Antihistamines for atopic dermatitis (eczema): systematic review and network meta-analysis of randomised trials

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ABSTRACT

OBJECTIVE

To systematically synthesise the benefits and harms of add-on oral antihistamines for managing atopic dermatitis (eczema).

DESIGN

Systematic review and network meta-analysis of randomised trials.

DATA SOURCES

Medline, Embase, CENTRAL, the United States Food and Drug Administration, and the European Medicines Agency databases from database inception to 5 May 2025.

STUDY SELECTION

Randomised trials assessing add-on oral H1 antihistamines, H2 blockers, mast cell stabilisers (nedocromil sodium and sodium cromoglycate), or their combinations. Paired reviewers independently screened records, extracted data, and assessed risk of bias using a modified Cochrane Risk of Bias tool version 2.

METHODS

Random effects bayesian meta-analyses synthesised atopic dermatitis severity (oSCORAD—objective scoring atopic dermatitis, 0-83; minimal important difference 8.2; lower better), itch severity (numerical rating scale, 0-10; minimal important difference 3; lower better), sleep disturbance, atopic dermatitis related quality of life, and harms. The network meta-analysis GRADE (Grading of Recommendations Assessment, Development and Evaluation) and Core GRADE approaches informed certainty of evidence ratings.

RESULTS

47 trials enrolled 6230 children and adults with primarily moderate to severe atopic dermatitis. With moderate certainty, compared with placebo, adding a first generation or second generation H1 antihistamine likely resulted in a small reduction in atopic dermatitis severity (mean difference -1.87, 95% credible interval -3.47 to -0.27) and itch severity (-0.89, -1.41 to -0.37). Although statistically detectable, these effects are well below established minimal important differences (smallest change in an outcome that a patient would identify as important). With low certainty, all studied interventions may not improve sleep disturbance or reduce atopic dermatitis exacerbations. First generation agents probably increase cognitive impairment and may increase treatment discontinuation because of adverse events (risk difference 66 more per 1000, 95% credible interval 0 to 231 more; moderate certainty). Second generation agents differ in their risk of cognitive impairment (range of mean effects 0 more per 1000 for loratadine, 16 more per 1000 for levocetirizine, and 17 more per 1000 for cetirizine).

CONCLUSIONS

Among patients with atopic dermatitis, adding H1 antihistamines probably results in a clinically unimportant reduction in atopic dermatitis severity and itch severity, and may not reduce sleep disturbance or atopic dermatitis exacerbations. First generation agents increase cognitive impairment and may increase treatment discontinuation because of adverse events. Cognitive impairment risk differs among second generation agents. These findings provide evidence against routine antihistamine use in atopic dermatitis management and will inform updated clinical guidelines.

SYSTEMATIC REVIEW REGISTRATION

PROSPERO CRD42022345643.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Oral antihistamines are used by one in five patients for managing atopic dermatitis (eczema) in recent UK estimates and nearly half in recent estimates in the United States

Comprehensive analyses are needed examining the benefits and harms of these over-the-counter drugs and addressing patient important atopic dermatitis outcomes

Evidence based assessments of oral antihistamines are necessary for optimal management of atopic dermatitis

WHAT THIS STUDY ADDS

This network meta-analysis of 47 randomised trials enrolled 6230 children and adults with mainly moderate to severe atopic dermatitis

Oral second generation H1 antihistamines result in a slight, likely not clinically important, reduction in eczema severity and itch severity

Oral first generation H1 antihistamines probably increase cognitive impairment with limited or uncertain efficacy

Introduction

Atopic dermatitis (eczema) is a chronic and relapsing inflammatory skin disease affecting 13% of children

and 7% of adults.[1 2] Characterised by intense itching and skin inflammation, atopic dermatitis impairs patient and family quality of life, mental health, and social relationships.[3 4] Oral H1 antihistamines are a common add-on treatment for more than 20% of patients with atopic dermatitis according to recent UK estimates and 47% according to recent estimates in the United States.[5-12] These systemic drugs are also the most prescribed among patients with atopic dermatitis who are pregnant or lactating.[13] Their presumed mechanism of action—similar to other allergic conditions such as allergic rhinitis and urticaria—is to inhibit histamine activity released from mast cells and basophils, and therefore inhibit local neuronal, vascular, and inflammatory cell activation that manifests as itch and skin inflammation.[14 15] However, current understanding is that atopic dermatitis associated itch predominantly involves histamine independent pathways.[16]

Oral H1 antihistamines are typically classified by when they were developed. First generation agents, such as chlorpheniramine, diphenhydramine, and hydroxyzine, are lipophilic, readily cross the blood-brain barrier and influence central nervous system neurotransmission. As a result, these drugs are associated with neurocognitive side effects and off-target anticholinergic effects, such as sedation.[17] Clinicians reasoned that histamine inhibition and sedation might reduce the frequent itch and sleep disturbance experienced by patients with atopic dermatitis. Second generation agents, such as cetirizine, desloratadine, fexofenadine, levocetirizine, and loratadine, are less lipophilic and more selective, thereby less likely to cause neurocognitive and off-target adverse effects. Both antihistamine generations are widely available over the counter (ie, without a prescription) worldwide for various indications.[17] Related drugs include ketotifen (classified as a first generation agent and a mast cell stabiliser) and sodium cromoglycate and nedocromil sodium (mast cell stabilisers). Not all agents are equally available internationally.

Despite their longstanding use, a clear evidence based role of oral antihistamines in treating atopic dermatitis remains unclear. A 2019 Cochrane review limited to placebo controlled trials yielded imprecise and inconclusive findings for 21-795 participants analysed across 25 trials.[18] To date, studies are lacking that have comprehensively synthesised the totality of evidence, including placebo controlled and head-to-head trials, in a single joint analysis. As part of the American Academy of Allergy, Asthma & Immunology and American College of Allergy, Asthma and Immunology Joint Task Force on Practice Parameters (AAAAI/ACAAI JTFPP) living guidelines for atopic dermatitis,[2] we systematically reviewed and performed a network meta-analysis[19] of placebo controlled and head-to-head randomised trials evaluating oral antihistamines and mast cell stabilisers for atopic dermatitis.

