

REVIEW ARTICLE

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

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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 H₁-antihistamines in the treatment of primary MCAS compared with placebo and other pharmacologic treatments.

Methods: We systematically searched five databases and three trial repositories and contacted an international panel of experts to identify published and unpublished trials.

Results: A total of 36 potentially relevant studies were identified. Of these, five crossover trials, enrolling a total of 71 patients (63 adults), met the eligibility criteria. All five of these studies were judged to be at moderate or high risk of bias. Two studies compared an H₁-antihistamine with placebo, two compared two different H₁-antihistamines, and one study compared H₁- and H₂-antihistamines with oral cromolyn sodium. Four of the five randomized controlled trials were historic (reported from 1983–1993), small (enrolling 8–15 patients), and used agents and/or dosing regimens that are now less commonly used in clinical practice (i.e. azelastine, chlorpheniramine, hydroxyzine, and ketotifen). The fifth trial, which enrolled 33 adults with cutaneous and systemic mastocytosis found 4 weeks of treatment with the second-generation H₁-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 in 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 H₁-antihistamines in treatment of primary MCAS.

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 D₂, 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 h 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 PGD₂ metabolite 11-beta-PGF-2- α) are elevated in a 24-h urine sample (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 effects of mediators released – for example, H₁- and/or H₂-antihistamines to mitigate the effects of histamine, and antileukotrienes 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 3- to 6-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 involves *KIT*-D816V-mutated monoclonal mast cells and include clonal disorders such as cutaneous mastocytosis or systemic mastocytosis, and monoclonal MCAS (1–5). Nonclonal MCAS also occurs (9). Secondary MCAS are associated with allergic diseases, chronic auto-immune urticaria, and some other chronic inflammatory or neoplastic disorders (1–5). Idiopathic MCAS is mast cell activation syndrome with no detectable monoclonal (*KIT*-mutated) mast cells and no underlying allergic, chronic inflammatory or neoplastic disease (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, H₁-antihistamines have been consistently recommended for relief of symptoms in MCAS, including cutaneous and systemic mastocytosis. However, the volume and quality of evidence supporting this recommendation is unclear (11–17).

H₁-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 H₁-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 H₁-antihistamines have been more commonly recommended than (newer) second-generation H₁-antihistamines. Use of first-generation H₁-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, nonsedating H₁-antihistamines such as cetirizine, desloratadine, fexofenadine, levocetirizine, and loratadine have become widely available in the past decade, and even newer H₁-antihistamines such as bilastine and rupatadine are now also available in many countries. Second-generation H₁-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 H₁-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, that is, randomized controlled trials (RCTs) which compared H₁-antihistamines with placebo or other pharmacologic agents. However, as 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 antimediation medications (4).

Types of interventions

We included studies investigating the use of systemic H₁-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-h 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 S1). There were no language, publication year, or publication status restrictions in our searches. To find ongoing 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; and 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 with 95% confidence intervals (95% CI). For continuous data, we hoped to calculate individual and pooled statistics as mean differences 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 >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 the following: age of patient (neonate/infant, child, and adult); type of mastocytosis; H₁-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 Fig. 1). 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 Table 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 Table 2a–c). Four RCTs

