H1-antihistamines for primary mast cell activation syndromes: a systematic review

Article Type: Review

H_1-antihistamines for primary mast cell activation syndromes (MCAS): a systematic review

Ulugbek B. Nurmatov[1], Edmund Rhatigan[2], F. Estelle R. Simons[3], Aziz Sheikh[1,4]

[1]Allergy and Respiratory Research Group,
Centre for Population Health Sciences
The University of Edinburgh, Medical School
Teviot Place, Edinburgh, EH8 9AG, Scotland

[2]Victoria Hospital Kirkcaldy,
NHS Fife, Kirkcaldy, Fife, KY2 5AH, Scotland

[3]Department of Pediatrics and Child Health,
Department of Immunology, University of Manitoba,
504D-715 McDermot Avenue
Winnipeg Manitoba MB R3E 3P4, Canada

[4]Division of General Internal Medicine and Primary Care,
Brigham and Women's Hospital/Harvard Medical School,
Boston, Massachusetts, USA

Corresponding author: Dr Ulugbek B. Nurmatov, Allergy & Respiratory Research Group, Centre for Population Health Sciences, The University of Edinburgh, Medical School, Doorway 3, Teviot Place, Edinburgh EH8 9AG, UK. Tel:+44(0)131 650 2677
E-mail: Ulugbek.Nurmatov@ed.ac.uk

Short title: H_1-antihistamines for MCAS

Key words: H_1-antihistamines, mastocytosis, primary mast cell activation syndrome, systematic review

ABSTRACT

Background: Primary mast cell activation syndromes (MCAS) are a group of disorders presenting with symptoms of mast cell mediator release.

Objectives: To assess the effectiveness and safety of orally-administered H_1-antihistamines in the treatment of primary MCAS compared with placebo and other pharmacologic treatments.

Methods: We systematically searched five databases, three trial repositories and contacted an international panel of experts to identify published and unpublished trials, enrolling a total of 71 patients (63 adults).

Results: 36 potentially relevant studies were identified. Of these, five crossover trials met the eligibility criteria. Five of these studies were judged to be at moderate or high risk of bias. Two studies compared an H_1-antihistamine with placebo, two compared two different H_1- antihistamines, and one study compared H_1- and H_2-antihistamines with oral cromolyn sodium. Four of the five RCTs were historic (reported from 1983-93), small (enrolling 8-15 patients), and used agents and/or dosing regimens that are now uncommonly used in clinical practice (i.e. azelastine, chlorpheniramine, hydroxyzine and ketotifen). The fifth trial, which enrolled 33 adults with cutaneous and systemic mastocytosis found four weeks of treatment with the second-generation H_1-antihistamine rupatadine, compared with placebo, resulted in significant improvements in quality of life, symptom control (itching, wheals and flares, flushing, tachycardia, and headache, but not gastrointestinal symptoms), and reduction of itching and whealing after standardized skin provocation to elicit Darier's sign.

Conclusions: There is an urgent need for large, well-designed, double-blind, placebo-controlled randomized trials investigating the effectiveness, cost-effectiveness and safety of second-generation H_1-antihistamines in treatment of primary MCAS.

PROSPERO registration: CRD42014007518

BACKGROUND

Mast cell activation syndromes (MCAS) are a group of disorders that typically present with symptoms of mast cell mediator release such as itching, flushing, whealing, flaring, angioedema, tachycardia, headache, and gastrointestinal manifestations including abdominal pain and diarrhea. These disorders are diagnosed when symptoms of mast cell mediator release are recurrent, accompanied by an increase in mast cell-derived mediators, and responsive to treatment with mast cell-stabilizing medications or mediator-targeting medications.[1-9]

Criterion 1 for diagnosis states that the term MCAS should be applied when there are clinical signs of severe recurrent or chronic systemic mast cell activation.

Criterion 2 for diagnosis of MCAS is met when an increase in mast cell mediators in biologic fluids can be documented. These mediators include tryptase, histamine, prostaglandin D_2, leukotrienes (LTC4 and LTD4), platelet-activating factor, pro-inflammatory cytokines, chemokines, and others. Criterion 2 is typically met when the total tryptase level is elevated in serum obtained at baseline, for example, at least 24 hours after complete resolution of anaphylaxis symptoms. This criterion is also met when histamine levels are elevated in plasma or when histamine and its metabolite N-methylhistamine (or less commonly, the prostaglandin PGD_2 metabolite 11-beta-PGF-2-alpha) are elevated in 24-hour urine.[1-10]

Criterion 3 for diagnosis of MCAS is met when symptoms such as itching, flushing, whealing, flaring, and angioedema are relieved by a mast cell-stabilizing medication such as cromolyn sodium that decreases mediator release, or by medications that prevent or reduce the effect of mediators that are released – for example, H_1- and/or H_2-antihistamines to mitigate the effects of histamine, and anti-leukotrienes to mitigate the effects of leukotrienes.[1-9] Such medications are typically given in a stepwise fashion on a regular daily or twice-daily basis for a three to six month trial period. If a patient responds appropriately to this treatment, it helps to confirm the diagnosis of MCAS.[1-9]

