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REVIEW

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An update on the use of antihistamines in managing chronic urticaria

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ABSTRACT

Introduction: Urticaria, a mast cell-mediated skin disease, manifests as acute or chronic, with the latter divided into spontaneous and inducible types and requires individualized management, including identifying triggers and comorbidities. Antihistamines, particularly the second generation group, form the mainstay of primary treatment plans consisting of dosage adjustments and/or in combination with other treatment modalities depending on underlying disease control.

Areas covered: A literature search was conducted using 'antihistamines,' 'urticaria,' 'pharmacogenomics,' 'genomics,' 'biomarkers' and 'treatment response' as key words. In this review, we focus on the comprehensive understanding and application of antihistamines in managing adult and adolescent patients with chronic urticaria.

Expert opinion: Using antihistamines to treat urticaria is set to change significantly, focusing more on personalized medicine and identifying key biomarkers to enhance treatment response prediction. These changes aim to make treatments more specific and cost-effective by avoiding unnecessary tests. Applying new approaches in everyday clinical care faces challenges like proving the biomarkers' reliability, updating current guidelines, and incorporating individualized treatments into standard procedures. Efforts should now concentrate on finding easy-to-use biomarkers, improving access to pharmacogenomics, understanding why some patients are resistant to treatment, and creating more specific treatment options based on patient needs.

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Urticaria; antihistamines; treatment response; biomarkers; pharmacogenomics

1. Introduction

Urticaria is primarily a mast cell-mediated skin disease characterized by itchy wheals and/or angioedema. It is classified as acute if lasting for six weeks or less, and chronic if persisting beyond six weeks [1]. Chronic urticaria (CU) manifests either as chronic spontaneous urticaria (CSU), characterized by spontaneous appearance without a certain trigger, or as chronic inducible urticaria (CIndU), where symptoms are triggered by specific and reproducible factors such as friction, heat, cold, sunlight exposure, pressure, exercise, or vibration [1]. The main mechanism involved in the activation of mast cells is considered as the autoimmune mechanism which has two endotypes: type 1 autoimmune (autoallergic) endotype is characterized by IgE-autoantibodies formed against autoallergens such as thyroid peroxidase and interleukin-24, and type 2b autoimmune endotype is characterized by IgG, IgA or IgM type autoantibodies against IgE or FcεRI [2,3].

The international urticaria guidelines suggest an individualized management approach in CSU which involves the following strategies: 1. ruling out differential diagnoses, 2. investigating causes by checking autoimmune urticaria markers, 3. identifying possible triggers such as stress and NSAIDs, 4. revealing comorbidities such as CIndU or other autoimmune diseases, 5. determining consequences of the disease such as anxiety, depression, fatigue, sexual, cognitive dysfunction and sleeping disorders, 6. detecting possible biomarkers of the disease and predictors of response to treatment and 7. following the course of the disease by determining the activity of the disease by Urticaria Activity Score (UAS) and Angioedema Activity Score (AAS), evaluation of control with Urticaria Control Test (UCT) and Angioedema Control Test (AECT) and assessing the burden of disease by CU-Quality of Life Questionnaire (CU-Q2oL) and Angioedema Quality of Life Questionnaire (AE-QoL) [1].

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Article highlights

- Urticaria, a mast cell-mediated disorder, is characterized by wheals and/or angioedema. Histamine is the major mediator released from mast cells and responsible for the signs and symptoms, and antihistamines are the primary treatment of chronic urticaria.
- Current evidence indicates that second-generation antihistamines (sg-AH) are effective for chronic urticaria and have fewer adverse effects compared to first-generation antihistamines.
- Pharmacogenetic testing might enable personalized antihistamine selection and dosing for chronic urticaria based on genetic markers, though current knowledge limits its immediate feasibility.
- Current guidelines lack specific recommendations for selecting sg-AH for urticaria, causing physicians to base choices on personal experience. In this review, we examine the efficacy and safety of standard-dose of antihistamines in managing urticaria.
- The international guideline suggests increasing sg-AH up to four times as second-line treatment, while certain national guidelines propose alternative strategies, such as combining different antihistamines. In this review, we compared the response rates between antihistamine updosing and combination therapies.
- High disease burden, concomitant spontaneous and inducible subtypes, together with high CRP/D-dimer levels predict nonresponse or poor response to sg-AH in chronic urticaria treatment.

Since histamine is the main mediator released from mast cells upon activation, antihistamines are the first choice of pharmacological treatment of urticaria. Treatment with antihistamines is carried out in accordance with the principle of as much as needed and as little as possible, taking into account the activity and control of the disease [4]. The aim of treatment is a continuous and safe treatment with complete symptom control and sustainable zero disease activity.

All international and national guidelines [1,5–8] recommend starting urticaria treatment with second-generation H1-antihistamines (sg-AH). First-generation H1-antihistamines (fg-AH) are no longer preferred in clinical practice in the treatment of urticaria due to their side effects such as anticholinergic and sedative effects, REM sleep disturbance, and multidrug interactions. However, the standard doses of antihistamines are inadequate in approximately 60% of the patients [9], and in this case current guidelines recommend dosage increment up to fourfold of standard dose [1,5,6]. High-dose antihistamine treatment leads to symptom control in a further 63% [10] and has been found to be safe in terms of the above-mentioned side effects, except for the increased risk of somnolence compared to standard-dose antihistamine treatment [11]. Approximately more than half (55%) [12] of patients do not respond to treatment with antihistamines (including updosing) and need a third-line treatment, i.e. monoclonal anti-IgE antibody (omalizumab). Omalizumab is administered subcutaneously once a month at a dose of 300 mg, and is a safe and effective treatment option for all types of CU even as a long term therapy given at higher doses [13–16]. However, in 15–30% of the patients the response to omalizumab treatment may be inadequate [17], and in this case, cyclosporine, is used as the fourth-line therapeutic option, in stepwise treatment recommendations despite its limiting adverse effect profile [18]. In the very refractory cases where cyclosporine does not work or is contraindicated, there are other new treatment options in the pipeline, many of them are currently being developed or tested in different stages of clinical trials [17]. During the COVID pandemic, patients with CU in clinical remission still face the risk of experiencing a urticaria relapse after vaccination [19].

Although approximately 50% of CU patients do not respond to antihistamines, half of them can be safely and economically treated by antihistamines. Given limited access as well as unavailability of omalizumab in many countries, it is unsurprising a great proportion of CU patients are being treated with various doses and combinations of antihistamines. However, effective use of antihistamines is only possible by knowing their mechanism of action, pharmacological properties, adverse effects and safety profile in higher doses. Therefore, with this review we aimed to provide detailed information about antihistamines starting from the basics of histamine, its effects, efficacy in CU, biomarkers of antihistamine response to the pharmacogenomics of antihistamines.

2. Pharmacological properties and classification of antihistamines

Histamine, a heterocyclic amine derived from the decarboxylation of l-histidine, is synthesized and released from the mast cells and basophils. It has both pro-inflammatory and anti-inflammatory actions that are determined by both the histamine receptor subtype and the cells stimulated. There are four types of histamine receptors: H1, H2, H3 and H4. The H1 receptors are responsible for the defensive action and immunoregulatory actions of histamine, along with acute and chronic allergic inflammation. They are expressed in many tissues and cells, including the nerves, endothelial cells, vascular smooth muscle cells, respiratory epithelium, hepatic cells, dendritic cells and lymphocytes [20–22]. When histamine binds to H1 receptors on small capillary venules, it leads to the formation of edematous and erythematous wheals or skin-colored swellings (angioedema). This occurs as a result of vasodilation and heightened vascular permeability, causing the leakage of plasma containing large molecular weight proteins, including immunoglobulins, into the interstitium [23]. Histamine also induces sensory nerve stimulation that leads to itch as well as the recruitment of eosinophils, basophils, neutrophils, and other immune cells that is evidenced by the mixed cellular infiltrate in histopathological specimens of the wheals [24,25].

The word ‘antihistamine’ refers only to the drugs acting on the H1 receptors; antagonists of the other histamine receptors are not antihistamines. The antihistamines are inverse agonists to the constitutionally active H1 receptors; they decrease the constitutional activity of histamine at H1 receptors and antagonize the effects of histamine on H1 receptors by stabilizing the H1 receptor in its inactive conformation [21]. Therefore, they are preferentially termed as ‘H1-antihistamines’ rather than ‘histamine antagonists.