Methods

Search strategy, inclusion and exclusion criteria

We conducted this systematic review and network meta-analysis according to Cochrane Collaboration[20] and Core GRADE (Grading of Recommendations Assessment, Development and Evaluation) guidance,[21-28] aligning with methods from previous AAAAI/ACAAI JTFPP systematic reviews.[29-32] We registered our protocol on PROSPERO (CRD42022345643) and report our review according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) network meta-analysis extension guidance[33] (see supplementary material).

We searched Medline, Embase, CENTRAL, the US Food and Drug Administration, and European Medicines Agency databases from inception to 5 May 2025 for published or unpublished randomised controlled trials in any language comparing adding versus not adding oral antihistamines, ketotifen, or mast cell stabilisers (nedocromil sodium and sodium cromoglycate), or randomised controlled trials comparing different add-on antihistamines, ketotifen, or mast cell stabilisers administered at any dose or frequency that included outcomes of interest studied for a minimum treatment duration of three days. We permitted any background treatments (eg, moisturisers, topical corticosteroids) that were received by all participants. To identify other potentially relevant trials, we manually searched the reference lists of other systematic reviews, conducted forward and backward citation analyses of all included studies using the Web of Science (all databases), and conferred with clinical experts.

Data collection

Paired and calibrated reviewers (AWLC, AW, MR, LB, IXZ) independently screened titles and abstracts, and reviewed full texts using Covidence (Veritas Health Innovation, Melbourne, Victoria, Australia). Following Cochrane guidance,[20] the same reviewers extracted data independently and in duplicate with standardised prepiloted forms, resolving disagreements by consensus, and if necessary, through discussion with a third reviewer (DKC). Reviewers extracted study bibliographical information, design, patient characteristics (including baseline atopic dermatitis severity as reported using validated measures or as defined by trial authors), intervention and comparator characteristics, outcomes according to the intention-to-treat principle, and sources of funding. When studies presented outcomes only in figures, we used WebPlotDigitizer 5.2 (Automeris LLC, California, USA; https://automeris.io/wpd/) to extract numerical data. For crossover trials, we analysed only the first period where possible or imputed between group standard deviations for approximating appropriate analyses according to Cochrane guidance.[20] We contacted authors for clarification when data were missing, unpublished, or unclear.

For trials that did not report means or standard deviations, we imputed data as described by Furukawa

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and colleagues,[34] Weir and colleagues,[35] and Cochrane guidance.[20] If a trial reported data as median and interquartile range or range, we assessed skewness, and if not present, we converted values to means and standard deviations according to Shi and colleagues[36] and Cochrane guidance.[20] If present, we estimated mean and standard deviation values using quantile estimation, Box-Cox transformation, or approximate bayesian computation, preferring the estimate that was the most consistent with other values within and between trials. If the instruments used to measure an outcome varied between trials, we followed GRADE guidance[37] and used linear transformation to convert each measure to the one most familiar to clinicians or most consistent across the included trials.[38]

Outcomes

Through discussion with our multidisciplinary AAAAI/ACAAI JTFPP atopic dermatitis guideline panel, including patient and caregiver partners, and aligning with previous JTFPP systematic reviews, we prioritised the following patient important outcomes[39]: clinician and patient reported atopic dermatitis severity, itch severity, sleep disturbance, atopic dermatitis related quality of life, atopic dermatitis exacerbations (flares), and adverse events (including cognitive impairment, adverse events leading to treatment discontinuation, and serious adverse events). We report outcomes as measured using validated patient reported outcome measures, including the objective scoring atopic dermatitis (oSCORAD) and the Dermatology Life Quality Index. We considered cognitive impairment to include any adverse event description of worsened memory or motor performance, confusion, delirium, psychosis, hallucinations, hyperactivity, or hypoactivity.

Risk of bias assessment

Paired and calibrated reviewers assessed risk of bias independently for each study outcome using a modified Cochrane Risk of Bias tool version 2 for randomised trials.[40] We subclassified "some concerns" judgments as "some concerns, probably high" and "some concerns, probably low." For crossover trials, we also considered the risk of bias arising from period and carryover effects. The domain with the highest risk of bias determined the overall risk of bias judgment for that study's outcome. If at least one domain was high or probably high risk, we considered the outcome at high risk of bias for that trial.

Data analysis

We performed bayesian random effects network meta-analysis using Markov chain Monte Carlo approaches.[41] We selected a bayesian approach because it accommodates data more flexibly, including incorporating external evidence and uncertainty (eg, heterogeneity priors and harms), rather than frequentist hypothesis testing approaches based on P values, and focuses on interpretation of estimated treatment effects relative to decision thresholds, which aligns well with the GRADE approach. For the mean treatment effects, we used minimally informative priors, defined as normal distributions centred at no effect (mean=0) with a standard deviation scaled to the range of the outcome measure. This approach ensures that the priors exert minimal influence on the posterior estimates while limiting implausible effect sizes.[41] Direct evidence was calculated from conventional pairwise meta-analyses using bayesian random effects approaches, indirect estimates from node split models, and network estimates from the full network meta-analysis model.[42 43] We summarised dichotomous outcomes using odds ratios and continuous outcomes using mean differences with 95% credible intervals (CrIs). Owing to the low number of serious adverse events in most trials, we summarised them using risk differences. When available trial data were insufficient to generate informative estimates for developing clinical recommendations, we assumed the risk of adverse effects from antihistamines would be comparable to that observed in other conditions, such as chronic urticaria.[44]

Following GRADE guidance, we supplemented estimates for cognitive impairment using meta-analyses of 132 randomised controlled trials involving 14 853 participants treated with antihistamines for chronic urticaria, incorporating these data using bayesian meta-analytic models.[44] To facilitate interpretation of outcomes, we used odds ratios to calculate absolute risk differences per 1000 participants using the median from all studies in which participants were assigned to placebo to calculate the baseline risk for each outcome.[20] To estimate the baseline risk among active interventions, we used transitive risk models.[45 46] For continuous outcomes, we compared mean differences with established minimal important differences (MIDs)—the smallest change in an outcome that a patient would identify as important. Unless otherwise specified, we present all treatment estimates in the main text in relation to placebo (with or without background topical treatments).