The proposed classification system of MCAS divides the syndromes into three categories: primary, secondary, and idiopathic.[1-5] Primary MCAS include clonal disorders such as cutaneous mastocytosis or systemic mastocytosis, and monoclonal MCAS.[1-8] Non-clonal MCAS also occurs.[9] Secondary MCAS include allergic diseases, induced or chronic auto-immune urticaria, and some chronic inflammatory and neoplastic disorders.[1-5] Idiopathic MCAS includes not only idiopathic mast cell activation syndrome, but also idiopathic anaphylaxis, spontaneous urticaria, and idiopathic angioedema.[1-5] In this review, we focus only on primary MCAS and specifically on cutaneous mastocytosis, systemic mastocytosis, and monoclonal MCAS. An algorithm has been proposed to facilitate diagnosis and management of mastocytosis.[10]

For more than three decades, H_1-antihistamines have been consistently recommended for relief of symptoms in mast cell activation syndromes, including cutaneous and systemic mastocytosis. However, the volume and quality of evidence supporting this recommendation is unclear.[11-17]

H_1-antihistamines are the most commonly used therapeutic intervention in MCAS. Approximately 40 medications in this class are available worldwide for oral administration.[12] Mastocytosis experts have typically recommended oral (old) first-generation, sedating H_1-antihistamines such as azelastine, chlorpheniramine, diphenhydramine, hydroxyzine and ketotifen for the prevention and treatment of symptoms.[1,2,4,5] However, azelastine and ketotifen have never been approved for oral use by some regulatory agencies such as the United States Food and Drug Administration (US FDA) and consequently have never been introduced for clinical use in the US or in many other countries. Overall, first-generation H_1-antihistamines have been more commonly recommended than (newer) second-generation H_1-antihistamines. Use of first-generation H_1-antihistamines in any disorder is difficult to track because most, including chlorpheniramine and diphenhydramine, are widely available for over-the-counter purchase without a prescription and are also widely used for self-medication of common allergic disorders such as allergic rhinitis and acute and chronic urticaria.

Second-generation, non-sedating H_1-antihistamines such as cetirizine, desloratadine, fexofenadine, levocetirizine, and loratadine have become widely available in the past decade, and even newer H_1-antihistamines such as bilastine and rupatadine are now also available in many countries. Second-generation H_1-antihistamines are therefore increasingly recommended over the older medications in this class for use in MCAS.[3,8,9,11,12]

In this systematic review, we sought to investigate the effectiveness and safety of H_1-antihistamines in the management of primary MCAS.

METHODS

We conducted the review according to the methods recommended by the Cochrane Collaboration,[18] and have in relation to reporting our findings followed the recommendations detailed in the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines.[19]

Criteria for considering studies for this review

Types of study

We appraised the literature by looking only at the highest forms of evidence; i.e. randomized controlled trials (RCTs) which compared H_1-antihistamines with placebo or other pharmacologic agents. However, since we anticipated a paucity of RCTs we also considered quasi-RCTs.

Types of participants

We were interested in studies conducted in any patients, including neonates, infants, and children[20] as well as adults diagnosed with primary MCAS (i.e. cutaneous mastocytosis, systemic mastocytosis, and monoclonal MCAS) according to the recently developed consensus criteria for MCAS.[1] We stipulated that at least two of the three criteria for diagnosis of MCAS needed to be met, namely:

- The presence of symptoms and signs relevant to severe recurrent or chronic systemic mast cell activation
- A documented increase in a mast cell derived mediator such as serum tryptase or plasma or urine histamine
- Response to treatment with one or more anti-mediator medications.[4]

Types of interventions

We included studies investigating the use of systemic H_1-antihistamines (i.e. oral, intramuscular and intravenous administration).

Types of outcome measures

We stipulated the following primary and secondary outcome measures:

Primary

- Clinical improvement: prevention or resolution of symptoms as assessed by any objective measure.
- Quality of life

Secondary

- Drug toxicity (adverse events)
- Symptom scores
- Number of hospital admissions
- Duration of hospital admissions
- Elevated serum tryptase levels (baseline)
- Elevated plasma and urine histamine levels and 24-hour urine N-methylhistamine levels (baseline)
- Cost-effectiveness.

Search methods for identification of studies

We searched the following international electronic databases: The Cochrane Central Register of Controlled Trials (CENTRAL) to October 2013, The Cochrane Database of Systematic Reviews and Database of Abstracts of Reviews of Effects (DARE) to October 2013, MEDLINE (Ovid SP, 1966 to October 2013), EMBASE (OVID SP, 1980 to October 2013), CINAHL (EBSCO host, 1982 to October 2013), ISI Web of Science (1945 to October 2013) (see Appendix 1). There were no language, publication year or publication status restrictions in our searches. In order to find on-going or unpublished studies we also searched three international trial repositories: www.clinicaltrials.gov; www.controlled-trials.com; and www.anzctr.org.au and contacted four international subject experts.