Antihistamines reverse local vasodilation and increase vascular permeability induced by histamine, thereby reducing local edema [21]. Besides blocking histamine action at the receptors on small blood vessels and sensory neurons, antihistamines indirectly decrease allergic inflammation by inhibiting the accumulation of inflammatory cells within tissues and suppressing the immune response to antigens through acting on nuclear factor-K beta and calcium channels as well [21,26].

The earliest antihistamines resembled histamine and consisted of an ethylamine group. Many different chemical series with similar or greater activities have been found including ethanolamines, ethylene diamines, alkylamines, piperazines, piperidines and phenothiazines [27]. In the 1980s, introduction of sg-AH provided a major advance in antihistamine development since these compounds are minimally or non-sedating due to their limited penetration of the blood-brain barrier [28].

First-generation antihistamines are poorly selective for H1 receptors; they have an affinity toward muscarinic, serotoninergic and alpha-adrenergic receptors and on cardiac potassium channels, which may lead to intolerable side effects such as constipation, dry mouth and blurred vision, and may be potentially fatal. Overdosing with fg-AH, for example diphenhydramine, may lead to anticholinergic effects, such as fever, flushing, tachycardia, hypotension, seizures, drowsiness, delirium, pupillary dilatation, urinary retention, respiratory depression and coma [20]. Fg-AH are lipophilic and cross the blood brain barrier; thus they have a potential to suppress to the central nervous system, causing psychomotor impairment, drowsiness, comatose state and even death. They have been associated with increased sedation, decreased sleep quality, hang-over symptoms the following day, decreased school or work performance; and increased drowsiness leading to car, boat and plane accidents. On the contrary, sg-AH are more selective toward H1 receptors and therefore are devoid of these side effects [20,26,29].

Cardiotoxicity has become a major concern in 1980s with an increasing number of reports showing an association between the consumption of astemizole and terfenadine and cardiotoxicity which was associated with prolongation of the QT interval [30]. Although these drugs are not available now, some fg-AH, such as promethazine, brompheniramine and chlorpheniramine may also be associated with a prolonged QTc and cardiac arrhythmias when taken in large doses or when overdosed [22]. Use of fg-AH in the elderly who have comorbid diseases and therefore polypharmacy, may pose a cardiac safety concern. The most frequently involved mechanism in cardiotoxicity induced by antihistamines is the blockade of hERG (Kv11.1) voltage-gated Kþ channels that leads to QT prolongation and ultimately to torsade de pointes [31]. No clinically significant cardiac effects have been reported for the sg-AH bilastine, cetirizine, levocetirizine, ebastine, fexofenadine, loratadine, desloratadine, mizolastine and rupatadine, even when higher doses are used [22,31].

Examples of fg-AH are chlorpheniramine, diphenhydramine, hydroxyzine, cyproheptadine, clemastine, promethazine, and doxepin [23,26,32] (Table 1). Because of these side effects and their relatively short half-lives, some of the fg-AH have been withdrawn from the market except for a few indications [29]. Randomized controlled trials revealed strong evidence for the use of sg-AH for chronic urticaria; they are as effective as fg-AH with less sedative side effects [26]. Sg-AH are cetirizine, levocetirizine, loratadine, desloratadine, fexofenadine, rupatadine, ebastine, mizolastine, acrivastine and bilastine (Table 1). This review will focus more on the pharmacological properties of the commonly used sg-AH. Besides their improved selectivity for histamine receptors and limited penetrance in the brain, the longer half-lives of sg-AH provide an ease for dosing that improves adherence to treatment [23,26,33,34].

3. Response rates and comparison between standard doses of antihistamines in urticaria

While the current EAACI/WAO/GA^{2}LEN guideline recommends using sg-AH over fg-AH for the treatment of urticaria, it does not make a recommendation on which sg-AH to choose due to the lack of well-designed clinical trials comparing the efficacy and safety of all modern sg-AH in urticaria. Therefore, urticaria treating physicians use sg-AH based on their personal preferences and experiences. In this section, we aimed to bridge this information gap and review the current evidence regarding use of these sg-AH in their standard dose to treat urticaria. We analyzed 30 clinical trials involving sg-AH in their standard doses for the treatment of chronic idiopathic/spontaneous urticaria. We included only randomized trials having a comparator group, either other sg-AH or placebo, sample size of at least 25 and published after 2000. We excluded single arm longitudinal studies, case-reports or case-series. Overall, we analyzed the data of 5144 patients, among them 3992 subjects received a sg-AH in standard dose while the remaining 1152 received placebo (see Table 2).

3.1. Studies depicting significant superiority of standard-dose sg-AH over placebo

All placebo-controlled studies demonstrated significant statistical superiority of the test sg-AH at standard dose over placebo, reaffirming their effectiveness and safety in treating chronic urticaria. Hide et al. [35] reported significant benefit with bilastine 20 mg OD or 10 mg OD in terms of tolerability and effectiveness, compared to placebo in treating urticaria. Two studies demonstrated the effectiveness and safety of levocetirizine 5 mg OD over placebo in treating urticaria [36,37]. The significant advantage of rupatadine 10 mg OD [38–40] and desloratadine 5 mg OD [41–43] over placebo was reported by 3 studies each. Two studies reported the significant advantage of fexofenadine 180 mg OD over placebo in terms of effectiveness, safety and tolerability [44,45]. Furthermore, Nelson et al. [45] reported significant improvement in the sleep quality and quality of life with fexofenadine.

3.2. Studies depicting statistically comparable benefit of different sg-AH in their standard doses

Overall, nine studies depicted statistically comparable effectiveness and safety of different sg-AH. Two studies demonstrated that bilastine 20 mg OD is equivalent to levocetirizine 5 mg OD in terms of efficacy and safety [46,47], and one study reported that bilastine (20 mg OD) and fexofenadine (180 mg OD) are comparable [46]. Levocetirizine was found to be comparable to bepotastine 10 mg BD [48], fexofenadine 180 mg OD [49] and ebastine 10 mg OD [50]. Mizolastine and loratadine were found to have comparable benefit in 2 studies [51,52], while another study demonstrated statistical equivalence between standard-dose loratadine and desloratadine in terms of clinical utility [53]. A study from France demonstrated that loratadine 10 mg OD is statistically comparable to emedastine difumarate 2 mg BD for the short-term treatment of chronic idiopathic urticaria [54].

Table 1. Summary of the properties of the first and second generation antihistamines [20,21].

Generation	Drug name	Standard adult daily dose (mg)	Elimination half-life (hours)	Time to reach maximum plasma concentration after a single dose (hours)	Time to action (hours)	Duration of action (hours)	Liver metabolization	Renal failure	Liver failure	Pregnancy considerations	Use in lactation*	Use in elderly	Clinically relevant drug interaction
fg-AH	Chlorpheniramine	24	27.9 ± 8.7	2.8 ± 0.8	3	24	+	Dose adjustment not needed-	Dose adjustment needed	Based on animal studies, the use is not expected to increase the risk of malformations. Human studies have reported associations with varied birth defects	Excretion in breast milk is not known. May cause drowsiness in newborn	Not recommended	Possible
fg-AH	Diphenhydramine	75–150	9.2 ± 2.5	1.7 ± 1.0	2	12	+	Dose adjustment not needed	Dose adjustment needed	Based on animal studies and available human data diphenhydramine is not expected to increase the risk of congenital anomalies	Excretion in breast milk is considered low. May cause drowsiness in newborn	Not recommended	Possible
fg-AH	Hydroxyzine	75–150	20 ± 4.1	2.1 ± 0.4	2	24	+	Dose adjustment not needed	Dose adjustment needed	Hydroxyzine showed adverse pregnancy effects in rodents. Limited published data during human pregnancy. Manufacturer contraindicates use in early pregnancy	Excretion in breast milk is not known. May cause drowsiness in newborn	Not recommended	Possible
sg-AH	Rupatadine	10	5.9	0.75	2	24	+	Dose adjustment needed	Dose adjustment needed	Based on animal data, therapy with rupatadine is not expected to increase the risk of congenital anomalies	Excretion in breast milk is not known	Be careful in liver function failure and polypharmacy	Possible
sg-AH	Fexofenadine	120–180	14.4	2.6	2	24	<8%	Dose adjustment needed	Dose adjustment not needed	Based on animal data and human data, fexofenaydne exposure during pregnancy is not expected to increase the risk of adverse outcomes	Excretion in breast milk is considered low	Safer to use	With p-glycoproteins
sg-AH	Loratadine	10	7.8 ± 4.2	1.2 ± 0.3	2	24	+	Dose adjustment needed	Dose adjustment needed	Based on animal data and human reports, loratadine is not expected to increase the risk of adverse pregnancy outcomes.	Excretion in breast milk is considered low	May have anticholinergic effects	Possible
sg-AH	Desloratadine	5	27	1–3	2	24	+	Dose adjustment needed	Dose adjustment needed	Based on animal and human data, the use during pregnancy is not expected to increase the risk of congenital anomalies	Excretion in breast milk is considered low	May have anticholinergic effects	Possible

(*Continued*)

Table 1. (Continued).

