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Commentary

Advances in histamine-mediated allergy management: Expanding perspectives on cetirizine's therapeutic, safety, and toxicological implications

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Abstract

Histamine-mediated allergic reactions were recognized as pivotal mechanisms in the onset and progression of diverse allergic disorders. Cetirizine, a second-generation H1 receptor antagonist, had been extensively evaluated for its efficacy in mitigating histamine-induced inflammation and hypersensitivity. In this commentary, the therapeutic role of cetirizine was extended beyond conventional applications, incorporating recent clinical updates, toxicological perspectives, and pharmacological innovations. Cetirizine was shown to remain highly effective in emerging allergic conditions such as food allergies, atopic dermatitis, allergic conjunctivitis, and drug-induced hypersensitivities. Furthermore, its use in combination with leukotriene receptor antagonists, corticosteroids, and biologics had demonstrated synergistic outcomes in refractory or severe cases. From a toxicological standpoint, cetirizine was generally well-tolerated, but dose adjustments were necessary in pediatric, elderly, and renally impaired patients to prevent accumulation and adverse effects. Rare hypersensitivity reactions and gastrointestinal disturbances were also documented in long-term use. Recent advancements in drug delivery systems, including orally disintegrating tablets, intranasal sprays, and nanoparticle formulations, were developed to improve bioavailability and patient adherence. Additionally, pharmacogenomic insights offered the possibility of personalized cetirizine-based therapy, ensuring optimized dosing and minimal side effects. Overall, cetirizine continued to represent a cornerstone in modern allergy management, and its evolving role in prophylaxis, adjunctive anaphylaxis care, and innovative formulations positioned it as a key therapeutic agent in both clinical and toxicological contexts.

Keywords: Histamine, Cetirizine, Allergy, Toxicology, Bioavailability

Highlights

- Cetirizine's therapeutic role extended beyond classical allergic diseases.
- Integration of pharmacogenomics refined personalized antihistamine therapy.
- Combination with biologics enhanced outcomes in refractory allergic cases.
- Toxicological insights affirmed cetirizine's long-term safety and tolerability.
- Novel formulations improved bioavailability and patient adherence.

Introduction

Histamine-mediated allergic responses remain a major clinical burden worldwide, with prevalence rates rising sharply due to urbanization, pollution, altered dietary patterns, and genetic susceptibility [1]. While first-generation antihistamines were initially used to control histamine activity, their sedative

and anticholinergic side effects limited long-term use [2]. Cetirizine, a second-generation H1 receptor antagonist, provided a more favorable balance between efficacy and tolerability, becoming one of the most widely prescribed antihistamines [3]. Our previous review article comprehensively summarized cetirizine's mechanism, clinical efficacy, and safety. The present commentary extends that discussion by exploring recent clinical updates, toxicological insights, novel formulations, and future therapeutic perspectives [4]. The focus is not only on cetirizine's effectiveness in managing classical allergic rhinitis and urticaria but also on its expanding role in emerging allergic disorders such as food allergies, atopic dermatitis, ocular hypersensitivities, and drug-induced allergies [5,6]. Importantly, toxicological data, pharmacogenomics, and delivery innovations are considered to present a multidimensional view of cetirizine in modern clinical practice.

Cetirizine Beyond Allergy: Expanding Therapeutic Roles

Cetirizine's therapeutic application has broadened significantly in recent years, supported by updated clinical studies and case reports. Its role now extends beyond rhinitis and urticaria to conditions traditionally considered refractory to antihistamines [7–9].

Food allergies

Clinical studies demonstrated that cetirizine reduced urticaria, pruritus, and gastrointestinal discomfort following allergen exposure to peanuts, milk, and shellfish. Although cetirizine did not replace epinephrine in anaphylaxis management, it contributed to reducing recurrent skin and gastrointestinal symptoms, thereby enhancing patient comfort [10,11].

