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Review Article

ROLE OF ANTIHISTAMINES IN ALLERGY INDUCED ASTHMA

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Abstract:

Asthma is a chronic disease that affects the airways. Asthma is characterized by inflammation and spasm of the airways. Allergic asthma is the most common form of asthma. Allergic asthma is triggered by inhaling allergens such as dust mites, pet dander, pollens, mold, etc. These allergens cause inflammation and swelling of the airways. This results in coughing, wheezing and chest tightness. The role of antihistamines in the therapy of asthma has been controversial from the beginning, over 30 years ago. It was only natural that after histamine was demonstrated to cause bronchospasm, and was closely related to the allergic phenomenon, the antihistamines should be expected to be effective in the therapy of asthma.

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INTRODUCTION

Asthma is a chronic disease that affects the airways. Asthma is characterized by inflammation and spasm of the airways. The airways are tubes that carry air in and out of your lungs. If you have asthma, the inside walls of your airways become sore and swollen. That makes them very sensitive, and they may react strongly to things that you are allergic to or find irritating.

Allergic asthma is the most common form of asthma. Allergic asthma is triggered by inhaling allergens such as dust mites, pet dander, pollens, mold, etc. These allergens cause inflammation and swelling of the airways. This results in coughing, wheezing and chest tightness.

Allergens are the key cause of allergic asthma and they can't be completely avoided. But the real culprit is the IgE antibody that is produced by the body in response to allergen exposure. The combination of the IgE antibody with allergens results in the release of potent chemicals. Thus, IgE is the root cause of allergic asthma. A new and exciting way to control allergic asthma is to take a medication that binds IgE and prevents it from setting off the inflammatory response. Only allergists or pulmonologists can prescribe and administer this medication.

The role of antihistamines in the therapy of asthma has been controversial from the beginning, over 30 years ago. It was only natural that after histamine was demonstrated to cause bronchospasm, and was closely related to the allergic phenomenon, the antihistaminesshould be expected to be effective in the therapy of asthma.

ASTHMA

DEFINITION:

Asthma is defined as a chronic inflammatory disease of the airways. The chronic inflammation is associated with airway hyperresponsiveness (an exaggerated airway narrowing response to triggers, such as allergens and exercise), that leads to recurrent symptoms such as wheezing, dyspnoea (shortness of breath), chest tightness and coughing. Symptom episodes are generally associated with widespread, but variable, airflow obstruction within the lungs that is usually reversible either spontaneously or with appropriate asthma treatment. (1)

EPIDEMOLOGY OF ASTHMA:

The recent substantial increase in the reported prevalence of asthma worldwide has led to

numerous studies of the prevalence and characteristics of this condition. (2) Foremost among these are 2 major international initiatives that have collected data using validated questionnaires, one among children, the International Study of Asthma and Allergies in Childhood, and the other among young adults, the European Community Respiratory Health Survey. Follow-up investigations for both of these studies have examined temporal trends within and across populations. During a mean of 7 years following phase I of the International Study of Asthma and Allergies in Childhood, (3) which in most participating countries was conducted between 1991 and 1993, the prevalence of asthma was stable or decreased in some areas of the world but increased substantially in many other areas, especially among children 13–14 years of age. (4) The Indian Study on Epidemiology of Asthma, Respiratory Symptoms and Chronic Bronchitis in Adults (INSEARCH) estimated the national burden of asthma at 17.23 million with an overall prevalence of 2.05% . In Kerala, Ernakulam records a highnumber of cases. About 10 per cent of the higher secondary students in the district suffer frombronchial asthma, according to a 2017 study by Amrita Institute of Medical Sciences, Kochi. In Thiruvananthapuram, a study in 2012 found 5 per cent of adolescents to be suffering from asthma.

TYPES OF ASTHMA: Two Types of Asthma:

- Chronic Asthma
- Acute Asthma

CHRONIC ASTHMA

Child-Onset Asthma

Asthma that begins during childhood is called child onset asthma. This type of asthmahappens because a child becomes sensitized to common allergens in the environment - most likely due to genetic reasons. The child is a topic - a genetically determined state of hypersensitivity to environmental allergens.

