Evolution, mechanism of action, and clinical applications of three generations of antihistamines

Evolución, mecanismo de acción y uso clínico de tres generaciones de antihistamínicos

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Highlights

- Antihistamine development has evolved from non-selective to highly selective drugs, improving efficacy and safety.
- Second-generation antihistamines provide safer alternatives to first-generation drugs, minimizing side effects while effectively treating chronic allergies.
- Third-generation antihistamines, active metabolites of second-generation drugs, offer superior efficacy and safety for long-term allergy management.

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SYSTEMATIC REVIEW

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ABSTRACT

Introduction: This review investigates the evolution, mechanisms of action, and clinical applications of three generations of antihistamines. **Materials and methods:** To identify relevant studies, an extensive search was performed across multiple databases, including PubMed, Web of Science, and Scopus, using a strategic combination of keywords and MeSH terms**.** The selection process yielded relevant scientific literature sources published between 1985 and 2024. **Results and discussion**: the study demonstrated that the initial step in the creation and development of antihistamines involved analysing the mechanisms of anaphylaxis and allergy. This analysis led to the discovery of histamine as a mediator of allergic reactions and subsequently to the synthesis of substances with antihistamine effects, resulting in the gradual discovery of three generations of antihistamines. These drugs are designed to block H1-histamine receptors to eliminate allergic manifestations. Due to their non-selective antihistamine activity, first-generation drugs have many side effects, primarily sedation, in addition to their intended therapeutic effects. Second- and third-generation drugs are selective for peripheral H1 receptors and have significantly fewer side effects. The third generation of drugs, as active metabolites of the second generation, demonstrate the highest efficacy and safety profile. First-generation medicines are used for emergency care in acute allergic reactions and to reduce local allergy manifestations, whereas second and third generations are used to treat symptoms of seasonal and chronic allergic rhinitis. **Conclusions:** The significance of the study lies in the potential application of its results in the clinical practice of allergists.

RESUMEN

Introducción. Esta revisión analiza la evolución, mecanismos de acción y aplicaciones clínicas de tres generaciones de antihistamínicos. **Materiales y métodos:** Se realizó una búsqueda sistemática en bases de datos como PubMed, MEDLINE, Web of Science y Scopus, utilizando términos clave y términos MeSH, abarcando literatura científica publicada entre 1985 y 2023. **Resultados y discusión:** El estudio revela que el desarrollo de antihistamínicos se originó en la investigación de los mecanismos de anafilaxia y alergia, identificando la histamina como mediador clave. Esto condujo a la síntesis de sustancias antihistamínicas y al surgimiento de tres generaciones de fármacos. Estos fármacos bloquean los receptores H1 de histamina para aliviar los síntomas alérgicos. La primera generación, aunque eficaz, presenta efectos secundarios como sedación debido a su acción no selectiva. Las generaciones posteriores, más selectivas para los receptores H1 periféricos, ofrecen mejor perfil de seguridad. La tercera generación, como metabolitos activos de la segunda, destaca por su eficacia y seguridad. Los antihistamínicos de primera generación se utilizan en situaciones agudas y para alergias locales, mientras que los de segunda y tercera generación son preferidos para la rinitis alérgica estacional y crónica. **Conclusiones:** La importancia del estudio radica en la posible aplicación de sus resultados en la práctica clínica de los alergólogos.

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INTRODUCTION

The prevalence of allergic diseases is an urgent issue for the healthcare industry worldwide. The most common of these are allergic rhinitis, bronchial asthma, contact dermatitis, and food and insect allergies, which cause acute reactions leading to disability and life-threatening consequences[1]. The worsening of this epidemiological situation is primarily caused by environmental pollution, climate change and the development of the chemical industry. Stopping or at least slowing down the effect of each of these factors is a difficult and lengthy process, therefore, a more appropriate and effective method of combating allergic diseases is to develop and improve products that act on allergens as their primary cause[2]. In this regard, the evolution of three generations of antihistamines is necessary to determine the current balance between the efficacy and safety of these drugs to adjust the direction in search of improving both indicators by eliminating or minimising existing risks. The wide variety of antihistamines complicates the comparison of their effectiveness and adverse reactions[3]. Therefore, given the complexity of the mechanism of action and the difference in properties, research on these drugs prioritised an analysis of a specific drug or generation of drugs. This approach provided comprehensive information on certain antihistamines, but the full picture of their evolution from the first to the third generation is still limited.

