\%$					
Test for overall effect: Z = 1.22 (P = 0.22)					
Test for subgroup differences: Not applicable					



Analysis 3.2. Comparison 3 Loratadine 10 mg versus desloratadine 5 mg, Outcome 2 Proportion of participants with 'good' or 'excellent' response whilst taking H1-antihistamines.

Review: H1-antihistamines for chronic spontaneous urticaria

Comparison: 3 Loratadine 10 mg versus desloratadine 5 mg

Outcome: 2 Proportion of participants with 'good' or 'excellent' response whilst taking H1-antihistamines

Study or subgroup	Loratadine n/N	Desloratadine n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Intermediate-term duration of intervention					
Gu 2002	24/79	18/79		43.5 %	1.33 [0.79, 2.26]
Hao 2003	31/106	32/105		53.6 %	0.96 [0.63, 1.45]
Zou 2002	0/20	4/21		2.9 %	0.12 [0.01, 2.03]
Subtotal (95% CI)	**205**	**205**		**100.0 %**	**1.04 [0.64, 1.71]**
Total events: 55 (Loratadine), 54 (Desloratadine)					
Heterogeneity: $Tau^2 = 0.07$; $Chi^2 = 3.31$, df = 2 (P = 0.19); $I^2 = 40\%$					
Test for overall effect: Z = 0.16 (P = 0.87)					
Test for subgroup differences: Not applicable					

Analysis 4.1. Comparison 4 Loratadine 10 mg versus mizolastine 10 mg, Outcome 1 Proportion of participants with complete suppression of urticaria whilst taking H1-antihistamines.

Review: H1-antihistamines for chronic spontaneous urticaria

Comparison: 4 Loratadine 10 mg versus mizolastine 10 mg

Outcome: 1 Proportion of participants with complete suppression of urticaria whilst taking H1-antihistamines

Study or subgroup	Loratadine n/N	Mizolastine n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Intermediate-term duration of intervention					
Guo 2003	10/23	18/23		21.3 %	0.56 [0.33, 0.93]
Liu 2003	68/104	68/104		47.6 %	1.00 [0.82, 1.22]
Yin 2003b	20/32	20/30		31.1 %	0.94 [0.65, 1.36]
Subtotal (95% CI)	**159**	**157**		**100.0 %**	**0.86 [0.64, 1.16]**
Total events: 98 (Loratadine), 106 (Mizolastine)					
Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 4.43$, df = 2 (P = 0.11); $I^2 = 55\%$					
Test for overall effect: Z = 0.97 (P = 0.33)					
Test for subgroup differences: Not applicable					

Analysis 4.2. Comparison 4 Loratadine 10 mg versus mizolastine 10 mg, Outcome 2 Proportion of participants with 'good' or 'excellent' response whilst taking H1-antihistamines.

Review: H1-antihistamines for chronic spontaneous urticaria

Comparison: 4 Loratadine 10 mg versus mizolastine 10 mg

Outcome: 2 Proportion of participants with 'good' or 'excellent' response whilst taking H1-antihistamines

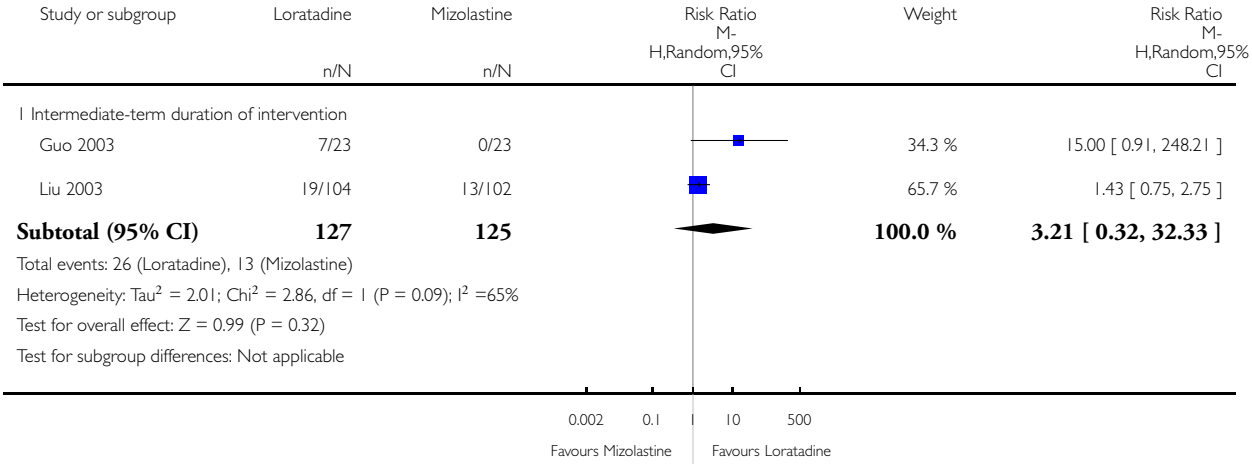
Study or subgroup	Loratadine n/N	Mizolastine n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Intermediate-term duration of intervention					
Guo 2003	4/23	4/23		14.1 %	1.00 [0.28, 3.52]
Liu 2003	12/104	16/102		46.1 %	0.74 [0.37, 1.48]
Yin 2003b	10/32	9/30		39.8 %	1.04 [0.49, 2.21]
Subtotal (95% CI)	**159**	**155**		**100.0 %**	**0.88 [0.55, 1.42]**
Total events: 26 (Loratadine), 29 (Mizolastine)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.49$, df = 2 (P = 0.78); $I^2 = 0.0\%$					
Test for overall effect: Z = 0.52 (P = 0.60)					
Test for subgroup differences: Not applicable					

Analysis 4.3. Comparison 4 Loratadine 10 mg versus mizolastine 10 mg, Outcome 3 Proportion of participants with at least 50% improvement in QoL whilst taking H1-antihistamines.