Generation	Drug name	Standard adult daily dose (mg)	Elimination half-life (hours)	Time to reach maximum plasma concentration after a single dose (hours)	Time to action (hours)	Duration of action (hours)	Liver metabolization	Renal failure	Liver failure	Pregnancy considerations	Use in lactation*	Use in elderly	Clinically relevant drug interaction
sg-AH	Cetirizine	10	7–11	1.0 ± 0.5	1	24	<40%	Dose adjustment needed	Dose adjustment needed	Based on animal and human data, the use is not expected to increase the risk of adverse pregnancy outcomes	Excretion in breast milk is considered low	May cause sedation	Unlikely
sg-AH	Levocetirizine	5	7 ± 1.5	0.8 ± 0.5	1	24	<15%	Dose adjustment needed	Dose adjustment needed	Based on animal and reported human data, the use is not expected to increase the risk of adverse pregnancy outcomes	There is not enough data however since it is an enantiomer of cetirizine, excretion in breast milk is considered low	May cause sedation	Unlikely
sg-AH	Bilastine	20	14.5	1.2	2	24	Not metabolized in humans	Dose adjustment not needed	Dose adjustment not needed	Information is limited. Based on animal and human data, no increased risk of adverse pregnancy outcome expected	Excretion in breast milk is not known.	Safer to use	With p-glycoproteins
sg-AH	Ebastine	10–20	10.3 ± 19.3	2.6 ± 5.7	2	24	+	Dose adjustment needed	Dose adjustment needed	Information is limited. Animal studies do not indicate direct or indirect harmful effects on embryonal/ fetal development, parturition or postnatal development	the amounts in milk are unlikely to affect a breastfed infant.	Be careful in liver failure and polypharmacy	Possible

*The percentage of drug concentration that penetrates into breast milk is typically categorized as follows: Low: Less than 1% of the maternal dose appearing in breast milk. Moderate: Between 1% to 10% of the maternal dose appearing in breast milk. High: Greater than 10% of the maternal dose appearing in breast milk.
Abbreviations: fg-AH, first-generation antihistamines; sg-AH, second-generation antihistamines.

Table 2. Characteristics of included studies concerning standard dose sg-AH in chronic urticaria.

Name of author, year, place of study	Type of study	Study participants and type of Urticaria	Interventions (n)	Study duration (weeks)	Study results	Remarks
(1) Shah et al., 2022, India [46]	Comparative, Three-Arm, Randomized Clinical Trial	18–60 years with a clinical history of CSU for at least 6 weeks during the last 3 months without an identifiable cause and urticaria activity score (UAS7) of ≥ 7.	Bilastine 20 mg OD (39) Fexofenadine 180 mg OD (35) Levocetirizine 5 mg OD (36)	2 weeks	• At week 2, 23 patients achieved well-controlled urticaria in the bilastine group, whereas 18 and 17 patients achieved well-controlled urticaria in the fexofenadine and levocetirizine arms, respectively. There was no statistical difference between any of the groups at week 2. • All drugs were safe and well tolerated.	Bilastine, Fexofenadine and Levocetirizine are effective, safe and well-tolerated at their standard doses.
(2) Sil et al., 2021, India [48]	Single-center, investigator-blind, randomized, active-controlled, parallel-group phase IV trial	Adult patients with CSU of either gender.	Bepotastine besilate 10 mg BD (30) Levocetirizine 5 mg OD (29)	6 weeks, fortnightly follow-up	• UAS7 and TSS reduced significantly ($p < 0.001$) in both treatment groups from 1st follow-up visit (bepostatine) and 2nd follow-up visits (levocetirizine). • At week 6, UAS7 (5.13 ± 8.21 vs 7.48 ± 8.96) and TSS (5.10 ± 4.06 vs 7.07 ± 4.48) were less with bepotastine than levocetirizine although not statistically significant. • Day-time sedation significantly more with levocetirizine ($p < 0.001$).	Bepotastine is comparable to levocetirizine with respect to its effectiveness with an edge in terms of side-effect (day-time sedation)
(3) Fayaz et al., 2021, India [55]	Single-blind randomized, parallel-group trial	Patients with CIU, 18–65 years, having symptoms ≥3 days per week in the last 6 weeks.	Loratadine 10 mg OD (25) Rupatadine 10 mg OD (26)	6 weeks, follow-up every 2 weeks	• Rupatadine is more efficacious than loratadine in the reduction of Total Leucocyte Count, Differential Count and Absolute Eosinophil Count, the key determinants of allergy. • Rupatadine also produced better improvement in Total symptom Score, Dermatology Life Quality Index in patients with CIU.	Rupatadine is superior to Loratadine for treating CIU, based on efficacy and safety parameters.
(4) Podder et al., 2020, India [58]	Double-blind RCT	CSU patients aged 18–65 years with moderate-to-severe disease (UAS 17 > 16)	Bilastine 20 mg OD (31) Levocetirizine 5 mg OD (27)	6 weeks, follow-up every 2 weeks	• Both drugs significantly improved UAS7, DLQI, and VAS at end-of-treatment (D42) compared to baseline (intra-group). • All parameters showed greater improvement with bilastine, but only UAS7 reduction was significant (bilastine > levocetirizine, $p = .03$). • Sedation was significantly less with bilastine ($p = .04$), while neither drug showed any serious adverse-effect.	Bilastine is a more effective and less-sedative therapy for CSU compared to levocetirizine, with similar effect on quality of life.
(5) Thi et al., 2019, Vietnam [49]	Open-label trial	Patients with chronic urticaria, aged >12 years	Levocetirizine 5 mg OD (52) Fexofenadine 180 mg OD (50)	2 weeks	• TSS reduced significantly in both groups at 2 weeks, compared to baseline [7.4 vs 2.3 for levocetirizine group and 8.0 vs 2.6 for fexofenadine group ($p < 0.05$)]. • No significant ADR reported in either group.	Levocetirizine and Fexofenadine are effective medications for CSU at their conventional dose, without any significant adverse reaction.
(6) Hide et al., Japan, 2019 [38]	Multi-center double-blind placebo controlled RCT	Patients with CIU, aged 12 to <65 years, total pruritus score (TPS) ≥ 2 for at least 3 consecutive days before drug administration	Rupatadine 10 mg OD (91) Placebo (94)	2 weeks	• TPS reduced significantly in those receiving rupatadine 10 mg, compared to placebo (mean TPS difference −1.956, $p < 0.001$). • No significant ADR was reported apart from somnolence in 20.9% patients (vs. 8.5% in placebo).	Rupatadine is safe and effective at a dose of 10 mg once daily, significantly better than placebo. It can be safely increased to 20 mg once daily, as necessary.

(*Continued*)

Table 2. (Continued).

