

Histamine H2-receptor antagonists for urticaria (Review)

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Histamine H2-receptor antagonists for urticaria

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ABSTRACT

Background

Urticaria is a common skin disease characterised by itching weals or hives, which can occur almost anywhere on the body. There are a number of different subtypes and a range of available treatment options. There is lack of agreement on the efficacy of H2-receptor antagonists used in the treatment of urticaria.

Objectives

To assess the safety and effectiveness of H2-receptor antagonists in the treatment of urticaria.

Search methods

We searched the following databases up to 7 October 2011: the Cochrane Skin Group Specialised Register, CENTRAL in *The Cochrane Library* (2011, Issue 4), MEDLINE (from 2005), EMBASE (from 2007), and LILACS (from 1982). We also searched online trials registries for ongoing trials.

Selection criteria

Randomised controlled trials of H2-receptor antagonists in people with a clinical diagnosis of urticaria of any duration or of any subtype. Studies including H1-antihistamines for chronic urticaria are the topic of a separate Cochrane review; thus, they were not included in this review.

Data collection and analysis

Two reviewers independently assessed trial quality and extracted and analysed data.

Main results

Four studies of a relatively small size, involving 144 participants, were included in this review. A combination of ranitidine with diphenhydramine was more effective at improving the resolution of urticaria than diphenhydramine administered alone (risk ratio (RR) 1.59, 95% confidence interval (CI) 1.07 to 2.36). Although there was a similar improvement in itching, weal size, and intensity, cimetidine provided no statistically significant greater overall improvement in symptoms of urticaria when compared to diphenhydramine. However, a combination of these medications was more effective than diphenhydramine alone (RR 2.02, 95% CI 1.03 to 3.94). Adverse events were reported with several of the interventions, i.e. ranitidine and diphenhydramine, causing drowsiness and sedation, but there was no significant difference in the level of sedation from baseline with either famotidine or diphenhydramine.

Authors' conclusions

The very limited evidence provided by this review was based on a few old studies of a relatively small size, which we categorised as having high to unclear risk of bias. Thus, at present, the review does not allow confident decision-making about the use of H2-receptor antagonists for urticaria. Although some of these studies have reported a measure of relief of symptoms of urticaria and rather minimal clinical improvement in some of the participants, the evidence was weak and unreliable. We have emphasised the lack of precision and limitations in the reported data where appropriate in this review.

PLAIN LANGUAGE SUMMARY

Histamine-blocking drugs for hives

Urticaria is a common skin disease characterised by itching weals or hives that can appear anywhere on the surface of the skin. Weals may be pinpoint in size or several inches in diameter. Most sufferers experience hives continuously or intermittently for less than six weeks, but they may last longer (when they are then called 'chronic'). Urticaria can also be accompanied by angioedema (swelling of a deeper layer of the skin). There are several varieties of urticaria, but the most common forms are acute urticaria and chronic urticaria. Common causes of acute urticaria are infections and adverse reactions to medications and foods, whereas in chronic urticaria the cause is often unknown. Intense itching is common, and it can lead to disturbed sleep and even depression, having a serious impact on a person's quality of life. As the face and other exposed body parts can be affected, hives and angioedema can prove embarrassing for the individual.

There are a range of treatment options for urticaria, of which the most well-known are the H1-antihistamines. This review evaluated the efficacy and safety of a similar category, the H2-antihistamines, and included 4 low-quality studies, which examined 144 participants. No firm conclusions could be drawn, but the combination of ranitidine with diphenhydramine appeared to be slightly more effective in reducing the symptoms of urticaria than diphenhydramine alone. In one study, cimetidine appeared to be as effective as diphenhydramine. However, the combination of both drugs was more effective than diphenhydramine alone. Drowsiness and sedation were reported with diphenhydramine, but there was no significant difference in the level of sedation with either famotidine or diphenhydramine. The studies were rather old and considered very few outcomes that were of importance to people with urticaria. Therefore, there is currently insufficient evidence to indicate whether this type of medication is effective or not.

BACKGROUND

Urticaria is a fairly common skin disease that can present in an array of different subtypes (Zuberbier 2009; see Table 1). The skin reaction is characterised by hives or weals, and it is usually accompanied by intense itching. It can be acutely disfiguring and a source of embarrassment for the sufferer, especially when it occurs on exposed parts of the body, such as the face and hands. Although rarely life-threatening, chronic urticaria may last for years or even decades, during which time it can severely impair the quality of life of the individual (Baiairdini 2011; Weldon 2006). It may even lead to depression, anxiety (Engin 2008), absenteeism from work, and "bad school performance" in children (Ferrer 2009).

Description of the condition

Prevalence and causes

Urticaria is reported to affect up to 20% of people at some time in their lives (Zuberbier 2009). It tends to occur more frequently in children and women between the ages of 30 to 60 years (Henderson 2000), although the chronic type is less common in children. The proportion of people who have this condition at any particular time varies, ranging from 0.5% to 1% of the population (Maurer 2011). This proportion might be explained by a number of factors including differences in the methods employed in the assessment, as well as geographical and cultural characteristics. The peak age of people with chronic spontaneous urticaria is between 20 and 40 years in most studies (Maurer 2011). However, in view of the diversity in classification of subtypes in some study populations, there is a degree of variability in some of the prevalence data. Up to three per cent of the people referred to hospital dermatology clinics in the UK complained of urticaria. The incidence

of hospital admissions in the UK for systemic allergic conditions, which include urticaria, has shown a steady increase over a recent 10-year period (Gupta 2003; Maurer 2011).

The underlying causes of the disease are both varied and complex, and the pathogenesis of the disease is still not clearly understood. Spontaneous urticaria is classified as either acute or chronic (Zuberbier 2009). Acute spontaneous urticaria has a duration of less than six weeks, whereas chronic spontaneous urticaria is continuously or intermittently present for at least six weeks. Acute spontaneous urticaria, which is generally more common, is said to be due to adverse reactions to medications, foods, infections, or inhalants. However, in more than half of those affected, the cause may not be clearly identified, and the precipitating factors may be unknown to the individual (Kulthanan 2008; Zuberbier 2009). The causes of chronic spontaneous urticaria are less clear (Charlesworth 2002; Zuberbier 2009). Evidence of an autoimmune cause has been demonstrated in approximately 45% of those affected, and it is still an area of active investigation (Kaplan 2009). In 35% to 40% of people with chronic spontaneous urticaria, autoantibodies against the FcεR1 (IgE receptor) are detected, and in 5% to 10%, auto-antibodies against IgE with or without antithyroid antibodies have been detected (Kaplan 2009; Philpott 2008). It has been reported that these antibodies induce histamine release from mast cells and basophils (Kaplan 2009; Philpott 2008). This apparent association between chronic urticaria and autoimmune disease has been more widely recognised; hence, this subtype has been classified as autoimmune chronic urticaria by some investigators.

The cause in the remaining 55% of those with chronic spontaneous urticaria is unknown; this group is characterised as 'idiopathic'. Other possible causative factors have been proposed; these include all kinds of chronic bacterial, viral, parasitic, or fungal infections, of which an *Helicobacter pylori* (*H.pylori*) infection is the most persistent (Abdou 2009; Kaplan 2009; Zuberbier 2009). However, it has been reported that *H. pylori* eradication has no significant effect on the course of chronic urticaria (Kaplan 2009; Shakouri 2010).

Clinical signs, symptoms, and diagnosis

Urticaria is characterised by eruptions of weals and/or angioedema, which can involve the skin, mucosa, and occasionally the upper respiratory tract. The degree of severity can vary quite markedly between individuals. The weals can arise quite suddenly, and they are usually accompanied by intense itching, having a fleeting nature with the skin returning to its normal appearance. This usually happens within 24 hours, but it may continue to recur for indefinite periods (Zuberbier 2009).

In some cases, there may be involvement of the deeper layers of the skin producing a rapid swelling of the dermis and/or subcutaneous tissue, which is called angioedema. This arises in a similar way to urticaria, but swelling is the major manifestation. The overlying

skin may be erythematous or normal, and there is less pruritus (itch), but pain or burning may be present. Resolution is slower than it is for weals and can take up to 72 hours. Angioedema may occur concurrently in some cases of acute spontaneous urticaria and in up to 50% of cases of chronic spontaneous urticaria (Greaves 2000; Zuberbier 2009).

Diagnosis of urticaria is usually made on the basis of a detailed history and physical examination. Although other investigations are rarely necessary, these may include measurements of differential blood counts, erythrocyte sedimentation rate, C-reactive protein; tests for infections; the Autologous Serum Skin Test (ASST- intra-dermal injection of autologous serum) to screen for autoantibodies; and physical stimulation tests for physical urticaria (Grattan 2007; Powell 2007; Zuberbier 2009).

