Efficacy and safety of combinations of H_1 antihistamines in the treatment of urticaria: A scoping review

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Abstract

The efficacy and safety of combining H_1 antihistamines (AHs) for treating urticaria are currently unclear. This scoping review aims to provide a comprehensive overview of the evidence regarding the efficacy and safety of H_1 AH combinations in the management of urticaria up to May 2023. The search encompassed databases such as PubMed, Web of Science, the Cochrane Central Register of Controlled Trials, and the China Biological Medicine Database. The inclusion criteria comprised randomised controlled trials (RCTs), non-randomised trials (NRTs), case reports, and case series focusing on urticaria treatment. Initially screening 12,887 studies, this review ultimately selected 109 studies involving 11,435 patients. These studies documented 43 different combination treatments across 11 types of urticaria. In comparison to monotherapy, combination therapy exhibited superior efficacy in 94 studies that reported treatment efficacy. Regarding adverse drug reactions (ADRs), 67 studies disclosed ADR incidences, with combination therapy showing lower ADR rates in 32 studies. Additionally, 7 studies reported similar ADR rates between combination therapy and monotherapy with AHs. Common ADRs included symptoms such as drowsiness, nausea, fatigue, dry mouth, dizziness, and headache, while less frequent side effects encompassed hypotension, otitis media, polyuria, rhinorrhoea, abnormal liver function, and rash. ADR rates ranged from 0% to 21% in the treatment group, and from 0.5% to 75% in the control group. Importantly, patients generally tolerated these ADRs well, with symptoms resolving upon discontinuation of treatment. The study's findings suggest that combining AHs leads to enhanced efficacy and reduced safety risks compared to monotherapy in the context of urticaria treatment. These results advocate for considering combination therapy as a viable option in clinical practice, especially for chronic urticaria cases. Nonetheless, caution is advised, and close monitoring for potential ADRs is crucial during treatment.

Key words: Adverse drug reactions, combination drug therapy, efficacy, H_1 antihistamines, urticaria.

Introduction

Urticaria is a common and diverse inflammatory skin condition characterised by the activation and release of histamine and other mediators from skin mast cells, resulting in transient wheals, angioedema, or both.[1–5] It can be triggered spontaneously or by various factors, affecting individuals of all ages, with a lifetime prevalence of up to 20% worldwide.[5,6] Urticaria can be classified as acute (lasting up to 6 weeks) or chronic (lasting more than 6 weeks) and as inducible (with identifiable triggers) or spontaneous (without specific triggers). While most cases are spontaneous, chronic urticaria is more prevalent in adult women, significantly impacting their quality of life.[4,7,8]

How to cite this article: Luo M, Shen K, Dong X, Zhang W, Tang F. Efficacy and safety of combinations of H_1 antihistamines in the treatment of urticaria: A scoping review. Indian J Dermatol Venereol Leprol. doi: 10.25259/IJDVL_1218_2023

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Received: November, 2023 **Accepted:** March, 2024 **EPub Ahead of Print:** June, 2024

DOI: 10.25259/IJDVL_1218_2023 **Supplementary available on:** https://doi.org/10.25259/IJDVL_1218_2023

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The treatment of urticaria typically involves first-line therapy with second-generation H_1 antihistamines (sgAHs) and alternative options such as omalizumab or cyclosporine-A for patients not responding adequately to sgAHs. Long-term use of corticosteroids is generally not recommended.[9] In recent years, emerging treatments have been studied to improve the management of urticaria. For example, up-dosing sgAHs up to four times the standard dose has shown better itch relief in patients with chronic urticaria refractory to conventional doses, as recommended by current guidelines.[10] In addition, research on biological agents and small molecule drugs including immunoglobulins, TNF-α inhibitors, IL-1 inhibitors and anti-NK-1R agents have provided promising results.[10,11] However, these therapies may carry more serious adverse drug reactions (ADRs), particularly in special populations such as pregnant women, children and the elderly, limiting their use as first-line treatments. Therefore, combining these agents with AHs as a second-line approach has been proposed.[12]