Review: H1-antihistamines for chronic spontaneous urticaria

Comparison: 4 Loratadine 10 mg versus mizolastine 10 mg

Outcome: 3 Proportion of participants with at least 50% improvement in QoL whilst taking H1-antihistamines

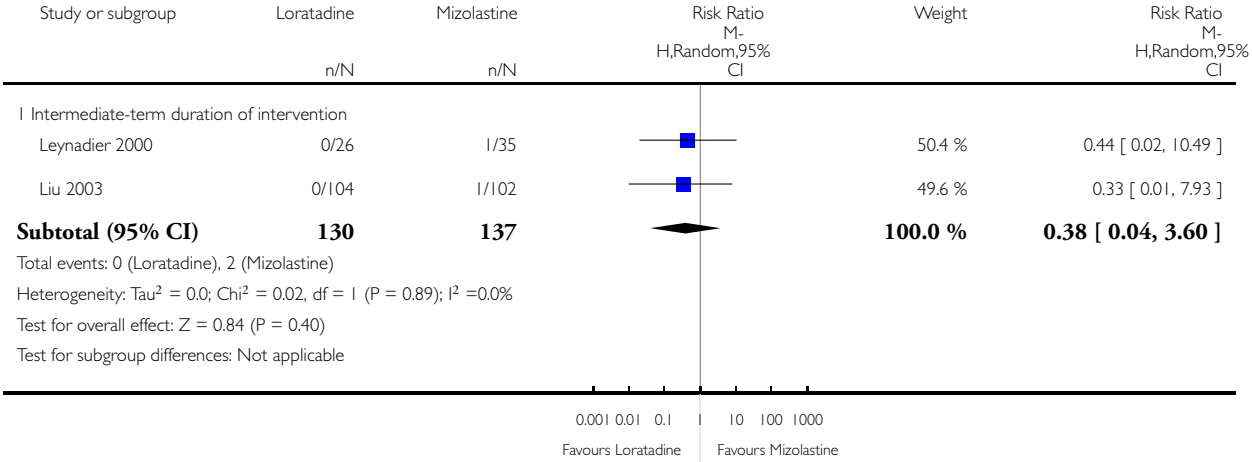


Analysis 4.4. Comparison 4 Loratadine 10 mg versus mizolastine 10 mg, Outcome 4 Serious adverse events (i.e. serious enough to require withdrawal of treatment).

Review: H1-antihistamines for chronic spontaneous urticaria

Comparison: 4 Loratadine 10 mg versus mizolastine 10 mg

Outcome: 4 Serious adverse events (i.e. serious enough to require withdrawal of treatment)

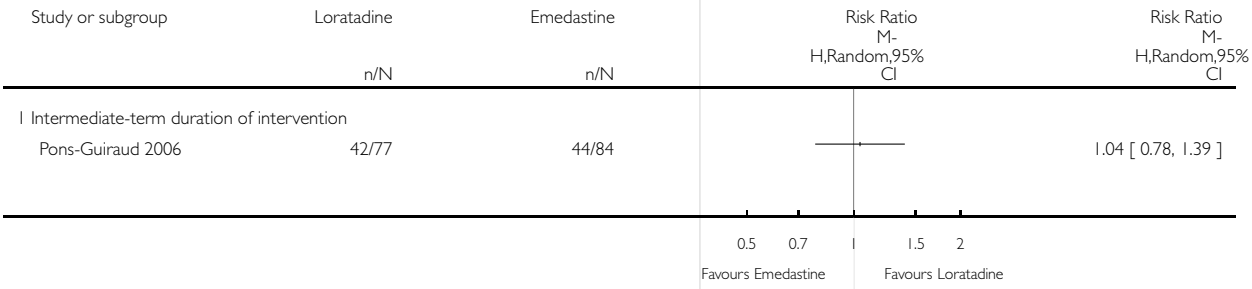


Analysis 5.1. Comparison 5 Loratadine 10 mg versus emedastine 2 mg, Outcome 1 Proportion of participants with complete suppression of urticaria whilst taking H1-antihistamines.

Review: H1-antihistamines for chronic spontaneous urticaria

Comparison: 5 Loratadine 10 mg versus emedastine 2 mg

Outcome: 1 Proportion of participants with complete suppression of urticaria whilst taking H1-antihistamines



Analysis 5.2. Comparison 5 Loratadine 10 mg versus emedastine 2 mg, Outcome 2 Proportion of participants with good or excellent response whilst taking H1-antihistamines.

Review: H1-antihistamines for chronic spontaneous urticaria

Comparison: 5 Loratadine 10 mg versus emedastine 2 mg

Outcome: 2 Proportion of participants with good or excellent response whilst taking H1-antihistamines

Analysis 5.3. Comparison 5 Loratadine 10 mg versus emedastine 2 mg, Outcome 3 Serious adverse events (i.e. serious enough to require withdrawal of treatment).

Review: H1-antihistamines for chronic spontaneous urticaria

Comparison: 5 Loratadine 10 mg versus emedastine 2 mg

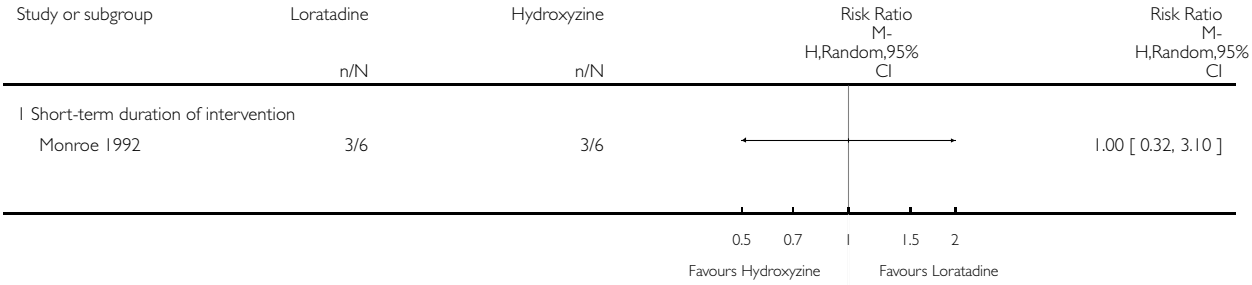
Outcome: 3 Serious adverse events (i.e. serious enough to require withdrawal of treatment)

Analysis 6.1. Comparison 6 Loratadine 10 mg versus hydroxyzine 25 mg, Outcome 1 Proportion of participants with complete suppression of urticaria whilst taking H1-antihistamines.

