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H1-antihistamines for chronic spontaneous urticaria: An abridged Cochrane Systematic Review

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Background: Chronic spontaneous urticaria is characterized by recurrent itchy wheals. First-line management is with H1-antihistamines.

Objective: We sought to conduct a Cochrane Review of H1-antihistamines in the treatment of chronic spontaneous urticaria.

Methods: A systematic search of major databases for randomized controlled trials was conducted.

Results: We included 73 studies with 9759 participants; 34 studies provided outcome data for 23 comparisons. Compared with placebo, cetirizine 10 mg daily in the short and intermediate term (RR 2.72; 95% confidence interval [CI] 1.51-4.91) led to complete suppression of urticaria. Levocetirizine 20 mg daily was effective for short-term use (RR 20.87; 95% CI 1.37-317.60) as was 5 mg for intermediate-term use (RR 52.88; 95% CI 3.31-843.81). Desloratadine 20 mg was effective for the short term (RR 15.97; 95% CI 1.04-245.04) as was 5 mg in the intermediate term (RR 37.00; 95% CI 2.31-593.70). There was no evidence to suggest difference in adverse event rates between treatments.

Limitations: Some methodological limitations were observed. Few studies for each comparison reported outcome data that could be incorporated in meta-analyses.

Conclusions: At standard doses, several antihistamines are effective and safe in complete suppression of chronic spontaneous urticaria. Research on long-term treatment using standardized outcome measures and quality of life scores is needed. (J Am Acad Dermatol http://dx.doi.org/10.1016/j.jaad.2015.06.048.)

Key words: chronic spontaneous urticaria; Cochrane; H1-antihistamines; review; treatment.

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The full version of the review is available in the Cochrane Library: 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. Cochrane Reviews are regularly updated as new evidence emerges and in response to feedback, and Cochrane Database of Systematic Reviews should be consulted for the most recent version of the review. See www.thecochranelibrary.com for information.

Disclaimer: The results of a Cochrane review can be interpreted differently, depending on people's perspectives and circumstances. The conclusions presented are the opinions of review authors, and are not necessarily shared by the Cochrane Collaboration.

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Chronic spontaneous urticaria (CSU), previously known as chronic idiopathic urticaria or chronic ordinary urticaria, is characterized by recurrent itchy wheals that appear for no identifiable reason. The condition is termed "chronic" when recurrent crops appear for more than 6 weeks.[1] There is a female to male predominance of 2:1[2] with a prevalence of between 0.5% and 1%.[3] The lack of predictability and frequency of symptoms often leads to distress and anxiety.

H1-antihistamines are the mainstay of treatment. These are usually classified as first- or second-generation according to their chemical structure and properties. Second-generation antihistamines tend to be less sedating.[4]

CAPSULE SUMMARY

- Chronic spontaneous urticaria is characterized by recurrent itchy wheals. First-line treatment is with H1-antihistamines.
- At standard doses, several antihistamines are effective and safe compared with placebo. Evidence for higher dosing is scarce.
- Further research is needed for longer duration of treatment using standardized and validated scores.

METHODS

Inclusion criteria

We included randomized controlled trials that evaluated the effectiveness of H1-antihistamines compared with placebo or another active treatment. Individuals of any age with a clinical diagnosis of CSU, chronic idiopathic urticaria, or chronic ordinary urticaria and use of H1-antihistamines at any dose, including topical interventions, were included. Terfenadine and astemizole were not included as they have been withdrawn from international markets because of safety issues. The interventions could be either single or combination therapy. The duration of intervention was categorized as short term (up to 2 weeks), more than 2 weeks to 3 months (intermediate term), and more than 3 months (long term).

Data extraction

Three authors extracted data independently using a data extraction form; any disagreements were resolved by consensus.

Searches

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 5 trials registers and checked articles for references to relevant randomized controlled trials. We contacted principal investigators for missing data.

Outcomes

We extracted data from studies based on 3 primary outcomes agreed on in the protocol of the review. These were the proportion of participants with complete suppression of urticaria, the proportion with good or excellent response while taking H1-antihistamines, and the proportion with 50% or greater improvement in quality of life (QoL) measures while taking H1-antihistamines.

We extracted data on 3 secondary outcomes: serious adverse events (requiring withdrawal of treatment), minor participant-reported adverse events not requiring withdrawal of treatment, and the proportion of participants who relapse within 1 month of stopping H1-antihistamines.