Classification of urticaria

The spectrum of clinical manifestations of the different subtypes of urticaria is very wide; therefore, classification can be problematic. But a recent guideline on definition, classification, and diagnosis, which was the result of a consensus meeting on urticaria, a joint initiative of the dermatology section of the European Academy of Allergology and Clinical Immunology (EAACI), the EU-funded Network of Excellence, the Global Allergy and Asthma European Network (GA²LEN) (<http://www.ga2len.net/>), the European Dermatology Forum (EDF) (<http://www.euroderm.org/>), and the World Allergy Organization (WAO) (<http://www.worldallergy.org/>), has been published (Zuberbier 2009). Urticaria (presenting with weals and/or angioedema) can be broadly divided into three main types (Zuberbier 2009) (and into a range of subtypes if the cause is due to a known allergen or provoking factor).

1. Spontaneous urticaria - including acute (lasting less than six weeks) and chronic (episodes persisting beyond this period)
 2. Physical urticaria - including (according to eliciting factors) cold contact, delayed pressure (latency of weals 3 to 12 hours), heat contact, solar, urticaria factitia (weals arising after mechanical shearing forces), and vibratory forces from machines
 3. Other - including aquagenic (induced by contact with water), cholinergic, contact, and exercise-induced anaphylaxis
- Autoimmune urticaria is classified as a form of chronic spontaneous urticaria.

Pathogenesis

Urticaria is triggered by the release of histamine and other inflammatory mediators from mast cells resident in the skin and circulating basophils (Philpott 2008). The existence of two distinct classes of histamine receptors (H1- and H2-) in the skin, and the important role they play in the pathogenesis of urticaria, has been known for some time (Greaves 1982). Approximately 15% of these histamine receptors are of the H2 subtype (Kaplan 2002).

H2-receptors are clinically important in reducing gastric acid secretion and other problems, such as reflux. Vascular permeability in the skin is controlled predominantly by H1-receptors (Kaplan 2002), but the importance of the role that H2-receptors play and what the triggers are in urticaria have not been clarified.

Treatment options

Although urticaria is a fairly common disease for which a range of treatments are available, there is inconsistency in the reported effectiveness of some of the interventions that are used in its treatment. Uncertainty about the precise cause means that treatment is principally directed at management strategies which focus on a reduction in the frequency of occurrence and severity of symptoms. These may be as simple as reassurance, promoting realistic expectations, and elimination of a cause if it is known.

A guideline on the management of urticaria was published recently (Zuberbier 2009b). Management is based on two principles: the identification and elimination of the underlying cause(s) and/or eliciting trigger(s), and the treatment aimed at providing symptom relief. The recommended first-line treatment algorithm for chronic urticaria includes the new generation of non-sedating H1-antihistamines. If standard dosing is not effective, increasing the dosage up to four-fold is recommended. For those who do not respond to the four-fold increase in dosage of non-sedating H1-antihistamines, it is recommended that second-line therapies should be added to the antihistamine treatment. In selecting second-line treatment, both their costs and risk/benefit profiles should be considered. Corticosteroids are not recommended for long-term treatment due to their unavoidable severe adverse effects (Zuberbier 2009b).

Complementary and alternative therapies have been considered, but they are still under evaluation.

Description of the intervention

H2-receptor antagonists (H2RAs) are a group of drugs that react with a type of histamine receptor called H2, which is found mainly in the cells lining the stomach (parietal gastric mucosa) (Keithley 1991). H2RAs are used clinically in the treatment of acid-related gastrointestinal conditions, such as peptic ulcer disease, gastro-oesophageal reflux, and dyspepsia.

H2RAs have also been used in the treatment of urticaria, generally in combination with H1-receptor antagonist therapy. There is a lack of agreement on the efficacy of H2RAs in the treatment of urticaria (Kozel 2004). The outcome may depend on which H1-receptor antagonist and H2RA is used and in which type of urticaria. The EAACI guideline treatment algorithm indicates that the efficacy of H2RA is only supported by low-level evidence (Zuberbier 2009b).

The combined effect may be due more to H1- and H2-antihistamine interactions at the level of liver metabolism with a resulting mutual increase in plasma drug concentration than to any genuine “synergic effect” (Jáuregui 2007).

Medications contained in this group include cimetidine, famotidine, ranitidine, roxatidine, lafutidine, and nizatidine, most of which are available as oral preparations. However, these medications have not been approved by the US Food and Drug Administration (FDA) for treating urticaria or angioedema. The preferred dosages and route of administration of these interventions varies between clinicians.

H2RAs are generally well-tolerated, except for some infrequent adverse drug reactions (ADRs), which include hypotension, headache, tiredness, dizziness, confusion, diarrhoea, constipation, rash, gynaecomastia in men, loss of libido, and impotence. Anaemia, leucopenia, or agranulocytosis are very rare side-effects.

How the intervention might work

There is still a degree of uncertainty as to the precise mode of action of H2RAs. Histamine is a potent mediator of immediate hypersensitivity reactions. Fifteen per cent of the histamine receptors in the skin are H2-receptors, and it is acknowledged that human skin mast cells, which store histamine also express H2-receptors (Lippert 2004). The H2RAs are reversible structural analogs (a chemical compound with a slightly altered chemical structure) of histamine that cause a decrease in the tonic activation rate of the receptor. Thus, these agents act as inverse agonists (agents that bind to the same receptor binding-site as an agonist for that receptor and reverse the activity of receptors) with a functional antagonism of histamine activity, hence, reducing the histamine activity on the receptor sites. In this way they may be able to block histamine release and curtail, or even prevent, symptoms of urticaria from occurring. It has also been suggested that one of these H2RAs, cimetidine, has an immunomodulator function (Nielsen 1996) and may have a role to play in chronic autoimmune urticaria.

Why it is important to do this review

Urticaria, especially the chronic type, presents a significant burden of disease for many people. It can be associated with major direct and indirect healthcare costs, resulting in consequent socioeconomic implications (Baiardini 2011; Maurer 2009; Maurer 2011). The degree of prevalence of urticaria and its effect on the quality of life makes urticaria an important disease from both an individual and a societal perspective. H2RAs appear to offer an additional way of treating people with urticaria. Uncertainties regarding long-term safety, coupled with a range of treatments of possibly questionable effectiveness, suggest that a systematic review is needed. In addition, this review might also help to clarify

which groups of people and/or which types and subtypes of urticaria might benefit from the use of H2RAs.

OBJECTIVES

To assess the effectiveness and safety of H2-receptor antagonists in the treatment of urticaria.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCT).

Types of participants

Participants of any age and gender with a clinical diagnosis of urticaria based on a detailed medical history and physical examination, including those with all generally recognised types, subtypes, and duration of urticaria.

Types of interventions

H2-receptor antagonists compared with placebo, any other active treatment, or against each other, at any dose or route of administration. Studies that examined H2-receptor antagonists as an additional intervention to any ongoing treatment were included. We avoided overlap with the Cochrane review in preparation on 'H1 antihistamines for chronic urticaria' (Stanway 2006) by excluding any studies that involve the use of H1-antihistamines for chronic urticaria in this review, regardless of whether they were combined with H2-antihistamines. Studies of H2-antihistamines have only been included if those studies do not contain a comparison against H1-antihistamines.

Types of outcome measures

Urticaria is a dynamic disease, and the symptoms are subject to daily and weekly fluctuation. So, whilst weal and hive counts can be valuable indicators, they do not address one of the most important outcomes for people: the effect of this disease on their daily activities. Although we recognise that many trials may not have reported the impact of urticaria on quality of life, we have specified this as our principal secondary outcome. However, we also included studies that had only reported time to cessation/urticaria activity scores.

Primary outcomes

1) Proportion of participants with resolution from urticaria (resolution of weals) in the immediate period (the first 24 hours) since the intervention was given in the study. Proportion of participants with resolution from urticaria (resolution of weals, no attacks in last seven days) in the short-term (up to six weeks) and long-term (longer than six weeks and up to six months) since the intervention was given in the study. Urticaria activity as evaluated in the study (both participant-reported and clinician-assessed).

2) We noted any reported adverse effects, systemic or local, any clinically diagnosed hypersensitivity, or other unacceptable or adverse events associated with any of the interventions. We categorised these as mild (not needing additional treatment), moderate (needing treatment or admission to hospital), and severe (life-threatening).

Because of the transient nature of urticaria, the outcome measures are likely to be based predominantly on participant self-reporting. The participant and clinician assessment outcome measure are considered separately and in combination. The outcome measures include those measures at the time points (the reference of the time point is with respect to the disease activity) measured while the treatment is ongoing.

Secondary outcomes

1) Proportion of participants with changes in their (participant-reported) quality of life (more than 50% improved/worsened/unaffected/less than 50% improved), assessed using any validated and internationally recognised generic or disease-specific scale in the immediate period (the first 24 hours), short-term (up to 6 weeks), and long-term (longer than 6 weeks and up to 6 months).

2) Reduction in urticaria symptoms, e.g. itching, (both participant-reported and clinician-assessed) expressed as percentage improvement from baseline in the immediate (the first 24 hours), short-term (up to 6 weeks), and long-term (longer than 6 weeks and up to 6 months).