A study of first- and second-generation antihistamines was conducted by Gumieniczek et al.,[1]. The chemical stability of diphenhydramine, azelastine and bepotastine in liquid and solid substances was experimentally determined in the study. Under the influence of high temperatures, ultraviolet/visible light, humidity, and changes in pH, the percentage of decomposition, kinetics of decomposition, and level of degradation of the drugs were determined. The results obtained are useful for the pharmaceutical industry, as they can be used in the production, storage and control of the use of drugs in the relevant dosage forms, but they do not reveal the evolution of the development of antihistamines in terms of improving their efficacy and safety. The principles of treatment of allergic conjunctivitis, allergic rhinitis and urticaria with the second-generation antihistamine bilastatin were investigated by Emeryk[2]. The properties of the drug and analysed its efficacy and safety were reviewed, but the study did not compare bilastine with other generations of drugs. Mehta et al.,[3] explored the molecular modelling of histamine receptors as one of the most recent advances in drug discovery. The review of theoretical studies focused on modern developments in docking and virtual screening, which have led to the discovery of new histamine receptor ligands for the treatment of allergic inflammatory disorders. This study assessed the technical advantages of molecular modelling but did not compare the efficacy and safety of new-generation drugs with those of previous generations.

The efficacy of pharmacotherapy and immunotherapy of allergic rhinitis was determined by a meta-analysis of clinical trials by Marko and Pawliczak[4]. According to the results of the study, the combination of intranasal antihistamines and intranasal glucocorticosteroids had the highest efficacy and safety. Similar conclusions were reached by Arcimowicz[5]. However, in addition to this method, the author also mentions ocular and combined intravenous antihistamines as effective treatments. These authors previously focused solely on treatment methods for allergic rhinitis, thus their findings do not fully address the questions raised in this study. In addition to analysing the efficacy of antihistamines, their side effects were examined in the context of safety. [4,5]

Studies on the central nervous system effects of antihistamines have yielded diverse findings. While these drugs may pose challenges in allergy treatment[6], they also offer potential benefits in managing insomnia[7] and motion sickness[8]. The rationale behind selecting the three generations of antihistamines reflects a strategic

evolution in pharmacological development to improve treatment efficacy and reduce side effects. First-generation antihistamines, originating in the 1940s, were chosen for their ability to block histamine receptors, effectively alleviating allergic symptoms. However, their non-selective action and ability to penetrate the blood-brain barrier led to significant sedative and central nervous system effects[9].
In response to these limitations, second-generation antihistamines emerged in the 1980s-1990s. These drugs were selected to be more selective in blocking peripheral H1 receptors, thereby reducing sedation and other central nervous system side effects. Examples such as loratadine and cetirizine exemplify this generation's focus on improved safety and efficacy.

The development of third-generation antihistamines from the late 1980s onward aimed to further refine these benefits[10]. This generation sought to enhance safety by avoiding cardiotoxicity issues seen in earlier drugs like terfenadine, while also improving efficacy through the use of active metabolites that could benefit patients with liver dysfunction. Drugs like fexofenadine and desloratadine illustrate these advancements, offering longer-lasting effects and reduced potential for central nervous system effects, thereby optimizing the therapeutic profile of antihistamines for modern clinical use in managing allergic conditions.

The research aims to investigate the mechanisms of action and areas of application for each of the three generations of antihistamines. The research objectives were formed, which studied the evolution of three generations of these drugs and finding a balance between the efficacy and safety of the investigated medicines.

MATERIALS AND METHODS

A comprehensive review of scientific literature on antihistamines was conducted. The study utilized PubMed, Google Scholar, Web of Science, and Scopus databases, selecting sources based on relevance, scientific value, and citation index. Search terms focused on the discovery, development, mechanism of action, therapeutic uses, side effects, and interactions of first-, second-, and third-generation antihistamines.

RESULTS AND DISCUSSION

A total of 61 scientific publications from 1985 to 2024 were reviewed to understand the evolving role of antihistamines in allergy management, their effectiveness, and safety profiles.

