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Overview on Newer Antihistaminic Drugs

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Abstract: *Allergic conditions such as allergic rhinitis, urticaria, and dermatitis are increasingly common and can significantly affect a person's daily life and overall well-being. Antihistamines have long been used to manage these conditions by blocking the effects of histamine, a key chemical responsible for allergic symptoms. However, older first-generation antihistamines are often associated with side effects like drowsiness, sedation, and reduced alertness, which limit their routine use. To address these drawbacks, newer antihistaminic drugs, including second- and third-generation agents, have been developed with improved selectivity and safety. These drugs provide effective relief from allergic symptoms while causing minimal or no sedation, thereby improving patient comfort and compliance. This review presents an overview of newer antihistamines, highlighting their mechanism of action, classification, advantages over older drugs, and their role in the treatment of allergic disorders.*

Keywords: Antihistamines, H1 receptor, Second-generation, Third-generation, Allergy

I. INTRODUCTION

Allergic diseases such as allergic rhinitis, urticaria, conjunctivitis, and atopic dermatitis are increasingly prevalent worldwide and represent a significant public health concern. These conditions can adversely affect daily activities, sleep quality, and overall well-being. The underlying mechanism of most allergic reactions involves the release of histamine from mast cells and basophils following exposure to allergens. Histamine plays a central role in mediating symptoms such as itching, sneezing, nasal congestion, and edema through its interaction with specific receptors in the body (Pawankar et al., 2013).

Antihistamines are among the most commonly prescribed drugs for the treatment of allergic disorders. They primarily act by blocking histamine H1 receptors, thereby reducing allergic symptoms. First-generation antihistamines, although effective, are associated with several limitations including sedation, impaired psychomotor performance, and anticholinergic effects due to their ability to cross the blood-brain barrier. These drawbacks have led to the development of newer antihistamines with improved pharmacokinetic and pharmacodynamic profiles (Simons and Simons, 2011).

1.1 Histamine and Its Physiological Role

Histamine is a low molecular weight biogenic amine that plays a central role in both physiological and pathological processes, particularly in allergic and inflammatory responses. It is synthesized from the amino acid histidine by the enzyme histidine decarboxylase and is primarily stored in mast cells and basophils. Upon exposure to allergens, histamine is rapidly released through a process known as degranulation, especially during immunoglobulin E (IgE)-mediated hypersensitivity reactions (Parsons and Ganellin, 2006; Thurmond et al., 2008).

In allergic conditions, the release of histamine is triggered when allergens bind to IgE antibodies present on the surface of mast cells. This interaction leads to activation of intracellular signaling pathways and subsequent release of histamine and other mediators such as leukotrienes and prostaglandins. Histamine then diffuses into surrounding tissues and exerts its effects by binding to specific histamine receptors located on target cells (Pawankar et al., 2013; Bousquet et al., 2012).

Histamine acts through four distinct receptor subtypes, namely H1, H2, H3, and H4 receptors, all of which belong to the family of G-protein-coupled receptors. Each receptor subtype is distributed differently in the body and mediates specific physiological functions (Parsons and Ganellin, 2006).

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The H1 receptor is primarily involved in allergic responses and is widely distributed in smooth muscle cells, endothelial cells, and the central nervous system. Activation of H1 receptors leads to vasodilation, increased vascular permeability, bronchoconstriction, and stimulation of sensory nerves, resulting in symptoms such as itching, redness, swelling, and sneezing. Due to its central role in allergy, the H1 receptor is the main target for antihistaminic drugs (Thurmond et al., 2008; Simons and Simons, 2011).

The H2 receptor is mainly found in gastric parietal cells, where it regulates the secretion of gastric acid. In addition, H2 receptors are present in cardiac tissue and play a role in modulating heart rate and contractility. Although not directly involved in allergic symptoms, H2 receptors contribute to various physiological functions and are targeted by drugs used in acid-related disorders (Parsons and Ganellin, 2006).

The H3 receptor is predominantly located in the central nervous system and functions as a presynaptic autoreceptor. It regulates the release of histamine and other neurotransmitters such as dopamine, serotonin, and acetylcholine. Through this mechanism, H3 receptors play a role in maintaining neurotransmitter balance and cognitive functions (Thurmond et al., 2008).

The H4 receptor is primarily expressed on immune cells, including eosinophils, mast cells, and T lymphocytes. It is involved in immune cell chemotaxis and inflammatory responses. Recent studies suggest that H4 receptors may play a significant role in chronic inflammatory and allergic conditions, making them a potential target for future therapeutic interventions (Bousquet et al., 2012; Thurmond et al., 2008).