While studies have suggested that combination therapy with AHs may not offer superior efficacy compared to increasing the dosage of a single AH, this conclusion needs validation through large-scale randomised, controlled and blinded trials.[11] Moreover, increasing the dosage of a single AH may lead to increased ADRs, whereas combining AHs with different mechanisms of action could potentially enhance efficacy and reduce safety concerns in patients. Unfortunately, there is a lack of comprehensive research in this area. To bridge this knowledge gap, our study aims to conduct a scoping review of the available literature investigating the efficacy and safety of combined H_1 AH use in the treatment of urticaria.

Methods

Methodological framework

We conducted a scoping review following the methodology proposed by Arksey and O'Malley,[13] which consists of five key steps: (a) identifying research questions, (b) searching and identifying relevant studies, (c) selecting studies for inclusion, (d) charting the data and (e) organising, summarising and reporting the results. The primary research question guiding this review was: 'Is the combination of H_1 AHs more effective and has fewer ADRs compared to monotherapy in the treatment of urticaria?'

Inclusion and exclusion criteria

Inclusion criteria: (1) Patients diagnosed with urticaria, (2) intervention involving a combination of H_1 AHs, (3) studies reporting outcomes, (4) study designs: Randomised controlled trials (RCT), non-randomised trials (NRT), cohort studies, retrospective cohort studies, case series or case reports and (5) studies published in English or Chinese.

Exclusion criteria: (1) Duplicate studies, (2) studies without relevant outcome measures, (3) studies involving combinations of two or more AHs with other drugs, (4) studies unrelated to the topic of this review (e.g., unrelated drugs or diseases), (5) animal tests or cell experiments and (6) studies with obvious errors in administered doses or missing information.

Search strategy

A systematic search was conducted for studies published up to May 2023 in multiple databases including Embase, PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science, China National Knowledge Infrastructure (CNKI) database, Wanfang database, Chinese Scientific Journals Full-Text database (VIP) and China Biological Medicine (CBM) database. Medical subject headings and free-text terms such as 'ketotifen,' 'cyproheptadine,' 'loratadine,' 'cetirizine,' 'fexofenadine,' 'desloratadine' and 'urticarial' were used in the search strategy. The detailed search strategy can be found in the Appendix.

Study selection and data extraction

All identified studies were imported into Endnote X9, a reference management software, for organisation and management. Duplicate studies were then removed to ensure that only unique studies were included in the review. Two reviewers then independently screened the titles and abstracts of the identified studies for eligibility. Discrepancies were resolved through discussion or involving a third reviewer. Data extraction forms were created to record relevant information including the first author, type of disease, year, gender, age, treatment regimen and duration, treatment outcomes and ADRs.

Synthesis and presentation of results

The results were synthesised and presented using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) guidelines, as outlined in the Appendix. The characteristics of the included studies were summarised in tables. In cases where the rates of treatment effectiveness and ADRs were not reported, a custom formula based on the methods reported by Li *et al*.[14] was used to calculate these rates.

Statistical analysis

Statistical analysis was conducted using SPSS 18.0 with *t*-tests for normally distributed data expressed as mean ± standard deviation and non-parametric tests for skewed distribution data expressed as median M (P25, P75). $P<0.05$ was considered statistically significant.

Results

Study selection and the baseline characteristics

A comprehensive search was conducted, resulting in identification of a total of 12,887 studies. After removing duplicates, a total of 109 studies were deemed eligible for inclusion in this review. These included 77 RCTs,[14–90] 22 NRTs,[91–112] 7 case reports,[113–119] and 3 case series.[120–122] The screening process is illustrated in Figure 1.

