Treatment of Allergic Rhinitis: Diphenhydramine vs. Fexofenadine

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Abstract

Allergic rhinitis is a growing allergic illness brought on by the inhalation of allergens, resulting in a list of symptoms, including sneezing, watery eyes, runny nose, etc. Among the many treatment options available, H_1-antihistamines are a popular choice for allergic rhinitis sufferers. First-generation antihistamines were the first to hit the market and were later discovered to be lipophilic, causing blood-brain barrier penetration and cognitive impairment. Second-generation antihistamines were later developed with lipophobic properties to eliminate any form of cognitive impairment. Both generations are readily available over-the-counter in tablet form, including two commonly used ones: diphenhydramine (Benadryl®) and fexofenadine (Allegra®). These medications claim to provide sufficient allergic symptom alleviation, creating a difficult situation for consumers to pick the right one. Taking a deeper glimpse at the availability, efficiency, and consequences of each one, the better option becomes obvious. Diphenhydramine is a first-generation antihistamine linked to sedation, learning impairment in children, motor vehicle and work-related accidents for adults, increased falling risks for the elderly, and intended overdosing. Meanwhile, fexofenadine ranks highly as a safe second-generation antihistamine with limited adverse effects, such as the rare development of cardiac arrhythmia with prolonged use, no cases of misuse, and a lack of cognitive impairment. Overall, fexofenadine is generally a safer alternative to diphenhydramine for treating the symptoms of allergic rhinitis because it does not penetrate the blood-brain barrier nor further leads to countless adverse effects related to cognitive impairment.

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Introduction

In the United States, around 40 million Americans suffer from allergic rhinitis year-round, and this number continues to climb with changes in households and the environment (Sullivan et al. 929). Allergic rhinitis brings forth countless symptoms that become irritating after a while when trying to function normally throughout the day. Therefore, medications and other therapeutic alternatives are sought after to manage the resulting symptoms of allergic rhinitis (Yanai et al. 2). By first starting with a broad view of allergies and gradually narrowing the conversation down to well-known H_1-antihistamines, the ultimate goal of this paper is to determine whether diphenhydramine or fexofenadine is the better and safer treatment option for allergic rhinitis. To arrive at a final and unbiased claim, data will be collected from multiple sources of literature, as well as from a local pharmacy, on the availability, efficacy, and consequences of each medication.

What is an Allergy?

An allergy can be defined as a condition that causes inflammatory responses due to the immune system not working properly (Holt et al. 12). When going outside on a spring day, people might experience an itchy nose or eyes due to pollen, and this would be an example of an allergy. Allergies occur when allergens, or foreign substances, enter the body through various methods of contact (**Fig. 1**), and the unknown substances enhance the release of histamine and other chemicals that cause inflammation (Holt et al. 13). Inflammation in itself is not a negative process as it rids the body of pathogens and helps with the healing process. With an allergy, however, the irritation brought on by the allergens can become intolerable and be followed by several allergic symptoms. Allergic symptoms may include nasal, ocular, and oral irritation and dermal symptoms, such as hives (Yanai et al. 1-2). As a result, just as there are numerous allergic

symptoms, there are numerous allergy types, each of which has specific allergens that cause the allergic inflammatory reaction.

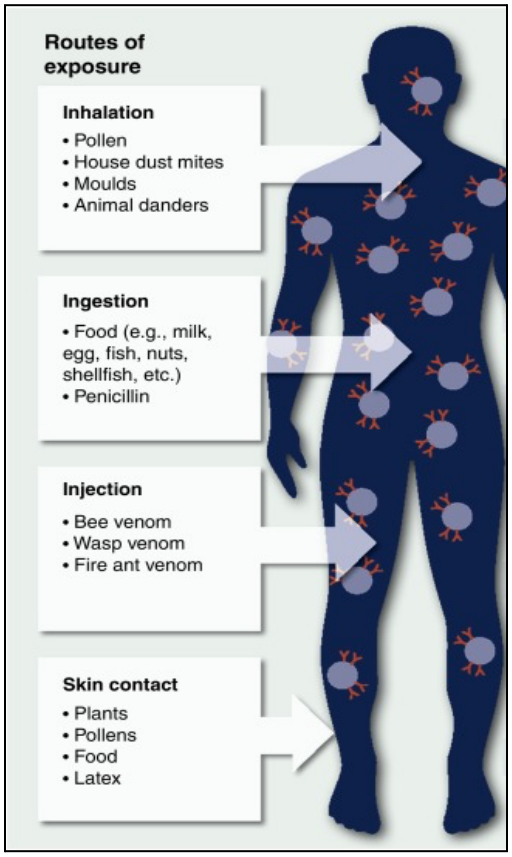

Figure 1. Illustration of Allergen Exposure Routes and Types (Larsen et al. 28)

Types of Allergies

As every individual may respond to allergens differently and have various symptoms, there may be many types of allergies to blame. From common household allergens like dust and pet dander to food and seasonal allergies, there are many different kinds of allergies. Allergens have an adverse effect on the body, which can result in mild to severe reactions that may be potentially life-threatening for each form of allergy.

Household Allergies

Household allergies result from persistent exposure to allergens, either indoors or outdoors, or insufficient sensitization to triggers. Inside the household, allergens, such as dust mites, mold, airborne fungi, and cockroach dander, can all lead to allergy and asthma development (Gent et al. 86-87). Dust, mold, fungus, and dander can hide and accumulate anywhere, especially on easily accessible surfaces to children, like carpeted floors. Although allergy and allergy-induced asthma development can emerge at any time of life, the most pivotal years of development are during childhood and infancy. According to a study performed by Gent and other researchers, insufficiently sensitized children with allergies and asthma experience worse irritation and wheezing symptoms when exposed to mold containing *Penicillium* than tolerant children (Gent et al. 90). Sensitization is a way of building tolerance, or IgE antibodies, to negative stimuli after repeated exposure slowly introduced in similar amounts. Thus, with high exposure to irritants unevenly over time, rather than a steadily controlled exposure, household allergies as well as allergen-mediated asthma will easily develop and only worsen symptoms for those susceptible.

Another allergen frequently found in households that causes troublesome symptoms for at-risk individuals is pet dander. Cats and dogs are the two most common pet species, and these four-legged companions both have a unique impact on IgE sensitization. According to Linneberg and fellow researchers, adults regularly exposed to cats in the home are more likely to develop IgE sensitization to the cat allergen (21). As a result, feline owners will develop an immunity to the resulting dander, which will slow the release of histamine and lessen inflammation and other allergic symptoms. On the other hand, dog owners respond to the accompanied dander differently in terms of building immunity to the allergens. Research shows no direct association

between owning a dog and developing IgE sensitization to canine dander (Linneberg et al. 21). Owning a dog may not be the best choice for susceptible individuals because IgE antibodies are unlikely to form with regular exposure and it will probably be necessary to administer or take medications to increase immunity or lessen symptoms. All in all, cats are wonderful pets to have in the house to help with IgE sensitization when compared to dogs.

Food Allergies

A food allergy is one of the most severe, though still relatively rare, kinds of allergies. More commonly encountered in youth, around 6% of children experience food allergies while less than 4% of adults are food allergy sufferers (Sicherer and Sampson 470). Food allergens are found in many recipes and menu items which makes it quite hard to avoid irritants if not properly informed of the contaminants. Some common allergy-inducing foods include peanuts, eggs, wheat, and shellfish. Sicherer and Sampson contend that food proteins are to blame for such allergies because the immune system does not develop the necessary tolerance, leading to irritation of the gastrointestinal tract, skin, or respiratory system (470). More specifically, pathogenesis-related proteins are to blame for over a fourth of all plant-food allergies, and the severity of food allergies is negatively influenced by widespread agricultural chemicals and other detrimental industrial activities (Shahali and Dadar 365). In industrialized countries around the world, agricultural chemicals are used on food-producing plants to remove bugs, as well as other predators, and to better the growth and appearance of the product. Although fresh foods are arguably more valuable and sought after for some, susceptible people can not say the same. Once a food source produced by a plant is consumed, agricultural chemicals are ingested in microscale amounts. For food allergy sufferers, the dangerous chemicals can act as adjuvants and have the potential to interact with the pathogenesis-related proteins already in the food, causing the

inability to develop sensitization and an increase in life-threatening symptoms (Shahali and Dadar 372-373). Altogether, food allergies are not common in most healthy adults, however, the growth of industrial activities slowly increases the rate and severity of allergic responses in susceptible individuals and affects how some become sensitized to food proteins.