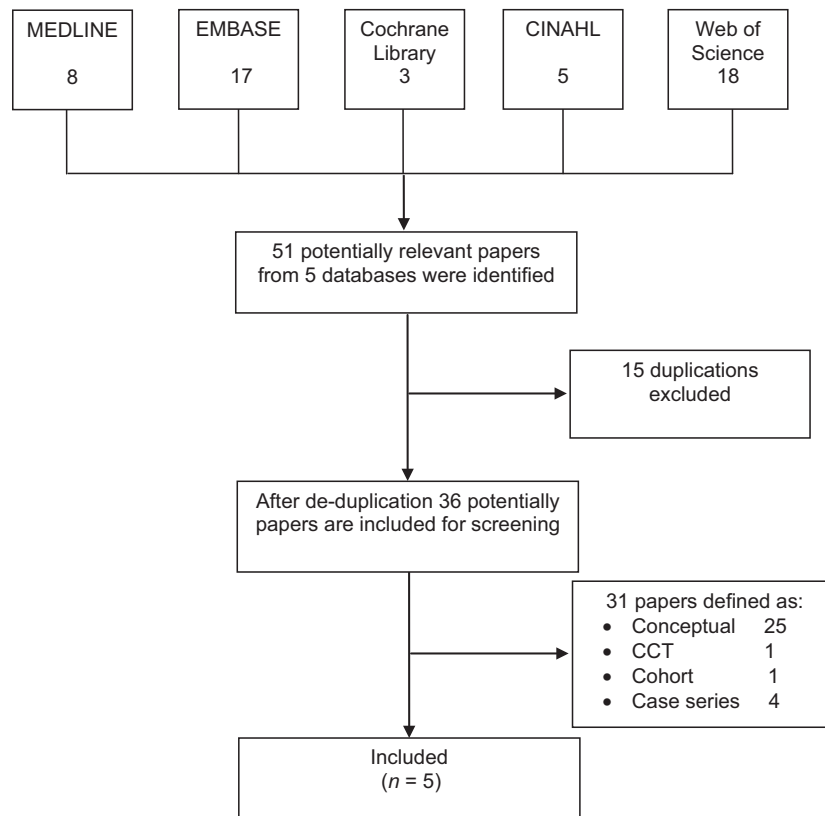


Figure 1 PRISMA flow diagram.

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 (Table 3a–c), but all considered the effect of H₁-antihistamines on symptoms in patients with primary MCAS.

Studies comparing H₁-antihistamine against placebo

Description of studies

There were two trials investigating H₁-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 10 cm visual analogue scale after standardized 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 4 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 H₁-antihistamine was required during the rupatadine phase compared with eight 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 3 months with placebo in 10 adults with urticaria pigmentosa, Czarnetzki (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 H₁-antihistamines against placebo. One study was of poor methodological quality and therefore needs to be interpreted with caution (14). In

Table 1 Detailed characteristics of included studies comparing (a) H₁-antihistamines vs placebo, (b) different types H₁-antihistamines and (c) H₁-antihistamines with different pharmacological therapies

Author (year) Country	Design	Population (age, gender and diagnosis)	Intervention	Outcome	Notes
(a)					
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 et al. (2013) (17) Germany	Double-blind, randomized, placebo-controlled crossover study	33 Adults (23 female), 3 females later excluded 20–70 years-old, mean age 49.4 years 7 with chronic stable maculopapular cutaneous mastocytosis and 23 with indolent systemic mastocytosis and skin involvement	2 Consecutive 28 day treatment periods (Min: 25 days, Max 30 days) (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
(b)					
Kettelhut et al. (1989) (15) USA	Double-blind, randomized, placebo controlled crossover trial	8 Children (2 female) 1–8 years 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 and 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 h urine collection for quantitative urinary histamine and routine urinalysis	Two consecutive 6- week trial arms with the first 2 weeks serving as the washout period
Friedman et al. (1993) (16) USA	Double-blind, randomized, three period crossover trial	15 Patients (10 female) 25–65 years, mean age 44.1 years 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)	(1) Patients recorded a daily symptom diary (Scale 0–3) At baseline and at end of each treatment period (Day 28): (1) Physical examination and assessment for adverse events were performed (2) Plasma histamine levels measured (3) Extinction dilution skin tests were performed with histamine and morphine sulphate; areas of wheals and flares were calculated	2-Week washout period following first two of three treatment periods in which no study drugs taken

Table 1 (continued)

Author (year) Country	Design	Population (age, gender and diagnosis)	Intervention	Outcome	Notes
(c) Frieri et al. (1985) (13) USA	Double-blind, randomized, double crossover trial	8 Adults (7 female) 33–65 years 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

contrast, the findings of Siebenhaar et al. (17). are promising and point to the likely effectiveness of H₁-antihistamines in adults with primary MCAS.

Studies comparing H₁-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 H₁-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 H₁-antihistamine chlorpheniramine 12 mg twice daily was compared with the H₁-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 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 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 H₁-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 and azelastine was more effective in relieving abdominal pain and pruritus (16). These H₁-antihistamines caused varying degrees of sedation, which may or may not have affected allocation concealment and azelastine caused a bitter metallic taste.