Network nodes represent unique antihistamines or their combinations (eg, with H2 blockers). If the evidence showed little variability in effectiveness among the individual antihistamines, we performed additional analyses investigating overall class effects. To address potential limitations of network sparsity, we used between study priors informed by predictive distributions of between study heterogeneity from 14 886 Cochrane meta-analyses.[47 48] We confirmed the convergence of four chains in all cases with Gelman-Rubin statistics of less than 1.01 after a burn-in of 10 000, sampling of 50 000, and thinning of 10. Assessment of the deviance information criterion informed model fit.

We evaluated the certainty (quality) of the evidence using the GRADE approach for network meta-analysis,[42 43] assessing risk of bias,[25] imprecision,[23] inconsistency,[24] indirectness,[26] publication bias,[25] intransitivity, and incoherence. We report our findings using standardised terminology.[49] We assessed and interpreted network meta-analysis findings according

to GRADE guidance using a target of certainty rating of an important effect (ie, relative to MIDs).[42] We categorised interventions as among the most effective (but not importantly different from placebo), not different from placebo, or among the most harmful, distinguishing between treatments with high or moderate certainty evidence versus those with low or very low certainty evidence.[42] We assessed inconsistency by visually inspecting forest plots for the magnitude of differences in point estimates, overlap of CrIs, and the relation of the estimates to the aforementioned thresholds. We assessed publication bias using the GRADE approach.[25 50] We used node splitting models and followed GRADE guidance to assess for local incoherence and to obtain indirect estimates. We assessed incoherence by comparing the direction and magnitude of point estimates and the overlap of the 95% CrI between the direct and indirect estimates in comparison to the network estimate. If the direct and indirect estimates are incoherent and do not dominate the network estimate, we rate down the certainty according to GRADE and use the direct or indirect estimate as the best estimate of the relative effect between two comparisons based on whichever has the highest certainty.[42 43] We assessed intransitivity by inspecting the distribution of potential effect modifiers comprising comparisons.[51]

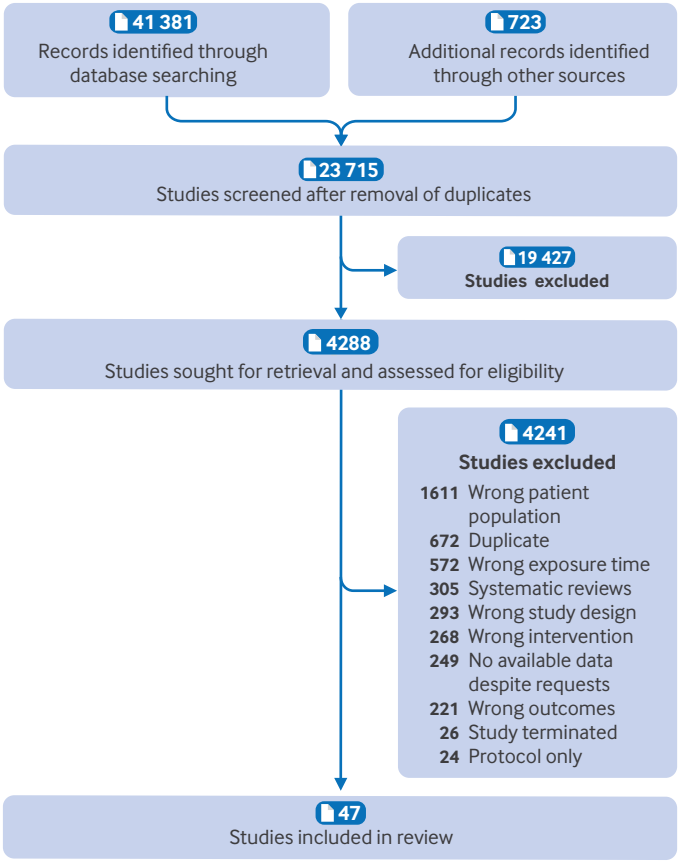

Fig 1 | PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) study selection and flow diagram of systematic review of randomised clinical trials analysing antihistamines and mast cell stabilisers for atopic dermatitis (eczema)

We analysed prespecified subgroups: age (paediatric *v* adult), risk of bias (low *v* high), trial design (parallel *v* crossover), duration of treatment (<12 weeks *v* ≥12 weeks), and baseline severity. We additionally assessed subgroups based on the presence of background treatments (moisturisers or topical corticosteroids *v* none or not reported). We initially assessed subgroups using pairwise comparisons and proceeded with random effects (network) meta-regression if effect modification appeared possible or if there were insufficient data to perform pairwise comparisons. We appraised the credibility of the subgroup effects using the Instrument for assessing the Credibility of Effect Modification Analyses (ICEMAN).[52] For each intervention and outcome with a potential statistical subgroup interaction, ICEMAN assesses whether the effects are within or between study, similarity of effect modification among trials, sample size, whether the direction of effect modification is consistent with a priori hypotheses, number of effect modifiers tested, whether a random effects or fixed effects model was used, and whether continuous variables were dichotomised. The overall credibility of the subgroup is rated as very low, low, moderate, or high. ICEMAN is not used if there is no subgroup effect detected, which may be a limitation of the available sample size. We hypothesised that treatment effects would be greater among older participants, in studies at high risk of bias, in crossover trials, in trials of shorter duration, among participants with greater atopic dermatitis severity, and among trials using background treatments. Sensitivity analyses used alternative reported MIDs.

We conducted analyses using R version 4.3.2 (R Foundation for Statistical Computing, Vienna, Austria).