Allergic Rhinitis

The most common allergy type that many people have probably experienced is allergic rhinitis. Allergic rhinitis is a growing condition that is thought to affect around 40 million Americans currently (Sullivan et al. 930). There are two main types of allergic rhinitis, seasonal and perennial, and both deal with the mucosal membranes. Seasonal allergic rhinitis (SAR) and perennial allergic rhinitis both irritate the throat, nose, and eyes. As the name implies, seasonal allergic rhinitis occurs only a few times a year, mainly in the spring. Airborne pollen is the major allergen that causes seasonal discomfort (Schmidt 71). As for perennial allergic rhinitis, this condition is more along the lines of being chronic as it can occur for a year or longer, and some of the main allergens include dust mites and mold—household allergies previously mentioned. Overall, allergic rhinitis of either kind can become quite annoying for susceptible individuals, so it is important to find a safe treatment method to alleviate the symptoms.

There are many different kinds of allergies brought on by numerous allergens that are virtually impossible to avoid. The dander from pets or dust in homes, foods like peanuts, and the outdoors are all places where common allergens conceal. Each allergen is associated with a particular sort of allergy, with allergic rhinitis being the most prevalent. A variety of symptoms brought on by allergic rhinitis, whether it be seasonal or chronic, cause chaos for a large number of people around the globe.

The History of Allergies, Diagnosis Methods, and Treatments

Information about allergens and the different allergic diseases improved over the past century as environmental, biological, and chemical research advanced. While treatment options and diagnosis methods continue to advance and develop, recent environmental findings reveal a pattern in allergen formation related to human activities that exacerbate allergic rhinitis symptoms. All of this information is valuable for understanding the background of allergic rhinitis as well as the history of allergies in general.

Evolution of Allergies

Over the years, researchers have discovered an abundance of allergy triggers, most originating from human activities. Industrial facilities, farming techniques, and motor vehicles are just a few factors to blame for the rigorous changes in the earth's environment and overall air quality. Furthermore, the development of poor outdoor conditions has altered the air quality and cleanliness of indoor facilities, such as workspaces and homes, causing a disturbance to susceptible individuals with allergic rhinitis.

Climate Change

Seasonal and insect allergies rapidly increase as the climate changes. Global warming is arguably the number one cause of climate change. Due to the large production of greenhouse gasses and industrial practices, global temperatures, and CO_2 concentrations in the atmosphere have significantly increased, causing alterations in the seasons. Warmer temperatures and growing CO_2 concentrations cause extended pollen seasons as plants' growth patterns change and more pollen is produced (Pacheco et al. 1368). An increase in pollen production stimulates seasonal allergic rhinitis and asthma in those susceptible. Seasonal allergy and asthma medications thus become increasingly desired for long periods, causing a burden on many

families and individuals; appropriate medications are not always cheap. In addition to expanding pollen seasons, warmer temperatures allow stinging insects to live and repopulate for an extended duration (Bielory et al. 486). This in turn poses a threat to those who are severely allergic to certain insect venoms, requiring an epinephrine pen to prevent life-threatening consequences. All and all, human industrial activities present many threats to the earth's overall climate; these man-made problems offer unfavorable situations for those suffering from seasonal and insect allergies.

Climate change is a global problem that affects pollen production and other allergens differently regarding location. According to Schmidt, around 10-30% of the world's population suffers from seasonal allergies, and research suggests that urban areas cause a notable increase in temperatures and levels of CO_2 compared to rural areas (71). This comes as no surprise as city areas include denser populations and many surfaces, such as closely packed roads and skyscrapers, that hold in heat. With larger populations comes an enlarged number of greenhouse gasses in the atmosphere as well. As for extended pollen seasons, areas further to the north experience an increase in days of pollen spikes, specifically looking at a map of North America. During a study between 1995 and 2009, Schmidt states that airborne pollen samples from east Texas to Saskatoon, Canada allowed for the discovery of increasing pollen seasons by 13 to 27 days, increasing while getting closer to Canada (72). Therefore, a single area is not to blame on the map for growing pollen seasons caused by warmer temperatures and high CO_2 levels. Geographical differences have a lot to do with altering peoples' exposure to certain allergens, whether plant-based or not. Thus, climate change is a growing international problem that must be calmed to keep allergies and the need for medications to a minimum.

Most effects of climate change are witnessed outdoors, however, some nonindustrial indoor air pollutants are a threat to susceptible individuals. A home or a workplace is supposed to offer safety from the dangers of the outdoors, right? Well, that is not always the case. On average, Americans spend around 22 hours indoors every single day, whether that be at home, work, or other buildings, and there are many indoor pollutants, such as ozone (O_3) and nitrogen dioxide (NO_2), that cause health problems (Bernstein et al. 585). O_3 has multiple side effects when inhaled for long periods, even in small amounts. Side effects of O_3 inhalation include airway inflammation, decreased exercise capacity, and enhanced allergic response because O_3 acts as an adjuvant; outdoor O_3 sources are to blame for the increased amount in homes and workspaces (Bernstein et al. 585-586). Moving to NO_2, many residences in the United States use gas to cook and to provide heat which leads to an increase in NO_2 exposure. According to Bernstein and other researchers, NO_2 inhalation leads to unfavorable respiratory effects for susceptible individuals as an unwanted allergen or irritant; furthermore, female adults and children are most sensitive to NO_2 exposure with infants being placed at a higher risk of developing asthma (586). Homeowners and workers are at a higher risk of experiencing pollutant side effects due to the lack of proper ventilation. Some workspaces are overstaffed with low ventilation, causing pollutants to accumulate, and the workers will most likely experience anywhere from slight to severe health problems eventually. Overall, indoor environments are greatly influenced by outdoor conditions and the burning of fuels inside and outside homes or workplaces.

Diagnosis Methods

As the number of known allergens has increased over the years with research, so have the ways to detect individuals' sensitivity. Finding out allergen sensitivity helps susceptible

individuals find appropriate ways to treat and avoid symptoms of allergic rhinitis. Physical symptoms, such as sneezing or itchy eyes, provide an easy way to determine an irritant, however, advanced ways of testing offer an alternative to discovering an array of allergens.

Skin Prick Testing

One of the most popular options for diagnosing Immunoglobulin E (IgE) mediated allergic rhinitis, or determining individuals' allergen sensitivities, happens to be skin prick testing. During a skin prick test, a small amount of allergen extract is placed on either the surface of the patient's back or inner arms and then the area of skin containing the extract is lightly scratched. After 15 minutes, the sensitivity of certain allergens is determined by the diameter of the wheals, or welts, present, and the inflammation indicates that there are IgE antibodies hard at work (Carr et al. 342). The advantages of discovering allergies from skin prick testing include learning which allergens to avoid, developing medical plans, and knowing which extracts to use for immunotherapy treatments. While skin prick testing has many advantages, several disadvantages arguably make this method of testing not ideal. According to Carr and many colleagues, at least one week before skin prick testing occurs, patients have to stop taking any antihistamines (342). This can become dangerous for any individual with severe allergies and asthma, as allergen exposure could easily occur during one week and life-threatening symptoms could arise. Additionally, skin prick testing subjects patients to allergens up close, aggravates skin conditions like eczema, and, depending on the patient, may even result in minor discomfort (Siles and Hsieh 586-587). Altogether, skin prick testing provides incredible benefits that help form healthy habits in terms of treating and avoiding allergens resulting from the environment, foods, animals, insect strings, etc. However, for certain individuals, this style of testing proves to be an unrealistic and ineffective option for discovering allergen sensitivities.