Review: H1-antihistamines for chronic spontaneous urticaria

Comparison: 6 Loratadine 10 mg versus hydroxyzine 25 mg

Outcome: 1 Proportion of participants with complete suppression of urticaria whilst taking H1-antihistamines

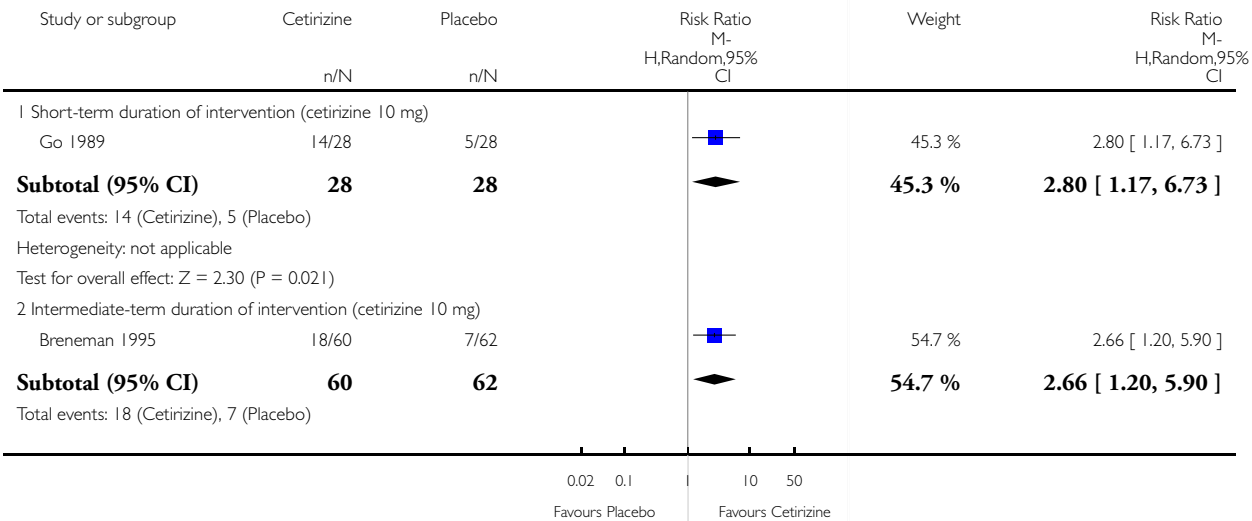


Analysis 7.1. Comparison 7 Cetirizine 10 to 20 mg versus placebo, Outcome 1 Proportion of participants with complete suppression of urticaria whilst taking H1-antihistamines.

Review: H1-antihistamines for chronic spontaneous urticaria

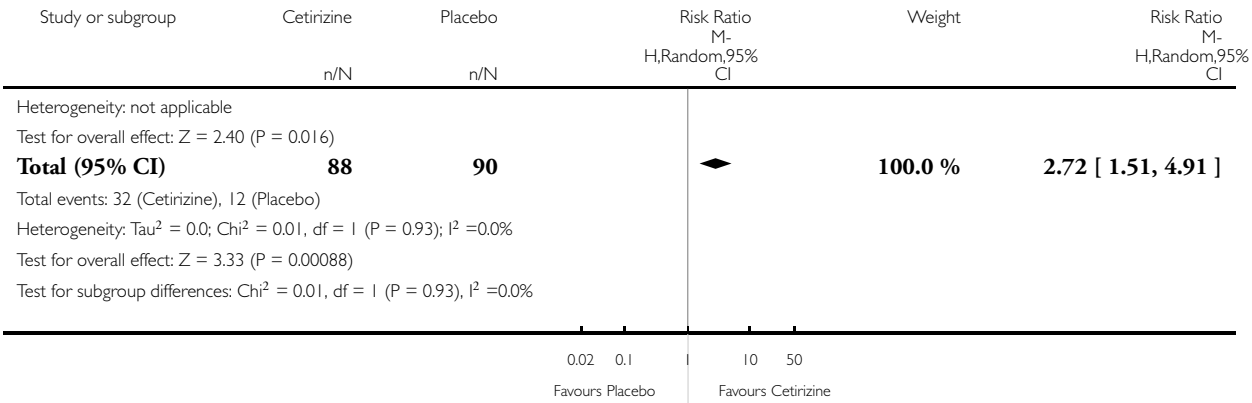
Comparison: 7 Cetirizine 10 to 20 mg versus placebo

Outcome: 1 Proportion of participants with complete suppression of urticaria whilst taking H1-antihistamines



(*Continued* . . .)

(. . . *Continued*)

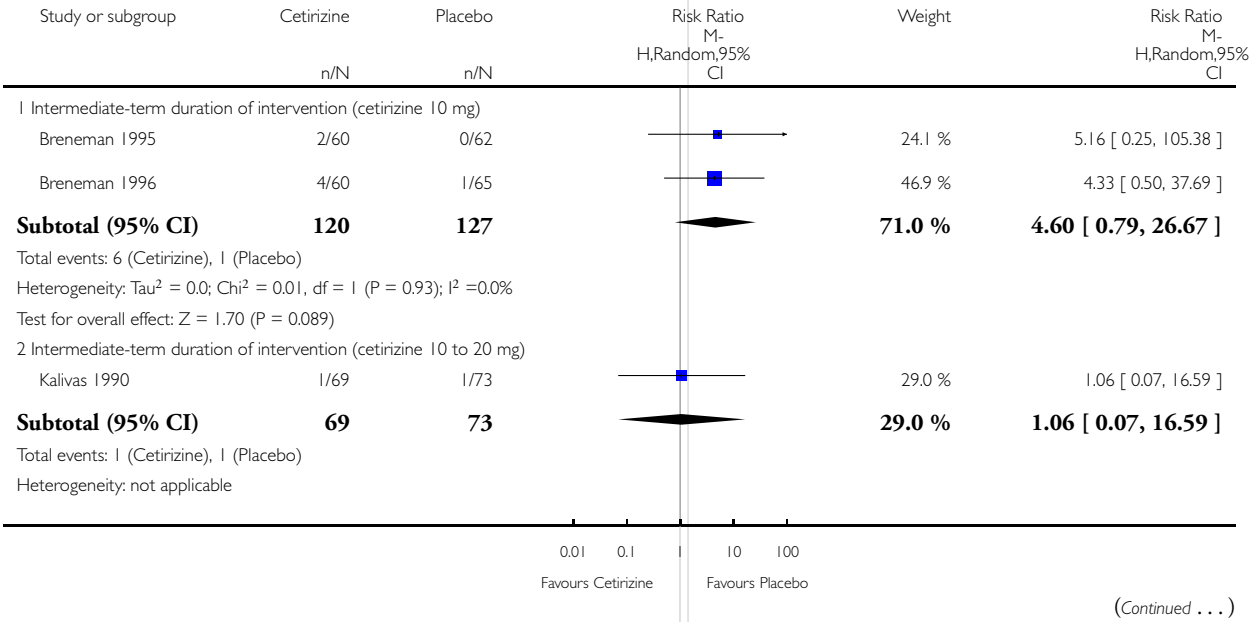


Analysis 7.2. Comparison 7 Cetirizine 10 to 20 mg versus placebo, Outcome 2 Serious adverse events (i.e. serious enough to require withdrawal of treatment).