Name of author, year, place of study	Type of study	Study participants and type of Urticaria	Interventions (n)	Study duration (weeks)	Study results	Remarks
(7) Hide et al., Japan, 2017 [35]	Multi-center double-blind placebo controlled RCT	Patients with documented CSU aged 18–74 years	Bilastine 20 mg OD (101) Bilastine 10 mg (100) Placebo (103)	2 weeks	• TSS reduced significantly in Bilastine 20 mg group, compared to placebo demonstrating its superiority ($p < 0.001$). • Bilastine 10 mg also reduced TSS significantly vs. placebo ($p < 0.001$) • Improvement started from day 1 and it was maintained, DLQI also improved with Bilastine treatment. • Bilastine was found to be safe and tolerable.	Two-week treatment with bilastine (20 or 10 mg) once daily was significantly more effective and tolerable in Japanese patients with CSU (vs. placebo), demonstrating an early onset of action.
(8) Goyal et al., 2017, India [50]	Open-label comparative longitudinal study	Patients with documented CSU, aged 10–70 years	Ebastine 10 mg OD (50) Levocetirizine 5 mg OD (50)	4 weeks	• 50% and 70% patients achieved complete urticaria remission (UAS7 = 0) at end-of-treatment with Ebastine 10 mg OD and Levocetirizine 5 mg OD ($p > 0.05$) • Levocetirizine 5 mg showed more side effects like dryness of mouth and sedation as compared to ebastine.	The effectiveness of Ebastine is comparable to levocetirizine at licensed dose for CSU. However, adverse effects are more frequent with levocetirizine.
(9) Dakhale et al., India, 2016 [62]	Double-blind RCT	Patients with CSU, aged 18–65 years, with history of urticarial wheals and/or angioedema for ≥3 days per week for 6 consecutive weeks without any obvious cause.	Rupatadine 10 mg OD (30) Olopatadine 10 mg OD (30)	6 weeks	• In olopatadine group, there was significantly higher reduction in mean total symptom score [MTSS] ($p = 0.01$), number of wheals ($p < 0.05$), size of wheals ($p < 0.05$), intensity of erythema ($p < 0.05$) and change in eosinopil count ($p = 0.015$), compared to rupatadine. • Adverse effects were less in the olopatadine group, vs rupatadine.	Olopatadine is a better choice in chronic spontaneous urticaria in comparison to rupatadine due to its better efficacy, safety and cost effectiveness profile.
(10) Dakhale et el, India, 2014 [56]	Double-blind RCT	Patients with CSU, aged 18–65 years, with history of urticarial wheals and/or angioedema for ≥3 days per week for 6 consecutive weeks without any obvious cause.	Cetirizine 10 mg OD (35) Rupatadine 10 mg OD (35)	6 weeks	• Both drugs reduced MTSS (mean total symptom score), MNW (mean number of wheals), and pruritus significantly, but it was significantly more with rupatadine ($p < 0.05$). • No drug reported any significant adverse effect.	Rupatadine is a more attractive therapeutic modality compared to cetirizine for the treatment of CSU.
(11) Mahawar et al., India, 2014 [59]	Open-label trial	Patients with documented CSU, 14–70 years, either gender.	Levocetirizine 5 mg OD (77) Olopatadine 5 mg BD (77)	6 weeks	• Both drugs reduced UAS significantly ($p < 0.05$) at all visits and olopatadine reduced UAS more than levocetirizine at 2 weeks ($p < 0.05$). • Each drug reduced DLQI score significantly. Levocetirizine reduced more DLQI than olopatadine, but the difference was not significant ($p > 0.05$). • Olopatadine was associated with more side-effect profile, and most common side-effect was somnolence in both groups.	Levocetirizine is a marginally superior drug as compared with olopatadine for long-term treatment of CIU in Indian population.
(12) Sil et al., India, 2013 [63]	Accessor blind, parallel-group, active controlled phase IV trial	Adults (>18 years) suffering from chronic urticaria.	Olopatadine 5 mg BD (54) Levocetirizine 5 mg OD (51)	9 weeks (continuously for first 4 weeks and then on demand basis for last 5 weeks).	• UAS and TSS values declined significantly with both drugs over the treatment period but the reduction was greater with olopatadine. • Adverse event profiles were comparable with sedation being the commonest complaint.	Olopatadine is a safe and more effective alternative to levocetirizine in the treatment of CU.

(*Continued*)

Table 2. (Continued).

Name of author, year, place of study	Type of study	Study participants and type of Urticaria	Interventions (n)	Study duration (weeks)	Study results	Remarks
(13) Maiti et al., India, 2011 [57]	Single-blind randomized parallel group trial	Patients aged 12–60 years suffering from CSU	Rupatadine 10 mg OD (35) Levocetirizine 5 mg OD (35)	4 weeks	• In rupatadine group, there was 27.9% decrease ($p = 0.027$) in DC eosinophil, 35.6% decrease ($p = 0.036$) in AEC, 15.3% decrease ($p = 0.024$) in serum IgE, 28.2% decrease ($p = 0.02$) in Total Symptom Scoring, and 27.3% decrease ($p = 0.006$) in Aerius Quality of Life Questionnaire score. • Global efficacy score of rupatadine was found to be significantly greater ($p = 0.009$) than levocetirizine. • Adverse effects were more with levocetirizine.	Rupatadine is a better choice in CIU in comparison to levocetirizine being more effective and safe.
(14) Zuberbier et al., Germany, 2010 [47]	Multicentre, double-blind placebo controlled RCT	Male and female patients with documented history of moderate-to-severe CIU, having symptoms for at least 3 days per week for 6 weeks.	Bilastine 20 mg OD (173) Levocetirizine 5 mg OD (165) Placebo (184)	4 weeks	• Bilastine significantly reduced patients' mean reflective and instantaneous TSS from baseline to a greater degree than placebo ($p < 0.001$); from day 2 onwards of treatment. • The DLQI, general discomfort, and sleep disruption were also improved significantly in bilastine-treated patients as compared to placebo-treated patients ($p < 0.001$ for all parameters). • Comparison with levocetirizine indicated both treatments to be equally efficacious as well as equally safe and well tolerated.	Bilastine 20 mg is a novel effective and safe treatment option for the management of CU, comparable to levocetirizine.
(15) Anuradha et al., 2010, India [60]	Open-label trial	CIU patients aged between 12–60 years	Loratadine 10 mg OD (30) Levocetirizine 5 mg OD (30)	4 weeks	• TSS reduction significantly more in Levocetrizine group (13.3%), compared to Loratadine group (4.8%), [$p < 0.001$] • Minor ADRs noted in both groups [Loratadine (19%) > Levocetirizine (12%)- drowsiness, headache, gastric irritation, dry mouth. Drug discontinuation not needed.	Levocetirizine is superior to loratadine for CSU in terms of efficacy and safety.
(16) Potter et al., Germany and UK, 2009 [61]	Multi-center, double-blind RCT	Adult patients (>18 years) with documented CIU, having episodes at least 3 times per week for 6 consecutive weeks during 3 months prior to inclusion.	Levocetirizine 5 mg OD (438) Desloratadine 5 mg OD (448)	4 weeks	• Levocetirizine led to a significantly greater decrease in pruritus severity than desloratadine after 4 weeks ($p = 0.004$) • Additionally, levocetirizine decreased pruritus duration and the mean CIU composite scores to a significantly greater extent than desloratadine. • Levocetirizine increased the patients' global satisfaction after 4 weeks ($p = 0.021$), compared to desloratadine.	Levocetirizine 5 mg was significantly more efficacious than desloratadine 5 mg in the treatment of CIU symptoms.

(*Continued*)

Table 2. (Continued).