Blood Testing

Blood testing is an alternative for people who are unable to submit to skin prick testing. Blood testing is a fresh alternative that confirms an allergic diagnosis and tests a large range of allergens, anywhere from insect venoms to foods. The allergy blood testing process is quite simple as it only requires a normal blood drawing of a few vials (Siles and Hsieh 586). Thus, blood testing is arguably a more convenient and less painful option as the patient does not get pricked multiple times, either on the back or arms, with a following wait time of 15 minutes. Additionally, blood testing does not expose patients directly to allergens, allows people with severe dermal issues to safely get tested, and does not require the patients to stop taking any histamine suppressants before testing (Siles and Hsieh 586-567). Blood testing establishes a realistic alternative with many benefits for those who could not tolerate the negatives of skin prick testing while diagnosing allergic diseases mediated by IgE. As Siles and Hsieh discuss, the main downsides to allergy blood testing are slight bruising and discomfort at the testing site, and the tests are not clinically relevant while dealing with conditions that are not IgE mediated (586-567). Overall, blood testing appears to be a safer alternative for multiple groups of recipients to diagnose allergic diseases mediated by IgE, and this method only has a few minor disadvantages. To grasp a deeper understanding of everyone's allergies, this method of testing displays the importance of furthering research to discover testing options to accommodate everyone.

Treatments Now and Then

Upon receiving an allergy diagnosis or experiencing common allergy symptoms, the first step is to find a suitable treatment plan to manage the symptoms. Over the past few decades, treatment options for various allergy-related illnesses have greatly improved, with more

accessible and affordable solutions available to the average person. Depending on the individual, treatments range from at-home cures to therapeutic choices—either accessible over the counter or endorsed by healthcare providers.

Earliest Treatments

Treatment choices in the early stages of allergen discovery were limited, inadequate for some people, and somewhat problematic. Individuals who experienced any source of an allergic response, such as itching or sneezing, were typically advised to avoid allergens before or after sensitization (Holgate and Polosa 220). As the allergen source is not always known and allergens, like dust mites, are inevitable, using this technique can be challenging. Furthermore, sensitivity to allergens is linked to pregnancy and the first few years of childhood. Looking at early food allergy management, pregnant or nursing mothers were urged to steer clear of allergenic foods, like peanuts and seafood, as the likelihood that the child will acquire an allergy rises; around the age of three, it is best to introduce new foods to children to allow sensitization (Sicherer and Sampson 473-474). Therefore, allergen avoidance is still a great choice when plausible, nevertheless, it can be insufficient and difficult to practice when allergens are found readily in households and foods.

Initial H_1-antihistamines, also known as first-generation antihistamines, were developed in the early 1900s. These first-generation medications, such as chlorpheniramine, were the first specialized treatments for allergic rhinitis (Holgate and Polosa 222). However, because the full impact of these early medications was not yet understood, using them was followed by numerous complications. Due to the ability to penetrate the blood-brain barrier, H_1-antihistamines cause sedative and anticholinergic side effects (Holgate and Polosa 222). Such side effects are problematic in real-world situations because a person's cognitive and motor functions become

impaired. H_1-antihistamines are still available today, but based on a person's lifestyle and line of work, side effects may be problematic and ineffective, especially when abused.

Current Solutions

Numerous medical advances have been made since the first treatments were available to inhibit allergens and irritating symptoms. During the 1980s, less than half a century ago, second-generation antihistamines were created to treat allergic rhinitis (Slater et al. 32). Several second-generation antihistamines, including fexofenadine (Allegra®) and cetirizine (Zyrtec®), help to lessen histamine-mediated symptoms and are currently accessible over the counter in countless stores—sold in pill or liquid forms. Second-generation antihistamines do not cross the blood-brain barrier, ruling out the negative impacts of the sedative factor, unlike first-generation antihistamines. However, there are a few adverse effects still present. For some individuals, second-generation antihistamines can cause minor central nervous system impairment, appetite stimulation, weight gain, and more severely, cardiac arrhythmia, specifically associated with terfenadine and astemizole (Slater et al. 36-37). Second-generation antihistamines are a much safer option for treatment even though some people experience side effects because a variety of other medications can be taken concurrently with the antihistamines, and there are no associated cognitive issues that would affect one's daily life. The wide variety of second-generation antihistamines available on the market today allows individuals to experiment with different options to find the best one. Overall, second-generation antihistamines provide a practical, stable medicinal option for the treatment of allergic rhinitis.

Currently, another considerable method for controlling allergies is the immunotherapy approach. Allergen-specific immunotherapy consists of weekly subcutaneous injections of patient-specific allergens for a course of three to five years (Senti et al. 7). The injections are

either received at the prescriber's facility or short classes are available for at-home administration. As a result, this treatment technique offers users a convenient, easy-to-use alternative. Depending on the patients' reactivity, the allergen extracts used for the weekly injections are made straight from raw materials like pollen, grass, or animal dander. With repeated years of injections, this type of therapy induces immunological tolerance, which helps to prevent the rapid release of histamine—the main substance responsible for common allergy symptoms (Larsen et al. 29-31). Although it offers successful long-term effects, three to five years of immunotherapy treatment can be quite a hassle to keep up with and afford. To help solve these problems, current research is taking place to make allergen-specific immunotherapy an ideal and affordable method for patients. One possible advancement of allergy immunotherapy is injecting the specialized allergen extracts directly into lymph nodes to shorten the treatment time to only three years or less (Senti et al. 1). Less extract and supplies would be required for administration with shorter treatment duration, lowering the cost. Furthermore, allergy immunotherapy research foreshadows that oral tablets and drops may be a less painful, more effective option to overcome allergic rhinitis in the long run (Larsen et al. 32). Altogether, allergen-specific immunotherapy provides a fantastic alternative to long-term allergic rhinitis treatment, but the length and cost of the procedure may discourage patients; however, further study may uncover a solution to overcome these drawbacks.

Recently growing in popularity, air purifiers are a non-medicinal solution for managing allergic rhinitis and even allergen-induced asthma. Air purifiers within households contain high-efficiency particulate absorbing (HEPA) filters that help reduce indoor pollution and allergens. More specifically, air purifiers have been proven to reduce house dust mite (HDM) concentrations and particulate matter (PM) concentrations (Jia-Ying et al. 219). Fewer allergens

in the home lead to fewer allergic responses and associated symptoms, like nasal congestion. Although there is not much research on the air purifiers' general clinical efficiency, nasal congestion, and other mild allergic symptoms get better when indoor air pollution and allergens from bedding and other household items are reduced.

All in all, there has been a significant advancement in the understanding of allergic diseases, testing procedures, and at-home and medical treatments over the past century. From an environmental perspective, climate change causes a rise in allergens like pollen that cause symptoms of seasonal allergic rhinitis. Skin prick testing and blood sampling tests offer a way to diagnose and recognize these allergens which helps to point susceptible individuals in the right direction when searching for an appropriate treatment method. Today, treatment methods differ from the earliest options and now include allergy-related immunotherapy, different generations of antihistamines, and air purifiers. The evolution of allergies, diagnosis methods, and treatments have considerably improved for allergic rhinitis sufferers.

Antihistamines

Antihistamines are one of the most popular treatments among individuals who suffer from allergic rhinitis. As the name suggests, antihistamines prevent the release of histamine and attachment of the histamine to its receptors; thus, the physiological functions of histamine in the body are relevant to comprehend. Antihistamines come in a variety of forms and are widely accessible to the general public today. The generation of each antihistamine, either first-generation or second-generation, is the main difference between those on the market. Each antihistamine also has a unique history, chemical structure, and set of therapeutic properties to thoroughly evaluate.

What is Histamine?

First identified in 1911, histamine is a naturally occurring, pro-inflammatory chemical that the body produces and releases (Bachert 15). Specifically, regarding allergic rhinitis, histamine plays a large part in the immune system. Mast cells and basophils, a type of leukocyte, are responsible for the primary storage, production, and release of histamine; T cells, monocytes, and dendritic cells are also capable of producing and secreting histamine in smaller amounts (Jutel et al. 735). When an antigen triggers an allergic reaction in a susceptible individual, too much histamine is released which increases vascular permeability and leads to excessive inflammation. Although inflammation plays a crucial role in the body's ability to recover and rid itself of pathogens, increased amounts cause unwanted allergy symptoms, such as swollen eyes, itching, and hives. Furthermore, histamine involves four different heptahelical G-protein-coupled receptors, including H_1-receptors, H_2-receptors, H_3-receptors, and H_4-receptors (Jutel et al. 737). In terms of allergic rhinitis, histamine is mainly mediated by H_1-receptors that are expressed in central nervous system (CNS) neurons, smooth muscle cells, endothelial and epithelial cells in the cardiovascular system, and multiple leukocyte types (F. Simons and K. Simons 1140-1141). Accordingly, H_1-antihistamines are a popular treatment option for allergic diseases as it prevents excessive production and secretion of histamine, slows the binding of histamine to H_1-receptors, and helps rid allergic symptoms.