Discovery and Development of Antihistamines

The creation and development of antihistamines is an example of a substantiated and consistent scientific approach. The starting point was the study of the phenomenon of anaphylaxis, the results of which helped to systematise existing knowledge and form an understanding of allergy as an acute pathological reaction to a specific stimulus (allergen-antigen)[9]. After the introduction of the term "allergy", its development mechanism clarification was started, which determined a biologically active substance, histamine[10]. In 1907, Windaus and Vogt isolated histamine from animal and human tissues and studied its functions in the body[11]. In 1920, histamine was first described and experimentally confirmed in 1937 as a contributor to allergic reactions, which consisted of activation of an acute inflammatory response to an allergenic stimulus, expressed by smooth muscle spasm, dilation and increase in capillary permeability, respectively, lowering of pressure and development of oedema[12, 13]. Confirmation and substantiation of the close relationship between the development of allergies and histamine led scientists to the next logical step – the search for substances with antihistamine effects.

Continuing the research on the synthesis of clinically safe antihistamines world researchers, over the next 10 years (in the 1940s), achieved the production of drugs that had an impact on allergic manifestations and symptoms of anaphylaxis, which are now known as first-generation antihistamines[14, 15]. The pharmacological effect of the first generation of antihistamines was a non-selective blockade of histamine receptors (H-receptors). Despite the high efficacy of these drugs in reducing inflammation, a significant drawback was their blood-brain barrier cross capabilities, thus penetrating the central nervous system and blocking endogenous histamine receptors[16]. This property led to adverse reactions, the most common of which were drowsiness, dizziness, inhibition and impaired cognitive processes. Antihistamines of this generation include diphenhydramine, promethazine, chloropyramine, squifenadine, ciprofentadine, ketotifen, dimethindene, clemastine and mebhydroline.

Obtaining evidence of the heterogeneity of histamine receptors, in the early 60s of the twentieth century, their types were established and the location of each was determined [17]. This made it possible to identify a link between the manifestations of allergic reactions and the effect of histamine on type 1 (H1) receptors [18]. Given this, the adverse reactions of first-generation antihistamines were associated with the non-selective blockade of histamine receptors, whose action extended to H3[19]. Therefore, when developing second-generation drugs, the scientific vector aimed to create compounds whose interaction extends to the first type receptor. From the '80s to the '90s, the following drugs were synthesised using this principle: terfenadine, astemizole, loratadine, acrivastine, cetirizine and ebastine.

In the late 1980s and until the beginning of the 21st century, antihistamines known as third-generation drugs were developed and approved. In addition to improving the safety and efficacy profile, their development aimed to solve the problem of drug transformation in the body, which is typical for the second generation of drugs. With the exception of cetirizine and acryvastine, the second generation of drugs are prodrugs, so their therapeutic efficacy depends on the condition of the liver, where they are converted to the active form[20]. Therefore, in case of any liver pathology, the therapeutic effect of these drugs will be reduced. Third-generation drugs – fexofenadine, desloratadine, norastemizole and cetirizine – enter the body as active metabolites of second-generation drugs – terfenadine, loratadine, astemizole and hydroxyzine, respectively, so they are effective for patients with concomitant liver disease. The history of the development of antihistamines demonstrates that a clear understanding of the pathogenesis of allergy, a thorough study of pharmacological properties and their consistent improvement have ensured and maintained this group of drugs in one of the main places in the treatment of allergic diseases. At the same time, despite the obvious advantages of second and third-generation drugs, first-generation drugs have not left the global pharmaceutical market and still occupy a certain niche in it, which is primarily due to the increase in the number of allergic diseases in the world[21].

To determine the balance between the efficacy and safety of antihistamines, it is worth studying their pharmacological properties, and investigating the mechanism of action, which will allow us to identify the desired (therapeutic) and undesirable (side) effects.

Mechanism of Action of First-Generation Antihistamines

The mechanism of action of first-generation antihistamines is the blockade of H1 receptors, which are located in the smooth muscles of the bronchi, arteries, capillaries, heart, central nervous system neurons and intestines; and H3 receptors, which are located in the neurons of the central nervous system, upper respiratory tract, cardiovascular system and gastrointestinal tract [22, 23]. Thus, blockade of H-receptors activates

antihistamine activity, which reduces or eliminates allergy symptoms, including reduction or prevention of smooth muscle spasms, reduction of capillary permeability, reduction or elimination of tissue oedema, reduction of itching and hyperaemia; and concomitant effects associated with blockade of H3 receptors, m-cholinergic receptors and blockade of H1 receptors in the central nervous system. The blockade of H3 receptors in the brain and inhibition of central cholinergic structures decreases the secretion of exocrine glands, which increases the viscosity of the secretion, and dryness of the oral mucosa and provides the effect of local anaesthesia – short-term numbness of the oral mucosa. At the same time, there are antiparkinsonian, antiemetic, antidopamine, and antitussive effects; decreased gastrointestinal motility, urinary tract tone, increased heart rate, impaired accommodation, and increased intraocular pressure[24].