Review: H1-antihistamines for chronic spontaneous urticaria

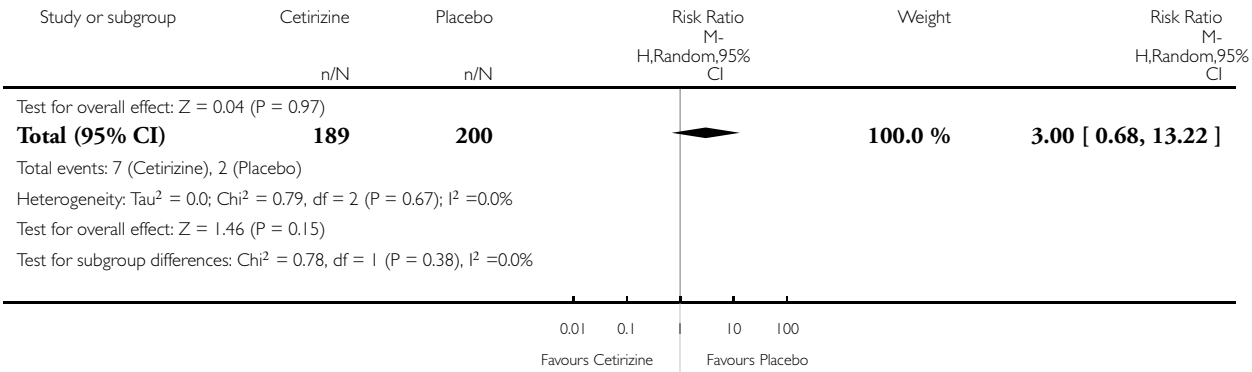
Comparison: 7 Cetirizine 10 to 20 mg versus placebo

Outcome: 2 Serious adverse events (i.e. serious enough to require withdrawal of treatment)



(*Continued* . . .)

(. . . *Continued*)

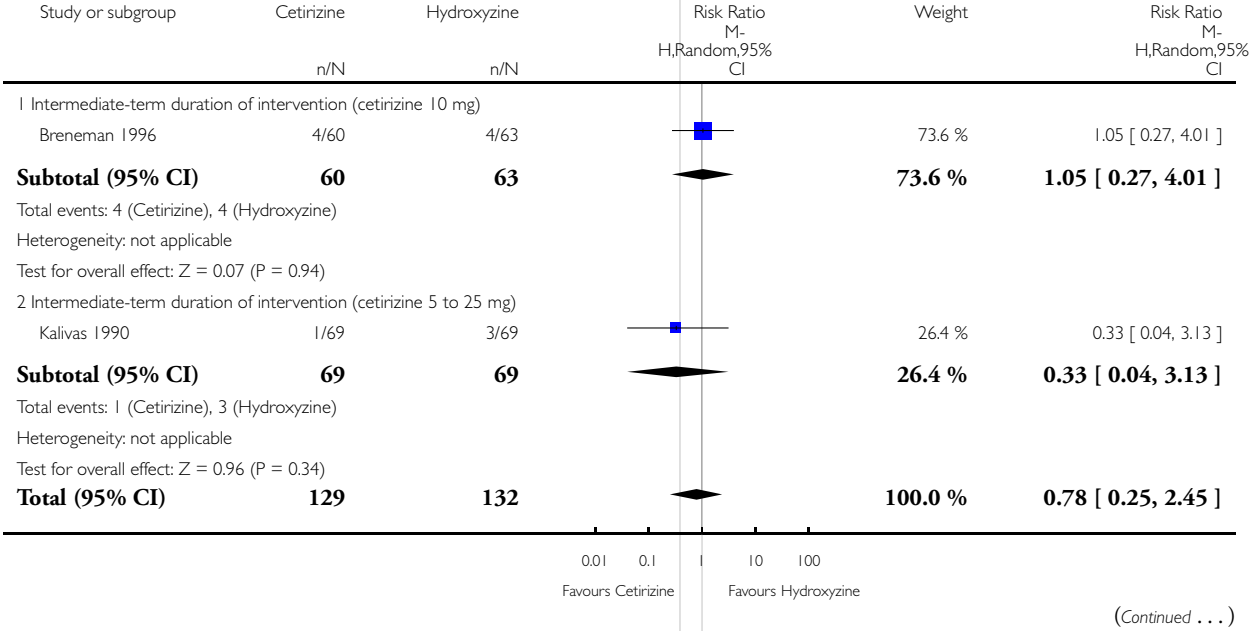


Analysis 8.1. Comparison 8 Cetirizine 10 mg versus hydroxyzine 25 mg, Outcome 1 Serious adverse events (i.e. serious enough to require withdrawal of treatment).

Review: H1-antihistamines for chronic spontaneous urticaria

Comparison: 8 Cetirizine 10 mg versus hydroxyzine 25 mg

Outcome: 1 Serious adverse events (i.e. serious enough to require withdrawal of treatment)



(*Continued* . . .)

(. . . *Continued*)

Study or subgroup	Cetirizine n/N	Hydroxyzine n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Total events: 5 (Cetirizine), 7 (Hydroxyzine)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.75$, df = 1 (P = 0.39); $I^2 = 0.0\%$					
Test for overall effect: Z = 0.43 (P = 0.67)					
Test for subgroup differences: $Chi^2 = 0.74$, df = 1 (P = 0.39), $I^2 = 0.0\%$					

Analysis 9.1. Comparison 9 Desloratadine 5 to 20 mg versus placebo, Outcome 1 Proportion of participants with complete suppression of urticaria whilst taking H1-antihistamines.