Classes of Antihistamines

H_1-antihistamines are currently available in a huge range to the general public. First-generation antihistamines and second-generation antihistamines are the two major classes, or generations, of H_1-antihistamines. First-generation antihistamines have been the first to be widely available, and as medical studies advanced, second-generation antihistamines started to

appear in stores. Both are easily accessible and have unique therapeutic qualities that help to treat many symptoms caused by allergic illnesses.

First-Generation

Sometimes referred to as 'old'-generation antihistamines, first-generation H_1-antihistamines were discovered around 83 years ago and became available to the public shortly after (Kay 623). While appearing in the 1940s, first-generation antihistamines did not have to go through the newer and more efficient drug studies and clinical trials required today. Moreover, first-generation antihistamine pharmacokinetic and pharmacodynamic data regarding individuals' biological factors, like age, were lacking due to the absence of regulatory agencies and clinical pharmacology research at the time (F. Simons and K. Simons 1141). As the name implies, first-generation H_1-antihistamines act as H_1-receptor blockers for histamine. First-generation H_1-antihistamines are inverse agonists and act at the H_1-receptor sites, mainly in the respiratory mucosa, as powerful competitive inhibitors for histamine which causes the antihistamines to become lipophilic; with the ability to dissipate in lipids or fats, first-generation antihistamines can easily cross the blood-brain barrier (Kay 624-625). Cognitive and motor functions are highly susceptible to being negatively affected by medications once passed through the blood-brain barrier. First-generation antihistamines are responsible for sedative effects that lead to a decline of ordinary functions, such as alertness, memory, and learning—having the potential to affect people's everyday lives and activities (F. Simons and K. Simons 1143). Currently, first-generation antihistamines are still on the market and are deemed safe as more trials and pharmacology studies have been completed that backup the safety; however, due to the sedative factor, there are still many potential adverse effects to keep in mind while ingesting the first generation of antihistamines.

Second-Generation

Over the last semi-centennial period, second-generation H_1-antihistamines were generated to help alleviate countless allergic diseases by manipulating the composition of first-generation H_1-antihistamines. Since the discovery of first-generation antihistamines, the protocols for medicinal studies and clinical trials have increased significantly. Appropriately, the pharmacokinetics of the more recent antihistamines were carefully examined, taking into consideration a wide range of people with distinctive characteristics as well as a variety of interactions, such as drug-food interactions, with other ingested materials (F. Simons and K. Simons 1141). With an increase in investigations and trials, the beneficial effects of second-generation antihistamines were made known. Thought of as a major improvement, the newer generation of antihistamines acts highly lipophobic, meaning the medications do not penetrate the blood-brain barrier as easily or at all while still acting as H_1-receptor blockers for histamine (Kay 622). Without the blood-brain barrier penetration, second-generation antihistamines point to an absence of cognitive or motor impacts like the older generation of antihistamines. The adverse effects that follow the sedative factor of the first-generation antihistamines, such as poor performance of everyday tasks, are also not present with the newer generation as the sedative effect does not occur as severely or at all (Kay 622). Ultimately, second-generation H_1-antihistamines were crafted to offer a non-sedative and arguably safer option for those who suffer from allergies.

Over-the-Counter H_1-Antihistamines

With the large range of allergic diseases currently on the rise, multiple H_1-antihistamines are available on pharmacy and grocery store shelves alike, marketed to help relieve several symptoms. Varieties of both first-generation and second-generation antihistamines are available

over-the-counter and heavily advertised to the public through social media platforms. Searching the internet or watching television, it is common to spot ads for both antihistamine types as each claim to treat multiple allergic rhinitis symptoms. Before taking any H_1-antihistamine, it is important to consult a doctor or pharmacist about the specifics or conduct appropriate research because each medication has health benefits as well as possible side effects.

Background and Health Properties

Regarding the treatment of allergic rhinitis and its accompanying symptoms, the four H_1-antihistamines mentioned below are discussed in terms of their background, health properties, and other significant details:

Cetirizine

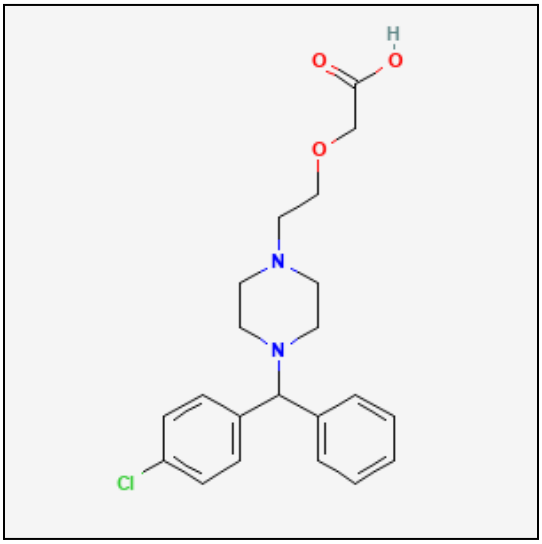

Figure 2. Chemical Structure Depiction of Cetirizine (*PubChem*)

Frequently referred to by its trade name, Zyrtec®, cetirizine is a popular second-generation H_1-antihistamine used for the treatment of allergic rhinitis. Looking at the chemical background of cetirizine, it comes from hydroxyzine as it is structurally the carboxylated metabolite of such, meaning the process of metabolism changes the structure (**Fig. 2**); cetirizine exhibits low-to-moderate lipophilicity due to its molecular composition (Curran et

al. 525). With low-to-moderate lipophilicity, the medication is least likely to cross the blood-brain barrier and cause cognitive and motor impacts. Altogether the possibility is unlikely, in some patients, the 'moderate' lipophilicity of an average 10 mg dose of cetirizine takes effect and causes a slight increase in sleepiness (Yanai et al. 3). An increase in sleepiness could prohibit one's ability to operate any form of machinery or complete everyday tasks. As for health properties, cetirizine alleviates many symptoms of allergic rhinitis with the most common being hives and other forms of itchy inflammation on the skin's surface. According to research completed by Slater and other colleagues, wheal and flare examinations proved that cetirizine was effective in the treatment of allergic symptoms visible on the skin as it offers 24-hour coverage, faster onset, and greater effectiveness in comparison to other second-generation antihistamines (Slater et al. 41). Ultimately, cetirizine is a great second-generation antihistamine to choose while dealing with hives and other forms of skin inflammation caused by allergies; however, it is possible to encounter sleepiness while consuming a normal dose of the medication which could be concerning for some individuals.

Loratadine

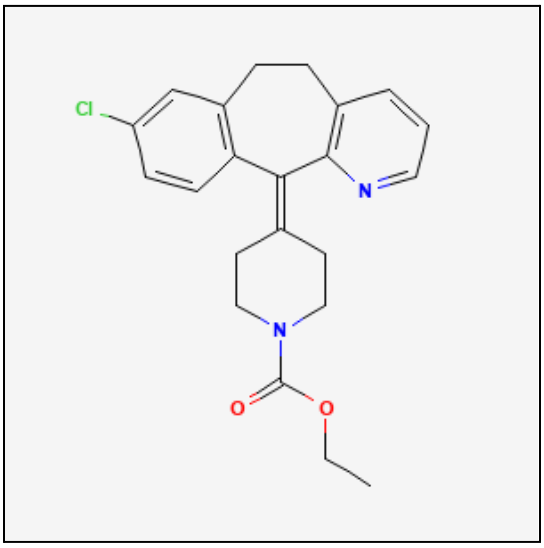

Figure 3. Chemical Structure Depiction of Loratadine (*PubChem*)

Loratadine, also known as Claritin®, is another well-liked second-generation H_1-antihistamine that is useful in treating allergic rhinitis. This medication is structurally defined as a benzocycloheptapyridine (**Fig. 3**) that is fast acting and well-tolerated for many individuals (Haria et al. 617-618). Like other fellow second-generation H_1-antihistamines, loratadine does not cross or barely crosses, depending on the individual or dosage, the blood-brain barrier. As a result, the Food and Drug Administration (FDA) of the United States has categorized loratadine as a non-sedating antihistamine (Slater et al. 36). Without sedating effects, there are no direct links to impairment of one's cognition or ability to display regular motor functions. In one study, conducted by Haria and colleagues, only 1% of the 55,000 patients receiving a daily dose of 10 mg of loratadine to address seasonal allergic rhinitis reported adverse effects, such as headaches and sleepiness (630). To significantly and safely deal with allergic symptoms, the over-the-counter recommended dose of loratadine is 10 mg by mouth, and the medication stays effective for 24 hours. Loratadine is successful at reducing nasal discharge, itchiness, and congestion as well as sneezing and eye-related symptoms throughout the day (Prenner et al. 761). Therefore, for those suffering from allergic rhinitis, loratadine would be an effective, nonsedating alternative to help manage nasal and ocular symptoms.