Name of author, year, place of study	Type of study	Study participants and type of Urticaria	Interventions (n)	Study duration (weeks)	Study results	Remarks
(17) Ortonne et al., 2007, France [41]	Multi-center, placebo-controlled, double-blind RCT	Patients aged >18 years with active moderate-to-severe CIU	Desloratadine 5 mg OD (65) Placebo (77)	6 weeks	• The mean score for the number of wheals was significantly lower in the desloratadine group than in the placebo group on days 14 and 42 ($p <$ or = 0.016). • Overall improvement in CIU (complete, marked, or moderate therapeutic response) was also greater at the end of the study in the desloratadine group compared with placebo ($p < 0.001$), which started as early as day 1 of treatment. • Adverse effects were comparable between both groups.	Once-daily desloratadine 5 mg is well tolerated and superior to placebo in reducing pruritus and wheals associated with CIU. It provided rapid and sustained symptomatic relief.
(18) Gimenez-Arnau et al., 2007, Spain [39]	Multi-center, placebo-controlled, double-blind RCT	Male and female patients with minimum 6-week history of CIU, aged 12–65 years, having an active flare for at least 3 days/week.	Rupatadine 10 mg OD (110) Placebo (111)	4 weeks	• A 57.5% ($p < 0.005$) significant MPS (mean pruritus score) reduction from baseline, was observed at week 4 with 10 mg rupatadine compared to placebo (44.9%). • No significant adverse effects were reported with rupatadine.	Rupatadine 10 mg is a fast, long-acting, efficacious and safe treatment option for moderate-to-severe CIU, significantly better than placebo.
(19) Dubertret et al., 2007, France [40]	Randomised, double-blind, placebo-controlled, parallel-group, international, dose-ranging study	Male and female patients with documented CSU, aged 12–65 years, having symptoms at least 3 days per week over the last 6 weeks.	Rupatadine 10 mg OD (73) Placebo (69)	4 weeks	• Rupatadine10 mg significantly reduced the mean pruritus score (MPS) from baseline by 1.52 ($p < 0.05$), compared to reduction of 1.14 with placebo, reflecting significant reductions in pruritus severity of 62.7% compared with 45.8% with placebo. • Mean total symptom score (MTSS) reduced significantly with rupatadine 10 mg, compared to placebo ($p < 0.05$) over the 4-week period. • Incidence of ADRs was comparable between rupatadine and placebo treated groups.	Rupatadine 10 mg is a fast-acting, efficacious and safe treatment for moderate-to-severe CIU, significantly better than placebo.
(20) Pons-Guirau et al., 2006, France [54]	Double-blind RCT	Patients aged 18–64 years, having CIU for at least 3 months	Loratadine 10 mg OD (77) Emedastine difumarate 2 mg BD (84)	4 weeks	• The efficacy of the two drugs was similar in terms of mean change in total urticaria symptom score (– 5.57 ± 3.15 with emedastine vs. 5.67 ± 3.26 with loratadine), proportion of symptom-free patients (52.4% vs. 54.5%) after 4 weeks treatment. • The most common adverse event was somnolence (7 with emedastine and 2 with loratadine).	Emedastine is well tolerated, and as effective as loratadine in the short-term treatment of chronic idiopathic urticaria.

(*Continued*)

Table 2. (Continued).

Name of author, year, place of study	Type of study	Study participants and type of Urticaria	Interventions (n)	Study duration (weeks)	Study results	Remarks
(21) Kapp and Pichler, 2006, Germany [36]	Randomized, double-blind, placebo-controlled, parallel, multicenter study	Patients with moderate-to-severe CIU having episodes at least 3 times per week for a period of 6 weeks during the previous 3 months.	Levocetirizine 5 mg OD (81) Placebo (85)	4 weeks	• Pruritus severity scores improved significantly with levocetirizne, compared to placebo ($p < 0.001$). • The number and size of wheals were considerably reduced compared with placebo over 1 week and over the total treatment period ($P = 0.001$). • Levocetirizine significantly improved the QoL and work-productivity. • No unexpected adverse events were reported.	Levocetirizine, 5 mg once daily, is an effective and safe treatment for CIU, significantly better than placebo.
(22) Nettis et al., 2006, Italy [37]	Randomized, double-blind, placebo-controlled study	Adult patients with CIU, >18 years age	Leocetirizine 5 mg OD (53) Placebo (53)	6 weeks	• Levocetirizine was superior to placebo in reducing the mean total symptoms score as well as individual symptoms, the number of daily episodes and the number of weals, the overall severity of symptoms and the quality of life. • The significant beneficial effects of levocetirizine lasted only during the active trial, while at follow-up there was a significant worsening of all the variables (week 7). • No significant adverse effects reported.	Levocetirizine 5 mg once daily is an effective agent in patients with chronic idiopathic urticaria, significantly better than placebo. There is rapid onset of action but effect is limited to duration of treatment.
(23) Kaplan et al., 2005, U.S.A. [44]	Randomized, double-blind, parallel-group, placebo-controlled study	Male and female patients (>12 years) with CIU, with history of urticarial wheals at least 3 days per week for the 6 consecutive weeks before first visit.	Fexofenadine 180 mg OD (167) Placebo (92)	4 weeks	• Mean number of wheals (MNW) and pruritus severity score improved significantly more with fexofenadine, compared to placebo (both p's < 0.001). • There were no significant differences in the frequency of treatment-emergent adverse events between the 2 treatment groups.	A once-daily dose of fexofenadine hydrochloride, 180 mg, offered effective, well-tolerated relief for the management of CIU, significantly better than placebo.
(24) Handa et al., 2004, India [64]	Double-blind RCT	Patients aged 17 to 65 years, with CIU (urticarial wheals for at least two days per week for six consecutive weeks before entry).	Cetirizine 10 mg OD (52) Fexofenadine 180 mg OD (45)	4 weeks, with follow-up at 2 weeks	• The treatment response in both the groups at the end of treatment period was- symptom free [cetirizine 27(51.9%), fexofenadine 2 (4.4%)], partial improvement [cetirizine 19 (36.5%), fexofenadine 19(42.2%)], no improvement [cetirizine 6(11.5%), fexofenadine 24(53.3%)]. • Adverse effects were comparable with both drugs.	Cetirizine seems to have therapeutic advantage over fexofenadine in the treatment of CIU.
(25) Yin et al., 2003, China [52]	Randomized, open-label, parallel comparative clinical trial	Adult patients (>18 years) with documented CIU.	Mizolastine 10 mg OD (32) Cetirizine 10 mg OD (32) Loratadine 10 mg OD (32)	4 weeks, with follow-up at 2 weeks	• The efficiency rates of mizolastine, cetirizine and loratatine were 90.0%,85.3%,90.6% at14th day and 96.7%,94.2%,93.8% at 28th day, respectively. ($p > 0.05$) • The recurrent rates of mizolastine, cetirizine and loratatine were 40.0%, 35.3% and 28.1% respectively. • No obvious and notable adverse effects occurred with either drug.	All the three antihistamines (mizolastine, cetirizine and loratadine) have high clinical efficacy and safety in the treatment of chronic idiopathic urticaria.

(*Continued*)

Table 2. (Continued).

Name of author, year, place of study	Type of study	Study participants and type of Urticaria	Interventions (n)	Study duration (weeks)	Study results	Remarks
(26) Monroe et al., 2003, U.S.A. [42]	Randomized, double-blind, placebo-controlled, parallel-group, multicenter trial	Patients aged 12 years or older, of either sex and any racial group, with documented CIU, having a flare for 3 weeks or more before screening, with urticarial lesions visible 3 days or more per week.	Desloratadine 5 mg OD (116) Placebo (110)	6 weeks	• Compared with placebo, desloratadine significantly improved the total CIU symptom score as well as pruritus, the number of hives, and the size of the largest hive. • Overall, global CIU status improved significantly with desloratadine; interference with sleep was reduced and the performance of daily activities improved. • Adverse effects were comparable in both groups.	Desloratadine is a well-tolerated and effective treatment of CIU, significantly better than placebo.
(27) Hao et al., 2003, China [53]	Multiple-center, double-blind comparative clinical trial	Adult patients with documented diagnosis of CIU	Desloratadine 5 mg OD (106) Loratadine 10 mg OD (106)	4 weeks	• The effective rates of desloratadine group and loratadine group were 23.81% and 32.08% at 7th day, 62.86% and 59.43% at 14th day after treatment and 88.78% and 83.02% by the end of treatment respectively. • Adverse effects (mouth dryness, dizziness and headache etc.) were comparable in both groups.	Both desloratadine and loratadine are effective and safe treatment for CIU, statistically comparable.
(28) Ring et al., 2001, Germany [43]	Multicenter, randomized, double-blind, placebo-controlled study	Patients aged 12–79 years with CIU, having a moderate-to-severe flare at the time of recruitment.	Desloratadine 5 mg OD (95) Placebo (95)	6 weeks	• Desloratadine was superior to placebo in controlling pruritus and total symptoms after the first dose and maintained this superiority to the end of the study. • Measures of sleep, daily activity, therapeutic response, and global CIU status were also significantly better with desloratadine. • No significant adverse effects were reported.	Desloratadine 5 mg daily is a safe and effective treatment for CIU with significant benefits over placebo. Onset of action is rapid within 24 hours.
(29) Nelson et al., 2000, U.S.A. [45]	Double-blind, randomized, placebo-controlled study	Chronic urticaria patients aged 12–65 years, with moderate-to-severe pruritus	Fexofenadine 60 mg BD (90) Placebo (79)	4 weeks	• Fexofenadine was statistically superior to placebo for reducing pruritus and number of wheals ($p < 0.01$). • Additionally, patients receiving fexofenadine experienced significantly less interference with sleep and daily activities than patients receiving placebo ($p <$ or = .0014). • No patient developed any treatment emergent adverse event.	Fexofenadine significantly reduced pruritus severity, number of wheals, and interference with sleep and normal daily activities in patients with chronic urticaria compared with placebo. Twice-daily doses of 60 mg or greater were most effective.
(30) Leynadiar et al., 2000, France [51]	Double-blind comparative trial	Adult patients suffering from CIU	Mizolastine 10 mg OD (26) Loratadine 10 mg OD (35)	4 weeks	• The reduction in the number of episodes per week (5. 6 ± 16.3 and 6.4 ± 12.4 for mizolastine and loratadine, respectively) and the reduction in the symptom severity score, measured using a Visual Analogue Scale (VAS), were comparable (30.2 ± 39.0 mm and 30.5 ± 28.5 mm for mizolastine and loratadine, respectively). • No notable adverse effects occurred.	Both Mizolastine and loratadine are comparable with respect to safety, efficacy and tolerability in CIU.