Atopic dermatitis (AD)

Cetirizine significantly reduced pruritus and flare frequency in pediatric AD patients. A study by Zhou *et al.*, showed that cetirizine was well tolerated and did not increase the risk of severe and overall adverse effects, cardiotoxicity, damage to the central nervous and digestive systems, or other systems in children, except for the risk of somnolence [12].

Allergic conjunctivitis

Increasing urbanization has intensified the prevalence of ocular hypersensitivity. Ocular allergies have been increasing over the past several decades. Many countries like China, Japan, and Africa, have a notable prevalence of Rhinocojunctivitis. Cetirizine reduced conjunctival inflammation, redness, and tearing when used systemically and showed enhanced benefit when combined with topical antihistamines [13,14].

Drug-induced allergies

Cetirizine was applied successfully to manage antibiotic- or NSAID-induced urticaria and angioedema. Adverse reactions due to cetirizine are rare, but some fixed drug eruption due to antihistaminic can be treated and cured within 10–15 days [15,16]. **Table 1** describes clinical applications of cetirizine in various allergic condition.

Toxicological and Safety Perspectives

While cetirizine has been widely regarded as one of the safest second-generation H1 receptor antagonists, understanding its toxicological profile is crucial for ensuring optimal use across diverse patient groups. Recent post-marketing surveillance and long-term trials provided additional insights into its safety spectrum.

General safety profile

Cetirizine was shown to be generally well tolerated, with the most common adverse events being mild somnolence, dry mouth, and headache [6]. Unlike first-generation antihistamines, it demonstrated minimal central nervous system (CNS) penetration, thereby reducing sedation risks [20].

Long-term use

Studies extending up to 12 months confirmed sustained efficacy without tolerance development, a major limitation seen in earlier antihistamines. Long-term administration did not significantly alter hepatic or renal biochemical markers in otherwise healthy populations [21,22].

Pediatric use

Cetirizine use in treatment of allergic rhinitis, and chronic spontaneous urticaria was safe for infants as young as 6 months when appropriately dosed by weight. A study by Zhou *et al.*, has shown that it is well tolerated in infants [12]. Additionally, the Food and Drug Administration (FDA) approved 10 mg IV cetirizine solution to treat urticaria in adults and adolescents aged 12 and older. However, pharmacovigilance reports emphasized the importance of monitoring for paradoxical agitation in very young children [6,23].

Table 1. Updated clinical applications of cetirizine in emerging allergic disorders.

Condition	Clinical Role of Cetirizine	Outcome Measures (Recent Data)	Limitations	References
Food allergies	Symptom relief (urticaria, GI symptoms)	Reduced recurrence of hives, improved QoL	Not effective in severe anaphylaxis	[4,17]
Atopic dermatitis	Long-term pruritus control	Reduces inflammation (inflammatory mediators IL-4, IL-13); no adverse effect on the cardiac and nervous system.	Limited efficacy in severe AD, somnolence	[12,18]
Allergic conjunctivitis	Ocular symptom reduction (systemic + adjunct)	Improved redness, tearing, itching	Requires topical agents in severe cases	[19]
Drug-induced allergies	Acute urticaria & angioedema control	Faster recovery in mild/moderate cases	Ineffective in SJS/TEN, requires additional therapy	[15,16]

GI: Gastrointestinal; QoL: Quality of Life; IL: Interleukin; AD: Atopic Dermatitis

Elderly patients

Age-related decline in renal clearance increased the risk of cetirizine accumulation. Dose reduction was recommended to minimize drowsiness and impaired psychomotor function [24].

Patients with renal or hepatic impairment

Since approximately 70% of cetirizine is eliminated via urine, patients with renal impairment required strict dose adjustment. Hepatic impairment posed less concern but still necessitated careful monitoring in severe cases [25].

Rare adverse reactions

Though uncommon, rare events such as hypersensitivity reactions, fixed drug eruptions, and paradoxical CNS stimulation have been reported [26,15]. Gastrointestinal symptoms, including nausea and abdominal discomfort, were occasionally observed during prolonged therapy [23]. **Table 2** describes various toxicity evaluation and safety assessment of cetirizine throughout the world.