Review authors checked and entered the outcome data (numeric and nonnumeric) into RevMan data analysis software.[5] We used the Cochrane Collaboration's tool for assessing risk of bias, and rated the Cochrane risk of bias domains for each included study as low risk of bias, high risk of bias, and unclear if the risk of bias was uncertain or unknown.[5] We reported data according to a treatment by allocation principle whenever possible, and according to section 16.2.2 of the *Cochrane Handbook for Systematic Reviews of Interventions*.[6] If authors only presented a per-protocol analysis we assessed dropout imbalance between the trial arms. In the absence of intention-to-treat data, we used available case population data (per protocol) and reported this accordingly. We have presented continuous outcomes with a change from baseline or standardized mean difference and dichotomous outcomes as risk ratios (RR) with 95% confidence intervals (CI). Where we identified clinically similar studies that exhibited no worse than moderate heterogeneity ($I^2 < 60\%$), we pooled the data into a meta-analysis using a Mantel-Haenszel or inverse-variance (dichotomous or continuous data, respectively) method with a random effects model. We conducted subgroup analyses based on the duration of the intervention.

RESULTS

We identified 1080 references from our electronic database searches up to June 2014. In total, 73 studies (82 records) were included in the qualitative analysis

Abbreviations used:

CI: confidence interval
CSU: chronic spontaneous urticaria
QoL: quality of life
RR: risk ratio

(Fig 1). Of the 73 included studies, 34 yielded data for 23 comparisons (online supplementary material available at http://www.jaad.org).

The total number of randomized participants was 9759 comprising adults or mixed groups including adolescents (ie, >12 years old) and was predominantly female.

Interventions

The comparisons included first- and second-generation antihistamines; montelukast, a leukotriene receptor antagonist[7]; and doxepin, a sedative tricyclic antidepressant.[8]

Seventeen studies included a short-term duration of intervention[9-25] and the duration of intervention was not explicitly stated in 1 study[26] but we categorized this as short term on the basis of information given in the abstract report. One study[27] was of very short duration (5 hours) and the remaining 55 studies were intermediate-term duration. No studies had a long-term duration (>3 months). Sample sizes varied from several hundred participants to fewer than 25.

No study provided complete clarity on every item in our risk of bias assessment. Of the 73 included studies, 37 (50%) had at least 1 element of selection bias, performance and detection bias, attrition bias, or reporting bias that we rated as at high risk of bias **[F2-4/C]** (Fig 2). Other issues that could suggest a high risk of bias (eg, potential conflicts of interest, pharmaceutical funding or support) were also assessed. There were some notable methodological limitations in the included studies. Only 12 studies demonstrated clear and adequate randomization methods, and only 5 had adequate allocation concealment. Blinding of participants and personnel was adequate in 22 studies and blinding of outcome assessors adequate in 14. In 20 studies, the distribution or high number of dropouts or losses to follow-up could have introduced bias. In all, 24 studies were judged to be at low risk for selective reporting. 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.

Studies on cetirizine (10 mg daily)

Four studies compared cetirizine 10 mg versus placebo.[10,28-30] There was clear evidence that cetirizine increased the cessation of urticaria (RR 2.72; 95% CI 1.51-4.91; $P < .001$; $I^2 = 0\%$). One study[28] reported an increase in good response after treatment was seen in 45 of 60 (cetirizine) and 29 of 62 (placebo) participants ($P = .001$). Seven participants in 3 studies[28-30] withdrew because of adverse events, and 2 while taking placebo, that suggested a possible increase caused by cetirizine over the intermediate term; however, this was not statistically significant (RR 3.00; 95% CI 0.68-13.22; $P = .15$; $I^2 = 0\%$). Two studies[21,31] compared cetirizine 10 mg versus loratadine 10 mg. Both reported a similar proportion of participants with complete suppression of urticaria in each group. Overall, combining data from both studies, the RR was 1.05 (95% CI 0.76-1.43; $P = .77$; $I^2 = 0\%$) indicating no evidence of a difference. Two studies were identified that compared cetirizine 10 mg versus hydroxyzine 25 mg.[29,30] Both studies reported the number of participants who withdrew because of an adverse event with no evidence of a difference (RR of withdrawal 0.78; 95% CI 0.25-2.45; $P = .67$; $I^2 = 0\%$). One study compared cetirizine 10 mg versus fexofenadine 180 mg[32] and found that cetirizine increased the suppression of urticaria: 27 of 59 (cetirizine) compared with 2 of 57 (fexofenadine) ($P < .001$). One study compared cetirizine 10 mg versus levocetirizine 5 mg[33] and reported no difference in the suppression of urticaria or response to treatment. One study compared cetirizine 10 mg versus mizolastine 10 mg[31] and reported no difference in the complete suppression of urticaria or at least good response to treatment ($P = .60$).