Data abstraction

Two reviewers (UN and ER) independently scrutinized all titles and abstracts of articles generated by the search strategy detailed above and designated each study as either potentially included or excluded or unsure according to the agreed inclusion criteria. Both reviewers (UN and ER) then independently assessed the full manuscripts of all studies classified as potentially included. Consensus was achieved and no recourse to additional independent reviewers (FERS and AS) was needed. Data were then independently abstracted by both reviewers onto a customized data extraction sheet. The following data were extracted: authors; country and setting; year, participants (gender, mean age and range); description of intervention; outcome measures (primary and secondary); withdrawals and losses to follow-up; and adverse events.

Quality assessment

Critical appraisal of the included studies was performed independently by both reviewers (UN and ER). The methodological quality of the included RCTs and quasi-RCTs was assessed using the methods detailed in section eight of the *Cochrane Handbook for Systematic Reviews of Interventions*.[18] We focused on using the following seven domains to assess quality: adequate sequence generation; allocation concealment; blinding of participants and personnel; blinding of outcome assessment; the addressing of incomplete outcome data; the absence of selective reporting and the absence of other sources of bias. Each parameter of included trial quality was graded: A – low risk of bias; B – moderate risk of bias; C – high risk of bias. Where differences existed the two authors (UN and ER) were able to agree on a consensus position without recourse to adjudication by other reviewers (FERS and AS).

Data synthesis

There were insufficient comparable data to permit meta-analysis. We therefore first undertook a descriptive summary of data and then undertook a narrative synthesis of the body of evidence uncovered. Had sufficient data been available, we planned to use Review Manager for data analysis and quantitative data synthesis. For dichotomous data, we planned to calculate individual and pooled statistics as relative risks (RR) with 95% confidence intervals (95% CI). For continuous data, we hoped to calculate individual and pooled statistics as mean differences (MD) and/or standardized means differences with 95% CI.

We planned to consider if meta-analysis was appropriate in the presence of significant clinical or statistical heterogeneity. We planned to test for heterogeneity using the I^2 statistic. Significant heterogeneity would have been assumed if the I^2 was greater than 40% (i.e. more than 40% of the variability in outcome between trials could not be explained by sampling variation).[21] If able to pursue a meta-analysis, we would have used fixed effect or random effects modeling depending on whether or not the data were found to be homogenous. In the absence of any substantial statistical or clinical heterogeneity, we planned to report a fixed-model derived pooled effect. We intended to conduct, wherever possible, quantitative analyses of outcomes on an intention-to-treat basis. We would then have assessed evidence of publication bias graphically using Funnel plots and statistically using Begg and Egger tests.[22-23] In the event of statistical and clinical heterogeneity we had planned to undertake subgroup analyses based on: age of patient (neonate/infant, child and adult); type of mastocytosis; H_1-antihistamine used; and the route of administration.

RESULTS

Our searches identified 36 potentially relevant papers, from which we identified five trials in which a total of 71 patients were enrolled (see Figure 1 PRISMA flow diagram). Four studies were RCTs that included 63 adult participants, and the remaining study was a RCT of eight children.[13-17] The key characteristics of these trials are summarized in Tables 1a-c. Contacting experts and undertaking detailed searches of the bibliographies of included papers did not lead to identification of any additional studies.

Quality assessment of these trials revealed that none were judged to be at low risk of bias (see Tables 2a-c). Four RCTs were judged to be at moderate risk of bias;[13,15-17] and the fifth was judged to be at a high risk of bias.[14]

A range of outcomes were seen across the trials (Tables 3a-c), but all considered the effect of H_1-antihistamines on symptoms in patients with primary MCAS.

Studies comparing H_1-antihistamine against placebo

Description of studies

There were two trials investigating H_1-antihistamines against placebo. Both were conducted in adults with primary MCAS; in the first, ketotifen[14] was evaluated and in the second rupatadine[17] was studied (see Table 1a). In the rupatadine trial, 33 patients were enrolled and a number of evaluations were performed.[17] Firstly, the quality of life of participants was assessed using a validated instrument (ItchyQoL). Secondly, pruritus was measured using a validated 10cm visual analogue scale after standardised skin provocation testing to elicit Darier's sign . Thirdly, symptoms including itching, flushing, whealing, flaring, tachycardia, headache and gastrointestinal manifestations were evaluated using a 5-point Likert scale (i.e. none, mild, moderate, severe and very severe).

Main findings

In the double-blind placebo-controlled crossover RCT of rupatadine, Siebenhaar et al. reported that four weeks of once daily rupatadine 20 mg significantly improved the mean total symptom specific quality of life (16.1% reduction in ItchyQoL; p=0.004), and resulted in significant improvement in the domains of symptoms (17.4% reduction; p=0.007), functions (10.6% reduction; p=0.022) and emotions (18.5% reduction; p=0.006). In three patients (10%), treatment with a rescue H_1-antihistamine was required during the rupatadine phase compared with 8 patients (27%) during the placebo phase.[17] A total of 40 treatment emergent adverse effects were reported by 28 participants; 20 during treatment with rupatadine and 20 with the placebo. The authors provided little detail about these adverse effects other than noting that none were deemed serious.