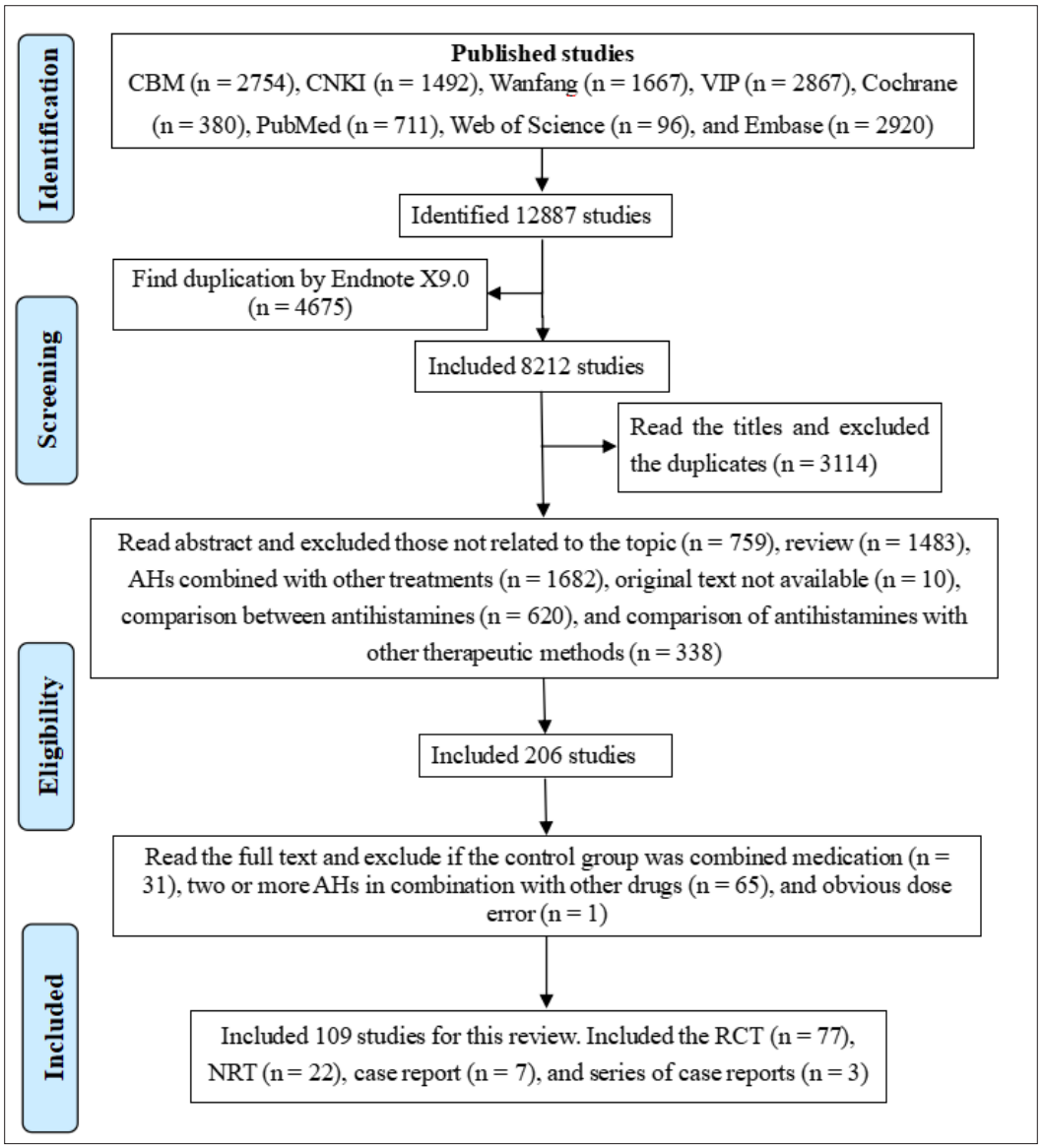

Figure 1: PRISMA flowchart of study selection and inclusion process. AHs: H_1 antihistamines, RCT: Randomised controlled trials, NRT: Non-randomised trials, CNKI: China National Knowledge Infrastructure, VIP: Chinese Scientific Journals Full-Text database, CBM: China Biological Medicine.