Review: H1-antihistamines for chronic spontaneous urticaria

Comparison: 9 Desloratadine 5 to 20 mg versus placebo

Outcome: 1 Proportion of participants with complete suppression of urticaria whilst taking H1-antihistamines

Study or subgroup	Desloratidine n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 Short-term duration of intervention (desloratadine 5 mg)				
Hoxha 2011	3/34	0/12		2.60 [0.14, 46.97]
2 Short-term duration of intervention (desloratadine 10 mg)				
Hoxha 2011	11/34	0/12		8.54 [0.54, 134.83]
3 Short-term duration of intervention (desloratadine 20 mg)				
Hoxha 2011	21/34	0/12		15.97 [1.04, 245.04]
4 Intermediate-term duration of intervention (desloratadine 5 mg)				
Di Lorenzo 2004	18/40	0/40		37.00 [2.31, 593.70]

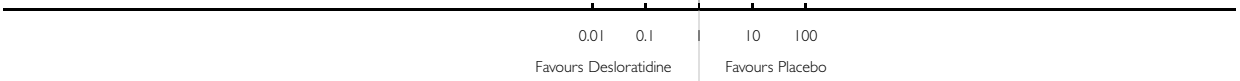
Analysis 9.2. Comparison 9 Desloratadine 5 to 20 mg versus placebo, Outcome 2 Serious adverse events (i.e. serious enough to require withdrawal of treatment).

Review: H1-antihistamines for chronic spontaneous urticaria

Comparison: 9 Desloratadine 5 to 20 mg versus placebo

Outcome: 2 Serious adverse events (i.e. serious enough to require withdrawal of treatment)

Study or subgroup	Desloratidine n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Intermediate-term duration of 5 mg of intervention					
Monroe 2003	3/116	2/110		49.9 %	1.42 [0.24, 8.35]
Nettis 2004	0/25	0/25			Not estimable
Ring 2001	3/95	2/95		50.1 %	1.50 [0.26, 8.78]
Subtotal (95% CI)	**236**	**230**		**100.0 %**	**1.46 [0.42, 5.10]**
Total events: 6 (Desloratidine), 4 (Placebo)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.00$, df = 1 (P = 0.97); $I^2 = 0.0\%$					
Test for overall effect: Z = 0.59 (P = 0.55)					
Test for subgroup differences: Not applicable					

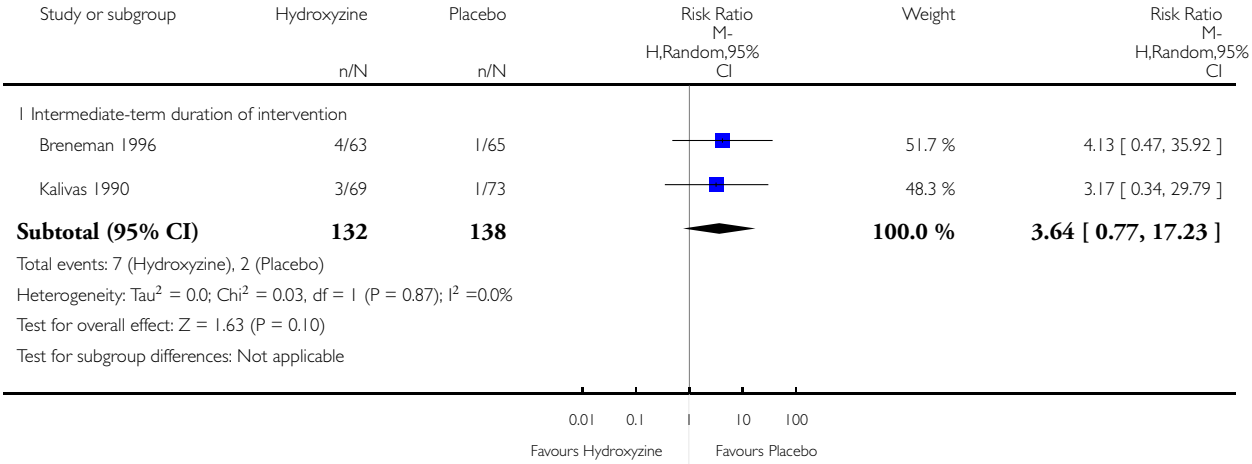


Analysis 10.1. Comparison 10 Hydroxyzine 25 mg versus placebo, Outcome 1 Serious adverse events (i.e. serious enough to require withdrawal of treatment to withdrawal).

Review: H1-antihistamines for chronic spontaneous urticaria

Comparison: 10 Hydroxyzine 25 mg versus placebo

Outcome: 1 Serious adverse events (i.e. serious enough to require withdrawal of treatment to withdrawal)



Analysis 11.1. Comparison 11 Levocetirizine 5 to 20 mg versus placebo, Outcome 1 Proportion of participants with complete suppression of urticaria whilst taking H1-antihistamines.

Review: H1-antihistamines for chronic spontaneous urticaria

Comparison: 11 Levocetirizine 5 to 20 mg versus placebo

Outcome: 1 Proportion of participants with complete suppression of urticaria whilst taking H1-antihistamines