In the small crossover RCT comparing ketotifen 2 mg twice daily for three months with placebo in 10 adults with urticaria pigmentosa, Czarnetzki et al.[14] reported a significant reduction in pruritus and wheals; however, this study was judged to be at high risk of bias with little detail on how an adequate sequence was generated and whether the outcome was blinded; indeed, 40% of the patients experienced tiredness while taking ketotifen, which may have compromised allocation concealment.

Summary of evidence

We found limited evidence evaluating H_1-antihistamines against placebo. One study was of poor methodological quality and therefore needs to be interpreted with caution.[14] In contrast,

the findings of Siebenhaar et al.[17] are promising and point to the likely effectiveness of H_1-antihistamines in adults with primary MCAS.

Studies comparing H_1-antihistamines

Description of studies

We found two crossover RCTs in this category (see Table 1b). In one small study undertaken in eight children with cutaneous mastocytosis, the first-generation H_1-antihistamines ketotifen and hydroxyzine were compared.[15] This study was only of moderate quality as it was unclear how the random sequence was generated and how participants and investigators were blinded.[15] In the second study in 15 adults with urticaria pigmentosa, the first-generation H_1-antihistamine chlorpheniramine 12 mg twice daily was compared with the H_1-antihistamine azelastine 4.4 mg or azelastine 8.8 mg twice daily and placebo twice daily.[16]

Main findings

In the pediatric study,[15] hydroxyzine 2 mg/kg four times daily was found to be significantly more effective than ketotifen 1 mg three times daily in improving symptoms ($p<0.05$) especially flushing and abdominal pain ($p=<0.01$) The risk of sedation was similar with both agents ($p>0.20$).

In the adults with urticaria pigmentosa, there was no significant difference between chlorpheniramine 12 mg bid and azelastine 4.4 mg or 8.8 mg bid in terms of overall symptom reduction;[16] however, azelastine (4.4 mg dose) was more efficacious in reducing abdominal pain ($p<0.01$) and pruritus (both 4.4 mg and 8.8 mg doses) ($p<0.05$) and also at reducing the cutaneous wheal and flare response to histamine. Chlorpheniramine was associated with less fatigue than azelastine 8.8 mg. Additionally, two patients on azelastine dropped out of the trial because of the moderate-to-severe bitter metallic taste.

Summary of evidence

There was little evidence comparing different H_1-antihistamines in the treatment of primary MCAS. Two published trials of moderate quality suggested that in children, hydroxyzine was more effective than ketotifen for symptom relief,[15] and that in adults,[16] azelastine and chlorpheniramine had comparable overall effectiveness, azelastine was more effective in relieving abdominal pain and pruritus.[16] These H_1-antihistamines caused varying degrees of sedation, which may or may not have affected allocation concealment and azelastine caused a bitter metallic taste.

Studies comparing H_1-antihistamines against other pharmacologic agents

Description of studies

Only one study was found in this category: a placebo-controlled RCT in eight adults with systemic mastocytosis, in which treatment with the H_1-antihistamine chlorpheniramine 4 mg administered with the H_2-antihistamine cimetidine 200 mg, both given four times daily, were compared with cromolyn sodium 200 mg four times daily (see Table 1c).[13] Little detail was provided on how the randomisation sequence was generated thereby introducing a moderate risk of bias.

Main findings

There was no difference in the individual symptom scores ($p>0.05$) of the participants between the two treatment regimens, nor was there a difference between patient and physician evaluations of disease status at the end of both cycles of treatment ($p>0.50$).[13] Three of the four patients with nausea improved on cromolyn sodium. Similarly, five of the six patients with pruritus and four of the six patients with urticaria improved with the co-administration of an H_1-antihistamine and an H_2-antihistamine. There was no significant difference in adverse effects; fatigue was reported by five patients on cromolyn sodium and two on H_1-/H_2-antihistamines, and one patient on H_1- and H_2-antihistamines was withdrawn after mild liver function test abnormalities were identified.