The blockade of H1 receptors in the central nervous system, which is determined by the blocking of first-generation antihistamines to penetrate the blood-brain barrier, causes sedation, drowsiness, impaired coordination of movements, and a decrease in cognitive function[25].

Pharmacokinetics and Clinical Use of First-Generation Antihistamines

According to pharmacokinetic properties, molecules of first-generation antihistamines bind to plasma proteins by up to 100% (98-99%). Most of the drug is metabolised in the liver by hydroxylation and conjugation to glucuronides, and the rest is excreted unaltered in the urine during the day. The drug is distributed by the body and has good penetrating properties – easily dissolving in lipids, it penetrates the blood-brain barrier to the central nervous system, during breastfeeding it enters maternal milk and causes a sedative effect in children. The maximum activity of the drug develops in one hour, the half-life is from one to four hours, and the therapeutic effect lasts from four to six hours[26].

Among the second-generation antihistamines, all but cetirizine and acryvastine are prodrugs. The main representatives of prodrugs are loratadine and ebastine. Terfenadine and astemizole were withdrawn from the pharmaceutical market due to significant side effects on the cardiac system – ventricular arrhythmias and tachycardia, the development of which was provoked by blocking potassium channels controlling myocardial membrane repolarisation[27].

Mechanism of Action of Second-Generation Antihistamines

The pharmacodynamics of prodrugs and antihistamines that are already active metabolites differ only in the presence of metabolite activation in the first stages, which occurs with the help of the cytochrome P450 isozyme CYP 3A4 in the liver. The already active metabolites have selective antihistamine activity at peripheral H1 receptors, and they do not have a significant effect on H2 and H3 receptors. Second-generation drugs demonstrate antipruritic and anti-exudative properties[28]. At an early stage of an allergic reaction, they inhibit its active development, at a later stage – limit the release of inflammatory mediators, reduce the level of migration of eosinophils, neutrophils and basophils, relieve smooth muscle spasm, reduce capillary permeability, prevent or inhibit the development of tissue oedema, and eliminate skin reactions. Due to their selectivity, the drugs do not inhibit norepinephrine reuptake, do not cause anticholinergic and antiserotonergic effects, do not affect the cardiovascular system, have almost no sedative effect in therapeutic doses, and do not interact with alcohol and psychotropic drugs[29].

Pharmacokinetics and Clinical Use of Second-Generation Antihistamines

The antihistamine effect after taking second-generation drugs occurs 1-3 hours after administration, the peak activity is observed in 8-12 hours, the therapeutic effect lasts for 24 hours, after discontinuation of

treatment the effect lasts up to three days, the half-life is 7-10 hours in adults and 5-6 hours in children. The drug molecules are up to 100% (90-93%) bound to plasma proteins. Except for prodrugs, a small amount of the drug is metabolised in the liver by O-desalkylation to form a pharmacologically inactive metabolite; approximately 60% of the drug is excreted unchanged in the urine and 10% in the faeces. After a 28-day course of administration, no tolerance to the drug was observed[30, 31].

Mechanism of Action and Clinical Use of Third-Generation Antihistamines

Third-generation antihistamines, as active metabolites of second-generation drugs, are selective antagonists of peripheral H1 receptors that do not have a sedative effect, as they do not cross the blood-brain barrier well and, accordingly, rarely enter the central nervous system[32]. In addition to anti-allergic properties, these drugs demonstrate anti-inflammatory properties, inhibiting mediators of systemic allergic inflammation, in particular, reducing the release of chemokines and pro-inflammatory cytokines IL-4, IL-6, IL-8, IL-13, reduce the level of expression of adhesion molecules in endothelial cells (P-selectin), inhibit superoxide radical formation, reduce chemotaxis, inhibit the activation of eosinophilic granulocytes and reduce bronchial hyperreactivity[33, 34].