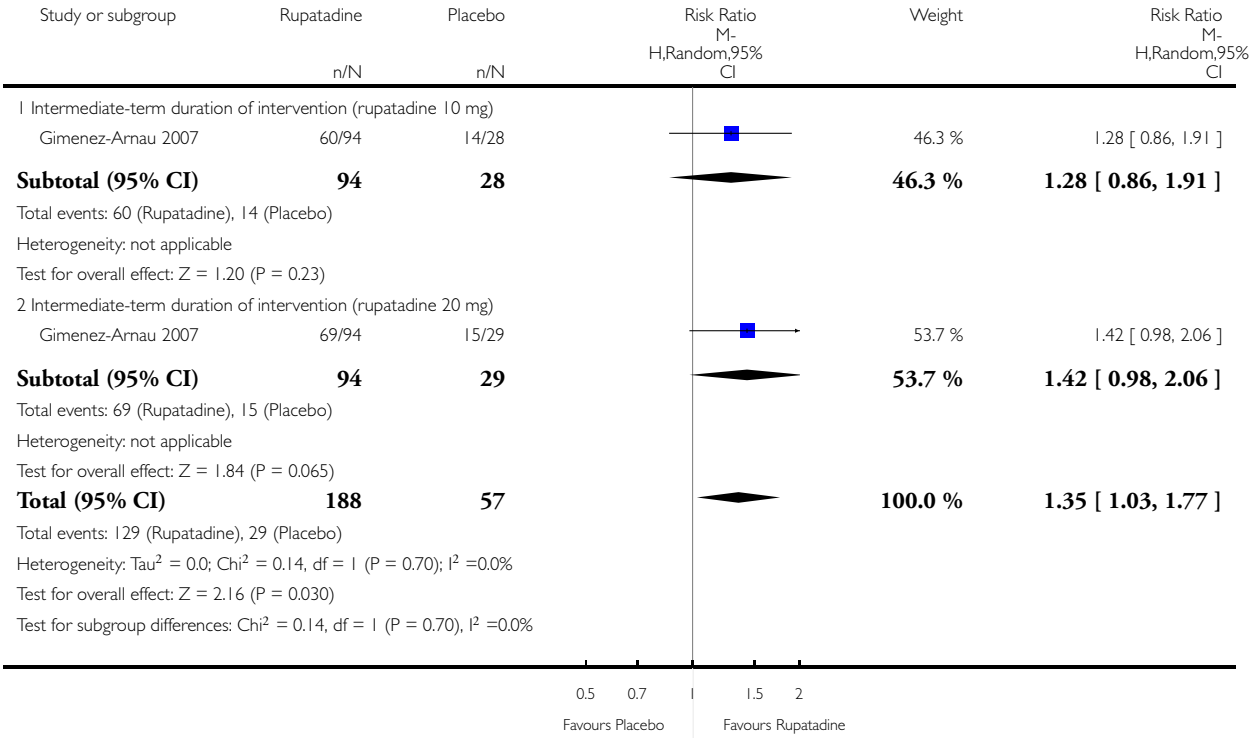
Study or subgroup	Levocetirizine n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 Short-term duration of intervention (levocetirizine 5 mg)				
Hoxha 2011	9/37	0/12		6.50 [0.41, 104.06]
2 Short-term duration of intervention (levocetirizine 10 mg)				
Hoxha 2011	17/37	0/12		11.97 [0.77, 185.38]
3 Short-term duration of intervention (levocetirizine 20 mg)				
Hoxha 2011	30/37	0/12		20.87 [1.37, 317.60]
4 Intermediate-term duration of intervention (levocetirizine 5 mg)				
Nettis 2006	27/51	0/49		52.88 [3.31, 843.81]

Analysis 12.1. Comparison 12 Rupatadine 10 to 20 mg versus placebo, Outcome 1 Proportion of participants with 'good' or 'excellent' response whilst taking H1-antihistamines.

Review: H1-antihistamines for chronic spontaneous urticaria

Comparison: 12 Rupatadine 10 to 20 mg versus placebo

Outcome: 1 Proportion of participants with 'good' or 'excellent' response whilst taking H1-antihistamines



APPENDICES

Appendix 1. Skin Group Specialised Register search strategy

(Urticaria or hives) and (astemizole or brompheniramine or chlorpheniramine or cinnarizine or clemastine or cyclizine or cyproheptadine or dimenhydrinate or dimethindene or diphenhydramine or doxylamine or flunarizine or hydroxyzine or ketotifen or meclizine or methapyrilene or mianserin or pheniramine or promethazine or pyrilamine or terfenadine or tripelennamine or triprolidine or azelastine or bromodiphenhydramine or carbinoxamine or cetirizine or chlorodiphenhydramine or chlorphenamine or deschlorpheniramine or loratadine or desloratadine or dexbrompheniramine or dexchlorpheniramine or dimetindene or ebastine or embramine or fexofenadine or levocetirizine or meclozine or olopatadine or phenindamine or phenyltoloxamine or rupatadine or "H1 receptor antagonist*" or "H1 antagonist*" or "h1 antihistamine*")

Appendix 2. CENTRAL search strategy

#1 (urticaria):ti,ab,kw
#2 MeSH descriptor Urticaria explode all trees in MeSH products
#3 (hives):ti,ab,kw
#4 (#1 OR #2 OR #3)
#5 "H1 antihistamine*":ti,ab,kw
#6 ("H1 antagonist*"):ti,ab,kw
#7 MeSH descriptor Histamine H1 Antagonists explode all trees in MeSH products
#8 astemizole in Title, Abstract or Keywords in all products
#9 brompheniramine or chlorpheniramine in Title, Abstract or Keywords in all products
#10 cinnarizine or clemastine or cyclizine or cyproheptadine in Title, Abstract or Keywords in all products
#11 dimenhydrinate or dimethindene or diphenhydramine in Title, Abstract or Keywords in all products
#12 doxylamine or flunarizine or hydroxyzine or ketotifen or meclizine or methapyrilene in Title, Abstract or Keywords in all products
#13 mianserin or pheniramine or promethazine or pyrilamine in Title, Abstract or Keywords in all products
#14 terfenadine or tripelennamine or triprolidine in Title, Abstract or Keywords in all products
#15 "H1 receptor antagonist*":ti,ab,kw
#16 MeSH descriptor Astemizole explode all trees
#17 MeSH descriptor Brompheniramine explode all trees
#18 MeSH descriptor Chlorpheniramine explode all trees
#19 MeSH descriptor Cinnarizine explode all trees
#20 MeSH descriptor Clemastine explode all trees
#21 MeSH descriptor Cyclizine explode all trees
#22 MeSH descriptor Cyproheptadine explode all trees
#23 MeSH descriptor Dimenhydrinate explode all trees
#24 MeSH descriptor Dimethindene explode all trees
#25 MeSH descriptor Diphenhydramine explode all trees
#26 MeSH descriptor Doxylamine explode all trees
#27 MeSH descriptor Flunarizine explode all trees
#28 MeSH descriptor Hydroxyzine explode all trees
#29 MeSH descriptor Ketotifen explode all trees
#30 MeSH descriptor Meclizine explode all trees
#31 MeSH descriptor Methapyrilene explode all trees
#32 MeSH descriptor Mianserin explode all trees
#33 MeSH descriptor Pheniramine explode all trees
#34 MeSH descriptor Promethazine explode all trees
#35 MeSH descriptor Pyrilamine explode all trees
#36 MeSH descriptor Terfenadine explode all trees
#37 MeSH descriptor Tripelennamine explode all trees
#38 MeSH descriptor Triprolidine explode all trees
#39 (azelastine or bromodiphenhydramine or carbinoxamine or cetirizine):ti,ab,kw