Studies on desloratadine (5-20 mg daily)

Six studies compared desloratadine 5 to 20 mg versus placebo.[7,26,34-37] One did not provide efficacy data that could be included in our meta-analyses.[36] Another[26] investigated 3 doses of desloratadine (5, 10, and 20 mg) compared with placebo using a short-term duration of intervention and reported suppression of urticaria in 4 of 34, 11 of 34, 21 of 34, and 0 of 36 participants, respectively, suggesting a dose-response relationship. One study[34] used an intermediate term of intervention and reported complete suppression of urticaria in 18 of 40 (desloratadine 5 mg) and 0 of 40 (placebo) ($P < .001$). We did not pool across all dosages and durations of intervention, but because no participants in the placebo group exhibited suppression of urticaria, a Fishers Exact test was used to compare the two (53 of 142 desloratadine and 0 of 76 placebo). The 95% CI for the OR was between 7.12 and infinity ($P < .001$). Additional data obtained from the principal investigator of the study by Di Lorenzo et al[7] in 2004

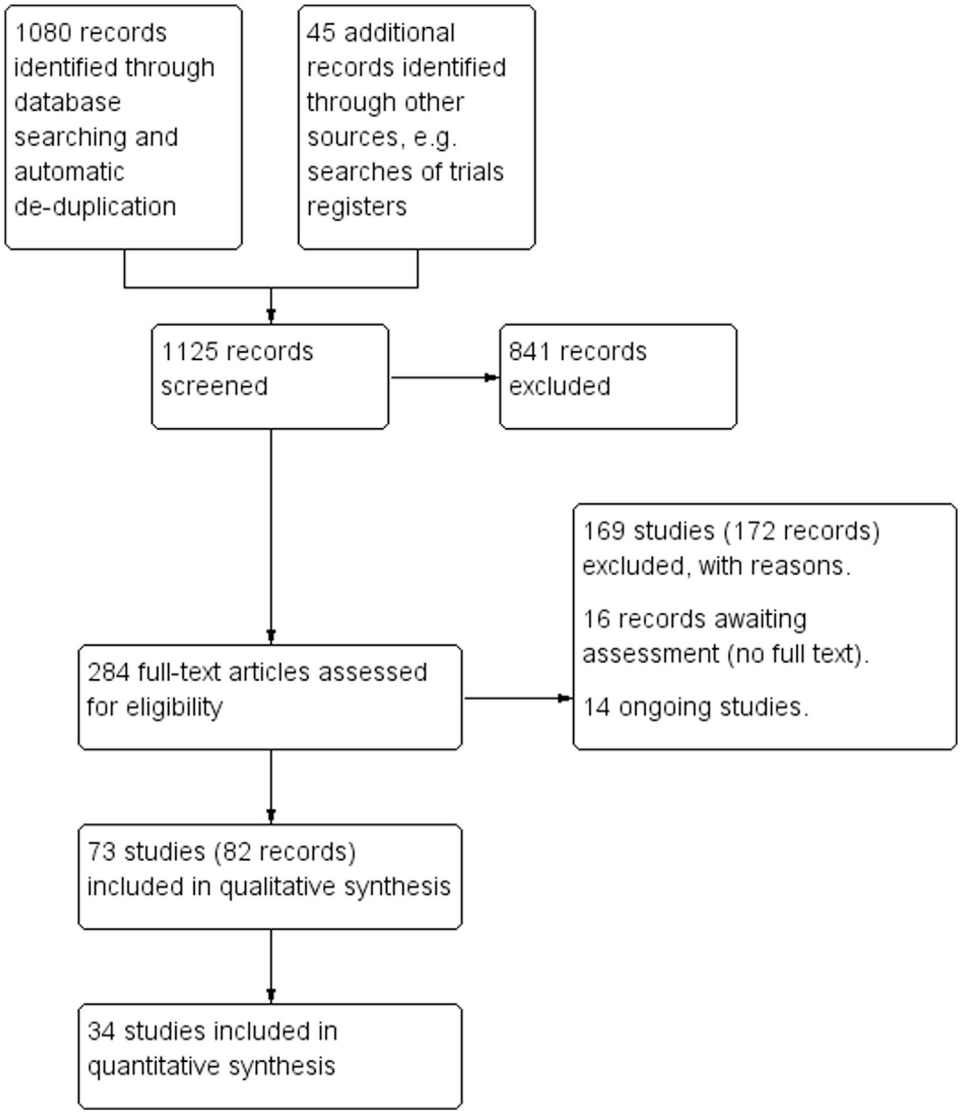

Fig 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) diagram of study flow.

indicated that 22 of 40 in the intervention group and 0 of 40 participants in the placebo group experienced an excellent response ($P < .001$). In all, 34 of 49 participants (desloratadine 5 mg) and 23 of 36 (placebo) exhibited an improvement in QoL.[36] There was no significant difference in withdrawals as a result of adverse effects between desloratadine 5 mg and placebo (RR 1.46; CI 0.42-5.1).[35,37] Two studies compared levocetirizine 5 to 20 mg with desloratadine 5 to 20 mg.