Among the included studies, 103 were conducted in China, while 2 studies were from Germany,[33,91] 1 from the United States,[115] 1 from Portugal[114] and 2 studies did not report nationality.[113,116] Collectively, the 109 studies involved a total of 11,435 patients with urticaria. Of these, the average age of onset for patients was reported in 101 studies, ranging from 1 to 85 years old. This information provides valuable insights into the demographics of the included patient population.

A total of 109 studies were conducted to address 11 different types of urticaria which included the following: urticaria (n = 7),[21,22,94,111,113,116,119] chronic idiopathic urticaria (n = 2),[27,122] chronic refractory urticaria (n = 4),[14,77,84,89] chronic spontaneous urticaria (n = 4),[33,56,105,110] refractory urticaria (n = 10),[45,49,61,64,75,76,101,104,106,108] pruritus urticaria (n = 1),[91] acute urticaria (n = 1),[118] intractable urticaria (n = 1),[117] urticaria (angioedema) (n = 1),[115] urticaria (mast cell proliferation) (n = 1)[114] and chronic urticaria (n = 77).[15-20,23-26,28-32,34-44,46-48,50-55,57-60,62,63,65-74,78-83,85-88,90,92,93,95-100,102,103,107,109,112,120,122]

Within these studies, a total of 43 combination therapy schemes involving AHs were reported. The breakdown of the combinations is as follows: 25[15,16,20,23,24,28,29,32,34,35,38,39,43,48,50,52,53,55,58,92,95,99,113,120,122] reported First-generation AHs (fgAHs) and Second-generation AHs (sgAHs) combination, 17[17,19,25,27,30,31,33,37,40,41,44,60,62,87,114,115,121] reported fgAHs and Third-generation AHs (tgAHs) combination, 17[14,22,47,57,59,63,67,69,72,74,77,80,82,89,93,105,112] reported sgAHs and sgAHs combination, 24[18,21,26,51,56,65,73,83-85,88,90,91,96-98,100,103,107,109-111,115,119] reported sgAHs and tgAHs combination, 23[36,42,45,46,49,54,61,64,66,68,71,75,76,78,79,81,86,94,101,102,104,106,108] reported tgAHs and tgAHs combination and 3[116-118] reported fgAHs

and sgAHs and tgAHs combination. Of all the studies, 94 reported the effective rate (rate of efficacy) of treatment and 67 reported ADR rates. For further details on the results of the AHs combinations, please refer to Tables 1 and 2.

In the studies analysed, a range of different approaches to medication administration was observed. In 26 studies, the frequency of administration was reduced in the treatment group compared to the control group.[15,16,20,24,27,28,30,31,35,37-41,43,48,53,82,87,92,95,99,105,114,120,122] However, in two studies,[33,107] both groups had an increase in the dose, reaching up to four times the conventional dosage. In two other studies,[83,109] only the dose of the treatment group was increased which was twice as much as the conventional dose. Interestingly, one study[71] increased the dose only in the control group, resulting in a dosage that was twice that of the conventional dose, but this led to an increase in the incidence of ADRs. The treatment duration varied among these studies with the longest course of treatment lasting for 1 year,[66] while the shortest duration being only 5 days.[33,113] The course of treatment was not reported in 15 studies.[37,38,53,61,75,76,91,103,104,107,114-116,118,119]

Clinical outcome of the study (efficacy and safety)

Of the total number of studies analysed, 94 of them reported the effective rate of the treatment under consideration. The effectiveness of the treatment varied among these studies with the lowest recorded effective rate being 60.4%[14] and the highest effective rate reaching 100%[79] in the combined group. In contrast, for the control group, the lowest effective rate observed was 37.3%,[14] while the highest effective rate stood at 99.5%.[92] Among the 94 studies, only 1 study showed a slightly lower efficacy with combination therapy (98% vs 99.5%),[92] but the difference was not statistically significant ($P > 0.05$). Several other outcomes were reported in these studies. Some studies indicated a reduction of inflammatory factors (n = 5),[49,63,71,76,106] improvement in quality of life (n = 1),[33] decrease in recurrence rate (n = 1),[21] amelioration of symptoms (n = 4),[114–116,118] presence of recurrent symptoms (n = 1),[119] relief from itching (n = 1),[91] no change in symptoms (n = 1)[113] and one study reported the treatment as ineffective (n = 1).[117]