Abbreviations: CU; chronic urticaria, CIndU; chronic inducible urticaria, CSU; chronic spontaneous urticaria, CIU; chronic idiopathic urticaria, sg-AH; second-generation antihistamines, RCT; randomized controlled trials, MNW; mean number of wheals, MTSS; mean total symptom score, MPS; mean pruritus score, ADR; adverse drug reactions, UAS7; urticaria activity score 7, TSS; total symptom score, QoL; quality of life, AEC; absolute eosinophil count, DC; differential count, OD; once daily, BD; twice daily, DLQI; Dermatology Life Quality Index, VAS; visual analog scale.

3.3. Studies depicting significant superiority of one sg-AH over another sg-AH at standard dose

We found 10 studies which reported significant superiority of one sg-AH over another sg-AH at standard dose. Fayaz et al. reported the superiority of rupatadine 10 mg OD over loratadine 10 mg OD in terms of safety, efficacy and improvement in patient's quality of life. Additionally, it also improved several biochemical determinants of allergy such as total leucocyte count, differential count and absolute eosinophil count [55]. Other studies also reported the superiority of rupatadine over cetirizine [56] and levocetirizine [57] at standard dose. Podder et al. [58] found bilastine 20 mg OD to be more effective and less sedative therapy for CSU, compared to levocetirizine 5 mg OD. Levocetirizine, one of the most commonly used sg-AH for CSU, was found to be superior to multiple antihistamines such as olopatadine [59], loratadine [60] and desloratadine [61] at standard doses, in terms of effectiveness and safety parameters. Olopatadine demonstrated its superiority over rupatadine [62] and levocetirizine [63] in 1 study each. Handa et al. [64] found cetirizine 10 mg OD to have therapeutic advantage over fexofenadine 180 mg OD, in terms of effectiveness, safety and cost-benefit.

As a summary, based on the reviewed studies, no definitive conclusion can be drawn regarding the superiority of any specific sg-AH; however, future prospective studies comparing a diverse range of sg-AH among a sizable cohort of chronic urticaria patients, sharing consistent demographic characteristics, disease endotypes, and severity, are necessary to ascertain comparative efficacy.

4. Response rates and comparison between updosing antihistamines and combinations of antihistamines

The utilization of sg-AH at standard licensed doses is established as the first-line treatment for urticaria, in accordance with international [1], American [5] and the other national guidelines [7,8]. Notwithstanding, discrepancies arise between these guidelines in the context of second-line treatment when standard sg-AH dosages fail to adequately manage urticaria symptoms. The international guideline advocates for a potential increase in sg-AH dosage by up to four times the standard amount. In contrast, the American guideline outlines five distinct options for second-line therapy, which may be employed individually or in combination. These include increasing the sg-AH dose from the first-line treatment and adding either another sg-AH, an H2-antihistamine, a leukotriene receptor antagonist, or a first-generation H1-antihistamine, the latter being recommended for bedtime use [5]. Regarding the other national guidelines, e.g. the Chinese guideline for second-line treatment of urticaria, it recommends either an increase in the dosage of sg-AH up to four times the standard amount or the combination of additional second-generation or first-generation antihistamines with the baseline first-line therapy [8], while Turkish guideline suggests switching to another sg-AH [7].

When standard doses of sg-AH are inadequate for effective urticaria symptom control, current evidence strongly supports the strategy of increasing sg-AH dosages up to four times, demonstrating good efficiency and safety. This approach applies to a range of sg-AH, including bilastine, cetirizine, levocetirizine, ebastine, fexofenadine, loratadine, desloratadine, mizolastine, and rupatadine [31]. In the international EAACI/GA2LEN/EuroGuiDerm/APAAACI guideline, combination of different sg-AH is not recommended, because this regimen is not superior to updosing the same sg-AH up to 4 times. Despite this, some studies recently have indicated that the combination of different sg-AH in second-line treatment can achieve comparable efficacy and safety to the practice of increasing sg-AH dosages (see Table 3). The only randomized controlled trial to compare combination sg-AH with sg-AH alone was reported by Wang and colleagues in 2019 [65], which included 234 patients with CU and grouped to experimental group and control group. Patient group treated with standard approved dose of levocetirizine together with standard approved dose of ebastine showed significantly better clinical efficacy compared with the control group treated with levocetirizine, also the decline of serum biomarkers TNF-α, IL-6, and IL-10, were significantly more obvious in experimental group, compared with control group after treatment [65]. In 2020, Zhang et al. [66] conducted a multicenter real-life pilot study to compare the clinical efficiency and safety of second-line treatments for CSU, as recommended in the international and American urticaria guidelines. With a sample size of 169, the study evaluated the long term (52-week) efficacy and safety of both 2-fold and 4-fold dose sg-AH, as well as equivalent doses of combined sg-AH. It also compared 4-fold dose sg-AH plus H2-antihistamine/leukotriene receptor antagonist with an equivalent dose of combination sg-AH plus H2-antihistamine/leukotriene receptor antagonist. Interestingly, both the updosing sg-AH group and the combination sg-AH group demonstrated effectiveness and safety in second-line treatment. At week 52, the rates of complete remission off therapy (no symptoms for at least four weeks in patients not taking any medications), the rates of complete remission on therapy (no symptoms in patients on therapeutic medications), and the rates of complete remission in both 'remission states' showed no significant differences between the updosing and combination therapy groups [66]. Even in the absence of statistical differences, it was observed that the response rate (complete remission both off therapy and on therapy) in the 2-fold dose sg-AH group was slightly higher than that in the 2-fold combination of different sg-AH group, with rates being 18.3% (31/169) versus 14.8% (25/169), respectively (Table 3). A larger retrospective study reported later by Ornek et al. [9]included 657 patients with CU, comprising 556 individuals with CSU and 101 with CIndU. Similar to the study by Zhang et al., approximately one-third of the patients responded to first-line treatment with standard approved dose sg-AH. In the context of second-line treatment, this study reported a numerically higher remission rate in patients receiving 2-fold dose sg-AH compared to those on a 2-fold combination of different sg-AH, specifically 46.3% (94/203) versus 35.8% (24/67), although these differences were not statistically significant. In addition to the 2-fold dose of sg-AH, this study identified the 4-fold dose of sg-AH as the second most commonly used second-line treatment option, which provided a remission rate of 29.4% (53/180). Another noteworthy

Table 3. Recent evidence on response rates comparison between updosing or combinations of antihistamines.