#40 (Chlorodiphenhydramine or chlorphenamine or Deschlorpheniramine):ti,ab,kw
#41 MeSH descriptor Loratadine explode all trees
#42 (desloratadine or loratadine or Dexbrompheniramine):ti,ab,kw
#43 (Dexchlorpheniramine or Dimetindene or ebastine or Embramine):ti,ab,kw
#44 (Fexofenadine or Levocetirizine or Meclozine or Olopatadine):ti,ab,kw
#45 (Phenindamine or Phenyltoloxamine or Rupatadine):ti,ab,kw
#46 MeSH descriptor Cetirizine explode all trees
#47 (#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46)
#48 (#4 AND #47)

Appendix 3. MEDLINE (Ovid) search strategy

1. randomised 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. exp Urticaria/ or urticaria.ti,ab.
12. hives.ti,ab.
13. or/11-12
14. exp Histamine H1 Antagonists/ or h1 antihistamine$.ti,ab.
15. astemizole.ti,ab. or exp Astemizole/
16. brompheniramine.ti,ab. or exp Brompheniramine/
17. chlorpheniramine.ti,ab. or exp Chlorpheniramine/
18. cinnarizine.ti,ab. or exp Cinnarizine/
19. clemastine.ti,ab. or exp Clemastine/
20. cyclizine.ti,ab. or exp Cyclizine/
21. cyproheptadine.ti,ab. or exp Cyproheptadine/
22. dimenhydrinate.ti,ab. or exp Dimenhydrinate/
23. dimethindene.ti,ab. or exp Dimethindene/
24. diphenhydramine.ti,ab. or exp Diphenhydramine/
25. doxylamine.ti,ab. or exp Doxylamine/
26. flunarizine.ti,ab. or exp Flunarizine/
27. hydroxyzine.ti,ab. or exp Hydroxyzine/
28. ketotifen.ti,ab. or exp Ketotifen/
29. meclizine.ti,ab. or exp Meclizine/
30. methapyrilene.ti,ab. or exp Methapyrilene/
31. mianserin.ti,ab. or exp Mianserin/
32. pheniramine.mp. or exp Pheniramine/
33. promethazine.ti,ab. or exp Promethazine/
34. pyrilamine.ti,ab. or exp Pyrilamine/
35. terfenadine.ti,ab. or exp Terfenadine/
36. tripelennamine.ti,ab. or exp Tripelennamine/
37. triprolidine.ti,ab. or exp Triprolidine/
38. azelastine.ti,ab.

39. bromodiphenhydramine.ti,ab.
40. Carbinoxamine.ti,ab.
41. exp Cetirizine/
42. cetirizine.ti,ab.
43. Chlorodiphenhydramine.ti,ab.
44. chlorphenamine.ti,ab.
45. Deschlorpheniramine.ti,ab.
46. exp Loratadine/
47. desloratadine.ti,ab.
48. loratadine.ti,ab.
49. Dexbrompheniramine.ti,ab.
50. Dexchlorpheniramine.ti,ab.
51. Dimetindene.ti,ab.
52. ebastine.ti,ab.
53. Embramine.ti,ab.
54. Fexofenadine.ti,ab.
55. Levocetirizine.ti,ab.
56. Meclozine.ti,ab.
57. Olopatadine.ti,ab.
58. Phenindamine.ti,ab.
59. Phenyltoloxamine.ti,ab.
60. Rupatadine.ti,ab.
61. H1 receptor antagonist$.ti,ab.
62. H1 antagonist$.ti,ab.
63. or/14-62
64. 10 and 13 and 63

Appendix 4. EMBASE (Ovid) search strategy

1. astemizole.ti,ab. or exp Astemizole/
2. brompheniramine.ti,ab. or exp Brompheniramine/
3. chlorpheniramine.ti,ab. or exp Chlorpheniramine/
4. cinnarizine.ti,ab. or exp Cinnarizine/
5. clemastine.ti,ab. or exp Clemastine/
6. cyclizine.ti,ab. or exp Cyclizine/
7. cyproheptadine.ti,ab. or exp Cyproheptadine/
8. dimenhydrinate.ti,ab. or exp Dimenhydrinate/
9. dimethindene.ti,ab. or exp Dimethindene/
10. diphenhydramine.ti,ab. or exp Diphenhydramine/
11. doxylamine.ti,ab. or exp Doxylamine/
12. flunarizine.ti,ab. or exp Flunarizine/
13. hydroxyzine.ti,ab. or exp Hydroxyzine/
14. ketotifen.ti,ab. or exp Ketotifen/
15. meclizine.ti,ab. or exp Meclizine/
16. methapyrilene.ti,ab. or exp Methapyrilene/
17. mianserin.ti,ab. or exp Mianserin/
18. pheniramine.mp. or exp Pheniramine/
19. promethazine.ti,ab. or exp Promethazine/
20. pyrilamine.ti,ab. or exp Pyrilamine/
21. terfenadine.ti,ab. or exp Terfenadine/
22. tripelennamine.ti,ab. or exp Tripelennamine/
23. triprolidine.ti,ab. or exp Triprolidine/

24. azelastine.ti,ab.
25. bromodiphenhydramine.ti,ab.
26. Carbinoxamine.ti,ab.
27. exp Cetirizine/
28. cetirizine.ti,ab.
29. Chlorodiphenhydramine.ti,ab.
30. chlorphenamine.ti,ab.
31. Deschlorpheniramine.ti,ab.
32. exp Loratadine/
33. desloratadine.ti,ab.
34. loratadine.ti,ab.
35. Dexbrompheniramine.ti,ab.
36. Dexchlorpheniramine.ti,ab.
37. Dimetindene.ti,ab.
38. ebastine.ti,ab.
39. Embramine.ti,ab.
40. Fexofenadine.ti,ab.
41. Levocetirizine.ti,ab.
42. Meclozine.ti,ab.
43. Olopatadine.ti,ab.
44. Phenindamine.ti,ab.
45. Phenyltoloxamine.ti,ab.
46. Rupatadine.ti,ab.
47. H1 receptor antagonist$.ti,ab.
48. H1 antagonist$.ti,ab.
49. exp histamine H1 receptor antagonist/
50. exp azelastine/
51. exp bromodiphenhydramine/
52. exp carbinoxamine/
53. exp desloratadine/
54. exp dexbrompheniramine/
55. exp dexchlorpheniramine/
56. exp dimetindene/
57. exp ebastine/
58. exp embramine/
59. exp fexofenadine/
60. exp levocetirizine/
61. exp meclozine/
62. exp olopatadine/
63. exp phenindamine/
64. exp phenyltoloxamine/
65. exp rupatadine/
66. h1 antihistamine$.ti,ab.
67. or/1-66
68. exp *urticaria/
69. urticaria.ti,ab.
70. hives.ti,ab.
71. or/68-70
72. random$.mp.
73. factorial$.mp.
74. (crossover$ or cross-over$).mp.
75. placebo$.mp. or PLACEBO/
76. (doubl$ adj blind$).mp.