Studies comparing H₁-antihistamines against other pharmacologic agents

Description of studies

Only one study was found in this category: a placebo-controlled RCTs in eight adults with systemic mastocytosis, in which treatment with the H₁-antihistamine chlorpheniramine 4 mg administered with the H₂-antihistamine cimetidine 200 mg, both given four times daily, were compared with

Table 2 Risk of bias of included studies comparing (a) H₁-antihistamines with placebo, (b) different H₁-antihistamines and (c) H₁-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
(a)								
Czarnetzki (1983) (14)	Unclear	Yes	Yes	Unclear	Unclear	Yes	Yes	C
Siebenhaar et al. (2013) (17)	Yes	Unclear	Yes	Unclear	Yes	Yes	Yes	B
(b)								
Friedman et al. (1993) (16)	Yes	Yes	Unclear	Unclear	Yes	Yes	Yes	B
Kettelhut et al. (1989) (15)	Unclear	Yes	Unclear	Yes	Yes	Yes	Yes	B
(c)								
Frieri et al. (1985) (13)	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	B

cromolyn sodium 200 mg four times daily (see Table 1c) (13). Little detail was provided on how the randomization 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 H₁-antihistamine and an H₂-antihistamine. There was no significant difference in adverse effects; fatigue was reported by five patients on cromolyn sodium and two on H₁-/H₂-antihistamines, and one patient on H₁- and H₂-antihistamines was withdrawn after mild liver function test abnormalities were identified.

Summary of evidence

There is little evidence comparing H₁-antihistamines with other agents in the treatment of primary MCAS. The only published study demonstrated no overall significant difference in symptom control when an H₁-antihistamine co-administered with an H₂-antihistamine was compared with cromolyn sodium in eight patients (13).

Discussion

Despite H₁-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 RCTs published between 1983 and 1993 in which study populations were small, ranging from 8 to 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 H₁-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 H₂-receptors rather than H₁-receptors, were not significantly improved. Interestingly, in two older studies (15, 16), the H₁-antihistamines hydroxyzine and azelastine were reported to reduce abdominal pain, despite the fact that H₂-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 stan-

Table 3 Summary of main findings of included studies comparing (a) H₁-antihistamines with placebo, (b) different H₁-antihistamines and (c) H₁-antihistamines with other pharmacological agents

Author (year)	Main findings
(a)	
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 et al. (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%) vs 8 (27%)
(b)	
Kettelhut et al. (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 hematological and biochemical testing not reported
Friedman et al. (1993) (16)	3 Withdrawals: 1st withdrew on day 9 of second period with disease exacerbation that was considered unrelated to the study. Two 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 ($P < 0.05$)
(c)	
Frieri et al. (1985) (13)	2 Patients on cromolyn sodium withdrew: 1st experienced severe generalized pruritus and dizziness after 24 h. 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 vs 3.2, respectively Three of 4 patients with nausea improved with cromolyn sodium. Five of 6 patients suffering from pruritus improved with H ₁ - and H ₂ -antihistamine therapy. Four 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

dards 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 H₁-antihistamines in the treatment of primary MCAS.

The main limitations of this review relate to the small numbers of RCTs published from 1983 to 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 H₁-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, and placebo-controlled randomized trials to investigate the use of this and other second-generation H₁-antihistamines in the treatment of primary MCAS. Dose-response studies are also needed, as up to four-fold doses of these second-generation H₁-antihistamines is now officially recommended worldwide in chronic spontaneous urticaria guidelines (24).

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Conflicts of interest

FERS is a member of the Uriach Medical Advisory Board. The other authors declare that they have no conflicts of interest.

Ethical approval

None.

Author 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.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Search strategy.

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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 (Neoclaritin 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 Tripelelnamine or Pyriline 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 claritin 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 H₁ antagonists or Neoclaritin or Telfast or Xyzal or Mizollen or Vallergran or Dimotane or Piriton or Periacin or Periacin 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 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 Tripeleminamine 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 claritin 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 tinset ped or optimine or stugeron or stugeron forte or sibelium or histadyl or polaramine or alomide or rizaben)

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*))