A total of 67 studies provided information on the incidence of ADR. Among these studies, combination therapy demonstrated a lower ADR incidence compared to monotherapy in 32 studies.[17,22,23,27,34,40,41,45,46,48,51-53,59,66,68-71,74,76,79,84,85,88,90,100,103,104,106,110,111] In seven studies,[16,18,20,26,28,58,67] the ADR incidence was found to be equal between the two treatment approaches. Thirty-four studies did not provide data on the incidence of ADR. In addition, six studies[31,35,38,44,87,91] mentioned the occurrence of ADRs but did not report the specific incidence rates. Only two studies[15,93] reported the incidence of ADR

Table 1: Results of combinations of H_1 antihistamines in randomised controlled trials and non-randomised trials

Intergenerational drug combination	Combination of AHs	Number of articles	Number of articles reporting efficacy	Number of effective articles (I > C)	Number of articles reporting the incidence of ADR	Number of articles on incidence of ADR (I < C)
fgAHs + sgAHs (n = 9)	Carritin + Cyproheptadine (n = 1); Loratadine + Ketotifen (n = 1); Cyproheptadine + Loratadine (n = 3); Mizolastine + Cyproheptadine (n = 9); Mizolastine + Ketotifen (n = 2); Mizolastine + Chlorphenamine Maleate (n = 1); Cetirizine + Promethazine (n = 3); Ebastine + Cyproheptadine + Dosepin (n = 1); Ebastine + Cyproheptadine (n = 1)	22	22	21	18	5
fgAHs + tgAHs (n = 8)	Levocetirizine + Hydroxy azine (n = 1); Desloratadine + Ketotifen (n = 1); Fexofenadine + Ketotifen (n = 1); Desloratadine Citrate + Ketotifen (n = 3); Desloratadine Citrate + Cyproheptadine (n = 1); Desloratadine Citrate + Chlorphenamine Maleate (n = 1); Levocetirizine + Ketotifen (n = 5); Fexofenadine + Chlorphenamine Maleate (n = 1)	14	13	13	5	4
sgAHs + sgAHs (n = 7)	Avastin + Loratadine (n = 4); Olotadine + Cetirizine (n = 1); Loratadine + Clomastine (n = 2); Ebastine + Lupatadine (n = 1); Loratadine + Cetirizine (n = 8); Statin + Loratadine (n = 1); Imestine + loratadine (n = 1)	17	16	16	10	4
sgAHs + tgAHs (n = 11)	Desloratadine + Ebastine (n = 2); Levocetirizine + Ebastine (n = 6); Betastin + Levocetirizine (n = 1); Desloratadine + Loratadine (n = 2); Desloratadine + Mizolastine (n = 2); Cetirizine + Desloratadine (n = 3); Desloratadine Citrate + Cetirizine (n = 2); Levocetirizine + Loratadine (n = 2); Fexofenadine + Loratadine (n = 1); Epistine + Fexofenadine (n = 1); Levocetirizine + Fexofenadine + Azolastine (n = 1)	23	21	21	16	10
tgAHs + tgAHs (n = 4)	Desloratadine Citrate + Fexofenadine (n = 10); Levocetirizine + Desloratadine Citrate (n = 3); Levocetirizine + Fexofenadine (n = 2); Levocetirizine + Desloratadine (n = 8)	23	19	19	16	9

AHs: H_1 antihistamines, ADR: adverse drug reaction, I: intervention group, C: control group, fgAHs: first-generation AHs, sgAHs: second-generation AHs, tgAHs: third-generation AHs, I<C: the effective rate of intervention group was higher than that of control group, I<C: adverse drug reactions in intervention group were less than those in control group.