Summary of evidence

There is little evidence comparing H_1-antihistamines with other agents in the treatment of primary MCAS. The only published study demonstrated no overall significant difference in symptom control when an H_1-antihistamine co-administered with an H_2-antihistamine was compared with cromolyn sodium in eight patients.[13]

DISCUSSION

Despite H_1-antihistamines being recommended and used in the management of primary MCAS,[1-9,11] this systematic review clearly demonstrates that there is little high quality evidence to support this widely held orthodoxy. We identified four RCT published between 1983 and 1993 in which study populations were small, ranging from 8-15 patients; in addition to the likely low power, a number of other methodological problems were identified. We did, however, identify one RCT published in 2013 that was of reasonably high quality and of reasonable size in the context of this body of literature.[17] In this study of 33 adults with mastocytosis, the second-generation H_1-antihistamine rupatadine was shown to be superior to placebo. A statistically significant improvement in the quality of life of participants, a significant reduction in whealing and itching on standardized skin provocation testing to elicit

Darier's sign, , and a significant reduction in symptoms (itching, flushing, tachycardia and headache), despite significantly less use of rescue medication, were all demonstrated. Moreover patients with the most severe symptoms appeared to derive the greatest benefit. Only gastrointestinal symptoms, which are due to the action of histamine at H_2-receptors rather than H_1-receptors, were not significantly improved. Interestingly, in two older studies,[15,16] the H_1-antihistamines hydroxyzine and azelastine were reported to reduce abdominal pain, despite the fact that H_2-antihistamine properties are not typically attributed to these medications.

The strength of this systematic review lies in its sound methodology in that it was conducted to international standards by performing a comprehensive search of five electronic databases of published research without language restrictions, three international trial repositories, contacting international experts in this field, and searching the bibliographies of the studies identified. As far as we are aware, this is the first systematic review to have investigated the role of H_1-antihistamines in the treatment of primary MCAS.

The main limitations of this review relate to the small numbers of RCTs published from 1983-2013, most of which were of poor or moderate quality due to small study sample sizes, heterogeneity of study populations and treatments studied, inconsistent descriptions of inclusion or exclusion criteria, inconsistent control arms, use of subjective outcome measures (some of which were not validated), and potential problems with allocation concealment. In addition, we were unable to conduct a meta-analysis because of the clinical and methodological heterogeneity of the participants studied.

Owing to the limited available data, we are unable to make any confident recommendations regarding choice of H_1-antihistamine or dosing; however, the findings from the one contemporary trial of moderately high quality suggest the urgent need for large, well-designed, double-blind, placebo-controlled randomized trials to investigate the use of this and other second-generation H_1-antihistamines in the treatment of primary MCAS. Dose-response studies are also needed, as up to four-fold doses of these second-generation H_1-antihistamines is now officially recommended worldwide in chronic spontaneous urticaria guidelines.[24]

Acknowledgements

AS was supported by The Commonwealth Fund, a private independent foundation based in New York City. The views presented here are those of the author and not necessarily those of The

Commonwealth Fund, its directors, officers, or staff. We thank the panel of experts for their time and contributions.

Author's contributions: FERS and AS conceived the idea for this study and together with UN drafted the protocol. UN undertook searches, and together with ER undertook data extraction, critically appraised studies. UN and ER drafted the manuscript and all authors commented on drafts of the article.

Funding: None.

Ethical approval: Not required.

Conflict of interests: FERS is a member of the Uriach Medical Advisory Board. The other authors declare that they have no relevant conflict of interests.

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Figure 1: PRISMA flow diagram