3) Time to resolution of urticaria (as defined by the study).

4) Sleep (reported by participant) - improved, worsened, or unaffected after treatment at end points mentioned in the study.

5) Incidental improvement in the symptoms of excessive gastric acid secretion - improved, worsened, or unaffected after treatment at end points mentioned in the study.

Search methods for identification of studies

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

Electronic searches

We searched the following databases up to 7 October 2011:

- the Cochrane Skin Group Specialised Register using the search terms (urticaria or wheal* or flare* or hive*) and ((histamine and antagonist*) or (H2 and antagonist*) or (H1 and antagonist*) or steroid* or (tricyclic and antidepress*));
- the Cochrane Central Register of Controlled Trials (CENTRAL) in *The Cochrane Library* using the search strategy in Appendix 1;
- MEDLINE (from 2005) using the search strategy in Appendix 2;
- EMBASE (from 2007) using the search strategy in Appendix 3; and
- LILACS (Latin American and Caribbean Health Science Information database, from 1982) using the search strategy in Appendix 4.

The UK and US Cochrane Centres (CCs) have ongoing projects to systematically search MEDLINE and EMBASE for reports of trials which are then included in the Cochrane Central Register of Controlled Trials. Searching has currently been completed in MEDLINE to 2004 and in EMBASE to 2006. Further searching was undertaken for this review by the Cochrane Skin Group to cover the years that have not been searched by the UK and US CCs.

Ongoing Trials Registers

We searched for reports of trials on 7 October 2011 using the search term 'urticaria' in the following ongoing trial registers.

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

Searching other resources

Correspondence

The reference lists of relevant articles were examined, and as most of the studies were more than 10 years old, investigators of included studies were not contacted.

Language

There were no language or date restrictions in the electronic searches, and, if required, we would have arranged to translate any studies not in the English language.

Data collection and analysis

Selection of studies

Three review authors (ZF, NH, and EvZ) independently assessed the titles and abstracts of studies resulting from the searches. We obtained full copies of all relevant and potentially relevant studies, those appearing to meet the inclusion criteria, and those for which there were insufficient data in the title and abstract to make a clear decision (EvZ and ZF). The full-text papers were assessed independently by two review authors (EvZ and ZF), and any disagreements on the eligibility of included studies were resolved through discussion and consensus or, if necessary, through the third review author. Those studies that at first appeared to meet the eligibility criteria but which on further scrutiny turned out not to meet them were excluded, and the reasons for their exclusion have been noted in the 'Characteristics of excluded studies' tables.

Data extraction and management

Study details were entered into the 'Characteristics of included studies' tables in Review Manager 5.1 (RevMan 2011). Data were extracted independently and in duplicate by two review authors (ZF and EvZ) and only included if there was a consensus; any disagreements were resolved by consultation with the third review author.

The following details were extracted if reported:

1. trial methods - method of allocation, masking of participants and outcomes, exclusion of participants after randomisation, and proportion of losses to follow-up;
2. participants - country of origin, study setting, sample size, age, gender, and inclusion and exclusion criteria;
3. intervention - type, concentration, dose, route, and frequency;
4. control - type, concentration, dose, route, and frequency;
5. outcomes - primary and secondary outcomes mentioned in the 'Types of outcome measures' section of this review; and
6. adverse effects. We noted any adverse effects related to any clinically diagnosed hypersensitivity or other adverse reactions/side-effects to the interventions.

If stated, the sources of funding were recorded.

Assessment of risk of bias in included studies

Two review authors (ZF and EvZ) independently assessed the risk of bias in the selected trials using the Cochrane Collaboration's tool for assessing risk of bias, as described in section 8.5 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). The gradings were compared, and any inconsistencies in the assessments between the reviewers were discussed and resolved. The following domains were assessed as 'low risk of bias', 'high risk of bias', or 'unclear risk of bias':

- (a) sequence generation;
- (b) allocation concealment;
- (c) blinding (of participants, personnel, and outcome assessors);
- (d) incomplete outcome data addressed;
- (e) free of selective outcome reporting; and
- (f) free of other bias.

We also categorised and reported the overall risk of bias 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; or
- high risk of bias (plausible bias that seriously weakens confidence in the results) if one or more criteria were not met.

These assessments are reported in the 'Risk of bias' tables, which form part of the '[Characteristics of included studies](#)' tables in the review.

Measures of treatment effect

We included the results from studies that met the inclusion criteria in this review.

If in future updates of this review sufficient data are available for any of the outcomes of interest, these will be included in a subsequent meta-analysis. The immediate period (the first 24 hours), short-term (up to 6 weeks), and long-term (longer than 6 weeks and up to 6 months) effects will be assessed separately.

Dichotomous data

For dichotomous outcomes, results will be expressed as risk ratios (RR) with 95% confidence intervals (CI). For studies reporting participant- or investigator-rated symptoms on categorical scales, the data will be made dichotomous by defining a cut-off at improved, worsened, and unaffected.

Continuous data

Mean differences (MD) with 95% CI will be used to express results for continuous outcomes where the same measurement scales have been used across trials, and standardised mean differences (SMD) will be used to express results for continuous outcomes where different but comparable measurement scales have been used across trials.

Time-to-event data

For time-to-event outcomes, hazards ratios will be calculated in future updates. The hazard ratio is derived from the log rank approach or log hazard ratios using the generic inverse-variance

method, depending on whether data is extracted from the primary studies or obtained from re-analysis of individual participant data.

Unit of analysis issues

The unit of analysis issues that might arise may be as a result of recurrences or relapses involving repeated observations on participants. If the studies had reported the proportion of participants who had relapsed, these were to be compared and analysed accordingly, following the advice provided in Section 9.3.4 of the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)).

Cross-over studies were not included largely due to uncertainty in the extent of carry-over effect of treatment as well as uncertainty defining a correspondingly appropriate wash-out period. However, if first period data are available in the future, these will be considered for inclusion, but no attempt will be made to pool these data with those from parallel group trials.

Dealing with missing data

We did not attempt to retrieve missing data from the investigators in any of the included trials. In view of the generally poor quality of their reporting, we have only provided a narrative synthesis of the data that was available.

Assessment of heterogeneity

Insufficient studies were included in this review, but for future updates - and if further trials are identified - the following methods will apply. We will assess clinical heterogeneity by examining the characteristics of the studies, the similarity between the types of participants, the interventions, and the outcomes as specified in the criteria for included studies. Heterogeneity will be assessed using I^2 statistic. If moderate levels of heterogeneity are detected for the primary outcomes (I^2 statistic > 50%), reasons for heterogeneity will be explored using subgroup analysis ([Higgins 2003](#)).

Assessment of reporting biases

If sufficient trials in the future are identified for inclusion in this review, publication bias will be assessed according to the recommendations on testing for funnel plot asymmetry ([Egger 1997](#)) as described in section 10.4.3.1 of the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)). If asymmetry is identified, we will try to assess other possible causes, which will be explored in the discussion if appropriate.

Data synthesis

We were unable to pool data from the included studies, but if further trials are identified the following methods of data synthesis will apply. We shall separately analyse studies that compare the

effectiveness of H2RAs against placebo, studies comparing H2RAs against another active intervention, and H2RAs in combination with other treatments against other active interventions.

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

We will use the fixed-effect model if there are sufficient numbers of studies investigating similar interventions; however, if there is substantial clinical diversity between the studies, we will use the random-effects model.

Number needed to treat (NNT) will be used to express the relative benefit (or otherwise) of the various treatment options where appropriate, for a range of plausible control event rates.

Where there are multiple intervention groups within a trial, pairwise comparisons will be made of similar active interventions versus no treatment, placebo, or another active intervention.

If there are insufficient clinically homogeneous trials for any specific intervention or if there is insufficient trial data that can be pooled, we will present a narrative synthesis.

Subgroup analysis and investigation of heterogeneity

In future updates if sufficient data are available, and if we identify at least moderate heterogeneity as defined above, we plan to carry out the following subgroup analyses:

- dosage and duration of treatment;
- type or subtype and severity of urticaria;
- type of H2-antagonist drug; and
- management before H2RA treatment.

Sensitivity analysis

In future updates if sufficient studies are included, we plan to conduct sensitivity analyses to assess the robustness of our review results by repeating the analysis with the following adjustments: exclusion of studies with unclear or inadequate allocation concealment, unclear or inadequate blinding of outcomes assessment, and completeness of follow up.