[26,38] No meta-analysis was possible for this comparison. The proportion of participants exhibiting suppression of urticaria in the desloratadine group (5, 10, and 20 mg) was 4, 11, and 21 of 34. The higher dose results in this small study might suggest that higher doses were more effective. The second study[38] found an increased chance of a good treatment response from levocetirizine 5 mg compared with desloratadine 5 mg (294 of 438 vs 256 of 448). Levocetirizine appeared to be more effective than desloratadine. In an intermediate-term duration of intervention study,[39] levocetirizine completely suppressed urticaria in 27 of 51 participants compared with placebo (0 of 51) ($P < .001$). In neither study were there withdrawals because of adverse effects. One study compared desloratadine 5 mg versus montelukast 10 mg.[7] There was an increase in complete suppression and response in the desloratadine group ($P = .008$ and $P < .001$, respectively). Adverse events were noted to be of low frequency, but a large number of withdrawals occurred because of lack of efficacy in the group not receiving desloratadine.

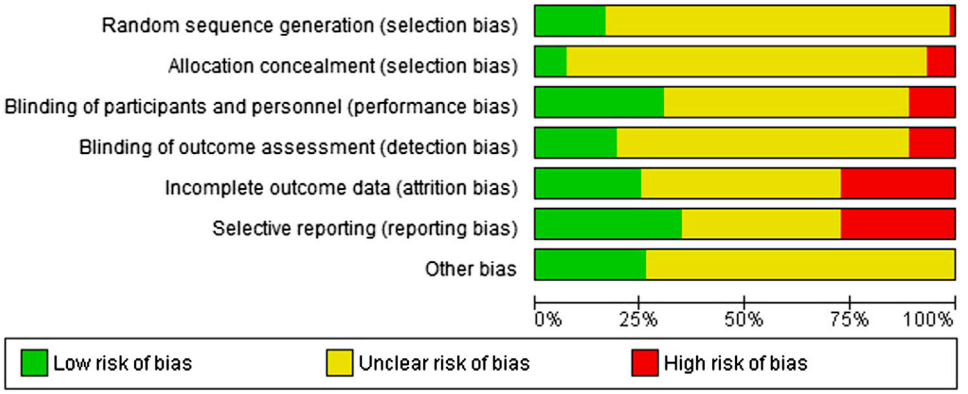

Fig 2. Graph of bias risk.

Three studies[40-42] with a total of 410 participants reported no significant difference in efficacy between loratadine 10 mg and desloratadine 5 mg (RR 1.04; CI 0.64-1.71). In 2 of these[41,42] with medications taken once daily over an intermediate-term duration, the RR for complete suppression of disease was 0.91 (CI 0.78-1.06; P = .22; I^2 = 0%). All 3 studies individually concluded that loratadine and desloratadine were safe and effective for CSU. No pooling of adverse events was carried out, but the main side effects reported included mouth dryness, dizziness, and headache.

Studies on loratadine (10 mg daily)

Two studies compared loratadine 10 mg and placebo.[20] A combined analysis suggested that loratadine may increase the chance of a participant experiencing a good response, expressed as a risk ratio (RR) of 1.86 (95% CI 0.91-3.79; P = .09; I^2 = 0%).