The distribution of third-generation antihistamines in the body is caused by the moderate binding of their molecules to blood plasma proteins (60-87%). When absorbed into the blood plasma, the drug concentration is determined in 30 minutes, and its maximum value is reached in 1-3 hours, depending on the active substance, the half-life ranges from 15 to 27 hours. The drug is almost not metabolised in the liver and, outside, most of it is excreted in bile, and up to 10% of it is excreted unchanged in the urine. During the 14-day course of administration, no clinically significant signs of cumulation of these drugs were detected[35, 36]. By determining the mechanism of action of antihistamines of each generation, it is possible to substantiate their therapeutic effect and side effects and, as such, determine the areas of application. The main indicators of the effectiveness of these medicines are antiallergic effect, selectivity, speed of onset of clinical effect, duration of action, absence, presence and type of interaction of drugs with food and other medicines, and reduction of antihistamine activity. Side effects include undesirable effects from various body systems and negative reactions when interacting with food and other medicines. The efficacy and side effects of antihistamines of each of the three generations are shown in (Table 1).

Analysing the efficacy and safety of first-generation antihistamines, it is possible to note that they have the lowest efficacy and safety profile compared to other generations.

Their main advantages are the availability of parenteral dosage forms and, compared to second-generation drugs, a faster onset of clinical effects. The disadvantages include a short duration of action, tachyphylaxis, drug interactions, and numerous side effects. The short duration of the drug's action necessitates prescribing it several times a day; a decrease in antihistamine activity with prolonged use necessitates changing the drug every 2-3 weeks; interaction with drugs enhances the sedative effect of the drugs and requires limiting their use during critical processes requiring concentration and cognitive activity; numerous side effects, including the development of haematological and skin allergic reactions, complicate the therapy process and may lead to early termination. An ambiguous disadvantage is non-selectivity, which, in addition to H1 receptors, allows the blocking of cholinergic, muscarinic and serotonin receptors.

Table 1. Efficacy and side effects of first, second and third-generation antihistamines

Performance indicators and side effects	First generation antihistamines	Second - generation antihistamines	Third - generation antihistamines
Anti-allergic effect	How histamine antagonists eliminate allergic symptoms by blocking H receptors.	How histamine antagonists eliminate allergic symptoms by blocking H receptors.	How histamine antagonists eliminate allergic symptoms by blocking H receptors.
Selectivity	Non-selective	Selectivity	Selectivity
Rate of clinical effect onset	1 hour	3 hours; the peak is reached after 8 - 12 hours	30 minutes; the peak is reached in 3 hours
Duration	Diphenhydramine, promethazine, chloropyramine, mebhydrolin, clemastine, squifenadine, ciprofentadine, ketotifen – 4-8 hours; Dimethindene, clemastine – up to 12 hours; Mebhydrolin – up to 24 hours.	More than 24 hours	Desloratadine – approximately 27 hours; Cetirizine – up to 24 hours; Fexofenadine – up to 15 hours.
Tachyphylaxis	Antihistamine activity with prolonged use (addiction) is increased.	No decrease in antihistamine activity with prolonged use.	No decrease in antihistamine activity with prolonged use.
Interaction of drugs with food and other medicinal products	The incidence of adverse reactions to the drug is reduced when taken with food. The effects of alcohol and substances that depress the central nervous system (tranquillisers, neuroleptics, and sedatives) increase the sedative effect of the drugs.	Do not potentiate the effect of alcohol. Terfenadine and astemizole in interaction with antifungal agents, macrolides, antidepressants and grapefruit juice increase the risk of cardiotoxicity associated with QT prolongation and heart rhythm disturbances. Loratadine does not interact with other drugs and does not cause cardiotoxicity.	Do not potentiate the effect of alcohol. The volume of drug absorption does not decrease with food. Concomitant use of theophylline reduces the clearance of drugs, which can lead to their accumulation and overdose. No data on the enhancement of the effect of sedatives when used in therapeutic doses is present.
Side effects	On the part of the nervous system: drowsiness, impaired concentration, irritability, nervousness, anxiety, insomnia, agitation, general weakness, fatigue, headache, impaired concentration of movements.	On the part of the nervous system: dizziness, drowsiness, headache, insomnia, cramps, increased fatigue.	On the part of the nervous system: headache, drowsiness, dizziness, increased fatigue.
	From the senses: pupil dilation, increased intraocular pressure, visual impairment, diplopia, acute labyrinthitis, tinnitus.		
	From the cardiovascular system: arterial hypotension, tachycardia, extrasystole.	From the cardiovascular system: tachycardia, palpation.	From the cardiovascular system: tachycardia, palpation.
	From the nervous system: agranulocytosis, thrombocytopenia, haemolytic anaemia changes in the blood formula.		
	From the digestive system: dry mouth, short-term numbness of the oral mucosa, anorexia, nausea, vomiting, diarrhoea, constipation, gastroesophageal reflux, pain in the epigastric region.	From the digestive system: nausea, vomiting, dry mouth, gastritis, increased appetite.	From the digestive system: nausea, dry mouth, diarrhoea.
	From the genitourinary system: frequent and/or difficult urination, urinary retention.		
	From the respiratory system: dryness of the nasal and throat mucosa, nasal congestion, thickening of bronchial secretions, feeling of tightness in the chest, difficulty breathing, shortness of breath.	From the liver and biliary tract: pathological changes in liver function.	From the skin and subcutaneous tissue: rashes, hives, itching.
	From the skin: hyperaemia, itching, polymorphic rashes, cyanosis of the skin and mucous membranes, urticaria.	From the skin: rashes, alopecia.	
	From the immune system: hypersensitivity reactions, including anaphylaxis, and angioedema.	From the immune system: hypersensitivity reactions, including anaphylaxis and angioedema.	From the immune system: hypersensitivity reactions manifested as angioedema, chest tightness, shortness of breath, hot flashes and other systemic anaphylactic reactions.
	Other undesirable effects: excessive sweating, chills, fever, hyperthermia, and photosensitivity.		