RESULTS

Description of studies

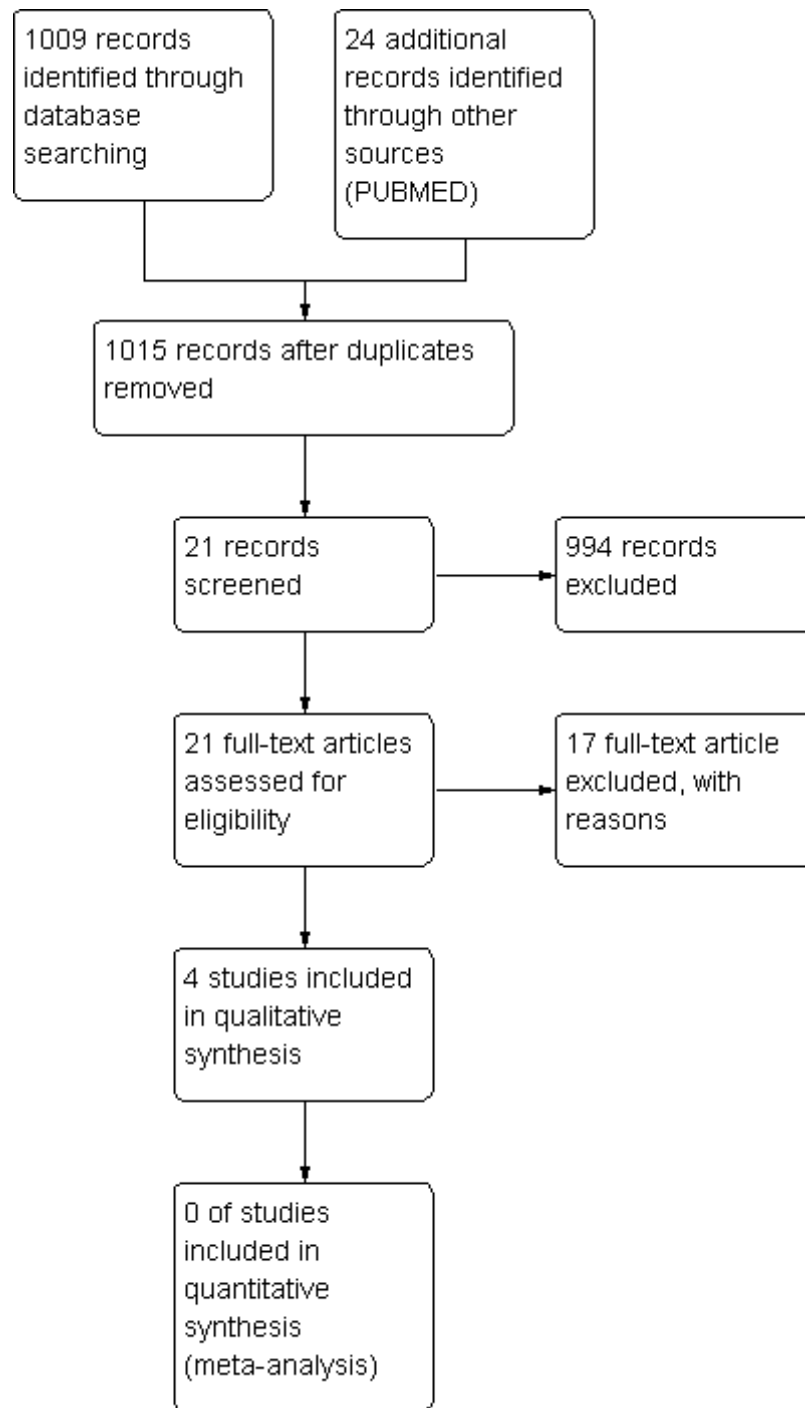
See: [Characteristics of included studies](#); [Characteristics of excluded studies](#).

Please see the 'Characteristics of included studies' tables and 'Characteristics of excluded studies' tables of this review.

Results of the search

The electronic searches retrieved 1015 references to studies. After examination of the titles and abstracts of these references, all of the studies which did not match our inclusion criteria and were clearly ineligible were eliminated from the review. Full-text copies of the remaining 21 potentially eligible trials were obtained and subjected to further evaluation. Seventeen studies were subsequently excluded, and the reasons for their exclusion are reported in the 'Characteristics of excluded studies' tables. For further details see the 'Study Flow Diagram' ([Figure 1](#)).

Figure 1. Study flow diagram



Included studies

Four trials involving 144 participants were included in this review: [Lin 2000](#); [Pontasch 1993](#); [Runge 1992](#); and [Watson 2000](#).

Characteristics of the trial setting and methods

All four studies were randomised, included an active control group, and had been conducted in the emergency departments of several general or university hospitals in the USA. Two of the trials were conducted over 15 years ago and two over 10 years ago.

Characteristics of the participants

All of the included studies considered participants with acute urticaria. Almost equal numbers of male and female participants were enrolled, and their ages ranged from 18 to 77, with a mean age of 30 years. Although participants with a broad range of allergic syndromes or acute allergic reactions were enrolled in two of the studies ([Lin 2000](#); [Runge 1992](#)), only the data from participants with urticaria were included in this review.

Duration of symptoms at enrolment varied between the studies: acute urticaria of less than 72 hours duration in [Watson 2000](#), of less than 1 week's duration in [Pontasch 1993](#), and less than 12 hours in [Runge 1992](#) and [Lin 2000](#). Only one of the included studies ([Lin 2000](#)) recorded some of the possible causes of urticaria in the participants, which were chiefly drug-related or as a result of food allergies.

Characteristics of the interventions

All of the included studies compared an H2-receptor antagonist with an H1 antihistaminic, i.e. diphenhydramine, or an H2RA against a combination of the two. Cimetidine was the active intervention in [Runge 1992](#), famotidine in both [Pontasch 1993](#) and [Watson 2000](#), and ranitidine in [Lin 2000](#). The intervention was administered intramuscularly in [Watson 2000](#), orally in [Pontasch 1993](#) and [Runge 1992](#), and intravenously in [Lin 2000](#).

Characteristics of the outcome measures

Only two of the studies ([Lin 2000](#); [Pontasch 1993](#)) addressed one of our primary outcomes, the resolution of urticaria, whereas most of the studies reported some of the adverse events associated with the interventions. The only secondary outcome for this review

which was addressed in the included studies was 'reduction of the symptoms of urticaria', and this was in only one study ([Pontasch 1993](#)).

All of the studies with the exception of [Lin 2000](#) and [Pontasch 1993](#) utilised participant-based, in addition to investigator-based, assessments for several of their outcomes.

The timing of outcome assessments varied markedly between the studies. These were carried out 30 minutes after the intervention in 2 of the studies ([Runge 1992](#); [Watson 2000](#)), at 1 hour and 2 hours in [Lin 2000](#), and in [Pontasch 1993](#) participants completed and submitted a follow-up questionnaire 10 days after discharge from the emergency department. In this questionnaire, participants recorded the time to relief of symptoms, their satisfaction and perception of the effectiveness of the drug (rated 1 to 10), and the occurrence of any adverse events.

A check-off cartoon of the body area was used by the investigators in [Lin 2000](#) to assess the extent of urticaria and erythema and the symptoms, which were rated as 'none-mild-moderate-severe'. In [Runge 1992](#), the participants and investigators made joint visual analogue scale (VAS) assessments of the degree of urticaria and symptoms of pruritus 30 minutes after the administration of the interventions. Outcome assessments of the total body surface covered by urticaria and weal intensity were made by the investigators, and the participants independently rated symptoms of pruritus using a VAS in [Watson 2000](#).

Excluded studies

Seventeen studies were excluded, and the reasons for their exclusion are reported in the '[Characteristics of excluded studies](#)' tables. We examined the three potentially eligible cross-over trials ([Kaur 1981](#); [Matthews 1979](#); [Sharpe 1993](#)). As the studies were 20 to 30 years old the relevant data for each participant at each intervention period was unlikely to be obtainable. We needed this information to carry out a paired analysis of the within-person effects of the interventions as recommended by [Elbourne 2002](#). We therefore made the decision to exclude them.

Risk of bias in included studies

We assessed each of the included studies for risk of bias, reported the judgements for the individual domains in the 'Risk of bias' table associated with each study, and we also presented these in the 'Risk of bias' graph in [Figure 2](#) and the 'Risk of bias' summary in [Figure 3](#).