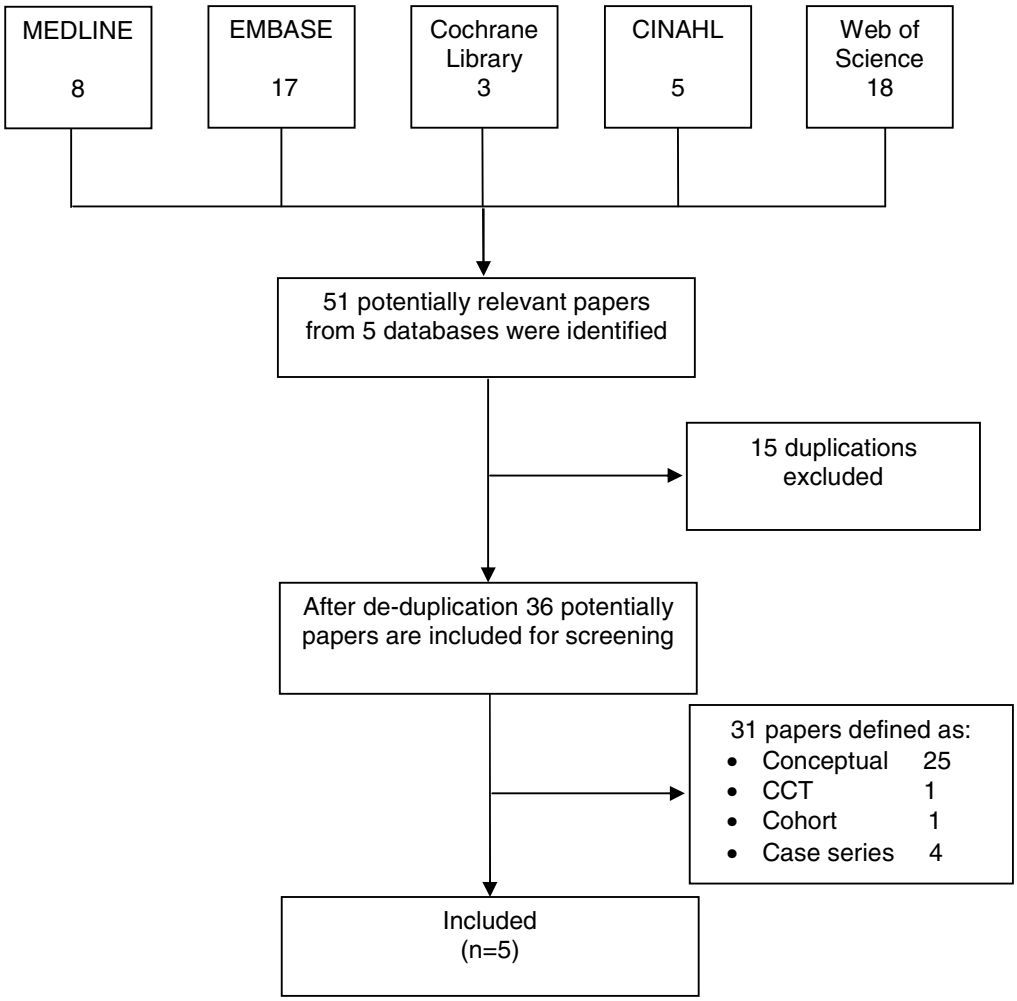

Table 1a: Detailed characteristics of included studies comparing H_1-antihistamines versus placebo

Author & Year; Country	Design	Population (Age, Gender and Diagnosis)	Intervention	Outcome	Notes
Czarnetzki 1983[14] Germany	Double-blind, randomized, placebo-controlled crossover study	-10 adults; 6 female -Urticaria pigmentosa	Three 30 day treatment periods (1) Ketotifen 2 mg twice a day (2) Placebo, twice a day.	Daily patient record of pruritus and intensity of whealing (scale of 0-3)	No details of washout period/process provided
Siebenhaar 2013[17] Germany	Double-blind, randomized, placebo-controlled crossover study	- 33 adults (23 female), 3 females later excluded. - 20-70 y/o, mean age 49.4 y. - 7 with chronic stable maculopapular cutaneous mastocytosis and 23 with indolent systemic mastocytosis and skin involvement.	2 consecutive 28 day treatment periods (Min: 25d, Max 30d). (1) Rupatadine 20 mg once a day (2) Placebo once a day	Patients assessed at baseline and end of 4 week treatment arms. (1) Patient evaluation of Quality of Life using validated ItchyQoL; questionnaire at the end of each 4 weeks of treatment. (2) Standardized skin provocation testing to elicit Darier's sign and assessment of pruritus severity using visual analog scale. (3) Evaluation of symptom severity using 5 point Likert scale.	No details of washout period/process provided

Table 1b: Detailed characteristics of included studies comparing different types H_1-antihistamines

Author & Year; Country	Design	Population (Age, Gender and Diagnosis)	Intervention	Outcome	Notes
Kettelhut 1989[15] USA	Double-blind, randomized, placebo controlled crossover trial	- 8 children (2 female) - 1-8 y - Cutaneous mastocytosis; 6 with urticaria pigmentosa, 2 with diffuse cutaneous mastocytosis and increased mast cells in bone marrow aspirate, but normal bone marrow biopsy and no hepato-splenomegaly.	2 consecutive 6 week trial arms consisting of a 2-week washout followed by a 4-week treatment period. (1) ketotifen liquid 1 mg twice a day & hydroxyzine placebo four times a day. (2) hydroxyzine liquid 2 mg/kg four times daily and ketotifen placebo twice daily.	Patients assessed at 2 week intervals (1) Plasma histamine levels, complete blood count and biochemistry tests (2) Assessment of daily symptom diary (0-3) and side effects at beginning and end of each trial arm (3) 24 hr urine collection for quantitative urinary histamine and routine urinalysis. .	Two consecutive 6 week trial arms with the first two weeks serving as the washout period
Friedman 1993[16] USA	Double-blind, randomized, three period crossover trial	- 15 patients (10 female) - 25-65 y, mean age 44.1 y - 15 had histologic evidence of mastocytosis (urticaria pigmentosa), 15 had elevated plasma histamine levels, and 12 had elevated number of bone marrow mast cells.	3 consecutive trial periods; comprising a 2-week wash-out and a 4-week treatment period. (1) Chlorpheniramine, 12 mg, twice a day (and 2 doses of placebo twice a day) (2) Azelastine, 4.4 mg twice a day (and 2 doses of placebo twice a day) (3) Azelastine, 8.8 mg twice a day (and 2 doses of placebo twice a day)	2 week washout period following first two of three treatment periods in which no study drugs taken.	