Overall, histamine is a key mediator that links immune responses with clinical manifestations of allergy. Its wide range of physiological actions and receptor-mediated effects highlight its importance in both normal body functions and disease states. Understanding the role of histamine and its receptors is essential for the development and rational use of antihistaminic drugs in the treatment of allergic disorders (Simons and Simons, 2011; Church and Maurer, 2015).

1.2 Mechanism of Action of Antihistamines

Antihistamines primarily exert their therapeutic effects by interacting with histamine H1 receptors, which are G-protein-coupled receptors (GPCRs) involved in mediating allergic responses. Unlike earlier assumptions that these drugs act as simple antagonists, modern pharmacological understanding recognizes antihistamines as inverse agonists, which bind to the H1 receptor and stabilize it in its inactive conformation. This reduces both the basal (constitutive) activity of the receptor and its activation by histamine, thereby providing more effective and sustained suppression of allergic responses (Leurs et al., 2002; Simons and Simons, 2011).

Upon exposure to allergens, immunoglobulin E (IgE)-mediated activation of mast cells and basophils leads to the release of histamine and other inflammatory mediators. Histamine binds to H1 receptors located on endothelial cells, smooth muscle cells, and sensory nerve endings, resulting in vasodilation, increased vascular permeability, bronchoconstriction, and stimulation of sensory nerves. These effects collectively contribute to the clinical manifestations of allergic reactions such as erythema, edema, itching, and sneezing. Antihistamines inhibit these responses by preventing histamine from binding to H1 receptors and by reducing receptor signaling pathways (Parsons and Ganellin, 2006; Thurmond et al., 2008).

At the molecular level, activation of H1 receptors leads to stimulation of phospholipase C (PLC) via Gq proteins, resulting in the generation of inositol triphosphate (IP3) and diacylglycerol (DAG). This cascade increases intracellular calcium levels and activates protein kinase pathways, which further amplify inflammatory responses. Antihistamines interfere with this signaling cascade by stabilizing the inactive receptor state, thereby inhibiting downstream intracellular events and reducing inflammation (Leurs et al., 2002; Church and Maurer, 2015).

In addition to blocking histamine-mediated effects, newer antihistamines exhibit anti-inflammatory properties independent of H1 receptor antagonism. These include inhibition of cytokine release, suppression of adhesion molecule expression, and reduction of eosinophil migration and activation. Such effects contribute to their efficacy in both early-phase and late-phase allergic responses, making them more beneficial in chronic allergic conditions (Canonica and Blaiss, 2011; Bousquet et al., 2012).

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Pharmacokinetic characteristics also play a crucial role in the mechanism of action of antihistamines. Second- and third-generation antihistamines are designed to have low lipophilicity and are substrates for efflux transporters such as P-glycoprotein, which limits their entry into the central nervous system. As a result, these drugs primarily act on peripheral H1 receptors without significant central effects, thereby minimizing sedation and cognitive impairment (Simons and Simons, 2011; Wang et al., 2024).

Furthermore, newer antihistamines demonstrate a longer duration of receptor occupancy due to their high affinity and slow dissociation from H1 receptors. This prolonged receptor binding contributes to sustained therapeutic effects, allowing once-daily dosing and improved patient compliance. Some agents also exhibit rapid onset of action, providing quick relief from acute allergic symptoms (Church and Maurer, 2015; Scadding et al., 2021).

Overall, the mechanism of action of antihistamines involves a combination of H1 receptor inverse agonism, inhibition of intracellular signaling pathways, and additional anti-inflammatory effects. These multifaceted actions, particularly in newer antihistamines, result in effective control of allergic symptoms with improved safety and tolerability, making them essential agents in modern allergy management (Bousquet et al., 2012; Canonica and Blaiss, 2011).

1.3 Classification of Antihistamines

Antihistamines are primarily classified into different generations based on their pharmacokinetic properties, receptor selectivity, ability to cross the blood–brain barrier, and side effect profiles. This classification reflects the progressive development of these drugs from sedating agents to more selective and safer therapeutic options used in modern clinical practice (Simons and Simons, 2011).

1.3.1 First-Generation Antihistamines

First-generation antihistamines, also known as classical antihistamines, were the earliest agents developed for the treatment of allergic conditions. These drugs, including diphenhydramine, chlorpheniramine, and promethazine, are highly lipophilic in nature, allowing them to readily cross the blood–brain barrier. As a result, they bind not only to peripheral H1 receptors but also to central H1 receptors, leading to significant central nervous system (CNS) effects such as sedation, drowsiness, and impaired psychomotor performance (Simons, 2004).