Table 2: Summary results of combinations of H_1 antihistamines in case reports and case series reports

Number of articles	Combination of AHs	Intergenerational drug combination	Report the outcomes of treatment	Improved and effective	Report ADRs	No serious ADRs were reported
10	Fexofenadine + Cetirizine + Ketotifen (n = 1); Lupatadine + Desloratadine Citrate (n = 1); Mizolastine + Ketotifen + Levocetirizine (n = 1); Carritin + Chlorphenamine Maleate + Levocetirizine (n = 1); Hydroxy azine + Fexofenadine (n = 1); Levocetirizine + Ketotifen (n = 2); Ketotifen + Cetirizine (n = 1); Cetirizine + Cyproheptadine (n = 1); Loratadine + Chlorphenamine Maleate (n = 1)	sgAHs + tgAHs (n = 1); sgAHs + sgAHs (n = 0); fgAHs + tgAHs (n = 3); fgAHs + sgAHs (n = 3); fgAHs + sgAHs + tgAHs (n = 3);	10	6	2	2

AHs: H_1 antihistamines, ADR: adverse drug reaction, fgAHs: First-generation AHs, sgAHs: second-generation AHs, tgAHs: third-generation AHs

rates, but they provided information for only one of the treatment groups. The general ADRs reported included drowsiness, nausea, fatigue, dry mouth, dizziness and headache. Slightly more serious ADRs included hypotension, otitis media, polyuria, rhinorrhoea, abnormal liver function, rash, loss of appetite and pain in other parts of the body. These ADRs were observed in different combinations of fgAHs and sgAHs, fgAHs and tgAHs, sgAHs and sgAHs, sgAHs and tgAHs and tgAHs and tgAHs, respectively. The incidence rates of ADRs ranged from 0% to 21% in the treatment group, while in the control group it varied from 0.5% to 75%. It is worth noting that all ADRs were found to be tolerable by the patients and resolved after discontinuation of the treatment. For more detailed information, please refer to Tables 1–3 in the supplementary materials.

Common combination therapy schemes

In a total of 99 Randomised controlled trials (RCTs) and Non-randomised trials (NRTs), several combination therapies were identified. These included cyproheptadine and mizolastine in nine studies,[16,32,35,43,48,53,55,92,99] levocetirizine and ketotifen in five studies,[17,19,25,40,114] loratadine and cetirizine in eight studies,[22,47,57,59,63,67,74,93] levocetirizine and ebastine in six studies[51,65,70,85,98,100] and loratadine citrate and fexofenadine in ten studies.[45,49,61,64,75,76,101,104,106,108] When compared to monotherapy, combination therapy demonstrated superior efficacy with statistical significance ($P < 0.05$). Furthermore, there was no significant difference observed in the incidence rates of ADR between the two treatment approaches ($P > 0.05$). Detailed results can be found in Table 3.

Discussion

Specific efficacy and safety of combinations of AHs on urticaria

This scoping review summarises the evidence related to the clinical efficacy and safety of combination therapy with AHs in the treatment of patients with urticaria. Our research questions focused on describing the current literature on H_1 AHs combinations for the treatment of urticaria. We found that most studies only looked at the results of AHs combination therapy in general which is usually associated with higher efficacy rates and fewer ADRs than monotherapy. However, the sample size of up to 368 cases in all the studies was not sufficient to draw firm conclusions and therefore our conclusions can only be taken as an inference.

Specifically, combination therapy with AHs is known to be effective in treating urticaria, at least when compared to monotherapy which has better efficacy and fewer ADRs. Although individual studies have reported higher ADRs with combination therapy compared to monotherapy, combination therapy does exert a synergistic effect. It is important to note that urticaria exists in multiple types with the major types being acute urticaria (AU) and chronic urticaria (CU). There are significant differences in the aetiology and treatment of these two types. AU typically subsides within a week of onset, but approximately 40% of patients may progress to develop CU which has a much longer treatment time and may resolve naturally after several years.[6] Of the studies we included in our review, only one[118] reported on AU as a case report, while the remaining studies focused on CU and other subtypes.