Table 1c: Detailed characteristics of included studies comparing H_1-antihistamines with different pharmacological therapies

Author & Year; Country	Design	Population (Age, Gender and Diagnosis)	Intervention	Outcome	Notes
Frieri 1985[13] USA	Double-blind, randomized, double crossover trial	- 8 adults (7 female) - 33-65 y - Systemic mastocytosis; 7 had urticaria pigmentosa, 6 had elevated bone marrow mast cells, 7 had abnormalities on bone scans and 6 had hepato-splenomegaly.	2 consecutive 10 week treatment periods. (1) Cromolyn sodium 200 mg by mouth four times a day + chlorpheniramine and cimetidine placebos four times a day. (2) chlorpheniramine 4 mg four times a day + cimetidine 300 mg four times a day + cromolyn sodium placebo four times a day.	Patients evaluated at 5 week intervals. (1) Plasma and urine histamine levels. (2) Complete blood count, liver function tests (3) Urinalysis (4) Patient and physician assessment of disease status; using numerical 1-5 scale. (5) Patient symptom diary (0-4 scale)	2 consecutive 10 week treatment periods with a 2 week washout and crossover period at end of week 10.

Table 2a: Risk of bias of included studies comparing H_1-antihistamines with placebo

Author & year	Adequate sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data addressed?	Free of selective reporting	Free of other bias	Grade
Czarnetzki 1983[14]	Unclear	Yes	Yes	Unclear	Unclear	Yes	Yes	C
Siebenhaar 2013[17]	Yes	Unclear	Yes	Unclear	Yes	Yes	Yes	B

Table 2b: Risk of bias of included studies comparing different H_1-antihistamines

Author & year	Adequate sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data addressed?	Free of selective reporting	Free of other bias	Grade
Friedman 1993[16]	Yes	Yes	Unclear	Unclear	Yes	Yes	Yes	B
Kettelhut 1989[15]	Unclear	Yes	Unclear	Yes	Yes	Yes	Yes	B

Table 2c: Risk of bias of included studies comparing H_1-antihistamines with other pharmacological therapies

Author & year	Adequate sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data addressed?	Free of selective reporting	Free of other bias	Grade
Frieri 1985[13]	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	B

Table 3a: Summary of main findings of included studies comparing H_1-antihistamines with placebo

Author & year	Main Findings
Czarnetzki 1983[14]	- 2 patients withdrew; 1 because of urgent eye surgery and 1 because of pregnancy. - Statistically significant symptom reduction with ketotifen; $p< 0.025$ (whealing) and $p< 0.010$ (pruritus) - 40% of participants experienced mild to moderate tiredness with ketotifen.
Siebenhaar 2013[17]	- 2 participants withdrew. One experienced severe bone pain while taking the placebo. The second experienced fatigue during rupatadine therapy. - 1 participant was withdrawn because of non- compliance. - 28 participants reported 40 treatment-emergent adverse effects; 20 with placebo and 20 with rupatadine; none considered severe. - Significant improvement in mean total ItchyQol score with rupatadine; 16.1% reduction $p<0.004$. Also statistically significant reduction in scores for the domains of symptoms, functions and emotions (17.4%, 10.6% and 18.5%, respectively). Those patients with a higher ItchyQoL total score, that is, poorer quality of life, received more benefit from rupatadine. - Significant reduction in Visual Analog Score for pruritus and whealing after standardized skin provocation testing to elicit Darier's sign during rupatadine treatment compared with placebo; 30.3% reduction $p= 0.041$. - Significant improvement in day-to-day itching, whealing, flaring, flushing, tachycardia, and headache, but not GI symptoms $p>0.05$. - Fewer patients required rescue therapy during rupatadine treatment; 3 (10%) versus 8 (27%).

Table 3b: Summary of main findings of included studies comparing different H_1-antihistamines

Author & year	Main Findings
Kettelhut 1989[15]	- 1 participant unable to complete final 2 weeks of second arm of trial. Authors judged sufficient data collected to include in final analysis. - Hydroxyzine was significantly more efficacious than ketotifen at reducing symptom scores; $p<0.05$. - Symptoms of flushing and abdominal pain were the most likely to improve with hydroxyzine; $p<0.01$. - No significant differences in plasma or urine histamine levels following treatment with either therapy - No significant difference in risk of sedation between the 2 agents; $p>0.20$ - Results of serum haematological and biochemical testing not reported.
Friedman 1993[16]	- 3 withdrawals: 1st withdrew on day 9 of second period with disease exacerbation that was considered unrelated to the study. 2 participants withdrew while taking azelastine, complaining of a severe bitter metallic taste. - Azelastine statistically superior at reducing wheal and flare response to intradermal histamine and morphine sulphate. - Mean plasma histamine levels reduced by both azelastine and chlorpheniramine, no statistical difference between the two agents. - No statistically significant difference between azelastine and chlorpheniramine in terms of overall symptom reduction and patient and physician global evaluation. However, azelastine significantly reduced pruritus and abdominal pain when compared to chlorpheniramine ($p<0.05$ and $p<0.01$). - Chlorpheniramine statistically associated with less fatigue ($p<0.05$).