Four studies were identified that compared loratadine 10 mg versus mizolastine 10 mg.[18,31,43,44] Three of these assessed complete suppression of urticaria and a good response but a difference between treatments was found for neither outcome (RR 0.86; CI 0.64-1.16; I^2 = 55%; P = .109; and RR 0.9; CI 0.56-1.43; P = .64; I^2 = 0%, respectively). Two of these studies[43,44] reported an improvement in QoL of at least 50% but without significant difference between the treatments (RR 3.21; CI 0.32-32.33; I^2 = 65%). There was no difference in numbers of withdrawals as a result of adverse events (RR 0.38; CI 0.04-3.6; P = .40; I^2 = 0%). A single study of loratadine 10 mg versus emedastine 2 mg[45] reported no difference in suppression of urticaria or response to treatment (RR 1.04; 95% CI 0.78-1.39; good response RR 1.09; 95% CI 0.96-1.24). No withdrawals attributable to the study medications occurred. Comparison of loratadine versus desloratadine is detailed above.

One study compared loratadine 10 mg versus hydroxyzine 25 mg[20] and found no difference in the suppression of urticaria (RR 1.00; 95% CI 0.32-3.10). Overall, 8 of 20 participants in the hydroxyzine group and 1 of 20 in the loratadine group reported sedation as a minor adverse event (P = .02).

Studies on hydroxyzine (25 mg daily)

Three studies were identified that compared hydroxyzine 25 mg versus placebo.[20,29,30] However, the small number of participants in each meant little evidence of any difference between the interventions in terms of efficacy. For adverse events there was similarly little evidence of differences between interventions.[29,30] One study mentioned above assessed hydroxyzine versus loratadine.

Studies on rupatadine (10-20 mg daily)

One study compared rupatadine 10 to 20 mg versus placebo over an intermediate-term duration of intervention (n = 122).[46] Meta-analysis of the pooled RR between rupatadine (at both doses) and placebo was 1.35 (95% CI 1.03-1.77; P = .03; I^2 = 0%); thus, rupatadine increased the chance of a good response but there was little evidence to indicate that 10 mg was more effective than 20 mg.

Other comparisons

One study[22] compared ebastine 10 mg versus placebo and found no statistically significant difference in efficacy (Fisher exact test P = .13).

Another compared fexofenadine 180 mg versus placebo.[47] Although no significant differences were found in suppression of urticaria (P = .272), at least a good response was more frequent with fexofenadine: 57 of 162 (fexofenadine) and 11 of 91 (placebo) (P < .001). Participants who were previously unresponsive to antihistamines were excluded, so this result may not be generalizable.

For ketotifen 1 mg (with chlorpheniramine 4 mg as required) versus placebo,[23] the requirement for chlorpheniramine dropped in significantly more participants taking ketotifen than placebo (94% vs 7%). For doxepin 10 mg versus pheniramine 22.5 mg,

8 of 28 and 3 of 28 participants experienced complete suppression of urticaria (doxepin and pheniramine, respectively; $P < .001$). A small study of azelastine 2 mg versus azelastine 4 mg[48] found no efficacy differences. For further details of these analyses, please see the full review within the Cochrane Library.[49]

DISCUSSION

The evidence indicates that several antihistamines are effective in suppressing CSU. The primary studies included in this review individually carry a varying risk of bias (Fig 2). For general use, to achieve complete suppression of urticaria, the evidence supports the use of cetirizine at 10 mg once daily for short- and intermediate-term duration. There may be benefit in using desloratadine at 5 mg once daily for at least an intermediate term of intervention and 20 mg desloratadine in the short term. Levocetirizine at 5 mg once daily in the intermediate term also appears to be effective at achieving complete suppression of CSU. This is based on the results of 3 trials. We rated 2 of these as carrying an unclear risk of bias in every domain, although the third study, while small, was relatively well conducted and reported. Although we included trials of various other drugs, the data are too sparse to draw firm conclusions about their relative efficacy.

There is some evidence to support the use of higher doses of antihistamines (eg, levocetirizine up to 20 mg) as recommended in the European guidelines[50] and future work should address these gaps.

Few of the included studies reported data that corresponded with the predetermined outcomes of this review. Primary outcome scores were variable, making direct comparisons difficult. We have drawn limited conclusions from single-study analyses, reported trial results narratively, or presented results from small meta-analyses of up to 3 studies. Overall there was mixed evidence and each comparison was rated as moderate or low quality.