According to the literature we retrieved, most patients with CU choose combination therapy with AHs, while patients with AU tend to receive monotherapy or combined treatment with traditional Chinese medicine (TCM).[123–126] While our review focused on the efficacy and safety of combination therapy with H_1 AHs for urticaria, it should be noted that further studies are needed to fill the gap in research on the effectiveness and safety of AHs as monotherapy or in combination with TCM for treating acute urticaria (AU). The studies included in our review primarily used second- and third-generation AHs for treating acute urticaria (AU).

It is important to emphasise that the results and conclusions presented in this study apply primarily to patients with CU. The paucity of reported studies and the lack of representativeness of the only study on AU included in our review make it difficult to determine the efficacy of combination therapy with AHs for treating AU. Further studies are needed to address these gaps in knowledge.

In our study, the combinations of sgAHs and tgAHs, sgAHs and sgAHs or tgAHs and tgAHs enhance immune function, reduce cardiac toxicity, improve anxiety and depression and overall quality of life while reducing inflammatory factors. Specifically, the combination of sgAHs and tgAHs effectively blocks histamine receptors without affecting the central nervous system. Studies have reported that the sgAHs ebastine is generally well-tolerated and has minimal adverse

Table 3: Comparison of effective rate and adverse drug reaction results of combinations of H_1 antihistamines

AHs combination therapy regimen	Results					
Mizolastine + Cyproheptadine (n = 9)	Effective rates (n = 9)		*P*	ADRs (n = 8)		*P*
	I	C	0.015	I	C	0.721
	92.97 ± 5.26[b]	79.33 ± 14.15[b]		12.50 (9.1, 13.41)[a]	10 (9.21, 17.5)[a]	
Levocetirizine + Ketotifen (n = 5)	Effective rates (n = 5)		0.013	ADRs (n = 2)		0.895; NA
	I	C		I	C	
	92.68 ± 4.57[b]	80.15 ± 7.53[b]		NA	NA	
Loratadine + Cetirizine (n = 8)	Effective rates (n = 7)		0.003	ADRs (n = 6)		0.143
	I	C		I	C	
	92.12 ± 7.00[b]	77.43 ± 7.68[b]		6.12 ± 4.50[b]	10.03 ± 2.97[b]	
Levocetirizine + Ebastine (n = 6)	Effective rates (n = 6)		0.003	ADRs (n = 4)		0.446
	I	C		I	C	
	96.18 ± 3.41[b]	81.31 ± 8.92[b]		4.95 ± 3.18[b]	6.65 ± 2.70[b]	
Desloratadine citrate + Fexofenadine (n = 10)	Effective rates (n = 7)		0	ADRs (n = 5)		0.065
	I	C		I	C	
	92.71 ± 2.82[b]	75.57 ± 3.00[b]		6.73 ± 2.39[b]	17.93 ± 11.46[b]	

AHs: H_1 antihistamines, ADR: adverse drug reaction, I: intervention group, C: control group, NA: not available/not applicable, [a] expressed as median M (P25, P75), [b] Expressed as mean ± standard deviation, n: represents how many articles in which the same H_1 antihistamine combination therapy regimen appears.

cognitive and psychomotor effects.[127] Therefore, combining these drugs significantly improves efficacy compared to monotherapy.

fgAHs and sgAHs or fgAHs and tgAHs reduce nocturnal itching, improve sleep quality and increase treatment adherence. However, fgAHs have a strong sedative effect, can cause drowsiness and may prolong the Q-T interval and induce Torsade de Pointes. To mitigate these effects, reducing the dose of fgAHs while concurrently using a sgAHs or tgAHs over the long term can improve efficacy compared to short-term treatment, effectively reducing sleepiness. Long-term therapy can also allow for reduced drug doses, lower medical expenses, minimise sensitivity and maintain immune function. Long-term therapy has been shown to improve treatment outcomes and reduce ADRs compared to short-term treatment.[92] It is important to note that the drowsiness effect of combined therapy is stronger in the initial course of treatment and tends to decrease with continued treatment.