In addition to their antihistaminic activity, these drugs also exhibit non-selective binding to other receptors, including muscarinic, α-adrenergic, and serotonergic receptors. This lack of selectivity results in a range of anticholinergic side effects such as dry mouth, blurred vision, constipation, and urinary retention. Furthermore, first-generation antihistamines have a relatively short duration of action, often requiring multiple daily doses, which can reduce patient compliance. Despite these limitations, they are still used in certain conditions such as motion sickness and insomnia due to their sedative properties (Church and Maurer, 2015).

1.3.2 Second-Generation Antihistamines (Newer Antihistamines)

Second-generation antihistamines were developed to overcome the limitations associated with first-generation drugs. These agents, including cetirizine, loratadine, and fexofenadine, are more selective for peripheral H1 receptors and exhibit minimal affinity for central receptors. Their relatively low lipophilicity and interaction with efflux transporters such as P-glycoprotein limit their ability to cross the blood–brain barrier, thereby significantly reducing sedation and other CNS-related adverse effects (Simons and Simons, 2011).

Pharmacokinetically, second-generation antihistamines have a longer half-life, allowing for once-daily dosing, which improves patient adherence to therapy. They also demonstrate rapid onset of action and sustained efficacy in controlling allergic symptoms. Additionally, these drugs have minimal interaction with other receptor systems, resulting in fewer side effects compared to first-generation antihistamines. Due to these advantages, second-generation antihistamines are widely recommended as first-line therapy for allergic rhinitis and chronic urticaria (Canonica and Blaiss, 2011).

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1.3.3 Third-Generation Antihistamines

Third-generation antihistamines represent a further advancement in antihistamine therapy. These drugs are either active metabolites or purified enantiomers of second-generation antihistamines, developed to enhance efficacy and minimize adverse effects. Examples include levocetirizine (active enantiomer of cetirizine) and desloratadine (active metabolite of loratadine).

These agents exhibit improved pharmacokinetic profiles, including higher receptor specificity, reduced variability in metabolism, and better safety margins. They maintain strong peripheral H1 receptor blockade while further minimizing central nervous system penetration. As a result, third-generation antihistamines offer enhanced efficacy with an even lower risk of sedation and drug interactions. Their improved tolerability makes them particularly suitable for long-term management of chronic allergic conditions (Canonica and Blaiss, 2011).

1.4 Limitations of First-Generation Antihistamines

First-generation antihistamines, although effective in alleviating allergic symptoms, are associated with several significant limitations that restrict their routine use in modern clinical practice. These limitations are primarily due to their non-selective receptor binding, high lipophilicity, and ability to cross the blood–brain barrier, resulting in undesirable central and peripheral effects (Simons, 2004).

One of the major drawbacks of first-generation antihistamines is their pronounced central nervous system (CNS) depression. Due to their easy penetration into the brain, these drugs block central H1 receptors, leading to sedation, drowsiness, fatigue, and impaired alertness. This effect can negatively impact daily activities such as driving, operating machinery, and performing tasks that require concentration and coordination. In some cases, especially in children and elderly patients, paradoxical excitation or confusion may also occur (Simons and Simons, 2011).

Another important limitation is their lack of receptor selectivity. First-generation antihistamines interact not only with H1 receptors but also with muscarinic, α-adrenergic, and serotonergic receptors. This non-specific action results in a variety of anticholinergic side effects, including dry mouth, blurred vision, constipation, urinary retention, and tachycardia. These adverse effects can be particularly troublesome in elderly patients and those with comorbid conditions such as glaucoma or prostatic hypertrophy (Church and Maurer, 2015).

In addition, these drugs have a short duration of action, typically requiring multiple daily dosing to maintain therapeutic effects. This frequent dosing schedule reduces patient compliance and increases the likelihood of missed doses. The variability in pharmacokinetics, including differences in metabolism and elimination among individuals, further complicates their clinical use (Simons, 2004).

First-generation antihistamines are also associated with cognitive and psychomotor impairment, which can affect learning ability, memory, and reaction time. This is particularly important in students and working individuals, where decreased cognitive performance can have a significant impact on productivity. Moreover, these drugs may potentiate the effects of other central depressants such as alcohol and sedative medications, increasing the risk of adverse events (Simons and Simons, 2011).

Another limitation includes their potential for drug interactions and reduced safety in long-term use. Due to their non-specific pharmacological activity, they may interact with other medications, leading to additive side effects or altered therapeutic responses. Furthermore, their sedative and anticholinergic properties make them less suitable for chronic conditions requiring prolonged therapy (Canonica and Blaiss, 2011).