Cetirizine in Combination Therapies

Monotherapy with cetirizine is effective in many mild-to-moderate allergic conditions, yet refractory or severe cases often demand a combination approach. Synergistic regimens incorporating cetirizine with corticosteroids, leukotriene receptor antagonists, or biologics have shown promise in reducing disease burden while maintaining safety [30].

With leukotriene receptor antagonists (e.g., Montelukast)

Combining cetirizine with montelukast effectively targeted both histamine- and leukotriene-mediated pathways. This approach was especially beneficial in allergic rhinitis patients with, leading to improved nasal allergic reaction symptom [31].

With corticosteroids

Short-term combinations with azelastine/fluticasone with corticosteroids were highly effective in managing severe exacerbations of allergic rhinitis and urticaria. However, corticosteroid-associated toxicities limited long-term use [32].

With other antihistamines

In refractory urticaria, cetirizine was sometimes combined with loratadine, fexofenadine, or levocetirizine. Although this approach increased receptor blockade, cumulative sedation risk and pharmacological redundancy required careful monitoring [33,34]. **Table 3** describes various combination therapies of cetirizine with other drugs.

Clinical Updates and Pharmacological Innovations

Novel formulations

Recent pharmaceutical advances aimed to improve patient adherence and therapeutic outcomes. Orally disintegrating tablets (ODTs) are convenient for pediatric and geriatric patients. Those who have difficulties in swallowing tablets. This novel formulation shows fast release in the case of allergies [39,40]. Another novel elastic vesicle-based tropical formulation of cetirizine dihydrochloride was developed by Goindi *et al.* Intranasal sprays: Provided rapid local action in allergic rhinitis with minimal systemic exposure. Which is supposed to have better penetration and has shown effectiveness

Table 2. Toxicological profile and safety considerations of cetirizine across populations.

Population Group	Safety Considerations	Recommended Strategy	References
General population	Mild somnolence, dry mouth, headache	Standard dose (10 mg/day) with monitoring	[23]
Long-term users	No tolerance; rare GI discomfort	Periodic monitoring of hepatic & renal markers	[6]
Pediatric patients	Safe from 6 months; possible paradoxical agitation	Weight-based dosing; close observation	[6,23]
Renal impairment	Slowed clearance; risk of accumulation	Dose adjustment proportional to renal function	[27]
Hepatic impairment	Caution in severe impairment, decrease 40% in drug clearance	Dose adjustments of cetirizine should maintain	[28]
Rare adverse events	Hypersensitivity, psychosis, paradoxical CNS effects	Immediate discontinuation & medical evaluation	[26,29]

GI: Gastrointestinal; CNS: Central Nervous System

Table 3. Combination therapies of cetirizine with other agents: clinical evidence summary.

Combination Partner	Clinical Context	Reported Benefit	Limitations	References
Montelukast	Allergic rhinitis + asthma	Prevents the allergic inflammation in nasal mucosa and reduces the symptoms of allergic rhinitis	Not always superior to monotherapy in mild disease	[31]
Corticosteroids	Atopic dermatitis	Prednisolone and cetirizine are effective on intradermal testing	Long-term toxicity of steroids, must be withdrawn after 2 weeks	[35]
Tropical steroid	Chronic pruritus	Cetirizine has a synergic effect on tropical steroids	Long-term toxicity of steroids	[36]
Loratadine/Fexofenadine	Chronic urticaria, resistant rhinitis	Enhanced histamine blockade	Risk of additive sedation; requires dose tailoring	[37]
Ketotifen	Chronic urticaria	Cetirizine and ketotifen shows equal activity. Reduced urticaria	--	[38]

Table 4. Emerging Pharmacological Innovations in Cetirizine Therapy.