Fexofenadine

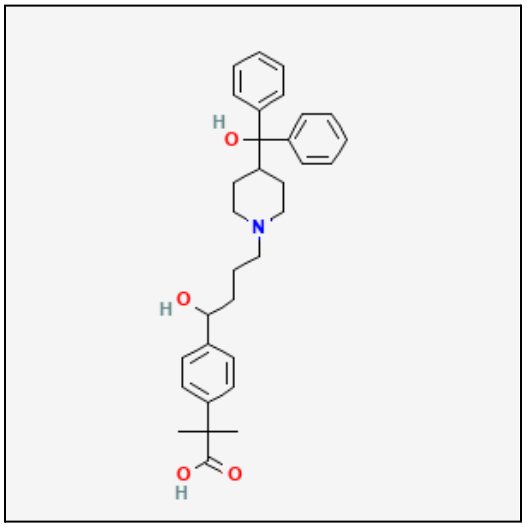

Figure 4. Chemical Structure Depiction of Fexofenadine (*PubChem*)

Another second-generation antihistamine, fexofenadine, often marketed as Allegra® when hydrochloric acid is included, is an effective medication to help reduce the bothersome symptoms of allergic rhinitis. Fexofenadine structurally contains a carboxyl group (**Fig. 4**) and is an active metabolite of the older antihistamine of terfenadine (Simpson and Jarvis 302). With this composition, there is very little chance that the drug will pass the blood-brain barrier and result in sedation or other cognitive problems. According to the studies completed by Yanai and other researchers, nearly 0% of sedation was present over 24 hours when subjects took a single 120 mg dose of fexofenadine (5). A lack of sedation caused by fexofenadine marks it as a safe option for the average consumer as there are little to no cognitive impairments. Proceeding, the health properties of fexofenadine mainly focus on the major allergic rhinitis symptoms that involve the mucous membrane. Taking 120 mg of fexofenadine once a day greatly reduces the amount of irritation and itching in the eyes, nose, and throat, as well as the need to sneeze (Simpson and Jarvis 303). Furthermore, a 120 mg or 180 mg dose of fexofenadine only has to be taken once every 24 hours to offer continuous relief. Due to the body's quick absorption of fexofenadine, the

onset of relief starts after about two hours (Simpson and Jarvis 302). Generally speaking, fexofenadine ranks highly on the list of treatments to manage symptoms of allergic rhinitis due to its absent sedation rate and numerous therapeutic advantages.

Diphenhydramine

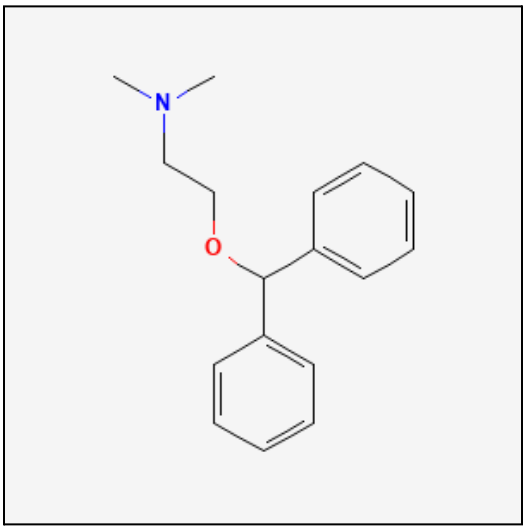

Figure 5. Chemical Structure Depiction of Diphenhydramine (*PubChem*)

The primary component of the over-the-counter drug Benadryl®, diphenhydramine, is a first-generation H_1-antihistamine effectively used in treating allergic rhinitis as well as other causes of inflammation. Midway through the 1940s, diphenhydramine was developed and has a simple and lipophilic structure (**Fig. 5**); with lipophilic qualities, diphenhydramine easily penetrates the blood-brain barrier (Pragst et al. 189). As the medication crosses the blood-brain barrier, consumers experience the sedation factor which can lead to cognitive and motor impairment. The half-life of a normal oral dose of 50 mg of diphenhydramine is approximately between 30 and 45 hours, meaning that the effects, both beneficial and adverse, can last and be felt for a few days (Yanai et al. 7). Somnolence is one of the main effects that patients experience, and this strong sense of fatigue can be considered positive or negative regarding the situation. If not planning to stay at home and rest, diphenhydramine can become dangerous if

taken before operating any type of machinery or performing any daily activity that requires complete alertness. Although, the use of diphenhydramine is not all bad as it effectively alleviates many allergic rhinitis symptoms, such as itchiness and irritation of the eyes, throat, and nose, as it works as a blockade for the H_1-receptors where histamine will bind (Pragst et al. 189). In general, diphenhydramine successfully manages all forms of inflammation and allergic symptoms, but if taken improperly, it can be dangerous.

All-inclusive, H_1-antihistamines are a well-liked form of therapy for allergic rhinitis as ocular, nasal, and oral symptoms are reduced when the release and binding of histamine slows. Over-the-counter varieties include common first-generation antihistamines, such as diphenhydramine, and second-generation antihistamines, such as cetirizine, loratadine, and fexofenadine, with each having distinct backgrounds, structures, and medicinal qualities. Indicated by the presence of sedation, the primary difference that sets the two apart is whether the drug passes the blood-brain barrier. The way an antihistamine affects an individual experiencing allergic rhinitis symptoms is crucial to study as each medication comes with benefits as well as potential risks.

Comparative Study of Antihistamines: Availability, Efficiency, and Consequences

The availability, efficiency, and consequences of diphenhydramine, a first-generation H_1-antihistamine, and fexofenadine, a second-generation H_1-antihistamine, were both assessed using a literature comparison approach that considers multiple sources of data. Availability refers to how simple it is for the average person to buy each medication in terms of cost and location. Efficiency refers to how well each antihistamine can eliminate allergic rhinitis symptoms, the pharmacokinetics, and further treatment advancements. Consequences refer to the adverse effects that each antihistamine can have on an individual seeking short-term or long-term therapeutic

properties for allergic rhinitis. Ultimately, the main goal of the study was to collect data to appropriately answer the following question: Which H_1-antihistamine, fexofenadine or diphenhydramine, is more effective and safe for managing allergic rhinitis?

Diphenhydramine vs. Fexofenadine

As previously evaluated, diphenhydramine is a first-generation H_1-antihistamine while fexofenadine is a second-generation H1-antihistamine. Currently, diphenhydramine and fexofenadine are both available over-the-counter and marketed to alleviate multiple symptoms evident in the eyes, nose, and throat caused by allergic rhinitis as well as other common allergic diseases. Both medications differ from one another in terms of expense, dosage requirements, effectiveness, and side effects.

Accessibility, Cost, and Drug Facts

Diphenhydramine and fexofenadine are easily accessible over-the-counter and found in pharmacies, grocery stores, gas stations, and other establishments open to the general public. Visiting a local CVS Pharmacy, specifically located at 105 E College Ave, Shelby, NC 28152, diphenhydramine and fexofenadine were both available in tablet form. As for diphenhydramine, the branded version of the medication in the form of diphenhydramine hydrochloride is trademarked as Benadryl®, and for a 24-tablet supply, the cost is $7.79 as of March 2023. As for fexofenadine, the branded version of the drug is trademarked as Allegra® which is specifically fexofenadine hydrochloride, and for a 30-tablet supply, the cost is $25.49 as of March 2023. Based on price alone, Benadryl® might appear to be the more obtainable option of the two, but the medication's benefits, as well as the drug instructions, warning, and other factors, must be considered before choosing one.