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

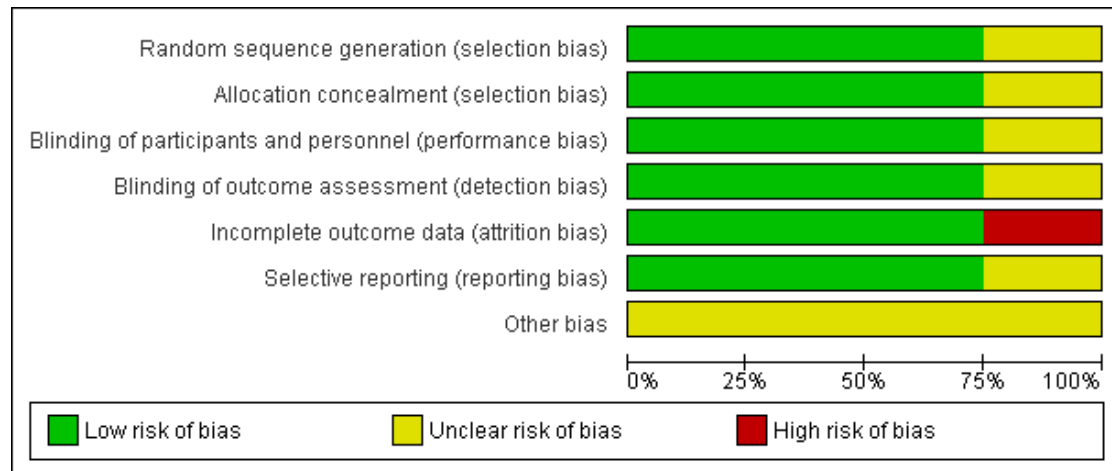


Figure 3. 'Risk of bias' summary: review authors' judgements about each 'Risk of bias' item for each included study

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Lin 2000	+	+	+	+	+	+	?
Pontasch 1993	+	+	?	?	-	+	?
Runge 1992	+	+	+	+	+	?	?
Watson 2000	?	?	+	+	+	+	?

We assessed the overall risk of bias in each study and categorised one of the studies (Pontasch 1993) as high risk of bias (plausible bias that seriously weakens confidence in the results) because we judged one or more domains as a 'high risk'. The losses to follow up/protocol deviation of Pontasch 1993 was 39%, and the incomplete data for outcomes which were prespecified for this review and the per-protocol analysis of the data posed a high risk of attrition bias. The remaining three studies were rated as unclear risk of bias (plausible bias that raises some doubt about the result) because one or more criteria were assessed as unclear.

Allocation

The methods used to generate the allocation sequence and how the sequence was concealed (so that participants and investigators enrolling participants could not foresee the upcoming assignment) are the most important and sensitive indicators that bias has been minimised in a clinical trial (Schulz 1995).

Sequence generation

The method used to generate the allocation sequence was described in sufficient detail to allow an assessment of whether it would produce comparable groups in Lin 2000, Pontasch 1993, and Runge 1992. Therefore, this domain was judged as low risk of bias for these three studies. Insufficient details were reported in Watson 2000 about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups; thus, this domain was judged as at unclear risk of bias.

Allocation concealment

Pharmacy-controlled or central allocation ensured that the intervention allocations could not have been foreseen in advance of, or during, enrolment in three studies (Lin 2000; Pontasch 1993; Runge 1992), which were judged low risk of bias for this domain. In Watson 2000 the report was unclear.

Blinding

The measures used to blind study participants and personnel from knowledge of which intervention a participant received were described in sufficient detail in Lin 2000, Runge 1992, and Watson 2000. Inadequate reporting in the other study (Pontasch 1993) did not permit a clear judgement to be made for this domain. Lack of blinding can also exert an influence on outcome measurement, and in view of the limited amount of information in this report, it was not possible to make a clear judgement of what impact the uncertainty of blinding may have had on outcome assessment for this study (Pontasch 1993), which was judged as unclear risk of

bias. This domain was clear for the three other studies, which were judged at low risk of bias.

Incomplete outcome data

In view of the 39% dropout rate and subsequent per-protocol analysis of the data, this domain was judged at high risk of bias in Pontasch 1993. The three remaining studies were judged to be at low risk of bias either because of the lack of dropouts or losses to follow up (Runge 1992; Watson 2000), or the number of dropouts was low and equitably balanced between intervention groups (Lin 2000).

Selective reporting

The protocols for the studies were not available, but the prespecified outcomes and those mentioned in the methods sections appeared to have been reported for Lin 2000, Pontasch 1993, and Watson 2000. However, in Runge 1992 two of the prespecified outcomes were not reported (pharyngeal tissue swelling and facial swelling), and although these were not outcomes for this review, this domain was judged as unclear risk of bias.

Other potential sources of bias

There was insufficient information to permit a clear judgement of the risk of bias for all studies regarding other potential sources of bias. None of the studies provided any declarations by the investigators of any potential conflicts of interest or any details of funding or support. In two of the studies (Pontasch 1993; Runge 1992), the use of antihistamines by the participants prior to the study was an exclusion criterion because the carry-over effect of antihistamines can last up to seven days. However, in Lin 2000 10 participants used antihistamines in the preceding 36 hours, and 3 of the participants in Watson 2000 took antihistamines in the 12 hours prior to the study.

Effects of interventions

(I) Cimetidine versus diphenhydramine

One study provided data for this comparison (Runge 1992).

Primary outcomes

Proportion of participants with resolution from urticaria (< 24 hours, up to 6 weeks, and long-term up to 6 months)

This was not assessed.

Adverse events

The single study investigated a combination of both diphenhydramine and cimetidine as a third comparison. Adverse events occurred in participants in all three of the intervention groups in this study. In the cimetidine-only group, these consisted of thrombophlebitis (two) and feeling “lightheaded” or “dizzy” (one). One participant in the diphenhydramine group felt a “burning sensation” at the intravenous line site. In the combined intervention group, two participants experienced a burning sensation, two felt “lightheaded” or “dizzy”, and one had nausea and chills.

Secondary outcomes

Proportion of participants with changes in quality of life

This was not assessed.

Reduction in urticaria symptoms

The investigators assessed this outcome as “clinically significant relief”, which was defined as a VAS change of 25+ mm before and after treatment, and as an improvement reported in 8/10 participants in the cimetidine group, 5/11 in the diphenhydramine group, and 11/12 in the combined therapy group. There were no statistically significant differences between the groups other than in the combined-medications group compared to the diphenhydramine group, with a result which favoured the combination therapy (RR 2.02, 95% CI 1.03 to 3.94, P value = 0.04, Mantel-Haenszel test).

Time to resolution of urticaria

This was not assessed.

Sleep

This was not assessed.

Incidental improvement in the symptoms of excessive gastric acid secretion

This was not assessed.

(2) Famotidine versus diphenhydramine

These interventions were compared in two studies (Pontasch 1993; Watson 2000), one of which (Pontasch 1993) also included an additional treatment arm in which the participants received cromolyn sodium. However, in view of the substantial number of dropouts (39%) in this study, the data are only presented as reported.

Primary outcomes

Proportion of participants with resolution from urticaria (< 24 hours, up to 6 weeks, and long-term up to 6 months)

In the per-protocol analysis in Pontasch 1993, 4 of 7 participants reported relief at 12 hours in the diphenhydramine group, compared to 1 of 6 in the famotidine group and 1 of 7 in the cromolyn sodium group.

Adverse events

Drowsiness induced by the interventions was participant-assessed using a VAS in Watson 2000, which reported that 30 minutes after administration there was no statistically significant difference in sedative effect between the famotidine and diphenhydramine groups (95% CI -46 to 7, P value > 0.10, two-tailed Student's t-tests). Participants in the famotidine group reported no change in sedation as assessed on the 100 mm VAS (0 mm, 95% CI -14 to 15, P value > 0.50, two-tailed Student's t-tests), while those in the diphenhydramine group showed a statistically non-significant increase in sedation of 20 mm (95% CI 27 to 47, P value > 0.10, two-tailed Student's t-tests). Drowsiness was also the adverse event reported in Pontasch 1993 in 3/7 in the diphenhydramine group, 3/6 in the famotidine group, and 1/7 in the cromolyn sodium group.

Secondary outcomes

Proportion of participants with changes in quality of life

This was not assessed.

Reduction in urticaria symptoms

The principal outcome in Watson 2000 was the change in patient-rated pruritus, and data were reported as VAS-assessed mean change scores. There was a reduction in mean VAS score of 36 mm in the famotidine group, compared to 54 mm in the diphenhydramine group. Based on these scores, the investigators reported that there was no significant difference between the groups in terms of a reduction of pruritus. No further data relevant to this outcome were reported.

Time to resolution of urticaria

This outcome was only assessed in [Pontasch 1993](#), and the data were presented per-protocol. In 6/7 in the diphenhydramine group the urticaria resolved after 3 days, compared to 5/6 in the famotidine group and 4/7 in the cromolyn sodium group.

Sleep

This was not assessed.

Incidental improvement in the symptoms of excessive gastric acid secretion

This was not assessed.

(3) Ranitidine combined with diphenhydramine versus diphenhydramine alone

One study compared these interventions and reported outcomes data ([Lin 2000](#)).

Primary outcomes

Proportion of participants with resolution from urticaria (< 24 hours, up to 6 weeks, and long-term up to 6 months)

Two hours after intravenous administration 25 out of 29 participants who received the combined interventions were free of urticaria, compared with 13 out of 24 participants in the diphenhydramine-only group (RR 1.59, 95% CI 1.07 to 2.36, P value = 0.02, Mantel-Haenszel test).

Adverse events

The investigators indicated that no adverse effects were observed in either of the intervention groups.

Secondary outcomes

Proportion of participants with changes in quality of life

This was not assessed.

Reduction in urticaria symptoms

This was not assessed.

Time to resolution of urticaria

This was not assessed.