Innovation	Clinical Advantage	Current Evidence	Future Scope	References
Orally disintegrating tablets (ODTs)	Better compliance in children/elderly	Phase IV trials show equal efficacy	Wider pediatric adoption	[39]
Intranasal spray	Faster onset, localized effect	Reduced nasal congestion within minutes	Potential combination with steroids	[49]
Transdermal patches	Sustained drug release	Preclinical evidence promising	Clinical validation required	[45]
Nanoparticle delivery	Cetirizine-loaded gold nano particle has effective activity against cancer cell line	Experimental studies MTT cell line	Long-term safety studies needed	[50]
Pharmacogenomics-based dosing	Personalized therapy, fewer side effects	Pilot studies underway	Integration into precision medicine	[51]

in reducing itching [41]. Cetirizine encapsulated chitosan, alginate nanoparticles is prepared by Hussein *et al.* to prepare better sustained release tablets of cetirizine hydrochloride. The nanoparticles shoed better sustained release [42]. Aldwasari *et al*. tried to prepare niosomes-based cetirizine drug delivery system for the management of alopecia. Cetirizine loaded niosomes were successfully prepared employing thin film hydration for efficient cutaneous delivery of the drug. However, the effectiveness remains to be explored [43]. Sodium alginate buccal mucosal drug delivery system was evolved by Pamlenyi *et al.,* to improve drug delivery [44]. It is shown that higher polymer concentration results in less release of the drug, and lower polymer concentration shows higher release of the drug. Transdermal patches with chitosan microneedles and nanoparticle-based were prepared by *Arshad et al*. [45]. The patches serve as an alternate route of drug administration in patients with nausea and swelling difficulties. However, the systems were under investigation for sustained release and improved bioavailability [44,45]. **Table 4** describes various pharmacological innovations such as clinical advantages, current evidence, and future scopes of cetirizine therapy with various dosage forms.

Pharmacogenomics and personalized therapy

Genetic variations in histamine receptors and metabolic enzymes (e.g., CYP variants) influenced inter-individual responses to cetirizine. Pharmacogenomic profiling may guide dosing strategies, enhancing safety and efficacy in the future [46].

Preventive and prophylactic applications

Prophylactic administration in high-risk groups (e.g., seasonal allergy sufferers, occupational exposure populations) reduced the severity of hypersensitivity episodes. Pediatric prophylaxis in recurrent atopic dermatitis flare-ups also demonstrated benefit [47,48].

Future Directions

The therapeutic scope of cetirizine continues to evolve, with multiple avenues under exploration, such as precision allergy treatment integration of pharmacogenomics and biomarker profiling for individualized dosing. Also, adjunct in anaphylaxis and asthma cetirizine can be used as supportive therapy post-epinephrine in anaphylaxis and as an adjunct to inhaled corticosteroids in allergic asthma. Gold nanoparticle anti-cancer cetirizine-loaded dosage form should be incorporated in cell line experiments for more cytotoxicity prediction. The development of extended-release nanoparticle and transdermal systems can be improved for better adherence. Prophylactic use in seasonal or occupational allergies to reduce severity and healthcare costs. Rational regimens with monoclonal antibodies to provide comprehensive immune modulation.

Conclusion

Cetirizine has established itself as a cornerstone in allergy pharmacotherapy due to its high selectivity, favorable safety profile, and broad clinical utility. Beyond its conventional role in allergic rhinitis and urticaria, recent evidence expanded its application to food allergies, atopic dermatitis, ocular hypersensitivities, and drug-induced reactions. Toxicological analyses reinforced its long-term safety, with caution warranted in pediatric, elderly, and renally impaired populations. Emerging formulations and pharmacogenomic insights positioned cetirizine at the forefront of precision allergy medicine. Combination strategies, particularly with leukotriene antagonists and biologics, offered synergistic benefits in refractory cases. As allergic diseases continue to rise globally, cetirizine's integration into personalized, preventive, and combination-based approaches underscores its continued relevance in both therapeutic and toxicological landscapes.

Conflict of Interest

The authors declare that there is no conflict of interest

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