77. (singl$ adj blind$).mp.
78. (assign$ or allocat$).mp.
79. volunteer$.mp. or VOLUNTEER/
80. Crossover Procedure/
81. Double Blind Procedure/
82. Randomized Controlled Trial/
83. Single Blind Procedure/
84. 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83
85. 67 and 71 and 84

Appendix 5. PsycINFO (Ovid) search strategy

1. double-blind.tw.
2. random$ assigned.tw.
3. control.tw.
4. 1 or 2 or 3
5. urticaria.ti,ab.
6. hives.ti,ab.
7. 5 or 6
8. 4 and 7

Lines 1-3 of this strategy are a therapy filter for PsycINFO (Ovid) created by the Health Information Research Unit at McMaster University.

WHAT'S NEW

Last assessed as up-to-date: 3 June 2014.

Date	Event	Description
15 July 2015	Amended	Correction to publication date of included study Zou 2002. Previously cited as 2003. 2002 is the correct publication year

CONTRIBUTIONS OF AUTHORS

Link with editorial base and co-ordinate contributions from co-authors, supervision (AS, CB).

Draft protocol (AS, SNC, CC, LB, CH).

Run search (AS, SNC, MS, CB).

Identify relevant titles and abstracts from searches (AS, SNC, MS, CB).

Obtain copies of trials (AS, MS, SNC, CB).

Select trials (AS, SNC, MS, CB, CC).

Extract data from trials (AS, CB, MS, SNC, CC).

Enter data into RevMan (CB, MS, BC).

Carry out data analyses and draft Effects of Interventions section of the review (BC, CB, MS).

Interpret data (BC, CB, MS, SNC).

Draft final review (CB, MS, SNC, BC).

Update review (MS, CB, SNC, BC).

Disclaimer

The views and opinions expressed therein are those of the review authors and do not necessarily reflect those of the National Institute for Health Research (NIHR), the National Health Service (NHS) or the Department of Health, UK.

DECLARATIONS OF INTEREST

Maulina Sharma: "I have represented the Cochrane Skin Group as a stakeholder for a NICE (National Institute for Health and Care Excellence) scoping workshop for chronic spontaneous urticaria: omalizumab 2014. I have received an honorarium as a speaker for a general practitioner (GP) educational event, which was donated to the charitable funds of the department. I have attended training and continuing medical education (CME) events that may have been sponsored in part by pharmaceutical industry. I have been a subinvestigator for clinical trials conducted in the Department of Dermatology, George Eliot Hospitals NHS Trust, Nuneaton, UK (2005 to 2006), in particular, the CUTE study (NCT00264303). I was not involved in writing of the results and received no payments for my involvement with the clinical trials."

Cathy Bennett: "I am the proprietor of Systematic Research Ltd, a company providing research services; I am an employee of this company and received a consultancy fee for the production of this review. I have also received consultancy fees for other Cochrane reviews and work in evidence-based medicine."

Stuart N Cohen: Nothing to declare.

Ben Carter: Nothing to declare.

Dr Karsten Weller was a clinical referee: "I received lecture fees or advisory board fees from Novartis, Uriach, FAES, MSD (Essex Pharma), UCB or was involved in clinical studies with drugs from these companies."

SOURCES OF SUPPORT

Internal sources

- Queen's Medical Centre, UK.

External sources

- The National Institute for Health Research (NIHR), UK.

The NIHR, UK, is the largest single funder of the Cochrane Skin Group

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We now use the term *chronic spontaneous urticaria*.

We changed the wording of the 'Types of participants' criteria to clarify that we mean angio-oedema without weals rather than angio-oedema without urticaria, as the latter uses the term 'urticaria' as a descriptor rather than a disease. We used 'autoinflammatory syndrome' rather than 'associated abnormalities,' as Muckle-Wells and Schnitzler's syndrome are not urticaria.

We clarified that we have included any first-generation ('sedating') or second-generation ('non-sedating') H1-antihistamines at any dose (including topical interventions and H2RAs given concomitantly) given as single therapy or as combination therapy. Comparators consisted of no treatment, that is, placebo, or another active (pharmacological) compound. We included studies that compared the same drug but at different doses, but we excluded non-pharmacological interventions such as acupuncture.

We collected additional data from the reports of studies, such as country and setting, to obtain further information about clinical heterogeneity between our included studies.

We did not carry out subgroup analyses on the basis of first-generation ('sedating') and second-generation ('non-sedating') antihistamines, as included studies with relevant outcome data were too few to allow meaningful comparisons.

We clarified that duration of intervention is categorised as follows: up to two weeks (short-term) and longer than two weeks up to three months (intermediate-term). Our analyses are now subgrouped by duration of intervention, as we are not looking for a cure but would like to identify which antihistamine will suppress or give good or excellent response for urticaria immediately and over the longest time.

We excluded studies that investigated the effects of astemizole or terfenadine (withdrawn from use).

We described moderate statistical heterogeneity as > 50% in the protocol, but we revised this in the full review to moderate heterogeneity at I^2 > 60%.

For some comparisons, we used Fisher's exact test because of the small number of participants,

We had stated that we would use funnel plots when at least three studies were included in the meta-analysis, but the *Cochrane Handbook for Systematic Reviews of Interventions* recommends a minimum of 10 studies for sufficient power.

We included in our methods section updated information about assessment of risk of bias using the 'Risk of bias' tool of The Cochrane Collaboration, and details about how we dealt with cross-over trials are provided in the Unit of analysis issues section.

NOTES

We provide brand names as a guide to the consumer and do not endorse any product over another.

INDEX TERMS

Medical Subject Headings (MeSH)

Cetirizine [therapeutic use]; Cyproheptadine [analogs & derivatives; therapeutic use]; Histamine H1 Antagonists [adverse effects; *therapeutic use]; Hydroxyzine [therapeutic use]; Loratadine [analogs & derivatives; therapeutic use]; Randomized Controlled Trials as Topic; Urticaria [*drug therapy]

MeSH check words

Humans