Patient and public involvement

As part of the living AAAAI/ACAAI JTFPP atopic dermatitis guidelines, patients, caregivers, and patient advocacy groups determined relevant patient important outcomes, established thresholds of important effects, and determined relevant subgroup and sensitivity analyses.[53] They reviewed the current manuscript and provided critical feedback. Patient and caregiver partners were also involved in generating the guideline's associated clinical recommendations. We also used established MIDs for patient important changes for each outcome.

Results

The systematic search identified 41 381 records, 4288 potentially relevant full texts, and ultimately included 47 unique randomised controlled trials[54-100] (fig 1). The studies included 6230 participants with a median reported mean age of 20 years (range of means 1-43). A median 52% of participants were female, 27 (57%) trials included paediatric participants, 31 (66%) were placebo controlled, 37 (79%) were parallel trial designs, and 36 (77%) trials reported using concomitant background treatments for all participants (ie, moisturisers or topical corticosteroids). Most trials reported

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Table 1 | Characteristics of included randomised trials of antihistamines for atopic dermatitis (eczema)

Study	Country	Study design	No of participants randomised	Age (years)*	No of female participants (%)	Baseline severity			Back-ground treatment	Randomised interventions and comparator
						Mild	Moderate	Severe		
Atherton 1982	UK	Crossover	30	5.50 (2-10)	11/29 (38)	x	x	x	TCS	Mast cell stabiliser, placebo
Benton 1990	UK	Crossover	20	34.00 (11.78)	14 (70)		x	x	TCS	Mast cell stabiliser, placebo
Berth-Jones 1989	UK	Crossover	28	28.60 (11-67)	NR	x	x		TCS	Terfenadine, placebo
Borelli 1967	Multinational	Parallel	75	31.00 (NR)	NR	NR			NR	Promethazine, placebo
Businco 1986	Italy	Crossover	31	NR (0.5-10)	17 (55)	x			NR	Mast cell stabiliser, placebo
Cambazard 2001	Multinational	Parallel	223	2.56 (0.9-5.9)	91 (41)		x		TCS	Cetirizine, placebo
Chunharas 2002	Thailand	Parallel	50	6.14 (2.88)	25/48 (52)			x	TCS	Loratadine, placebo
Daugbjerg 1984	Denmark	Crossover	34	6.40 (1-23)	17 (50)	x	X	x	TCS	Mast cell stabiliser, placebo
Diepgen 2002	Multinational	Parallel	817	1.42 (0.34)	301/795 (38)	x	x		TCS	Cetirizine, placebo
Doherty 1989	UK	Parallel	49	26.80 (16-58)	29 (59)	NR			TCS	Acrivastine Terfenadine, placebo
Falk 1993	Norway	Parallel	60	25.00 (18-35)	34 (57)			x	TCS	Dexchlorpheniramine, dexchlorpheniramine+ ketotifen
Fan 2012	China	Parallel	59	43.46 (13.19)	35 (59)		x		TCS	Mizolastine, placebo
Foulds 1981	UK	Crossover	21	20.40 (14-29)	12/20 (60)	NR			TCS	Cimetidine, cimetidine+ promethazine Promethazine
Frosch 1984	Germany	Crossover	18	23.00 (14-43)	13/16 (81)		x		TCS	Chlorpheniramine Chlorphe-niramine+cimetidine, placebo
Giannetti 1984	Italy	Parallel	22	NR	NR	NR			NR	Mast cell stabiliser, placebo
Hannuksela 1993	Finland	Parallel	178	29.70 (8.90)	125 (70)		x	x	TCS	Cetirizine, placebo
Iikura 1991	Japan	Parallel	128	1.00 (0.13)	31/91 (34)	x	x	x	Moisturiser and TCS	Ketotifen, placebo
Iikura 1992	Multinational	Parallel	121	NR	49 (40)	NR			NR	Ketotifen, placebo
Ishibashi 1989	Japan	Parallel	180	19.88 (7.77)	99 (55)	x	x	x	Moisturiser	Azelastine, ketotifen
Jung 1989	Multinational	Parallel	98	4.00 (1.00)	NR		x	x	Moisturiser	Cetirizine, placebo
Kawashima 2003	Japan	Parallel	411	26.60 (6.80)	186/400 (47)			x	TCS	Fexofenadine, placebo
Kawashima 2011	Japan	Parallel	305	10.45 (2.50)	131 (43)			x	TCS	Ketotifen, olopatadine
Klein 1980	United States	Parallel	20	8.65 (1.69)	7 (35)			x	Moisturiser	Cyproheptadine, hydroxyzine
La Rosa 1994	Italy	Parallel	23	7.00 (2.00)	12 (52)	x			TCS	Cetirizine, placebo
Langeland 1994	Norway	Crossover	16	24.80 (20-37)	7 (44)		x	x	TCS	Loratadine, placebo
Leon 1989	Mexico	Parallel	20	5.94 (2.99)	15 (75)		x	x	Moisturiser	Ketotifen, placebo
Lutsky 1993	Multinational	Parallel	236	9.00 (6-12)	94/192 (49)	NR			NR	Loratadine, terfenadine
Monroe 1992	United States	Parallel	41	NR (18-65)	31 (76)		x	x	NR	Hydroxyzine, loratadine, placebo
Munday 2002	Multinational	Parallel	155	7.00 (1-12)	85 (55)	x	x	x	Moisturiser and TCS	Chlorpheniramine, placebo
Nakagawa 2004	Japan	Parallel	163	9.00 (3.90)	63/147 (43)			x	TCS	Epinastine, ketotifen
Nakagawa 2006	Japan	Parallel	174	NR (7-15)	78/162 (48)		x		TCS	Fexofenadine, ketotifen
Nakayama 1980	Japan	Parallel	310	NR	146/309 (47)			x	Moisturiser	Azatadine, chlorpheniramine
NCT00375713	South Korea	Parallel	466	30.14 (10.34)	233/340 (69)	NR			TCS	Cetirizine, levocetirizine
NCT00884325	United States	Parallel	40	41.10 (20-68)	26 (65)		x	x	Moisturiser	Levocetirizine, placebo
NCT01840605	Japan	Parallel	303	10.30 (2.40)	141 (47)		x	x	TCS	Bepotastine, ketotifen
Patel 1997	Multinational	Parallel	118	28.52 (11.19)	83/116 (72)		x	x	NR	Cetirizine, loratadine
Ren 1996	China	Parallel	31	NR	18 (58)	NR			None	Astemizole, cetirizine
Satyanarayana 1975	India	Parallel	18	NR (10-60)	NR	NR			NR	Dimetindene, embramine
Sheng 2009	China	Parallel	92	36.76 (11.97)	47 (51)		x		None	Cetirizine, mizolastine, placebo
Simons 2007	Multinational	Parallel	510	1.62 (0.02)	191 (37)		x		NR	Levocetirizine, placebo
Tholen 1989	Germany	Crossover	29	5.30 (1.80)	NR			x	Moisturiser	Ketotifen, terfenadine
Toyoda 2007	Japan	Parallel	79	28.60 (18-42)	31 (39)			x	Moisturiser	Ranitidine, placebo
Veien 1995	Denmark	Parallel	47	NR	36 (77)	x	x		TCS	Clemastine, terfenadine, placebo
Wahlgren 1990	Sweden	Crossover	25	26.75 (6.36)	16 (64)	NR			TCS	Olopatadine, placebo
Yamanaka 2015	Japan	Parallel	20	22.50 (4.68)	4 (20)		x	x	Moisturiser	Olopatadine, placebo
Yoshida 1989	Japan	Parallel	284	9.41 (8.51)	133/255 (52)	x	x	x	Moisturiser	Clemastine, ketotifen
Zuluga de Cadena 1989	Colombia	Parallel	52	4.00 (2-6)	26/48 (54)	NR			Moisturiser	Hydroxyzine, terfenadine, placebo