Sleep

This was not assessed.

Incidental improvement in the symptoms of excessive gastric acid secretion

This was not assessed.

DISCUSSION

Summary of main results

Four studies, which examined 144 participants with an age range of 18 to 77 years, were included in this review. The majority of outcomes prespecified for this review were not addressed in the included studies. A combination of ranitidine with diphenhydramine was significantly more effective at improving the resolution of urticaria than diphenhydramine administered alone ([Lin 2000](#)). Although there was a similar improvement in itching, weal size, and intensity, cimetidine provided no statistically significant greater overall improvement in symptoms of urticaria when compared to diphenhydramine. However, a combination of these medications was more effective than diphenhydramine alone ([Runge 1992](#)). The time to resolution of urticaria was addressed in only one of the studies ([Pontasch 1993](#)), but the data were unusable due to a high percentage dropout rate (attrition bias).

Adverse events were reported with several of the interventions, i.e. ranitidine and diphenhydramine, causing drowsiness and sedation, but there was no significant difference in the level of sedation from baseline to 30 minutes after intervention with either famotidine or diphenhydramine.

Overall completeness and applicability of evidence

The studies included in this review, which evaluated a range of interventions and combinations, did not provide sufficient data to enable fair and reasonable comparisons to be made for any one single intervention against another for a specific outcome.

Quality of the evidence

Limitations in study design and implementation

Although study design in the included studies appeared to have been, at best, adequate, our study-level assessments of the risk of bias for a number of the domains in several of these studies revealed

some of the limitations in their implementation, which have been reported in the 'Risk of bias in included studies' section of this review. Both [Lin 2000](#) and [Runge 1992](#) included participants with a broad range of allergic syndromes or acute allergic reactions, but we could only include a subgroup that had urticaria. Only 53 of 100 participants were available for analysis in [Lin 2000](#) and 33 of 39 in [Runge 1992](#). Neither of these studies focused on antihistamines for urticaria, but on antihistamines for acute allergic reactions in general.

Inconsistency of results

The few key outcomes which were assessed in the included studies provided very limited data. None of these data could be pooled, which consequently did not allow any assessment of the effects of the interventions across the studies.

Indirectness of evidence

The participants in the included studies were in general a fairly representative sample as defined in the inclusion criteria; therefore, we did not have any significant concerns about the appropriateness of participants identified in the review.

Direct evidence of the effects of interventions on resolution of urticaria was only reported in one study ([Lin 2000](#)), which was relatively small in size. This does not provide sufficient evidence to enable confident clinical decision-making. Patient-preferred outcomes, such as change or improvement in quality of life, that would provide important direct evidence of the impact of these interventions on those with urticaria were not considered in any of the studies included in this review.

Imprecision of results

The small number of studies (of moderate to low quality) that were included in this review did not provide any data which could be pooled; therefore, any substantive assessment of the degree of precision of effect was not feasible. We have exercised caution when extracting and reporting data from the primary research studies, and we have indicated where appropriate any uncertainty with the reliability of the data and the conclusions which can be made from them.

Publication bias

Although it would be reasonable to assume that the comprehensive electronic searches employed in this review identified all existing randomised controlled trials thereby helping to limit bias in the conduct of this review, the absence of any other published trials over the intervening 10 years and the scant contribution of the 4 included trials to the outcomes specified for this review, might be a cause for concern about publication bias. Moreover, even though only a small number of trials were identified and an assessment of

publication bias could not be made, one cannot safely discount the possible existence of some unpublished studies with similar, i.e. null to very marginal, beneficial results or reporting additional side-effects.

Potential biases in the review process

We made every attempt to limit bias in the review process by ensuring a comprehensive search for potentially eligible studies. The authors' independent assessments of eligibility of studies for inclusion in this review and the extraction of data minimised the potential for additional bias beyond that detailed in the 'Risk of bias' tables. The incompleteness of some of the reports and our inability to obtain clarification of certain trial details or to resolve ambiguities in the reports may have contributed to some bias in their assessment, but where these conditions applied, this was explicitly stated in the text of our review.

Agreements and disagreements with other studies or reviews

We are unaware of any other published systematic reviews, but we have examined several evidence-supported guidelines on the treatment of urticaria. Although one of these guidelines ([Zuberbier 2009b](#)) concluded that the quality of evidence for the effectiveness of H2-receptor antagonists was very low and provides a weak recommendation for their use, the guideline developers concede that they did not conduct a "detailed assessment of the quality criteria for the individual studies". The BSACI guidelines ([Powell 2007](#)) concluded that H2-receptor antagonists are not recommended as monotherapy but "may be useful in combination with H1-antihistamines" referring to a relevant study by [Paul 1986](#), which was excluded from this review. The guidelines by [Grattan 2007](#) also concluded that an H2-antihistamine may sometimes give better control of urticaria than an H1-antihistamine taken alone, based on the studies by [Paul 1986](#) and [Bleehen 1987](#), both of which were excluded from our review.

AUTHORS' CONCLUSIONS

Implications for practice

The evidence presented in this review was based on a few old and relatively small (in sample size) studies, half of which were categorised as at high risk of bias. Although some of these studies have reported a measure of relief of symptoms of urticaria and rather minimal clinical improvement in some of the participants, the evidence for the effectiveness of these interventions was weak and unreliable and does not, at present, allow confident decision-

making about the use of H2-receptor antagonists used alone or when combined with H1-antihistamines for urticaria.

Until - and if - further evidence becomes available, clinicians should continue to base their decisions on the management of urticaria on therapeutic regimens recommended in relevant clinical guidelines (Powell 2007; Zuberbier 2009b) and in conjunction with an assessment of their patients' individual circumstances and preferences.

Implications for research

A review of histamine H2-receptor antagonists for urticaria provides an example where there is very limited and unreliable evidence, which is based on several old studies, of the effects of some of these interventions on the resolution and reduction of symptoms of urticaria. There is not enough evidence based on this review to answer the question of whether H2- plus H1-receptor antagonists are better than just H1-receptor antagonists alone.

Although we make no specific recommendations for future research, we suggest the following strategy should apply in general to any further trials which might consider investigating these interventions.

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

the risk of bias and the overall quality of the evidence. Although it is uncertain whether reported quality mirrors actual study conduct, it is noteworthy that studies with unclear methodology have been shown to produce biased estimates of treatment effects (Schulz 1995). Adherence to guidelines, such as the CONSORT statement, would help ensure complete reporting.

Outcomes collected in future trials should be primarily based on a standardised scale of the participant's assessment of the treatment efficacy and also have a greater emphasis on changes in quality of life as a result of the interventions.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Lin 2000

Methods	This was a prospective, double-blind, RCT. Setting Departments of Emergency Medicine and Medicine, Saint Vincent's Hospital & Medical Center of New York and New York Medical College, New York, NY, US Date of study May 1998 and April 1999 Duration of study 2 hours
Participants	Inclusion criteria of the trial - Adults (> 18 years) with acute allergic syndromes, i.e. acute urticaria, acute angioedema, acute unexplained stridor (loud wheezing), acute pruritic rash - Present for < 12 hours from the time of alleged allergen exposure - Due to ingested food; ingested, inhaled, or injected drug; or after contact with latex Exclusion criteria of the trial - Pregnancy Randomised 100 participants were randomised: 21 men and 27 women in the ranitidine and diphenhydramine group, and 15 men and 28 women in the diphenhydramine group Age The median age in the ranitidine and diphenhydramine group was 32.3 years (ranging from 19.6 to 79.4) and 31.7 years (ranging from 21.3 to 74.4) in the diphenhydramine group Baseline data The median duration of symptoms was 1 hour in the ranitidine and diphenhydramine group and 2 hours in the diphenhydramine group. Stridor, tongue swelling, or laryngoedema affected 5 participants in each group Antihistamines were taken by 10 participants in the preceding 36 hours of the study (by 4 in the ranitidine and diphenhydramine group and 6 diphenhydramine group) Withdrawals/dropouts There were 9 withdrawals/dropouts after randomisation: 1 participant was inadvertently studied twice and 8 were lost prior to administration
Interventions	Intervention A: 50 mg diphenhydramine and 50 mg ranitidine (H1 + H2) intravenously (48) Control intervention B: 50 mg diphenhydramine and normal saline solution (H1) intravenously (43) Supplemental medications, e.g. epinephrine, corticosteroids, bronchodilators and additional doses of antihistamines, were "administered at the discretion of the study physicians"
Outcomes	Assessments were at baseline and 1 hour and 2 hours relative to the experimental treatment Primary outcomes of the trial