The data presented in this table were derived from references[37-47].

Blocking of central serotonin and acetylcholine receptors leads to a sedative effect, which is enhanced by alcohol and other, mainly psychotropic, drugs[48]. At the same time, these drugs potentiate the effects of alcohol, narcotic substances, narcotic analgesics, monoamine oxidase inhibitors, hypnotics and sedatives.

The presence of sedative effect and other reactions associated with the impact on the nervous system influenced the revision of the areas of application of these products and expanded their use in the treatment of non-allergic diseases – migraines, motion sickness, anxiety, sleep disorders, extrapyramidal disorders (dystonia, tremor, myoclonias) and other disorders.

Central blockade of acetylcholine receptors can reduce certain symptoms of parkinsonism[49]. First-generation antihistamines are used in combination with antitussives to achieve a calming and hypnotic effect. The anticholinergic properties exhibited by the atropine-like reactions of the drugs show side effects such as dry mouth and nasopharynx, constipation, urinary retention, visual impairment, and tachycardia[50]. These properties can increase sputum viscosity, exacerbate glaucoma, and provoke obstruction in prostate adenoma. Given these properties, first-generation antihistamines are not recommended for use in bronchial asthma due to increased obstruction but are advisable for use in non-allergic rhinitis[51]. The central cholinolytic effect of the drugs determines the antiemetic and antiprotective effect of the first-generation drugs promethazine, diphenhydramine, meclizine, and cyclizine, stimulating vestibular receptors, which makes them effective in certain vestibular disorders (motion sickness, chorea) and postoperative vomiting. The effect of diphenhydramine on the cough centre in the medulla oblongata is responsible for its antitussive effect[52].

Due to a decrease in membrane permeability to sodium ions, first-generation antihistamines have a local anaesthetic effect, in particular, the anaesthetic effect of promethazine and diphenhydramine is stronger than that of novocaine[53]. The non-selectivity of first-generation antihistamines to histamine receptors caused numerous side effects and significantly narrowed the areas of their use in anti-allergy therapy. Currently, due to the variety of dosage forms, these drugs are used in emergency care in injectable form and to reduce local allergic manifestations in topical form. The sedative, antiemetic, antitussive, anaesthetic and other pharmacological effects of antihistamines extend the possibility of their use in the treatment of certain nervous disorders, nausea, and migraine, as part of anti-cold combination medicines and local anaesthetics. However, despite such a wide range of possible uses, the problem of predicting the therapeutic effect of drugs due to non-selective interaction with antihistamine receptors remains.