CSU can last for several years. We found no studies lasting over 3 months. Only 9 trials assessed whether responses were sustained after stopping the intervention. Trials with active treatment arms rather than a placebo, with comparisons of different doses over longer periods would be a more comprehensive way to gather relevant information. In future research, we would favor the use of standardized outcome scores such as the Urticaria Activity Score 7, which comprises the daily sum of 4-point scales (0-3) for number of wheals and pruritus over 7 days and is recommended in the European guidelines.[50] This, along with validated QoL scores for trial participants, would provide comparable data to help aid treatment decisions.

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ONLINE SUPPLEMENTARY INFORMATION

For full details, please see the full Cochrane Review.[S1]

COMPARISONS USED IN ANALYSES

A total of 73 trials met our inclusion criteria. Of these, only 34 trials provided outcome data for the following comparisons.[S2-S72]

- Loratadine 10 mg versus placebo (Belaich et al,[S2] 1990; Monroe,[S3] 1992).
- Loratadine 10 mg versus cetirizine 10 mg (Patel and Danzig,[S4] 1997; Yin et al,[S5] 2003).
- Loratadine 10 mg versus desloratadine 5 mg (Gu et al,[S6] 2002; Hao et al,[S7] 2003; Zou and Chen,[S8] 2002).
- Loratadine 10 mg versus mizolastine 10 mg (Guo et al,[S9] 2003; Leynadier et al,[S10] 2000; Liu et al,[S11] 2003; Yin et al,[S5] 2003).
- Loratadine 10 mg versus emedastine 2 mg (Pons-Guiraud et al,[S12] 2006).
- Loratadine 10 mg versus hydroxyzine 25 mg (Monroe,[S3] 1992).
- Cetirizine 10 mg versus placebo (Breneman et al,[S13] 1995; Breneman,[S14] 1996; Go et al,[S15] 1989; Kalivas et al,[S16] 1990).
- Cetirizine 10 mg versus hydroxyzine 25 mg (Breneman,[S14] 1996; Kalivas et al,[S16] 1990).
- Cetirizine 10 mg versus fexofenadine 180 mg (Handa et al,[S17] 2004).
- Cetirizine 10 mg versus levocetirizine 5 mg (Yin et al,[S18] 2003).
- Cetirizine 10 mg versus mizolastine 10 mg (Yin et al,[S5] 2003).
- Desloratadine 5 mg to 20 mg versus placebo (Di Lorenzo et al,[S19] 2004; Hoxha et al,[S20] 2011; Monroe et al,[S21] 2003; Nettis et al,[S22] 2004; Ortonne et al,[S23] 2007; Ring et al,[S24] 2001).
- Hydroxyzine 25 mg versus placebo (Breneman,[S14] 1996; Kalivas et al,[S16] 1990; Monroe,[S3] 1992).
- Levocetirizine 5 mg to 20 mg versus placebo (Hoxha et al,[S20] 2011; Nettis,[S72] 2006).
- Rupatadine 10 mg to 20 mg versus placebo (Gimenez-Arnau et al,[S25] 2007).
- Desloratadine 5 mg to 20 mg versus levocetirizine 5 to 20 mg (Hoxha et al,[S20] 2011; Potter et al,[S26] 2009).
- Ebastine 10 mg versus placebo (Peyri et al,[S27] 1991).
- Desloratadine 5 mg versus montelukast 10 mg (Di Lorenzo et al,[S19] 2004).
- Fexofenadine 180 mg versus placebo (Kaplan et al,[S28] 2005).
- Ketotifen 1 mg versus placebo (Phanuphak et al,[S29] 1987).
- Cetirizine 5 mg and hydroxyzine 25 mg versus placebo (Wan,[S30] 2009).
- Azelastine 2 mg versus azelastine 4 mg (Wu et al,[S31] 2008).
- Doxepin 10 mg versus pheniramine 22.5 mg (Ghosh and Haldar,[S32] 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 et al,[S10] 2000).
- Acrivastine 8 mg, chlorphen(ir)amine maleate 4 mg (Gale et al,[S33] 1989).