Is increasing the dose of a single AH more effective than combination therapy? In a study by Kuang et al.,[128] the treatment group received twice the conventional dose of loratadine, while the control group received a combination of loratadine and cetirizine. The results showed that combination therapy was more effective with no significant difference in ADRs between the two groups. Conversely, other studies have suggested that increasing the dose of a single sgAH is preferred over combining different sgAHs.[9,129] However, further research is required to confirm the optimal method of drug use through large, well-designed double-blind clinical trials.[130] Current evidence suggests that reduced treatment doses can also achieve better efficacy in the case of combination therapy. In our review, 26 studies reported that reducing treatment doses while using combination therapy resulted in improved efficacy compared to the control group with no significant difference in ADRs between the two groups. However, Schulz et al.[91] reported lower efficacy with combinations of more than two AHs compared to increasing the dose of a single AH, possibly due to unknown interactions. Future research should aim to confirm the most effective method of drug use.

Discussion on the efficacy and safety risk of combination therapy for urticaria

In our review, all studies except one reported better efficacy with combination therapy than monotherapy. Most ADRs were mild and reversible. Common side effects included drowsiness, dry mouth, dizziness, headache and stomach discomfort which were generally well-tolerated by patients. More serious ADRs such as hypotension, otitis media, abnormal liver function, rash and pain in other parts of the body occurred with the combination of fgAHs and sgAHs, fgAHs and tgAHs, sgAHs and sgAHs and tgAHs and tgAHs, respectively. However, these ADRs returned to normal immediately after discontinuation of the therapy. Combination therapy did not significantly increase the occurrence of ADRs compared to monotherapy. It is important to note that there may be a higher risk of nephrotoxicity with combination therapy and patients receiving combination treatment may also be at a higher risk of treatment failure.[131,132] In addition, it is crucial to closely monitor liver function when using sgAHs.[14,69,74] Recent guidelines do not recommend the use of fgAHs for the treatment of urticaria due to their significant side effects on the central nervous system which can impair daily activities, especially in special patient groups.[133] Therefore, the occurrence of ADRs should not be ignored when using combinations of AHs.

Future Research

There are several areas that require further research: (1) Evaluating the economic benefits of combination therapies, (2) investigating whether lowering drug doses or reducing

dosing intervals in combination therapies leads to a lower incidence of ADRs, (3) studying the drug interactions in combination therapies, and (4) assessing drug safety in special populations such as very aged persons or those who are pregnant.

Limitations

Our analysis filled the gap in the literature regarding the combined application of two or more AHs in the treatment of urticaria. However, we did not evaluate publication bias and most of the studies included in our review were conducted in China. Therefore, this conclusion may only be applicable to patients with urticaria in China and caution should be exercised when extrapolating these findings to patients in other countries.

Conclusion

In conclusion, the reviewed studies have consistently demonstrated that combination therapy with two H_1 AHs is more effective than AH monotherapy for treating urticaria with the exception of one study. Most ADRs associated with such therapy were mild and reversible and no new safety concerns were observed. The most common combinations were mizolastine and cyproheptadine, levocetirizine and ketotifen, loratadine and cetirizine, levocetirizine and ebastine and desloratadine citrate and fexofenadine.

This review offers valuable guidance to healthcare providers for selecting appropriate combination therapies with AHs for treating urticaria, particularly CU. While combination therapy may be preferred for most CU cases, AU may be treated with AH monotherapy or in conjunction with TCM. However, the use of combination therapy with AHs should always be individualised, considering patient-specific characteristics and closely monitored for response and adverse events.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

Financial support and sponsorship

Nil

Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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