The second generation of antihistamines, unlike the first, has selectivity for H1 receptors, so it has almost no sedative and cholinolytic effects[54]. The advantages of these medicines are the time of clinical effect onset, and duration of action, which is achieved due to the accumulation of the drug and its metabolites in the body and, accordingly, slow excretion, and no decrease in antihistamine activity with prolonged use. The disadvantages include cardiotoxicity, interaction with certain drugs that increase the risk of its development, reduced therapeutic effect in patients with liver function disorders, lack of parenteral dosage forms of most drugs and side effects. The risk of cardiotoxicity due to the blocking of potassium channels in the heart muscle, which causes prolongation of the QT interval and heart rhythm disturbances, was inherent in terfenadine and astemizole. Due to the severity of the impact of these products on the cardiovascular system, these products were withdrawn from the pharmaceutical market. Loratadine, acrivastine, cetirizine and ebastine do not show cardiotoxicity and do not interact with other medicinal products. Compared to most second-generation drugs that start to act by metabolising, bamipine can be used as a topical antihistamine in gel form, which allows it to relieve allergic skin reactions after insect or jellyfish stings, frostbite, sunburn and thermal burns[55].

Second-generation drugs have fewer and less frequent side effects than the previous generation, making them safer and more effective for treating allergies and allergic diseases such as symptoms of seasonal and chronic

allergic rhinitis (rhinorrhoea, itchy nose, sneezing), nasal symptoms of conjunctivitis, itching, urticaria of various types (idiopathic, chronic, cholinergic, acquired cold urticaria), pollinosis, allergic dermatitis, eczema, hay fever, symptomatic dermographism, herpes in pregnancy. Third-generation antihistamines have the highest efficacy and safety profile due to the preservation of all the advantages of their predecessors and the elimination of their main disadvantages. As active metabolites of second-generation drugs, they eliminate the problem associated with a decrease in the therapeutic effect in patients with liver function disorders and do not affect the QT interval[56]. Deep skin penetration contributes to the effective elimination of skin allergies. Due to their pharmacokinetic properties, the drugs are hardly metabolised in the body, and their excretion rate depends on the condition and function of the kidneys. Apart from the risks of accumulation and overdose when taken together with theophylline, no other drug interactions were identified. Following all these characteristics, third-generation antihistamines can be effectively used for long-term therapy of seasonal and year-round allergic rhinitis, rhinoconjunctivitis with prolonged exacerbations, various types of urticaria (including chronic idiopathic urticaria), atopic and allergic contact dermatitis.

Balancing Efficacy and Safety of Antihistamines

Determining a balance between efficacy and risks in the form of side effects is the main task of pharmacology in the development and introduction of medicines. When creating antihistamines, the success of scientists was in pinpointing the mediator of allergic reactions – histamine – and the complication is that histamine, as the target of the therapeutic process, is also a universal regulator of most vital body functions[26]. Therefore, the development of each subsequent generation of antihistamines was aimed at increasing the rationality of using histamine receptor blockers. A way to determine the balance between the efficacy and safety of medicines is the theoretical and post-marketing results of collecting information on the side effects of medicines. Thus, despite numerous side effects, first-generation drugs remain relevant in anti-allergy therapy primarily due to the availability of injectable forms for emergency care in case of life-threatening allergic reactions[39]. At the same time, two second-generation drugs were withdrawn from circulation due to adverse cardiac effects that posed direct risks to the patient's life.

Personalized Medicine and Antihistamine Use

The fact that not only third-generation drugs and second-generation injectable forms but also all other antihistamines have retained their place in the pharmaceutical market is explained by the demand for personalised medicine, which, unlike the principles of universalisation of healthcare services, does not look for a single drug but uses a wide range of products to select the optimal properties that will provide the desired therapeutic effect, including the individual clinical situation of each patient[15].

Patient-specific factors significantly influence the use and effectiveness of antihistamines in personalized medicine. Age plays a crucial role, with children and elderly patients experiencing distinct challenges. Children may metabolize antihistamines differently, affecting dosing and side effects, while older adults are more susceptible to certain adverse effects like sedation and anticholinergic symptoms due to altered drug metabolism. Comorbidities such as liver or kidney disease, cardiovascular conditions, and neurological disorders also impact treatment choices. Patients with hepatic impairment may struggle with metabolizing certain antihistamines, requiring alternatives with different metabolic pathways[19]. Renal dysfunction can affect drug elimination, potentially necessitating adjusted dosing to avoid accumulation and side effects. Cardiovascular and neurological conditions can influence medication tolerance and efficacy, necessitating careful selection to mitigate risks. Treatment adherence is another critical factor influenced by dosing frequency, side effects, perceived efficacy, and cost, all of which can vary significantly between antihistamine types and formulations. Personalized approaches to antihistamine therapy must therefore account for these diverse patient factors to optimize treatment outcomes effectively.