Recent Evidence	Type of urticaria	Treatment groups	Response rates	Comparison on response rates	Comparison on side effects
Zhang et al. 2020 [66]	CSU	Standard dose sg-AH	35.5% (60/169)	/	/
		2-fold dose sg-AH vs. 2-fold combination sg-AH	18.3% (31/169) vs.14.8% (25/169)	No significant difference	No difference
		4-fold dose sg-AH vs. 4-fold combination sg-AH	1.8% (3/169) vs.3% (5/169)	No significant difference	No difference
		4-fold dose sg-AH + H2-antihistamine/leukotriene receptor antagonist vs. 4-fold combination sg-AH + H2-antihistamine /leukotriene receptor antagonist	6.5% (11/169) vs.6.5% (11/169)	No significant difference	No difference
Ornek et al. 2022 [9]	CU	Standard dose sg-AH	43.1% (283/657)	/	/
		4-fold dose sg-AH	29.4% (53/180)	/	/
		2-fold dose sg-AH vs. 2-fold combination sg-AH	46.3% (94/203) vs.35.8% (24/67)	No significant difference, updosing group demonstrated better outcomes than the combination group	No difference
		Updosing sg-AH (2-fold +4-fold) vs. 2-fold combination sg-AH vs. sg-AH +first-generation H1-antihistamine	38.3% (147/383) vs.35.8% (24/67) vs. 37.5% (6/16)	No significant difference	No difference
Kim et al. 2023 [67]	CU	4-fold dose sg-AH vs. 4-fold combination sg-AH	40% (10/25) vs.10.7% (3/28)	Updosing group demonstrated significantly ($p = 0.03$) better outcomes than the combination group	No difference

Abbreviations: CU, chronic urticaria; CSU, chronic spontaneous urticaria; sg-AH, second-generation antihistamines.

observation from the study is that when the 2-fold and 4-fold dose sg-AH groups were combined into a single group and compared with the group receiving a 2-fold combination of different sg-AH and the group treated with standard dose sg-AH plus a first-generation H1-antihistamine, the remission rates in these three groups were 38.3% (147/383), 35.8% (24/67), and 37.5% (6/16), respectively. Very recently, a 4-week, randomized, open-label trial is published by Kim and colleagues [67]. The study firstly compared two second-line treatment regimens for CU in a prospective approach including four-fold dose of sg-AH and a combination of four different sg-AH. After four weeks of second-line treatment, the control status of urticaria in patients, as assessed by specialists, was categorized as well controlled, partly controlled, or uncontrolled. The proportion of patients assessed as well-controlled in the four-fold dose of sg-AH group was marginally higher than that in the combination of four different sg-AH group, though the difference was not statistically significant (57.7% (15/26) vs. 46.4% (13/28), $p = 0.616$). However, when considering the proportion of patients with a Urticaria Activity Score over 7 days (UAS7) of 0 after four weeks, the four-fold dose of sg-AH group had a significantly higher percentage compared to the combination of four different sg-AH group (40% (10/25) vs. 10.7% (3/28), $p = 0.030$). In this study, the updosing group, compared to the combination group, not only demonstrated a significant advantage in completely controlling urticaria symptoms but also showed no difference in the incidence of adverse reactions between the two high-dose sg-AH treatment groups.

The primary constraints of these investigations are notably marked by their relatively limited participant numbers and the lack of uniform implementation of patient-reported outcome measures (PROMs). A critical concern observed across these studies is the inconsistent usage of key efficacy evaluation tools such as the Urticaria Activity Score over a period of 7 days (UAS7) and the Urticaria Control Test (UCT) [38,68]. This inconsistency underscores the necessity for future research endeavors to concentrate on the harmonization of PROMs. Furthermore, there is an imperative need for the development and execution of meticulously structured, long-term, head-to-head prospective randomized controlled trials. These trials should be specifically designed to provide a comprehensive and robust comparison of the effectiveness and safety profiles of increased dosing (updosing) strategies versus combination therapies utilizing second-generation H1-antihistamines, thereby offering more substantial and reliable data for clinical application in urticaria treatment.

5. Pharmacogenomics of antihistamines in chronic urticaria

Patients with chronic urticaria not only exhibit varying response rates to antihistamines but will also experience different susceptibility to adverse effects of antihistamines, which interferes with optimal treatment regimens [69].

Individual variation in effectiveness and sensitivity to antihistamines may in large part be explained by genetic alterations. Pharmacogenomics is the study of the relationship between an individual patient's genetic makeup and drug response, and although only explored to a small extent, holds promise for

optimizing antihistamine therapy in CU. Specifically, if robust genetic markers could be identified it would be possible to genotype a patient with CU before initiation of antihistamine therapy to guide the choice and dosing of specific drugs.

Several genetic polymorphisms influencing primarily drug metabolism (enzyme activity), drug transport, and target receptor activity have been linked to antihistamine response in CU [29]. Particularly, the cytochrome P450 (CYP) enzyme system, primarily responsible for antihistamine metabolism in the liver, is highly susceptible to genetic variations. For example, individuals carrying the CYP3A5 × 1/*1 allele have high metabolic activity and low transporter activity, whereas the opposite is true for CYP3A5 × 1/*3 carriers, resulting in altered concentrations of rupatadine in the gastrointestinal tract and blood [70]. Also, subjects with the 2677AA/3435CC genotype of the plasma membrane drug transporter ABCB1 have been shown to attain lower plasma concentrations of fexofenadine than individuals carrying other variants [71], although results have been conflicting [72]. Moreover, plasma concentrations of fexofenadine have been associated with a polymorphism in the drug transporter SLCO2B1 and several haplotypes of genes encoding the drug transporters ABCB1 and ABCC2, which may lead to differences in drug efficacy and sensitivity of fexofenadine [73]. Further, a histamine H1 receptor gene polymorphism, the CC genotype of the – 17C/T site, has been shown to confer altered responsiveness to azelastine therapy, albeit in patients with allergic rhinitis [74]. Finally, polymorphisms in several genes encoding the high-affinity IgE receptor on mast cells (FCER1A), calcium channels involved in mast cell degranulation (CACNA1C and ORAI1), complement receptors related to mast cell activation and degranulation (C5AR1), and Th2 lymphocyte function (CRTH2), have been associated with overall susceptibility to CU as well as to differential response and sensitivity to antihistamines in patients with CU [29].

It is possible that pharmacogenetic testing will be implemented in the clinical evaluation of the individual patient's possible response to, and risk of adverse effects of, antihistamines in CU in the future. However, in the context of the present knowledge this is not feasible. Rather, further identification of a set of relevant genetic markers associated with specific therapeutic response will allow us to select the most appropriate antihistamine and dosage for each patient.

6. Biomarkers for antihistamine response in urticaria

While histamine is the primary mediator released from mast cells and H1-antihistamines are the recommended first-line therapy for CU, there is substantial variation in individual response rates between patients. Notably, over half (55%) of patients do not experience relief from antihistamine treatment [12]. Given the significant impact of uncontrolled CU on patients' quality of life, there arises a critical necessity for specific biomarkers to predict the response to antihistamines. Such biomarkers could facilitate a proactive adjustment of treatment strategies, thus mitigating the consequences of uncontrolled disease activity. In this regard, specific clinical and biochemical markers have been studied in recent years that aim to predict treatment response or nonresponse to antihistamines (see Table 4).

A recent systematic review analyzed various predictors of treatment response in CSU [75]. There was strong or robust evidence that suggests high Urticaria Activity Score 7 or

Table 4. Clinical and biochemical parameters predicting nonresponse or poor response to second generation antihistamines.

Clinical or biochemical parameter	Publication	Details
High disease burden	Ulambayar, 2019 [76]	Higher UAS7 predicts poor response to sg-AH ($p = 0.024$)
	Curto-Barredo, 2018 [77]	Higher baseline UAS7 in sg-AH refractory patients ($p = 0.035$)
	Magen, 2011 [88]	Higher baseline UAS in sg-AH resistant cases ($p < 0.001$)
	Ornek, 2022 [9]	Lower baseline UCT scores in AH-refractory CSU patients ($p < 0.001$)
		Lower baseline UCT scores in AH-refractory CIndU patients ($p < 0.001$)
CRP	Kolkhir, 2018 [78]	CRP (≥5 mg/L) higher in sg-AH nonresponders ($p < 0.001$)
	De Montjoye, 2021 [79]	CRP levels higher in sg-AH nonresponders ($p < 0.0001$)
	Magen, 2011 [88]	Higher CRP levels in sg-AH -resistant cases ($p < 0.001$)
D-dimer	Asero, 2013 [84]	Elevated D-dimer levels more frequently observed in sg-AH-resistant cases ($p < 0.001$)
	De Montjoye, 2021 [79]	D-dimer levels higher in sg-AH nonresponders ($p = 0.009$)
	Kolkhir, 2017 [85]	D-dimer levels higher in nonresponders ($p < 0.001$)
Concomitant CSU-CIndU	Curto-Barredo, 2018 [77]	Higher sg-AH doses required and frequent treatment after 5 years observed in CSU with concomitant CIndU ($p < 0.05$)
	Magen, 2011 [88]	Concomitant CIndU more commonly observed in sg-AH-resistant group ($p = 0.014$)
	Ornek, 2022 [9]	CSU with accompanying CIndU patients were more refractory to AH as compared to isolated CIndU ($p = 0.017$)

Abbreviations: CIndU, chronic inducible urticaria; CRP, C-reactive protein; CSU, chronic spontaneous urticaria; sg-AH, second-generation antihistamines; UAS, Urticaria activity score; UCT, Urticaria control test.