Overall, despite their effectiveness in controlling allergic symptoms, the multiple limitations associated with first-generation antihistamines—particularly sedation, poor selectivity, short duration of action, and adverse effects—have led to a shift toward the use of newer, safer antihistaminic agents in clinical practice.

1.5 Need for Newer Antihistamines

The development of newer antihistamines was primarily driven by the need to overcome the limitations associated with first-generation agents, particularly their sedative effects, poor receptor selectivity, and unfavorable safety profiles.

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Although first-generation antihistamines were effective in controlling allergic symptoms, their ability to cross the blood–brain barrier and interact with multiple receptor systems significantly limited their clinical utility, especially in patients requiring long-term therapy (Simons, 2004).

One of the most important reasons for the development of newer antihistamines is the need to minimize central nervous system (CNS) side effects. Sedation, drowsiness, and impaired cognitive function associated with older drugs can interfere with daily activities, reduce productivity, and increase the risk of accidents. This is particularly relevant for individuals who require sustained alertness, such as students, drivers, and working professionals. Newer antihistamines were therefore designed to have low lipophilicity and limited penetration across the blood–brain barrier, resulting in minimal or no sedation (Simons and Simons, 2011).

Another key factor is the need for greater receptor selectivity. First-generation antihistamines exhibit non-specific binding to various receptors, including muscarinic and adrenergic receptors, leading to multiple adverse effects. In contrast, newer antihistamines demonstrate high selectivity for peripheral H1 receptors, thereby reducing unwanted side effects and improving tolerability. This selective action enhances the safety profile of these drugs, making them more suitable for a wide range of patients, including the elderly and those with comorbid conditions (Church and Maurer, 2015).

The requirement for longer duration of action and convenient dosing also contributed to the development of newer agents. First-generation antihistamines often require multiple daily doses due to their short half-life, which can negatively affect patient compliance. Newer antihistamines possess longer half-lives, allowing once-daily dosing, which improves adherence to treatment and overall therapeutic outcomes (Canonica and Blaiss, 2011).

In addition, there was a need to develop drugs with improved safety for long-term use. Allergic conditions such as chronic urticaria and perennial allergic rhinitis often require prolonged treatment. Newer antihistamines exhibit a better safety profile with fewer adverse effects, minimal drug interactions, and reduced risk of toxicity, making them more appropriate for chronic therapy (Simons and Simons, 2011).

Furthermore, the increasing prevalence of allergic diseases worldwide has emphasized the importance of effective and well-tolerated medications. Patients today require treatments that not only control symptoms but also maintain quality of life without causing additional discomfort or impairment. Newer antihistamines fulfill these expectations by providing effective symptom relief with minimal side effects (Pawankar et al., 2013).

Overall, the need for newer antihistamines arises from the demand for safer, more selective, and patient-friendly drugs that can provide effective management of allergic disorders without compromising daily functioning. This has led to the development of second- and third-generation antihistamines, which are now widely accepted as the preferred therapeutic options in modern clinical practice.

II. AIM AND OBJECTIVES

2.1 Aim

The primary aim of this review is to provide a comprehensive overview of newer antihistaminic drugs, focusing on their pharmacological properties, mechanism of action, clinical applications, and advantages over conventional first-generation antihistamines.

2.2 Objectives

The specific objectives of this review are:

- To study the role of histamine in allergic disorders and its physiological significance.
- To explain the mechanism of action of newer antihistaminic drugs.
- To classify antihistamines with emphasis on second- and third-generation agents.
- To compare newer antihistamines with first-generation drugs in terms of efficacy and safety.
- To evaluate the clinical uses of newer antihistamines in the management of allergic conditions.
- To analyze the advantages and limitations of newer antihistaminic drugs.

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- To review recent advances and developments in antihistamine therapy.
- To highlight the importance of newer antihistamines in improving patient compliance and quality of life.

III. METHODOLOGY

This review was conducted using a structured approach to collect and analyze relevant information on newer antihistaminic drugs.

3.1 Study Design

A narrative review design was adopted to summarize and interpret existing literature on newer antihistamines.