Antihistamines and Sleep Disorders

Given that the sedative effect of antihistamines could not be fully negated, doctors and scientists have used its effect to expand the areas of application for the treatment of sleep disorders. Wesselhoeft et al.,[57] conducted a statistical analysis of sleeping pill use among adolescents and young people in Scandinavia. The study's strength lies in its comprehensive data collection across multiple countries, allowing for comparative analysis. However, it's limited by its focus on a specific demographic and geographic region, which may not be generalizable to other populations. The study revealed an increase in sedative antihistamine use from 2012 to 2018, with the largest increase in Sweden (13 out of 1000 people), followed by Norway (7.5 out of 1000 people), and Denmark (2.5 out of 1000 people). These findings not only reflect sleep problems in Nordic countries but also highlight the off-label use of antihistamines for their sedative effects rather than their intended anti-allergic purpose.

Chaudhry and Susser[58] investigated the treatment of insomnia during pregnancy, highlighting the need to address this issue in a specific and vulnerable population. The strength of their work lies in the comprehensive review of relevant literature. However, the review may be limited by the quality and quantity of available research on this sensitive topic. The authors assessed the effectiveness of various drug therapies, including hypnotics, sedatives, and antihistamines. While this review provides valuable insights, it's important to note that the efficacy and safety of these treatments may vary among pregnant women.

Burgazli et al.,[59] conducted a systematic review on the efficacy and safety of hydroxyzine for insomnia in adults. The strength of this study is its systematic approach and focus on a specific antihistamine. However, it may be limited by the quality and quantity of available studies on hydroxyzine for this indication. The authors assessed efficacy through sleep initiation, maintenance, and quality, while safety was evaluated based on side effects, with dry mouth being the most common. The review concluded that hydroxyzine could be considered for short-term insomnia treatment in adults when other therapies are contraindicated or ineffective. However, this conclusion should be interpreted cautiously, considering potential publication bias and the need for long-term safety data.

While the findings of these studies[57-59] suggest potential benefits of antihistamines in sleep disorders, it's important to note their limitations. The Wesselhoeft study focuses on a specific region and age group, the Chaudhry and Susser review addresses a specialized population, and the Burgazli et al.,[59] review concentrates on a single antihistamine. Additionally, none of these studies provide long-term safety data on the use of antihistamines for sleep disorders.

Considering these factors, it can be concluded that sedation as the main side effect of antihistamines, subject to necessary precautions, does not pose a direct threat to the patient's life and may have therapeutic potential in providing calming and hypnotic effects. However, further research is needed to establish long-term safety and efficacy across diverse populations and to develop clear guidelines for their use in sleep disorders.

Emerging Therapies and Future Research in Antihistamines

Despite significant advancements in antihistamine development, research in this field remains dynamic and promising. Recent studies are focusing on emerging therapies that could revolutionize allergy management. For instance, the long-term effects of newer generation antihistamines on chronic allergy management are being explored, with a focus on developing extended-release formulations or combination therapies for sustained relief[60]. Additionally, potential applications of antihistamines in non-allergic conditions like pruritus, inflammatory bowel disease, and certain neurological disorders are under investigation, which could broaden their therapeutic utility. Advancements in nanotechnology and other drug delivery technologies may enable more targeted delivery of antihistamines, enhancing efficacy and minimizing side effects. The interplay between antihistamines and the gut microbiome is also being investigated, potentially leading to novel strategies for modulating immune responses and mitigating allergies[39]. Furthermore, combining

antihistamines with immunotherapy or other treatments could offer a more comprehensive approach to allergy management[61]. These active research areas hold promise for enhancing our understanding and expanding the therapeutic applications of antihistamines in the future.

CONCLUSIONS

The evolution of antihistamines, driven by research on histamine's role in allergies, has led to three generations of drugs with increasing selectivity and safety. While first-generation antihistamines effectively block H1 and H3 receptors, their non-selective action results in various side effects, limiting their use primarily to emergency care and topical applications. Second- and third-generation drugs, with improved selectivity for peripheral H1 receptors, offer enhanced safety and efficacy in managing chronic allergic conditions such as rhinitis, urticaria, and dermatitis. The choice of antihistamine should be individualized, considering factors such as patient characteristics, disease severity, and potential drug interactions. Despite the comprehensive nature of this review, it is important to acknowledge the potential limitations associated with accessing all available literature sources, which may have impacted the scope of the analysis.

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