NR=not reported; TCS=topical corticosteroid.
*Mean (standard deviation or range).

including participants with moderate to severe atopic dermatitis. Four trials investigated antihistamines at more than twofold daily doses.[58 59 61 69] Table 1 summarises the characteristics of the included trials. We found consistent effects between trials reporting the use of background treatments compared with those not reporting their use (see supplementary material).

Individual outcomes of most randomised controlled trials were at overall probably low risk of bias. We did not detect strong evidence of publication bias.

Outcomes

Figure 2 presents the network plots for atopic dermatitis severity by class of treatments and individual drugs. The supplementary material presents all other network plots for the remaining outcomes. Network plots permit visualisation of the geometry of the network and visually summarise the number of trials directly comparing each intervention and the number of participants analysed for each intervention. We found consistency in treatment effects among individual antihistamines within classes, and therefore present overall class effects in our analyses (see supplementary material). Figure 3 presents the GRADE summary table of comparative effects of antihistamines on patient important atopic dermatitis outcomes. The main results are summarised below and the supplementary material presents the complete GRADE network meta-analysis evidence profiles and classification of interventions.

AD severity

Twenty seven randomised controlled trials[54 55 58 59-62 64 65 67-70 72 73 75-77 82 83 86 88 91 96 97 99 100] (n=3541) informed effects on atopic dermatitis severity, presented as

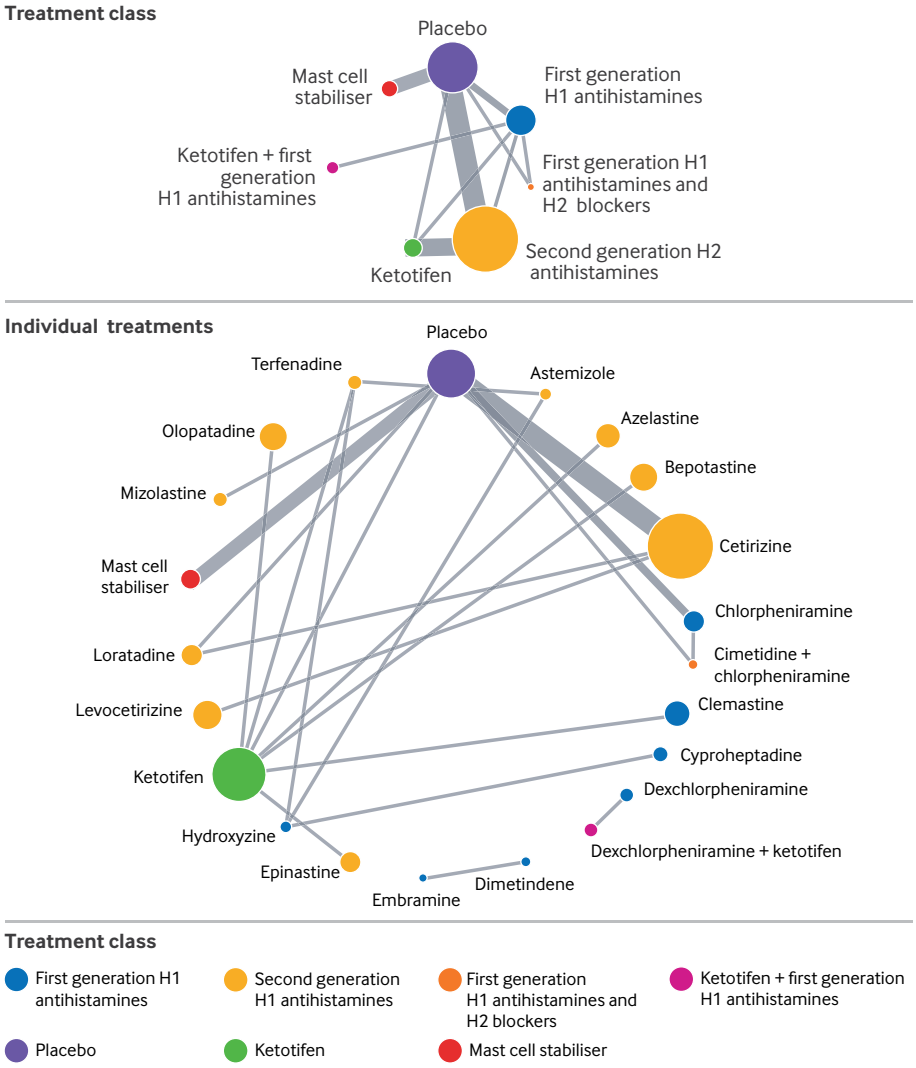

Fig 2 | Network plot of randomised trials examining effects of add-on antihistamines and mast cell stabilisers on clinician reported atopic dermatitis severity organised by treatment class and individual treatments. Solid lines indicate direct treatment comparisons, with line width proportional to number of trials. Circles (nodes) represent individual treatments, with node size proportional to number of participants. Seventy seven per cent of trials reported use of background treatments (primarily moisturisers and topical corticosteroids) among all participants