Figure 6. Front and Back Photograph of Benadryl® Packaging (*CVS Pharmacy*)

Looking at the packaging for Benadryl® (**Fig. 6**), the first-generation antihistamine claims to temporarily soothe itchy, watery eyes, sneezing, runny nose, and itchy throat—all typical symptoms of allergic rhinitis. As far as dosing instructions, adults and children 12 years old and over are directed to take 1 to 2 of the 25 mg tablets every 4 to 6 hours, taking no more than 6 within 24 hours. Highlighted in bright pink, the warnings are clearly stated as the medication should not be taken with any other drug containing any traces of diphenhydramine. The product's box also mentions the sedative effect, urging users to avoid alcohol and use care when operating machinery or running a vehicle after taking a typical dose of Benadryl®. Therefore, the user can comprehensively study all of the drug information, including instructions, facts, and warnings, before consuming.

Figure 7. Front and Back Photograph of Allegra® Packaging (*CVS Pharmacy*)

Glancing at the packaging for Allegra® (**Fig. 7**), the second-generation antihistamine claims to temporarily relieve itchy, watery eyes, sneezing, runny nose, and itchy nose and throat; once again, all typical symptoms of allergic rhinitis. Regarding dosage guidelines, adults and children 12 years old or over are instructed to take 1 of the 180 mg tablets once a day, taking no more than 1 tablet within 24 hours. Bolded at the top, the warnings for the medication are clearly stated, and users are urged to not consume the drug more than directed, with fruit juices, or concurrently with antacids containing aluminum or magnesium. Allegra® is labeled as non-drowsy on the front of the container as well.

Altogether, diphenhydramine and fexofenadine are two highly sought medications used to relieve allergic rhinitis symptoms. Both can easily be considered the 'better option' when it comes to cost or accessibility for the average person. Not to mention, there are other brands available that might offer a better price as the two compared are popular name brands. Nonetheless, it is crucial to look at both sides of the packaging before choosing and consuming the medication to see all the information about the drug, including the dosage instructions, uses, and warnings.

Proven Effectiveness

Given that both diphenhydramine and fexofenadine are presently on the market and intended to treat allergic rhinitis, it is fair to say that each one has excellent medicinal qualities, regardless of the type, first- or second-generation. Symptom relief provides evidence of efficiency, which is strongly correlated with each drug's pharmacokinetics. From a more recent take on the effectiveness of diphenhydramine and fexofenadine, research highlights the numerous curing properties that both medicines possess regarding COVID-19.

Symptom Relief and Pharmacokinetics Overview

As a first-generation antihistamine, diphenhydramine has offered relief from allergic rhinitis symptoms for many people for decades. 82% of people with allergic rhinitis are thought to take antihistamines, 65% of those taking first-generation antihistamines like diphenhydramine, and 35% selecting second-generation antihistamines like fexofenadine out of 82% (Sullivan et al. 930). The high percentage of consumers proves that diphenhydramine is an effective drug that alleviates sneezing, runny nose, itchy or watery eyes, etc. The half-life of diphenhydramine is thought to be around 30 to 45 hours, the half-life in the plasma is thought to be 6 to 8 hours, and the half-life in the brain is thought to be 30 to 40 hours in the brain (Yanai et al. 7). Looking at the half-life values alone, the half-life of diphenhydramine in the brain is five times longer than the half-life in the plasma; understandably so because diphenhydramine penetrates the blood-brain barrier, or slowly diffuses from the cerebrospinal fluid to the brain matter, and causes sedation. Moreover, a large percentage of a normal dose of diphenhydramine is metabolized by the liver, and only around 1% of the unchanged drug is excreted with urine (Pragst et al. 189). Just focusing on the positives, diphenhydramine acts as a prominent antihistamine for the treatment of allergic rhinitis and has been for many generations.

For children 12 years old and above, adults, and the elderly, second-generation antihistamines like fexofenadine are a great choice for allergic rhinitis treatment. Fexofenadine has proven efficiency in treating symptoms of allergic rhinitis related to histamine, including sneezing, itchy throat, nasal drainage, etc., and is considered to have a high safety rating (Ten Eick et al. 130). The high safety rating has a lot to do with the pharmacokinetics of the drug. In children, the half-life of fexofenadine ranges around 17.6 hours while the half-life for adults is around 14.4 hours; additionally, fexofenadine is minimally metabolized in the body, as approximately 5% is metabolized by the liver, and excreted through the kidneys (Ten Eick et al. 126). This explains why a 120 mg or 180 mg dose of the drug is enough for 24 hours. Furthermore, as previously mentioned fexofenadine has a high absorbance rate as noticeable relief occurs just 2 hours after ingestion (Simpson and Jarvis 302). Overall, fexofenadine is a highly effective and safe medication that is great for all ages (excluding children 11 and under) to help overcome bothersome allergic rhinitis symptoms.

COVID-19 Treatment

The SARS-CoV-2 virus, responsible for COVID-19, hit the United States in the first few months of 2020, leading to a significant number of viral cases, fatalities, and an overall pandemic. Researchers scrambled to develop vaccines and medications to address the virus as it produced a wide range of symptoms, including fever, chills, nasal congestion, breathing issues, cough, and other flu or cold-like symptoms (So et al. 1). Many people resorted to the well-known antihistamines available in stores for relief because some of the symptoms were similar to those of allergic rhinitis. Recent studies have found that diphenhydramine has antiviral properties against SARS-CoV-2, and in older individuals, the use of diphenhydramine has been shown to reduce the positivity of SARS-CoV-2 (So et al. 1). Diphenhydramine may thus be proved to be a

useful medication to recommend for people with mild COVID-19 cases with further research. Much like diphenhydramine, some people turned to fexofenadine to help alleviate COVID-19 symptoms, such as nasal congestion. Although, fexofenadine might have more potential in acting as a treatment for COVID-19. Fexofenadine may have antiviral properties as well, according to recent research published in 2020 by Piplani and other colleagues, as the medication may be able to combat the SARS-CoV-2 helicase (14). If the helicase of the virus is confronted by the antihistamine with antiviral properties, then the body would theoretically be able to overcome the virus quicker than normal. Yet, more research on fexofenadine's interaction with the SARS-CoV-2 helicase is required to prove the antiviral properties at play. All in all, fexofenadine and diphenhydramine are excellent antihistamine options for treating the cold and flu-like symptoms caused by the SARS-CoV-2 virus; moreover, additional research may reveal that both medications work well as antivirals to cure the problematic virus.

Adverse Effects

Although diphenhydramine and fexofenadine have positive medicinal properties as H_1-antihistamines to treat allergic rhinitis, each can potentially become dangerous. Due to the sedative properties, misuse, or overdosing, a broad range of negative effects may occur to consumers. The majority of these negative effects are brought on by ingesting diphenhydramine, nonetheless, fexofenadine can also potentially be threatening to individuals' general health.

Sedation, Misuse, and Accidental Overuse

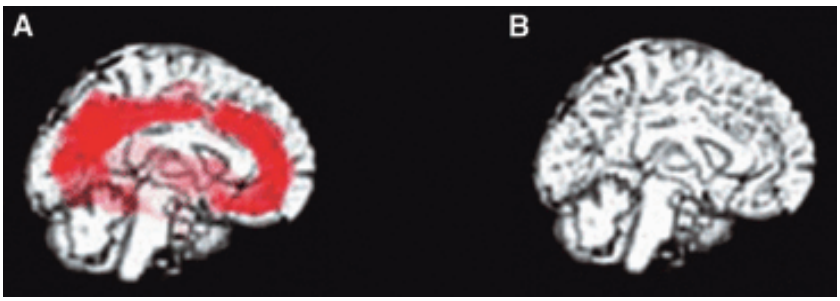

Figure 8. Blood-brain barrier penetration of diphenhydramine vs. second-generation antihistamine (Church et al. 460)

As previously mentioned, first-generation antihistamines are known to easily penetrate the blood-brain barrier, causing users to experience sedation. Diphenhydramine, a first-generation antihistamine, is associated with cognitive and motor impairment because of the sedative effect after substantially penetrating the brain (**Fig. 8**). In children, the extended use of diphenhydramine is concerning as it is linked to impaired learning which entails decreased learning performance, verbal learning, decision-making, and psychomotor speed (Ten Eick et al. 124). In one study, children and adults took first-generation antihistamines, such as diphenhydramine, second-generation antihistamines, such as fexofenadine, or a placebo tablet. In terms of learning and performance capability, the individuals taking the second-generation antihistamines were less affected in comparison to those taking the first-generation antihistamines (Ten Eick et al. 137). Furthermore, allergic rhinitis in general, along with the use of antihistamines, affects the educational success of children and teenagers alike. In the UK, a study found that teenagers suffering from allergic rhinitis and taking diphenhydramine, or other sedative first-generation antihistamines, were 70% more likely to receive examination grades one or more letter grades under healthy teens in the class (Church et al. 461). Thus, the penetration of the blood-brain barrier that occurs when taking diphenhydramine has the potential to make children and adolescents fall behind in school or behind in learning critical life skills.