- Acrivastine 8 mg, clemastine 1 mg, placebo (Juhlin et al,[S34] 1987).
- Acrivastine 8 mg, hydroxyzine hydrochloride 20 mg (Salo et al,[S35] 1989).
- Azelastine 2 mg, azelastine 4 mg, azelastine and cimetidine (histamine H2-receptor antagonist [H2RA]) 2 mg (Wu et al,[S31] 2008).
- Cetirizine 10 mg, placebo (Juhlin,[S36] 1991).
- Cetirizine 10 mg plus placebo, terfenadine 60 mg, placebo (Go et al,[S15] 1989; Kint et al,[S37] 1989).
- Cetirizine 10 mg, terfenadine 120 mg, placebo (Garavaglia et al,[S38] 1995).
- Cetirizine 10 mg, placebo (cross-over) (Goh et al,[S39] 1991); non-cross-over (Alomar et al,[S40] 1990).
- Cetirizine 10 mg versus rupatadine 10 mg (Dakhale et al,[S41] 2014).
- Chlorphen(ir)amine 4 mg, chlorphen(ir)amine 4 mg plus cimetidine 400 mg (H1 + H2 antagonist), placebo (Marks,[S42] 1980).
- Cimetidine 200 mg plus chlorphen(ir)amine 4 mg, chlorphen(ir)amine 4 mg plus placebo, placebo (Commens and Greaves,[S43] 1978).
- Desloratadine 5 mg, placebo (Bronsky,[S44] 2001; Monroe et al,[S21] 2003; Ortonne et al,[S45] 2004; Ortonne et al,[S23] 2007; Ring et al,[S24] 2001).
- Desloratadine 5 mg, desloratadine 10 mg, desloratadine 20 mg (NCT00536380[S46]).
- Desloratadine 5 mg, desloratadine 20 mg (Weller et al,[S47] 2013).
- Desloratadine 5 mg and placebo, desloratadine 5 mg and montelukast 10 mg, placebo (Nettis et al,[S22] 2004).
- Fexofenadine 60, 120, 180, and 240 mg; placebo (Paul et al,[S48] 1998).
- Fexofenadine 60 mg, placebo (Thompson et al,[S49] 2000).
- Fexofenadine hydrochloride (HCl) 180 mg, levocetirizine 5 mg (Godse et al,[S50] 2007).
- Fexofenadine HCl 20, 60, 120, and 240 mg; placebo (Finn et al,[S51] 1999; Nelson et al,[S52] 2000).
- Fexofenadine 180 mg, placebo (Degonda et al,[S53] 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 et al,[S54] 1981).
- Ketotifen 1 mg, fluoxetine 20 mg (selective serotonin reuptake inhibitor–type antidepressant) (Sener et al,[S55] 1999).
- Levocetirizine 5 mg, bilastine 20 mg (Zuberbier et al,[S56] 2010).
- Levocetirizine 5 mg, desloratadine 5 mg (Potter et al,[S26] 2009).
- Levocetirizine 20 mg, levocetirizine 15 mg plus hydroxyzine 50 mg (Staevska et al,[S57] 2014).
- Loratadine 10 mg, levocetirizine 5 mg (Anuradha et al,[S58] 2010).
- Loratadine 10 mg, placebo (Monroe et al,[S59] 1988).
- Mizolastine 10 mg, loratadine 10 mg, placebo (Dubertret et al,[S60] 1999).
- Mizolastine 10 mg, placebo (Brostoff et al,[S61] 1996; Ollert et al,[S62] 1999).
- Mizolastine 10 mg in decreasing dose, mizolastine 10 mg daily (Wang et al,[S63] 2012).
- Nifedipine 10 mg, chlorphen(ir)amine 4 mg (Liu et al,[S64] 1990).
- Olopatadine 10 mg, olopatadine 5 mg, no medication (Makino et al,[S65] 2012).
- Oxatomide 30 mg, clemastine 1 mg (Beck et al,[S66] 1985).
- Oxatomide gel 5%, dechlorpheniramine cream (Locci and Del Giacco,[S67] 1991).
- Rupatadine 10 mg, levocetirizine 5 mg (Maiti et al,[S68] 2011).
- Rupatadine 10 mg, rupatadine 20 mg, placebo (Gimenez-Arnau et al,[S25] 2007).
- Rupatadine 5 mg, rupatadine 10 mg, rupatadine 20 mg, placebo (Dubertret et al,[S69] 2007).
- Terfenadine 60 mg, clemastine 1 mg, placebo (Hjorth,[S70] 1988).
- Terfenadine 60 mg, chlorphen(ir)amine 4 mg, placebo (Grant et al,[S71] 1988).

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