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	Atopic dermatitis severity oSCORAD (0-83)	Itch severity NRS (0-10)	Sleep disturbance NRS (0-10)	Atopic dermatitis exacerbation	Cognitive impairment	Discontinuation because of adverse event	Serious adverse event
	Mean difference (95% CrI)	Mean difference (95% CrI)	Mean difference (95% CrI)	Risk difference (95% CrI)	Risk difference (95% CrI)	Risk difference (95% CrI)	Risk difference (95% CI)
Overall baseline	35.38	6.29	3.87	124 per 1000	33 per 1000	8 per 1000	—
After placebo	27.52	4.13	2.48				
First generation H1 antihistamine	1.04 (-2.03 to 4.12)	-0.28 (-0.98 to 0.42)	—	89 fewer (118 fewer to 54 more)	66 more (0 more to 231 more)*	29 more (1 more to 131 more)	0 more (9 fewer to 9 more)
Second generation H1 antihistamine	-1.87 (-3.47 to -0.27)	-0.89 (-1.41 to -0.37)	-0.23 (-1.86 to 1.40)	28 more (70 fewer to 234 more)	Differs among agents †	1 fewer (4 fewer to 6 more)	20 fewer (46 fewer to 6 more)

High or moderate certainty evidence	Low or very low certainty evidence
Statistically detectable but not importantly different from placebo	Possibly statistically detectable but not importantly different from placebo
Not different from placebo	Possibly not different from placebo
Among the most harmful	Possibly among the most harmful

Fig 3 | Summary of comparative effects of oral antihistamines on patient important atopic dermatitis outcomes. GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach informed certainty of evidence ratings. Interventions categorised based on a non-zero effect, with effectiveness categories representing magnitude of treatment effect and certainty ratings reflecting trustworthiness of evidence. *Odds ratio 3.24 (95% CrI 0.99 to 10.64); risk differences presented for dichotomous outcomes to facilitate interpretation (see supplementary material for results in odds ratios). †Cognitive impairment differed among individual second generation H1 antihistamines: loratadine (risk difference 0 more per 1000, 95% CrI 6 fewer to 7 more; high certainty) is not different from placebo; cetirizine (17 more, 95% CrI 12 to 21 more; high certainty) and levocetirizine (16 more, 5 to 30 more; moderate certainty) increase cognitive impairment. No trials investigated bilastine, desloratadine, or rupatadine. CI=confidence interval; CrI=credible interval; NRS=numerical rating scale; oSCORAD=objective scoring atopic dermatitis

measured using oSCORAD (0-83; higher scores indicate greater severity based on extent of body surface involved and intensity of redness, swelling, oozing or crusting, scratch marks, skin thickening, and dryness; MID 8.2[101]). Subgroup analyses identified greater effects among trials at high risk of bias compared with those at low risk of bias (see supplementary material); therefore, we limit analyses to trials at low risk of bias. Second generation H1 antihistamines (mean difference -1.87, 95% CrI -3.47 to -0.27; moderate certainty) likely result in a statistically detectable, but not clinically important difference in atopic dermatitis severity because the effect size falls well below the MID. Similarly, first generation H1 antihistamines (1.04, -2.03 to 4.12; moderate certainty) likely result in no clinically important difference in atopic dermatitis severity. Fourfold doses may result in a greater reduction in atopic dermatitis severity (-4.34, -7.07 to -1.60; low certainty), but effect sizes fall below the MID (see supplementary material).

Itch severity

Twenty seven randomised controlled trials[54 56 57 60 61 63 64 67 69 73-75 77-79 81-84 91 92 94-99] (n=2667) informed effects on itch severity, presented as measured using a numerical rating scale (0-10; higher scores indicate greater severity; MID 3). Second generation H1 antihistamines (mean difference -0.89, 95% CrI -1.41 to -0.37; moderate certainty) likely result in a statistically detectable, but not clinically important difference in itch severity because the effect size falls well below the MID. First generation H1 antihistamines (-0.28, -0.98 to 0.42; moderate certainty) yielded similar findings. Increasing doses may not lead to greater improvement in itch severity, but the evidence is very uncertain (see supplementary material).

Atopic dermatitis related quality of life

One randomised controlled trial[98] (n=40) informed effects on atopic dermatitis related quality of life presented as measured using the Dermatology Life Quality Index (0-30; higher scores indicate greater impairment; MID 3). Levocetirizine may have little to no difference compared with placebo (mean difference 0.22, 95% CrI -3.05 to 3.49; low certainty). No other antihistamines provided evidence for this outcome.

Sleep disturbance

Four randomised controlled trials[54 61 79 91] (n=110) informed effects on sleep disturbance and are presented as measured using a numerical rating scale (0-10; higher scores indicate greater disturbance; MID 1). No trials investigated first generation agents for this outcome. All the investigated antihistamines may not importantly differ from placebo in improving sleep disturbance (low certainty).

Atopic dermatitis exacerbations

Thirteen randomised controlled trials[54 55 61 64 67 69-73 76 93 98] (n=987) informed effects on atopic dermatitis exacerbations. All investigated antihistamines may not importantly differ from placebo in reducing atopic dermatitis exacerbations.