	1) Investigator-assessed resolution of urticaria (check-off cartoon of body areas) and angioedema at 2 hours Secondary outcomes of the trial 1) Heart rate, blood pressure, and respiratory rates 2) Side-effects 3) Symptoms (none, mild, moderate, and severe)	
Notes	Only data on participants with acute urticaria (29 in the ranitidine and diphenhydramine group and 24 in the diphenhydramine group) were included	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 463): "Recruited patients were randomly assigned to treatment...on the basis of a random number assignment list." Comment: This was probably done.
Allocation concealment (selection bias)	Low risk	Quote (page 463): "Recruited patients were randomly assigned to treatment... Each treatment designation was placed in a sealed opaque envelope stored in a locked cabinet." Comment: A form of central allocation was probably done.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (page 463): "A staff member uninvolved with the patient's care then drew into a syringe either 50 mg of ranitidine solution or an equal volume of normal saline solution on the basis of a random number assignment list. Immediately after an intravenous injection of 50 mg of diphenhydramine was given, the unmarked syringe containing either saline solution or ranitidine was then given to the study physician, who was unaware of its contents." Comment: The report provides sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement. We judged this as at a low risk of bias
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (page 463): "A staff member uninvolved with the patient's care then drew into a syringe either 50 mg of ranitidine so-

		lution or an equal volume of normal saline solution on the basis of a random number assignment list. Immediately after an intravenous injection of 50 mg of diphenhydramine was given, the unmarked syringe containing either saline solution or ranitidine was then given to the study physician, who was unaware of its contents.” Comment: The outcomes were investigator-assessed. We judged that the intended blinding of participants and key personnel was probably effective and unlikely to introduce bias into the outcome assessment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	9/100 were not included in the analysis (1 was inadvertently studied twice, and 8 withdrew after the study medication had been obtained, but before administration). Another 9 were reclassified, but included on the basis of an intention-to-treat (ITT) analysis Comment: 9 dropouts were equally balanced between the 2 groups. We judged this as at a low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appear to have been reported Comment: We judged this as at a low risk of bias.
Other bias	Unclear risk	10 participants took antihistamines (4 in the ranitidine and diphenhydramine group and 6 in the diphenhydramine group) < 36 hours prior to the study. There was no declaration of potential conflicts of interest or funding support Comment: There was insufficient information to permit a clear judgement of the risk of bias

Pontasch 1993

Methods	This was an active-controlled, prospective, double-blind, RCT Setting This was a 2-centre study: Emergency Department, Fisher Titus Hospital, Norwalk; and E.D, Akron General Medical Center, Akron, US Date of study This was unspecified, but it was conducted over a 1-year period Duration of the study 5 days	
Participants	Inclusion criteria of the trial • With hives present less than a week Exclusion criteria of the trial • Pregnancy, underlying known malignancies, taking warfarin, benzodiazepines, antihistamines, corticosteroids, known allergies to the medications Randomised 33 participants were randomised: 5 men and 15 women; the gender of 13 participants was unclear Age Participants were aged from 19 to 87 years. Baseline data This was not stated. Withdrawals/dropouts There were 13 withdrawals/dropouts after randomisation: 8 were lost to follow up and 5 were non-compliant	
Interventions	A: Group I: diphenhydramine 25 mg orally 4 times a day (H1) (7) B: Group II: famotidine 20 mg orally twice a day (H2) (6) C: Group III: cromolyn sodium 200 mg orally 4 times a day (H1) (7) These were administered for 5 days.	
Outcomes	Only participant-assessed outcomes were measured by questionnaire 10 days after ED of the hospital discharge Primary outcomes of the trial 1) Time to relief of symptoms 2) Adverse effects 3) Patient satisfaction rated on a scale from 1 (dissatisfaction) to 10 (recommending repeat use) 4) Patient perception of effectiveness (scale 1 to 10, with 1 to 4 meaning not effective and 8 to 10 indicating that they would use again) Secondary outcomes of the trial These were not stated.	
Notes	-	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement

Random sequence generation (selection bias)	Low risk	Quote (page 730): "The hospital pharmacist randomized the distribution of medications." Comment: Pharmacy-controlled randomisation was probably done
Allocation concealment (selection bias)	Low risk	Quote (page 730): "The hospital pharmacist randomized the distribution of medications." Comment: A form of central allocation was probably done.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote (page 730): "...medications were provided in identical containers"; "The contents of the containers were unknown to the person compiling the questionnaires." Comment: It was unclear if the medications were similar in packaging and appearance. We judged that it was unclear if the outcome is likely to be influenced by the lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote (page 730): "...medications were provided in identical containers"; "The contents of the containers were unknown to the person compiling the questionnaires." Comment: It was unclear if the medications were similar in packaging and appearance The outcomes were participant-assessed. We judged that it was unclear if the outcome assessment was likely to have been influenced by the lack of blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	There were 13/33 (39%) losses to follow up/protocol deviation, incomplete data for outcomes that were prespecified for this review, and per-protocol analysis of this data. Comment: We judged this as at a high risk of bias.
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appear to have been reported Comment: We judged this as at a low risk of bias.

Other bias	Unclear risk	No pre-study wash-out was reported. However, taking antihistamines was an exclusion criterion. There was no declaration of potential conflicts of interest or funding support Comment: There was insufficient information to permit a clear judgement of the risk of bias
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Runge 1992

Methods	This was an active-controlled, prospective, double-blind, RCT Setting Department of Emergency Medicine, Carolinas Medical Center, Charlotte, North Carolina and Division of Emergency Medicine, University of Utah School of Medicine, Salt Lake City, US Date of study This was unspecified. Duration of study 2 days
Participants	Inclusion criteria of the trial 18 to 50 years presenting to ED with signs and symptoms of allergic reactions, i.e. pruritus, urticaria, throat tightness, or facial swelling of < 12-hour duration Exclusion criteria of the trial - Taking H1- or H2-antihistamines or corticosteroids, known allergy to study drugs, heart disease, pregnancy or lactation, asthma, chronic obstructive pulmonary disease, respiratory distress, or unstable vital signs Randomised 39 participants were randomised: 15 men and 24 women (only 33 with urticaria) Age The mean age of participants was 31.7 years (SD 9.3). Baseline data Pruritus: 89.5 mm on VAS scale $\pm$ 25.9 in diphenhydramine (DPN) group, 77.4 $\pm$ 25.6 in cimetidine (CTD) group, 81.9 $\pm$ 26.8 in DPN+CTD group Urticaria 51.8 mm on VAS scale $\pm$ 17.0 in DPN group 73.1 $\pm$ 16.6 in CTD group, 74.3 $\pm$ 14.3 in DPN + CTD group Withdrawals/dropouts None were reported.
Interventions	All medications were diluted in injectable saline and delivered intravenously A: Group I: 50 mg diphenhydramine (DPN) plus placebo (H1) (11) B: Group II: 300 mg cimetidine (CTD) plus placebo (H2) (10) C: Group III: 50 mg diphenhydramine plus 300 mg cimetidine (H1 + H2) (12) At discharge participants were given oral preparations of study medication

Outcomes	Evaluation was 30 minutes after treatment. Primary outcomes of the trial 1) Investigator-assessed degree of urticaria (VAS) 2) Investigator-assessed pharyngeal tissue swelling/facial swelling (VAS) 3) Participant-assessed symptoms of pruritus (VAS) 4) Participant-assessed throat tightness/facial swelling (VAS) Secondary outcomes of the trial 1) Adverse events 2) Pulse, respiratory rate, and blood pressure 5, 10, and 30 minutes after injections	
Notes	Only data from participants with acute urticaria (n = 33) was included	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 238): "...randomized by the pharmacies at each hospital" Comment: Pharmacy-controlled randomisation was probably done
Allocation concealment (selection bias)	Low risk	Quote (page 238): "A heparin lock adaptor was placed, and subjects were given the study medication intravenously from vials prepared, blinded, and randomized by the pharmacies at each hospital." Comment: A form of central allocation was probably done.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (page 238): "A heparin lock adaptor was placed...vials prepared, blinded, and randomized by the pharmacies at each hospital" Comment: The report provides sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received to permit a clear judgement. We judged this as at a low risk of bias
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (page 238): "A heparin lock adaptor was placed, and subjects were given the study medication intravenously from vials prepared, blinded, and randomized by the pharmacies at each hospital." Comment: Outcomes were investigator- and participant-assessed. We judged that the intended blinding of participants and

Runge 1992 (Continued)

		key personnel was probably effective and unlikely to introduce bias into the outcome assessment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts were reported and ITT analysis. Comment: We judged this as at a low risk of bias.
Selective reporting (reporting bias)	Unclear risk	Participant- and investigator-assessed outcomes of facial swelling and swelling of the throat were not reported, although they were prespecified in the methods section. However, these were not preselected outcomes in this review Comment: There was insufficient information to permit a clear judgement of the risk of bias
Other bias	Unclear risk	No pre-study wash-out was reported, but participants taking antihistamines were excluded There was no declaration of potential conflicts of interest or funding support Comment: There was insufficient information to permit a clear judgement of the risk of bias