3.2 Data Sources

Relevant data were collected from the following electronic databases:

- PubMed
- Google Scholar
- ScienceDirect

3.3 Search Strategy

Literature was searched using keywords such as:

- "Newer antihistamines"
- "Second-generation antihistamines"
- "Third-generation antihistamines"
- "H1 receptor antagonists"
- "Allergic disorders treatment"

3.4 Inclusion Criteria

- Articles published in English
- Studies related to newer antihistaminic drugs
- Review articles, clinical trials, and research papers
- Publications from the last 10–15 years

3.5 Exclusion Criteria

- Non-English articles
- Irrelevant or unrelated studies
- Duplicate publications
- Studies focusing only on first-generation antihistamines

3.6 Data Analysis

The collected data were analyzed and summarized based on:

- Classification of drugs
- Mechanism of action
- Clinical applications

IV. LITERATURE REVIEW

Antihistamines are widely used in the management of allergic conditions such as allergic rhinitis and urticaria. They act by blocking histamine-mediated responses and are considered first-line therapy in many allergic disorders. Their

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effectiveness in reducing symptoms like itching, sneezing, and nasal congestion has made them a cornerstone in allergy treatment (Farzam et al., 2023).

Modern antihistamines are now understood to function as inverse agonists at H1 receptors, stabilizing the receptor in its inactive state and thereby reducing the inflammatory response associated with allergic reactions. This mechanism provides more sustained symptom control compared to traditional antagonistic action (Linton et al., 2023).

First-generation antihistamines, although effective, are associated with significant central nervous system side effects due to their ability to cross the blood-brain barrier. This results in sedation, drowsiness, and impaired cognitive performance, limiting their use in routine clinical practice (Wang et al., 2024).

To overcome these limitations, second-generation antihistamines were developed with improved receptor selectivity and reduced penetration into the central nervous system. These drugs provide effective symptom relief with minimal sedation and are now widely preferred over older agents (Wang et al., 2024).

Newer antihistamines demonstrate high selectivity for peripheral H1 receptors and have low lipophilicity, which contributes to their reduced central nervous system effects. This pharmacological advantage improves patient compliance and overall safety (Abdullah et al., 2022).

Clinical studies have shown that second-generation antihistamines significantly improve nasal symptoms and quality of life in patients suffering from allergic rhinitis. They are effective in controlling both early and late-phase allergic responses (Vieira et al., 2026).

In the management of chronic urticaria, newer antihistamines have been found to reduce pruritus and wheal formation effectively. In cases where standard doses are insufficient, up-dosing strategies have been recommended and shown to be safe and beneficial (Podder et al., 2023).

Comparative studies indicate that newer antihistamines have a better safety profile than first-generation drugs, with fewer adverse effects and improved tolerability. This makes them suitable for long-term use in chronic allergic conditions (Li et al., 2022).

Research has also demonstrated that newer antihistamines have minimal effects on cognitive and psychomotor functions, allowing patients to maintain normal daily activities without impairment (Shamil et al., 2022).

Studies comparing different second-generation antihistamines suggest that most of these drugs have similar efficacy and safety profiles, although slight differences may exist in onset of action and duration of effect (Karger et al., 2023).

The use of newer antihistamines in pediatric populations has been supported by clinical evidence, showing that these drugs are both safe and effective in children with allergic disorders when used at recommended doses (Scadding et al., 2021).

Third-generation antihistamines, such as desloratadine and levocetirizine, represent an advancement over second-generation agents. These drugs are active metabolites or enantiomers that offer improved pharmacokinetics, enhanced efficacy, and reduced adverse effects (Wang et al., 2024).

Recent research has also explored combination therapy approaches, where antihistamines are used along with other agents such as leukotriene receptor antagonists. These combinations have shown improved symptom control in patients with moderate to severe allergic conditions (Wandana et al., 2026).

Dose optimization strategies, including the use of higher-than-standard doses of second-generation antihistamines, have been studied in patients with refractory symptoms. These approaches have demonstrated increased efficacy without significant safety concerns (Podder et al., 2023).

Emerging research indicates that antihistamines may have additional roles beyond allergy management, including anti-inflammatory and potential antiviral effects. This opens new avenues for their use in broader therapeutic applications (Travi et al., 2022).

V. CONCLUSION

Newer antihistaminic drugs have significantly improved the management of allergic disorders by offering effective symptom relief with a better safety profile compared to first-generation agents. Their high selectivity for peripheral H1

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receptors and minimal penetration into the central nervous system have reduced the incidence of sedation and cognitive impairment, making them more suitable for long-term use. Drugs such as cetirizine, loratadine, fexofenadine, desloratadine, and levocetirizine have become the preferred choice in clinical practice due to their efficacy, tolerability, and convenience of dosing.

In addition to their established role in treating conditions like allergic rhinitis and chronic urticaria, newer antihistamines continue to show potential in broader therapeutic applications. Ongoing research and development are expected to further enhance their pharmacological properties and expand their clinical utility. Overall, newer antihistamines represent a major advancement in allergy treatment, improving patient compliance and quality of life while maintaining a favorable safety profile.

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