Adverse effects

Cognitive impairment

Nineteen randomised controlled trials[56 62 65 71 72 75-77 80 83-86 89 90 93 96 97 99] (n=4607) informed effects on cognitive impairment. First generation H1 antihistamines (odds ratio 3.24, 95% CrI 0.99 to 10.64; risk difference 66 more per 1000, 95% CrI 0 to 231 more; moderate certainty) likely increase cognitive impairment. Differing effects were found among second generation H1 antihistamines. Loratadine (0 more, 6 fewer to 7 more; high certainty) does not increase the risk of cognitive impairment, while cetirizine (17 more, 12 to 21 more; high certainty) and levocetirizine (16 more, 5 to 30 more; moderate certainty) increase the risk of cognitive impairment.

Treatment discontinuation because of adverse events

Nineteen randomised controlled trials[55 61 62 64 67 69 72 74 75 77-79 83 90 91 93 96 97 99] (n=3485) informed effects on treatment discontinuation because of adverse events. First generation H1 antihistamines (odds ratio 4.61, 95% CrI 1.10 to 19.21; risk difference 29 more per 1000, 95% CrI 1 to 131 more; low certainty) may increase treatment discontinuation because of adverse events. With moderate certainty, second generation H1 antihistamines (0.90, 0.48 to 1.70; 1 fewer per 1000, 4 fewer to 6 more) and H2 blockers (0.26, 0.05 to 1.37; 6 fewer, 8 fewer to 3 more) likely do not increase treatment discontinuation because of adverse events.

Serious adverse events

Twelve randomised controlled trials[62 64-66 74 75 77 82 90 93 98 99] (n=2763) informed effects on serious adverse events. With high certainty, first generation H1 antihistamines (risk difference 0 more per 1000, 95% confidence interval 9 fewer to 9 more) and second generation H1 antihistamines (20 fewer, 46 fewer to 6 more) do not increase serious adverse events. The evidence is less certain for H2 blockers and combination treatments.

Other analyses

Subgroup analyses showed no credible treatment modifications based on age, trial design, treatment duration, baseline severity, or presence of background treatments. We observed moderately credible differences according to risk of bias in atopic dermatitis severity and therefore restricted analyses to trials with low risk of bias. Sensitivity analyses adjusting by baseline severity also proved consistent with the main analyses. Analyses using alternative MIDs for oSCORAD, including 13.1 to 24.2 in moderate atopic dermatitis and 17.9 to 23.2 in severe atopic dermatitis[102] instead of 8.7, or itch and sleep disturbance MIDs of 4 instead of 3, supported the inferences from the main analyses that, compared with placebo, adding antihistamines produced little to no patient important effect (see supplementary material).

Discussion

Principal findings

This systematic review and network meta-analysis including 6230 participants across 47 randomised controlled trials found that among patients with atopic dermatitis, adding a first or second generation H1 antihistamine did not importantly improve atopic dermatitis severity, itch, sleep disturbance, or atopic dermatitis exacerbation. First generation H1 antihistamines increased cognitive impairment, such as sedation and drowsiness, and first generation agents also increased treatment discontinuation because of adverse events. Bayesian analyses of cognitive impairment risk among second generation agents showed differences among individual antihistamines. Loratadine is no more impairing than placebo, while cetirizine and levocetirizine increase cognitive impairment. None of the studied antihistamines increased serious adverse events across the studied duration. The findings were consistent across participant age group, trial design, baseline atopic dermatitis severity, duration of treatment, and total daily doses received.

Strengths and limitations of this review compared with the existing literature

Compared with the inconclusive 2019 Cochrane review,[18] which was limited to placebo controlled trials and analysed individual antihistamines in isolation (up to 795 participants in the largest analysis), we analysed a larger body of evidence, 47 included trials (between 2667 and 4607 participants in main analyses), and present a systematic review and network meta-analysis evaluating all antihistamines investigated for atopic dermatitis. Given the similarity in treatment effects among individual drugs within antihistamine classes, we analysed them by class (ie, first generation, second generation as they are used in routine clinical practice) to enhance statistical power and enable comparisons of efficacy and safety. Our review also incorporates recent methodological advances, including GRADE for network meta-analysis and Core GRADE principles for structured evidence appraisal.[22] In contrast to the previous pairwise Cochrane meta-analysis, our analysis yielded several moderate certainty conclusions about the harms of antihistamines and their lack of important benefit in atopic dermatitis.

This review also differs from the Cochrane review[18] and similarly inconclusive older reviews[103] by focusing on outcomes and the magnitudes of change important to patients and caregivers, rather than statistical significance alone. Although some antihistamines yielded statistically detectable effects on atopic dermatitis outcomes, all fell well below established MIDs, indicating little patient important benefit and finding patient important harm with use of first generation agents.[6 103] This patient centred orientation of clarifying the role of antihistamines in atopic dermatitis aligns with priorities identified by international groups, including the James Lind

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Alliance Eczema Priority Setting Partnership[104] and the Skin Investigation Network of Canada,[105] enhancing the relevance and applicability of our findings. Together, the findings of this patient centred, large systematic review and network meta-analysis shift the evidence of antihistamines for atopic dermatitis from absence of evidence (a position of uncertainty) to evidence of absence (consequent certainty), thereby not supporting their role in the routine management of atopic dermatitis.

When considering evidence addressing antihistamines for conditions other than atopic dermatitis, the first generation antihistamines' increased risk for cognitive impairment, and adverse events causing treatment discontinuation are consistent with their association with anticholinergic adverse effects (eg, cognitive impairment and urinary retention).[52 106 107] The differences in cognitive impairment among second generation agents also align with known pharmacodynamic data and differential blood-brain barrier penetration.[108] The lack of patient important benefit in atopic dermatitis contrasts with the well established efficacy of antihistamines for treating allergic rhinoconjunctivitis and urticaria.[109]

Potential limitations exist inherent to the included randomised controlled trials. Trial populations differed in baseline severity. We addressed this limitation by analysing changes from baseline and conducting structured assessments using ICEMAN,[52] finding a consistent lack of effects across the spectrum of baseline severities. Additionally, sensitivity analyses adjusting for baseline severity proved consistent with the main analyses. However, subgroup analyses, while providing very little statistical support for clinically important effect modification, may be limited by low sample sizes for subgroups.