Watson 2000

Methods	This was an active-controlled, prospective, double-blind, RCT Setting Division of Emergency Medicine, Department of Surgery, Stanford University School of Medicine, Stanford, California, USA Date of study July 1995 to August 1997 Duration of study 30 minutes
Participants	Inclusion criteria of the trial - Age 18 to 55 years with acute urticaria, i.e. the presence of pruritic weals, < 72-hour duration Exclusion criteria of the trial - Known allergies to famotidine or diphenhydramine, pregnant or lactating, bronchospasm or pharyngeal oedema, unstable vital signs, angioedema Randomised 25 participants were randomised: 11 men and 14 women. Age The mean age (range) of participants was 29 ± 9 years in the famotidine group and 28

	± 6 years in the diphenhydramine group Baseline data - Participant-rated pruritus (mm) = 59 ± 29 in the famotidine group and 69 ± 29 in the diphenhydramine group - Participant-rated sedation (mm) = 33 ± 21 in the famotidine group and 26 ± 28 in the diphenhydramine group - Physician-rated body surface area (%) = 39 ± 30 in the famotidine group and 33 ± 19 in the diphenhydramine group - Intensity of urticaria (mm) = 56 ± 24 in the famotidine group and 55 ± 26 in the diphenhydramine group Withdrawals/dropouts There were no dropouts.	
Interventions	A: Group I: famotidine 20 mg intramuscular (H2) (15) B: Group II: diphenhydramine 50 mg intramuscular (H1) (10)	
Outcomes	Primary outcomes of the trial 1) Investigator-assessed percentage of total body surface area covered by urticaria using the 'Rule of Nines' 2) Investigator-assessed weal intensity (VAS) 3) Investigator-assessed reviewed vital signs 4) Participant-assessed symptoms of itching (VAS) 5) Participant-assessed drowsiness (VAS) Secondary outcomes of the trial These were not stated.	
Notes	Approximately half of the subjects in both groups required additional medication before discharge	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 186): "...a double-blind, randomized, controlled trial" Comment: There was insufficient detail reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during enrolment, was not reported Comment: There was insufficient information to permit a clear judgement of the risk of bias

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (page 186): “double-blind”, “subjects were administered either famotidine 20 mg i.m. or diphenhydramine 50 mg i.m. ..placed in blinded vials by the study pharmacists.” Comment: The report provides sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement. We judged this as at a low risk of bias
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (page 186): “double-blind”, “After completion of the pretreatment questionnaire, subjects were administered either famotidine 20 mg i.m. or diphenhydramine 50 mg i.m”, “placed in blinded vials by the study pharmacists” Comment: Outcomes were participant-assessed and investigator-assessed. We judged that the intended blinding of participants and key personnel was probably effective and unlikely to introduce bias into the outcome assessment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts were reported and ITT analysis. Comment: We judged this as at a low risk of bias.
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appear to have been reported Comment: We judged this as at a low risk of bias.
Other bias	Unclear risk	The pre-study wash-out period was not reported, but inclusion criteria specified urticaria history only < 72 hours. 2 in the famotidine group and 1 in the diphenhydramine group took H1RA in the 12 hours preceding the study. This has a potential impact as the effect modifier is unclear There was no declaration of potential conflicts of interest or funding support Comment: There was insufficient information to permit a clear judgement of the risk

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Blanca-Gomez 1984	This was not a RCT.
Bleehen 1987	This was a RCT, but participants had chronic urticaria and interventions included H2-antihistamines and H1-antihistamines. This study will be included in the Cochrane review on H1-antihistamines for chronic urticaria
Commens 1978	This was a RCT, but participants had chronic urticaria and interventions included H2-antihistamines and H1-antihistamines. This study will be included in the Cochrane review on H1-antihistamines for chronic urticaria
Cook 1979	This was a RCT, but participants had chronic urticaria and interventions included H2-antihistamines and H1-antihistamines. This study will be included in the Cochrane review on H1-antihistamines for chronic urticaria
Cook 1983	This was a RCT, but participants had chronic urticaria and interventions included H2-antihistamines and H1-antihistamines. This study will be included in the Cochrane review on H1-antihistamines for chronic urticaria
Diller 1983	This was a RCT, but participants had chronic urticaria and interventions included H2-antihistamines and H1-antihistamines. This study will be included in the Cochrane review on H1-antihistamines for chronic urticaria
Harvey 1981	This was a RCT, but participants had chronic urticaria and interventions included H2-antihistamines and H1-antihistamines. This study will be included in the Cochrane review on H1-antihistamines for chronic urticaria
Kaur 1981	This was a cross-over study. No data was available for each participant at each intervention period to permit a paired analysis of the within-person effects of the interventions as recommended by Elbourne 2002 .
Matthews 1979	This was a cross-over study. No data was available for each participant at each intervention period to permit a paired analysis of the within-person effects of the interventions as recommended by Elbourne 2002 .
Michell 1980	This was not a RCT.
Moscato 1990	This was reported as a RCT, but randomisation was by alternation (quasi-randomised controlled clinical trial)
Paul 1986	This was a RCT, but participants had chronic urticaria and interventions included H2-antihistamines and H1-antihistamines. This study will be included in the Cochrane review on H1-antihistamines for chronic urticaria
Paul 1987	The study included healthy subjects.

(Continued)

Sharpe 1993	This was a cross-over study. No data was available for each participant at each intervention period to permit a paired analysis of the within-person effects of the interventions as recommended by Elbourne 2002 .
Simons 1995	This was a RCT, but participants had chronic urticaria and interventions included H2-antihistamines and H1-antihistamines. This study will be included in the Cochrane review on H1-antihistamines for chronic urticaria
Wan 2009	This was a RCT, but participants had chronic urticaria and interventions included H2-antihistamines and H1-antihistamines. This study will be included in the Cochrane review on H1-antihistamines for chronic urticaria
Wozel 1990	This was a RCT, but participants had chronic urticaria and interventions included H2-antihistamines and H1-antihistamines. This study will be included in the Cochrane review on H1-antihistamines for chronic urticaria

RCT = Randomised controlled trial

ED = Emergency Department

DATA AND ANALYSES

This review has no analyses.

ADDITIONAL TABLES

Table 1. Glossary

Acute spontaneous urticaria	Spontaneous weals and/or angioedema < 6 weeks
Chronic spontaneous urticaria	Spontaneous weals and/or angioedema > 6 weeks
Physical urticaria	Cold urticaria - the eliciting factors are cold objects/air/fluids/wind Delayed pressure urticaria - the eliciting factor is vertical pressure (weals arising with 3 to 12 hours latency) Heat contact urticaria - the eliciting factor is localised heat Solar urticaria - the eliciting factors are UV and/or visible light Urticaria factitia/dermographic urticaria - the eliciting factor is mechanical shearing forces (weals arising after 1 to 5 minutes) Vibratory urticaria/ angioedema - the eliciting factor is vibratory forces (e.g. pneumatic hammer)
Other urticaria types	Aquagenic urticaria - the eliciting factor is water Cholinergic urticaria - the eliciting factor is increase of body core temperature due to physical exercises/spicy foods, etc Contact urticaria - the eliciting factor is contact with a urticariogenic substance Exercise-induced urticaria/anaphylaxis - the eliciting factor is physical exercise

HISTORY

Protocol first published: Issue 7, 2010

Review first published: Issue 3, 2012

Date	Event	Description
13 March 2009	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

Zbys Fedorowicz (ZF), Esther van Zuuren (EvZ) and Nianfang Hu (NF) were responsible for the following:

- organising the retrieval of papers (EvZ and ZF);
 - screening search results (ZF, EvZ and NF);
 - screening retrieved papers against the inclusion criteria (ZF, EvZ, and NF);
 - assessing risk of bias (EvZ and ZF);
 - data collection for the review (EvZ and ZF);
 - extracting data from papers (EvZ and ZF); and
 - obtaining and screening data on unpublished studies.
- EvZ and ZF entered the data into Review Manager and were responsible for the analysis and interpretation of the data.
 - EvZ, ZF and NF contributed to writing the review.
 - All review authors were responsible for designing and co-ordinating the review and for data management for the review.
 - NH and ZF conceived the idea for the review and are the guarantors for the review.

DECLARATIONS OF INTEREST

The authors of this review have no financial conflicts of interest, and they do not have any association with any parties who may have vested interests in the results of this review.

SOURCES OF SUPPORT

Internal sources

- No sources of support, Not specified.

External sources

- No sources of support, Not specified.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We made minor changes to the protocol in the process of conducting the review: The background section was updated, and the objectives were written more succinctly.

INDEX TERMS

Medical Subject Headings (MeSH)

Cimetidine [adverse effects; therapeutic use]; Diphenhydramine [adverse effects; therapeutic use]; Drug Therapy, Combination [methods]; Famotidine [adverse effects; therapeutic use]; Histamine H1 Antagonists; Histamine H2 Antagonists [adverse effects; *therapeutic use]; Randomized Controlled Trials as Topic; Ranitidine [adverse effects; therapeutic use]; Urticaria [*drug therapy]

MeSH check words

Humans