Adults who take sedative antihistamines may experience cognitive impairment that is slightly more risky or even life-threatening. This is because adults frequently find themselves behind the wheel of a motor vehicle and have to go to work, which occasionally involves working in an environment that demands absolute alertness. Accordingly, adults taking

diphenhydramine are more susceptible to a motor vehicle, aviation, and/or occupational crash as the ability to match other drivers' speed, reaction time, and steering ability is noticeably decreased (Sullivan et al. 930). In addition, a 2012 study by Sullivan and colleagues on motor vehicle crashes alone suggests that the annual statistics of first-generation antihistamine-related accidents include roughly 114,000 injuries, 900 fatalities, and approximately 510,000 accounts of property damage, resulting in costs of around 5 billion dollars (936). Therefore, taking first-generation antihistamines, like diphenhydramine, puts users' overall health, as well as wallets, in danger because damage costs from accidents can build up as repairs and hospital or emergency room visits will most likely be needed to treat the resulting injuries.

Continuing on the topic of operating a motor vehicle while taking antihistamines, two different studies were completed to analyze the effects of diphenhydramine, fexofenadine, and alcohol on one's driving abilities. In the first study completed by Weiler and other researchers, 40 participants, ranging in age from 25 to 44, were either given one dose of 60 mg of fexofenadine, 50 mg of diphenhydramine, a small amount of alcohol making the blood alcohol level 0.1%, or a placebo tablet (354). After being given the appropriate substance, each participant was allowed to drive using the Iowa Driving Simulator for 1 hour, and researchers evaluated each participant's overall driving performance focusing on the ability to switch lanes and maintain a certain speed (354). As far as results, participants who took fexofenadine and the placebo had similar results, and the participants who had diphenhydramine and alcohol had similar results, with diphenhydramine showing the poorest driving performance results (362). Altogether, within the first study, diphenhydramine proved to greatly impact participants' ability to operate a motor vehicle in terms of keeping a constant speed with other vehicles and switching lanes when needed during an emergency; this ranks even worse than the consumption of alcohol.

Fexofenadine had the same effect on driving performance as a placebo, ultimately meaning that participants' cognitive and psychomotor abilities were not affected at all. Bringing in the second study completed by Vermeeren and O'Hanlon, there were 24 participants (12 men and 12 women) ranging in age from 21 to 45 years old, and participants were given 120 mg or 240 mg of fexofenadine or a placebo over five days; a moderate amount of alcohol was received on the fifth day as well (306-307). To determine how fexofenadine by itself and fexofenadine combined with alcohol influence driving performance, participants underwent psychomotor tests and real driving tests one and a half hours to four hours after getting a daily dose of fexofenadine (Vermeeren and O'Hanlon 307). As a result, when taking 120 mg of fexofenadine, 60 mg in the morning and 60 mg in the evening, participants displayed greater driving performance than those with a placebo, and while taking fexofenadine with alcohol, there were no significant differences compared to consuming alcohol alone (Vermeeren and O'Hanlon 308). Thus, it is safe to claim that fexofenadine has no noticeable effects on a person's cognitive abilities or judgment while reacting to dangers. Looking at the results from both research studies, diphenhydramine showed to have considerable cognitive effects on participants' driving, even worse than small amounts of alcohol alone, and fexofenadine consistently displayed a lack of driving performance interference, even when taken along with alcohol.

First-generation antihistamines, such as diphenhydramine, have been one of the major culprits in many misuse and overuse situations. Although it is marketed as safe to the general population in the United States, Benadryl® specifically has been banned in some places, such as Zambia, due to the extensive dangers that can occur when the drug is misused (Wong 1078). Diphenhydramine could be defined as being 'misused' if the medication is taken along with alcohol or other sedatives, or if improper dosing is used; misuse could eventually result in death

if medical help is not sought out right away. Overdosing is sadly an issue with many medications in suicide attempts. For fexofenadine, no studies have found a connection between an overdose of the drug, and a resulting death, but this is not the case for diphenhydramine (Church et al. 462). As for diphenhydramine, an overdose has the potential to become lethal as individuals' bodies can not withstand the high amount of sedatives, and this results in the individual falling into an unawakening coma; intoxication of diphenhydramine depends on age and exact dosage (Church et al. 462). There have been multiple cases of death, either accidental or on purpose, that involve an overdose of diphenhydramine. Between 1992 and 2004, 55 fatal cases were directly linked to an overdose of diphenhydramine, found during the completion of autopsies (Pragst et al. 194). One of the cases involved a 22-year-old woman who committed suicide by ingesting a large quantity of diphenhydramine. At the scene, packaging for 10.5 g of 50 mg diphenhydramine tablets was found, and the autopsy justified the cause of death as an overdose as extremely high rates of the sedative were found in the blood (Pragst et al. 194). As knowledge on the effects of sedative, first-generation antihistamines grows, so do the future perspectives in forensic studies. With diphenhydramine suicides and accidental overdoses becoming a dangerous occurrence, antihistamine determination has become an important focus during clinical and forensic cases to better understand the cause of death (Katselou et al. 28). To ensure proper use and prevent unintentional overdoses, it is crucial to read all the cautions on a medication's packaging because diphenhydramine has been associated with multiple life-threatening cases.

Frequent Injuries

As previously stated, taking diphenhydramine before operating any kind of machinery, including a vehicle, can lead to accidents because the sedative impairs cognition and can cause confusion, dizziness, and other symptoms; injuries are common when mishaps occur. Although

many injuries occur from accidents while operating machinery, for older individuals, first-generation antihistamines can become dangerous inside the household. First-generation antihistamines, including diphenhydramine, are responsible for extremity weakness in older individuals, and combined with cognitive impairment and confusion, increase the risk of falling (Alvarez et al. 2). When first-generation antihistamines are inappropriately prescribed, it becomes especially worrying for elderly people who live alone because falling can necessitate the need for immediate medical care. Diphenhydramine and other first-generation antihistamines are directly associated with an increase in mortality, hospitalizations, and emergency room visits, and can often be addressed as 'high-risk' medications for older individuals (Alvarez et al. 2). Second-generation antihistamines, like fexofenadine, do not fall into the 'high-risk' category as none are linked to increased falling or injuries, offering a safer allergic treatment alternative for the elderly. Generally, injuries are more likely to occur when treating allergic rhinitis with first-generation antihistamines rather than second-generation antihistamines.

Cardiovascular Issues

Antihistamine	*Number*	*%*
Terfenadine	19	44.2%
Cetirizine	10	23.3%
Loratadine	7	16.3%
Fexofenadine	4	9.3%
Mizolastine	2	4.7%
Ebastine	1	2.3%
Total	43	100%

Figure 9. Reports of arrhythmia with the prospective antihistamine (De Bruin et al. 372)

In comparison to diphenhydramine, fexofenadine is arguably already the better antihistamine to treat allergic rhinitis looking at all of the previous data. Fexofenadine, however,

could potentially lead to the development of cardiovascular issues. Research argues that nonsedating antihistamines can increase the risk of developing cardiac arrhythmia, or an irregular heartbeat (De Bruin et al. 373). When cardiac arrhythmia develops, patients might experience heart flutters or a heart rate that is too fast or too slow. If cardiac arrhythmia goes unnoticed and/or untreated, it could potentially convert into fatal ventricular arrhythmia (De Bruin et al. 370). Thus, it is crucial to know which second-generation antihistamines are closely linked to the development of such cardiac problems. Looking above at **Figure 9,** out of 43 cases of reported development of cardiac arrhythmia, only 4 cases were thought to be caused by fexofenadine, coming out to 9.3% of cases (De Bruin et al. 372). Although not enough research has been completed to directly prove whether or not newer, second-generation antihistamines are responsible for the development of cardiac arrhythmia, it is still important to keep in mind when choosing a relief source for allergic rhinitis, especially if an individual has existing cardiovascular issues.