Some crossover trials reported results over the entire duration of the trial rather than by crossover period, introducing potential crossover effects. This effect was addressed through structured risk of bias assessments evaluating the effects of crossover effects (eg, duration of washout periods) and subgroup analyses comparing parallel versus crossover trials, which yielded consistent results. Additionally, the review includes nearly 60 years of trials, during which assessment and management of atopic dermatitis has evolved. Although many included trials were conducted before the advent of advanced targeted treatments,[30 31] such as biological agents and JAK inhibitors that are typically used in the minority of patients who are refractory to mid-to-high potency topical anti-inflammatories, the oral H1 antihistamines evaluated are longstanding agents with stable pharmacology and similar dosing in current practice,[17] and remain widely used (often over the counter) as add-on treatment for atopic dermatitis.[5-11] Further, the patients studied (mild to severe atopic dermatitis using moisturisers and mild to potent topical anti-inflammatory treatments) reflect most patients seen in current routine care.

Interpreting the evidence using contemporary MID thresholds and GRADE methods,[21 22] the consistency in observed effects in newer and older trials also supports application to present day clinical decision making. Therefore, these findings are directly relevant to modern atopic dermatitis management.

Implications for future research

Mechanistic studies have suggested that histamine signalling through H1 receptors drives itch in atopic dermatitis[106 107] and that histamine promotes inflammation by disrupting the skin barrier and impairing tight junction formation in keratinocytes.[110] However, our study found no clinically important differences in atopic dermatitis outcomes with various H1 antihistamines or with increasing doses. These findings support the idea that histamine is not a primary driver of atopic dermatitis related itch or inflammation, which is consistent with a growing understanding that may instead be predominantly mediated by non-histaminergic pathways, including interleukin 4, 13 and 31, JAK-STAT signalling, aryl hydrocarbon receptor, TRPV1, PDE4, and calcineurin.[30 31] While histamine H1 and H2 receptors may not play a central role in the immunopathogenesis of atopic dermatitis, this study opens new avenues for examining the specific role of mast cells, basophils, and other inflammatory cells in atopic dermatitis beyond histamine alone. This approach may help in developing future targeted treatments.

Additionally, while our current meta-analysis addresses atopic dermatitis, it remains unclear whether these findings can be extrapolated to contact dermatitis and hand eczema. Despite acknowledging that antihistamines are commonly used for these dermatoses, guidelines do not issue formal recommendations[111 112] or recommend antihistamines as an adjunct despite unclear evidence.[113] Clarifying the role of antihistamines in these related eczematous conditions remains essential for patients and their caregivers.

Implications for clinical practice

Our findings address the longstanding and common, but uncertain and controversial, use of antihistamines in atopic dermatitis. Despite widespread use, clinical practice and guidelines vary in recommending for[114] or against[115 116] adding oral antihistamines for atopic dermatitis, or stating no recommendation is possible owing to lack of evidence.[117] Most have relied on the earlier inconclusive Cochrane review[18] and have not incorporated a comprehensive network meta-analysis of randomised controlled trials. Our review's moderate and high certainty findings of harms and no clinically important benefit of oral antihistamines added to placebo with or without background topical treatments[31] can support stronger, more consistent recommendations in updated evidence based clinical practice guidelines.

Effective atopic dermatitis management should be individualised. Decisions about antihistamine use should reflect patient values, preferences, and goals. Considerations include minimising treatment burden,

avoiding unnecessary polypharmacy, and accounting for cost and over-the-counter availability. For patients where there were few, if any, effective alternatives for itch, antihistamine use may have been an acceptable compromise. In the context of our current understanding of itch pathways in atopic dermatitis, however, and the availability of topical anti-inflammatory treatments, biological agents, and small molecule drugs for patients with moderate to severe atopic dermatitis, particularly those whose quality of life is severely impacted, the use of antihistamines is now largely superfluous. The main scenario in which antihistamines may still have a role is in patients with associated allergic conditions that respond to antihistamines (eg, urticaria or rhinoconjunctivitis). For patients with atopic dermatitis and such coexisting allergic conditions, there may be a perceived benefit in continuing antihistamines despite their limited impact on atopic dermatitis specific symptoms and potential for adverse effects. Those wishing to take advantage of sedating effects, in the absence of proven sleep directed treatments, may also favour continuing first generation antihistamines; however, no data were reported on their effects in improving sleep disturbance. Conversely, people seeking maximal improvement in atopic dermatitis symptoms or those aiming to avoid antihistamine related adverse effects may favour avoiding antihistamines altogether and focusing their time, energy, and resources pursuing more effective and safe treatments (eg, higher potency topical anti-inflammatory treatments or systemic treatments).[2 30 31 118] Therefore, for almost all patients with atopic dermatitis, our findings support deprescribing and preventing polypharmacy with antihistamines.

Conclusions

This systematic review and network meta-analysis addresses the longstanding uncertainty surrounding the role of antihistamines in treating atopic dermatitis, showing they likely do not meaningfully improve patient important atopic dermatitis outcomes while probably increasing harms. Our findings do not support their use in routine atopic dermatitis management. We have provided a foundation for an evidence based change in practice, supporting the development of updated atopic dermatitis guidelines that prioritise efficacy, safety, and patient centred care.

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Transparency: The corresponding author affirms that the manuscript is an honest, accurate, and transparent account of the review being reported; that no important aspects of the study has been omitted; and that any discrepancies from the review as planned (and, if relevant, registered), have been explained.

Dissemination to participants and related patient and public communities: The findings from this review are incorporated directly into the AAAAI/ACAAI JTFPP atopic dermatitis living guidelines, which are shared with patient and caregiver audiences. As part of these efforts, key messages are shared through patient partner advocacy organisations and public-facing guideline materials to ensure people living with atopic dermatitis can access clear and actionable interpretations of the evidence.

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Supplementary file: Supplementary material