Table 3c: Summary of main findings of included studies comparing H_a-antihistamines with other pharmacological agents

Author & year	Main findings
Frieri 1985[13]	- 2 patients on cromolyn sodium withdrew: 1st experienced severe generalized pruritus and dizziness after 24 hours. 2nd experienced disease exacerbation (predominant symptoms of flushing and nausea) and withdrew after 7 days. - 1 patient developed mild liver function test abnormalities after 5 weeks of H_1- and H_2-antihistamine treatment. - 5 patients complained of fatigue (2 with H_1- and H_2-antihistamines, 3 with cromolyn sodium) - No statistically significant difference in patient symptom scores (assessed using a daily diary), between cromolyn sodium and combined H_1- and H_2-antihistamine therapy: mean symptom scores 3.1 versus 3.2, respectively. - 3 of 4 patients with nausea improved with cromolyn sodium. 5 of 6 patients suffering from pruritus improved with H_1- and H_2-antihistamine therapy. 4 of 6 patients with urticaria improved with H_1- and H_2-antihistamine therapy. - No significant differences in patient and physician assessment of disease status. - No significant change in plasma or urine histamine levels following either treatment.

Appendix 1

Search strategy: MEDLINE format

1. Mastocytosis, Cutaneous/ or Mastocytosis.mp. or Mastocytosis/ or Mastocytosis, Systemic/

2. urticaria pigmentosa.mp. or Urticaria Pigmentosa/

3. teleangiectasia macularis eruptiva perstans.mp.

4. monoclonal mast cell activation syndrom*.mp.

5. 1 or 2 or 3 or 4

6. MIANSERIN/ or METHAPYRILENE/ or FLUNARIZINE/ or CINNARIZINE/ or TERFENADINE/ or LORATADINE/ or ASTEMIZOLE/ or CETIRIZINE/ or DOXEPIN/ or PROMETHAZINE/ or TRIPELENNAMINE/ or PYRILAMINE/ or ANTAZOLINE/ or DOXYLAMINE/ or DIPHENHYDRAMINE/ or DIMENHYDRINATE/ or CLEMASTINE/ or

KETOTIFEN/ or CYPROHEPTADINE/ or MECLIZINE/ or HYDROXYZINE/ or CYCLIZINE/ or TRIPROLIDINE/ or PHENIRAMINE/ or DIMETHINDENE/ or BROMPHENIRAMINE/ or CHLORPHENIRAMINE/ or exp Histamine H1 Antagonists/ or (Neoclarityn or Telfast or Xyzal or Mizollen or Vallergan or Dimotane or Piriton or Periactin or Periactin or Tavegil or Ucerax or Atarax or Phenergan or Zaditen or Otrivine-Antistin or Valoid or tritoqualine or Tranilast or temelastine or proxicromil or protopine or picumast or NCO 650 or mirtazapine or mequitazine or lodoxamidetromethamine or dexchlorpheniramine or chloropyramine or carebastine or Actifed or Mianserin or Methapyrilene or Flunarizine or Cinnarizine or Epinastine or Emedastine or Azelastine or Terfenadine or Olopatadine or Mizolastine or Loratadine or Levocabastine or Fexofenadine or Ebastine or Desloratadine or Astemizole or Levocetirizine or Cetirizine or Acrivastine or Alimemazine Tartrate or Doxepin or Promethazine or Methdilazine or Tripelennamine or Pyrilamine or Antazoline or Phenyltoloxamine or Doxylamine or Diphenhydramine or Dimenhydrinate or Clemastine or Carbinoxamine or Ketotifen or Diphenylpyraline or Cyproheptadine or Azatadine or Oxatomide or Meclizine or Hydroxyzine or Cyclizine or Buclizine or Triprolidine or Pheniramine or Dimethindene or brompheniramine or Chlorpheniramine or antihistamin$ or Benadryl or Livostin direct or opatanol or emadine or relestat or optilast or nytol or dreemon or medinex or nightcalm or panadolnight or clarityn allergy or nyquil or sinequan or xepin or pbz-sr or tacaryl or hismanal or kestine or ebastel or clistin or dramamine or tussirex or antivert or tinsetped or optimine or stugeron or stugeron forte or sibelium or histadyl or polaramine or alomide or rizaben).mp.

7. ((randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti.) not (animals not (humans and animals)).sh.

8. 5 and 6 and 7

Search strategy: free-field format

(mastocytosis or systemic mastocytosis or cutaneous mastocytosis or monoclonal mast cell activation syndrome)

And

(Histamine H_1 antagonists or Neoclarityn or Telfast or Xyzal or Mizollen or Vallergan or Dimotane or Piriton or Periactin or Periactin or Tavegil or Ucerax or Atarax or Phenergan or Zaditen or Otrivine-Antistin or Valoid or tritoqualine or Tranilast or temelastine or proxicromil or protopine or picumast or NCO 650 or mirtazapine or mequitazine or lodoxamide tromethamine or dexchlorpheniramine or chloropyramine or carebastine or Actifed or

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And

(random* or placebo or multicenter or prospective) or ((controlled or clinical) SAME trial*) or ((single or double or triple or treble) SAME (mask* or blind*))