Results and Discussion

Regarding availability, both diphenhydramine and fexofenadine run about the same. Branded forms of both chemicals, such as Benadryl® and Allegra®, are readily available over-the-counter in grocery stores, gas stations, and well-known pharmacies like CVS Pharmacy. Collecting data from a local CVS Pharmacy, the price of a 24-tablet supply of Benadryl® came out to around $7.79 while a 30-tablet supply of Allegra® came out to $25.49. Benadryl® seems to claim the better availability title in terms of price at first glance, however, doing some math counters this argument. Each tablet of Allegra® works effectively for 24 hours, while each tablet of Benadryl® works for 4 to 6 hours. Not being able to take more than 6 tablets within 24 hours, the 24-count pack of Benadryl® would last a total of four days. Meanwhile, the 30-count pack of

Allegra® would last 30 days or an entire month. Benadryl® would be the better short-term option with Allegra® being long-term. Altogether, the availability in terms of locations to purchase the medications is equal for both parties. While regarding the costs of diphenhydramine and fexofenadine tablets, it would be the better option to choose Allegra® tablets as it offers a larger long-term supply, but Benadryl® offers a short-term cheaper option for buyers.

Concerning efficiency, diphenhydramine and fexofenadine both have a strong history of success in the treatment of allergy rhinitis. The packaging of Benadryl® and Allegra® simultaneously claim to treat the same mucosal symptoms: itchy, watery eyes, sneezing, runny nose, and itchy throat. Diphenhydramine is a largely used first-generation antihistamine that around 65% of antihistamine-using allergic rhinitis sufferers chose to alleviate symptoms (Sullivan et al. 930). Being that over half of all antihistamine-using allergic rhinitis sufferers pick first-generation antihistamines over second-generation antihistamines proves the effectiveness of the drug. Not to mention that diphenhydramine has lately undergone evaluation concerning the early 2020 COVID-19 pandemic. Diphenhydramine not only treats the cold or flu-like symptoms of the virus, but it also has newly discovered antiviral properties against the SARS-CoV-2 virus and even lowers elderly patients' viral existence (So et al. 1). Thus, diphenhydramine persists to be an effective medication in many aspects. Fexofenadine is a medication that can be used by people of all ages to treat the symptoms of allergic rhinitis and has high effectiveness ratings to go along with its high safety rating (Ten Eick et al. 130). With a half-life of around 14.4 hours for healthy adults, a single tablet of fexofenadine, more specifically Allegra®, provides 24 hours of successful symptom coverage (Ten Eick et al. 126). Accordingly, fexofenadine alleviates bothersome nasal, ocular, and oral symptoms better than some antihistamines. The cold and flu-like symptoms caused by COVID-19 are similar to those managed by fexofenadine. Much

like diphenhydramine, fexofenadine offers antiviral properties that help to oppose the helicase of SARS-CoV-2, demonstrating its efficiency for use in future treatments (Piplani et al. 14). When it comes to effectiveness, diphenhydramine and fexofenadine are similar in many ways because both medications effectively treat the typical mucosal symptoms of allergic rhinitis and even have antiviral qualities that should be noted for sufficient therapies in the future.

Finally, the potential consequences of each medication must be the primary criteria for comparing diphenhydramine and fexofenadine in the therapy of allergic rhinitis. Diphenhydramine readily crosses the blood-brain barrier, sedating the body and causing problems with cognition and motor function. One of the leading adverse effects of taking diphenhydramine happens to be motor vehicle crashes or machinery mishaps caused by cognitive and psychomotor impairment as many users easily disregard the sedation factor of the drug before completing everyday tasks (Sullivan et al. 930). Studies prove that the cognitive and psychomotor impairments of diphenhydramine affect drivers' abilities to react to normal situations encountered on the road. In one study, 40 participants were either given diphenhydramine, fexofenadine, a small amount of alcohol, or a placebo; using a driving simulator, participants' driving was worse than when alcohol was consumed (Weiler et al. 354). If drug facts are disregarded, diphenhydramine can become life-threatening. Diphenhydramine is unfortunately prone to drug abuse and overuse. When taken in large amounts or concurrently with other sedatives or alcohol, diphenhydramine works negatively in the body and can potentially cause death. Between 1992 and 2004, autopsies proved that 55 fatal cases were linked to the abuse of diphenhydramine, with one individual specifically consuming 10.5 grams of the drug in a successful suicide attempt (Pragst et al. 194). Given all of the available information, it is safe to conclude that diphenhydramine certainly has some adverse effects related to sedation,

abuse, and overuse. Although many allergic rhinitis symptoms happen to disappear with the use of diphenhydramine, without proper research and reading all of the drug facts before consuming, users can experience many adverse effects either by accident or with intent.

After collecting data from multiple sources of literature, fexofenadine stays true to its 'high safety rating' in multiple areas. Fexofenadine does not cross the blood-brain barrier like first-generation antihistamines, so sedation is not a problem with the medication. Accordingly, fexofenadine had the same impact on a person's driving as a placebo in driving tests in multiple studies, and in some cases, the medication even made drivers more attentive than usual (Vermeeren and O'Hanlon 307-308). Driving takes a lot of coordination and focus, thus proving that fexofenadine is a very safe option for individuals operating machinery or completing daily tasks. As for misuse and overuse, there have been no deaths linked to abusing fexofenadine in any way (Church et al. 462). Though fexofenadine has looked superior thus far, there is still one adverse effect to consider. Fellow second-generation antihistamines have been linked to cardiovascular problems, and fexofenadine is no different. A major long-term worry with fexofenadine is the possibility of developing cardiac arrhythmias, especially for elderly patients with pre-existing cardiovascular issues (De Bruin et al. 373). This condition is caused by an irregular heartbeat, and if left untreated, can ultimately result in death. However, in a study that looked at 43 cardiac arrhythmias cases linked to second-generation antihistamines, only 4 were caused by fexofenadine (De Bruin et al. 372). With a low percentage of cardiac related-issues, fexofenadine holds its spot as the safer option in comparison to diphenhydramine regarding potential consequences in the long run.

Conclusion

Given that allergens are present everywhere and have a wide range of negative health impacts, allergies are a serious threat to many Americans today. Allergic rhinitis, seasonal and perennial, specifically deals with large amounts of inflammation and histamine released in the body. As a result, susceptible individuals experience nasal, ocular, and oral symptoms that deal with the mucous membranes. There are many ways to help manage these irritating symptoms, including medications, immunotherapy, and the use of newer technology like air purifiers. Out of the choices, antihistamines are a popular medicinal pick among allergic rhinitis sufferers. While searching the shelves of any store, many over-the-counter antihistamines are available, either first or second-generation. First-generation antihistamines, such as diphenhydramine, penetrate the blood-brain barrier while second-generation antihistamines, such as fexofenadine, do not penetrate the blood-brain barrier. Due to the ability to cross the blood-brain barrier, diphenhydramine causes cognitive and psychomotor impairment—having the potential of turning into something worse or life-threatening. After conducting research and collecting data, diphenhydramine proves to be an unfavorable allergic rhinitis treatment if all drug facts are not read from the back of the packaging. Diphenhydramine has been linked to motor vehicle crashes, work-related accidents, poor school performance, physical falls and injuries, and intentional overdosing resulting in death. Thus, the use of diphenhydramine should be taken seriously and in a safe environment. On the other hand, fexofenadine seems to be the safer antihistamine of the two for the treatment of allergic rhinitis. Fexofenadine does not cross the blood-brain barrier, ultimately meaning it does not cause sedation. Accordingly, no studies have been able to identify links between fexofenadine and major injuries. The only main concern for the use of fexofenadine is the development of cardiovascular issues, however, this rarely occurs and

pertains to long-term use. Thus, individuals seeking allergic rhinitis treatment for more seasonal reasons would not have to worry. Overall, with evidence from multiple sources of credible literature, fexofenadine is arguably the superior antihistamine for allergic rhinitis in this comparison against diphenhydramine. Although both antihistamines could potentially lead to adverse effects, improper use of diphenhydramine by accident would have a much larger impact on a user than fexofenadine as it lacks connections and evidence with life-altering accidents.

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