Urticaria Activity Score (UAS), raised C-reactive protein (CRP) and raised D-dimer levels are predictive of poor response or nonresponse to sg-AH. There was also weak evidence for previous corticosteroid treatment, concomitant CIndU and lower Chronic Urticaria Quality of Life Questionnaire (CU-Q2oL) scores as poor response or non-response to sg-AH. Inconsistent evidence was demonstrated for comorbid allergic diseases, presence of angioedema, autologous serum skin test (ASST) positivity, chronic urticaria index, low blood eosinophil counts, antithyroid antibody positivity and raised erythrocyte sedimentation rate (ESR). Furthermore, the review also demonstrated that there was strong evidence for no association of age, sex, disease duration and serum C4 level with sg-AH responsiveness.

The two components recorded on the UAS7 are number of wheals and intensity of itch on a daily basis documented over a 7-day period. This is a patient reported outcome measure (PROM) commonly used in disease assessment, recommended by international guidelines [1]. High disease activity (i.e. high UAS7 or UAS scores) indicates severe disease, and carries a less favorable response outcome to sg-AH. To further elucidate, a prospective study with large sample size ($n = 283$) demonstrated a higher UAS7 score (OR = 1.023, $p = 0.024$) was a predictor of poor response to antihistamines [76]. This finding was echoed in another large-scale study ($n = 549$) that demonstrated refractory patients with significantly higher baseline UAS7 compared with non-refractory patients ($p = 0.035$) [77].

CRP is an inflammatory marker that has been demonstrated to be elevated in one-third of CSU patients [78]. Three retrospective studies with large sample size show that sg-AH-resistant CSU patients or poor responders had elevated levels of CRP. Of note, of 1019 CSU patients in a single study, 31% ($n = 313$) had a CRP level of ≥5 mg/L, and this pattern was seen significantly higher in sg-AH non-responders when comparing to responders ($p < 0.001$) [78]. Elevated CRP levels have also been shown to be associated with ASST positivity, high urticaria activity, and raised levels of inflammatory and coagulation markers [79].

The role of D-dimer in the pathogenesis of CSU has long been suspected, and subsequently studied and confirmed by various studies. It has been postulated that the activation of coagulation pathway is associated with tissue factor expressed by eosinophils [80]. Activation by eosinophil proteins of the coagulation pathway leads to thrombin generation and mast cell degranulation [81]. Elevated D-dimer levels have been found to be associated with a more severe disease with reduced response to antihistamines, paving the way for exploring treatment option with tranexamic acid and heparin before the advent of anti-IgE treatment [82]. Severe exacerbations are related to a strong activation of coagulation cascade and fibrinolysis [83]. In recent studies, there was clear evidence that D-dimer levels were statistically significantly higher in sg-AH non-responders [79,84,85]. In addition, higher D-dimer levels were also observed in patients with concomitant autoimmune condition and/or with autoantibodies, such as antithyroperoxidase antibodies [86].

CIndU may occur as a standalone disease, or as a concomitant feature with CSU, and for the latter, is a common comorbidity in the sg-AH-refractory subtype observed in the real-life AWARE study [87]. Concomitant CSU-CIndU has been associated with antihistamine-resistance, requiring more frequent treatment after 5 years or higher doses of sg-AH [9,77,88,89]. On the other hand, antihistamine refractory CIndU patients were found to have higher rates of increased anti-TPO levels and lower baseline UCT scores compared to antihistamine-responders [9]. The same study also highlighted Urticaria Control Test (UCT) ≤ 4 ($p < 0.001$), emergency referral ($p = 0.002$) and family history of CSU ($p = 0.008$) being significant risk factors for antihistamine refractoriness in CSU patients.

The importance of identifying more robust clinical and biochemical predictors of treatment response in CSU cannot be emphasized enough. There is clearly an unmet need in this regard. Many emerging biomarkers or predictors have been described with inconclusive evidence in view of sparsity of data. More research and studies are required to address this aspect of urticaria treatment. Treatment options must be individualized as every patient demonstrates unique phenotype and endotype. Based on this philosophy, treatment option may be tailored accordingly, therefore achieving therapeutic outcomes that are more effective and desirable. As the saying goes, one size does not fit all. And this should be aptly applied in the management of chronic urticaria.

7. Conclusions

In conclusion, sg-AH stand as cornerstone treatments for CU, offering both efficacy and safety profiles superior to their first-generation counterparts. Their reduced sedative effects and selective action on histamine receptors make them preferred options for long-term management. It is worth noting that while various sg-AH exist, there is currently no proven evidence suggesting superiority of one over another in treating CU. Therefore, the choice of antihistamine should be guided by individual patient factors and preferences. Here personalized medicine steps in, which is essential in CU management, necessitating consideration of patient age, pregnancy, lactation, and potential drug interactions, especially in elderly populations with compromised liver and renal function or polypharmacy. Additionally, discrepancies exist between guideline recommendations and actual clinical practice in the pediatric population due to insufficient evidence, highlighting the need for well-designed clinical trials targeting this specific patient group [90].

Assessing potential biomarkers such as disease severity, associated inducible urticaria, CRP levels, and D-dimer can aid in predicting antihistamine response. Recognizing that a significant proportion of patients may be refractory to antihistamine therapy underscores the importance of timely escalation to alternative treatments to alleviate the burden of persistent symptoms.

By integrating these considerations into clinical practice, healthcare providers can tailor treatment strategies to optimize outcomes for patients with chronic urticaria, ensuring effective symptom control and enhanced quality of life.

8. Expert opinion

The advances discussed, particularly in personalized medicine and the identification of biomarkers for treatment response, could significantly impact real-world outcomes in chronic urticaria. Implementation of these findings into clinical practice could lead to more tailored diagnosis and treatment guidelines, resulting in improved effectiveness and potentially cost savings by avoiding unnecessary treatments or optimizing therapeutic choices. However, barriers to adoption may include the need for further validation of biomarkers, updating existing guidelines, and integrating personalized medicine approaches into routine clinical workflows. Key areas for improvement include enhancing the reliability and specificity of biomarkers for predicting treatment response, ease of reaching pharmacogenomics, addressing gaps in understanding regarding the mechanisms underlying refractory chronic urticaria, and developing more targeted therapies based on individual patient characteristics. Further research holds significant potential for advancing our understanding of chronic urticaria and improving treatment outcomes. While there may not be a definitive end-point, ongoing studies could lead to the discovery of novel biomarkers, the development of targeted therapies, and advancements in personalized medicine approaches. Continued research efforts are essential for refining treatment strategies and addressing the unmet needs of patients with chronic urticaria. While chronic urticaria research is promising, there are also other areas within the field of management of chronic diseases such as drug interactions and efficacy that could be practically managed by integrating the pharmacogenomics approach to personalized medicine, however efforts should be made to make these approaches more available to the practicing physician. In the future, the field of chronic urticaria is likely to evolve toward more personalized and targeted approaches to diagnosis and treatment. Standard procedures may incorporate routine biomarker assessments to guide treatment decisions, and there may be greater emphasis on identifying and addressing the underlying causes of refractory disease. Additionally, advances in technology and data analytics could facilitate more comprehensive patient profiling and enable more precise therapeutic interventions. Overall, the field is expected to continue evolving toward improved outcomes and patient-centered care.

Abbrevations

CU	chronic urticaria
CIndU	chronic inducible urticaria
CRP	C-reactive protein
CSU	chronic spontaneous urticaria
fg-AH	first-generation antihistamines
sg-AH	second-generation antihistamines
UAS	Urticaria activity score
UCT	Urticaria control test

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