Adult-Onset Asthma

This term is used when a person develops asthma after reaching 20 years of age. Adult-onset asthma affects women more than men, and it is also much less common than child-onsetasthma. It can also be triggered by some allergic material or an allergy. It is estimated that up to perhaps 50% of adult-onset asthmas are linked to allergies

Exercise-Induced Asthma

Coughing, wheezing or feeling out of breath during or after exercise is called as exercise-induced asthma. Level of fitness also matters a lot. A person who is unfit and runs fastfor ten minutes is going to be out of breath. asthma.

Cough-Induced Asthma

Cough-induced asthma is one of the most difficult asthmas to diagnose. The doctor has to eliminate other possibilities, such as chronic bronchitis, post nasal drip due to hay fever, or sinus disease. In this case the coughing can occur alone, without other asthma-type symptoms being present. The coughing can happen at any time of day or night. If it happens atnight, it can disrupt sleep.

Occupational Asthma

This type of asthma is triggered by something in the patient's place of work. Factors such as chemicals, vapours, gases, smoke, dust, fumes, or other particles can trigger asthma. Itcan also be caused by a virus (flu), moulds animal products, pollen, humidity and temperature. Another trigger may be stress. (5,6)

ETIOLOGY:

Allergies

Common sources of indoor allergens include animal proteins (mostly cat and dog allergens), dust mites, cockroaches, and fungi. It is possible that the push towards energy- efficient homes has increased exposure to these causes of asthma. Allergic reactions triggered by antibodies in the blood often lead to the airway inflammation that is associated with asthma.

Tobacco smoke has been linked to a higher risk of asthma as well as a higher risk of death due to asthma, wheezing, and respiratory infections. In addition, children of mothers whosmoke - and other people exposed to second-hand smoke - have a higher risk of asthma prevalence. Adolescent smoking has also been associated with increases in asthma risk.⁽⁷⁾

Environmental Factors

Allergic reactions and asthma symptoms are often the result of indoor air pollution from mould or noxious fumes from household cleaners and paints. Pollution, sulphur dioxide, nitrogen oxide, ozone, cold temperatures, and high humidity have all been shown to trigger asthma in some individuals.

Obesity & Stress

Overweight adults - those with a body mass index (BMI) between 25 and 30 - are 38% more likely to have asthma compared to adults who are not overweight. People who undergo stress have higher asthma rates. Part of this may be explained by increases in asthma-related behaviours such as smoking that are encouraged by stress. However, recent research has suggested that the immune system is modified by stress as well.

Genes

It is possible that some 100 genes are linked to asthma - Genes linked to asthma also play roles in

managing the immune system and inflammation. Genetics may also be interacting with environmental factors. For example, exposure to the bacterial product endotoxin and having the genetic trait CD14 (single nucleotide polymorphism (SNP) C-159T) have remained a well-replicated example of a gene-environment interaction that is associated with asthma.

Airway Hyperreactivity

Researchers are not sure why airway hyperreactivity is another risk factor for asthma, but allergens or cold air may trigger hyperreactive airways to become inflamed.

CLINICAL MANIFESTATION

Signs and symptoms: Symptoms of asthma vary from person to person. There could be sudden outbursts of symptoms. Most common symptoms of asthma are:

- Dyspnoea or difficult breathing
- Wheezing
- Chest tightness
- Persistent coughing, more commonly at night. Most commonly cough with mucus orphlegm

During Asthma attack, the patient presents below symptoms:

- Very low blood pressure
- Abnormally rapid breathing
- Wheezing sounds may accompany both inspiration and expiration or expiration alone If the person is suffering from asthma for a prolonged period, Respiratory failure, a syndrome when the blood vessels around the air sacs fail to exchange gases of carbon dioxide and oxygen efficiently, may occur. The symptoms of Respiratory failure include:
 - Hyperinflation: Patients with long standing uncontrolled asthma may have a barrel-shaped chest caused by hyperinflation of lungs
 - Loss of consciousness
 - Skin and mucous membrane turning to blue in colour
 - Low blood pressure, which could lead to heart attack
 - Oxygen saturation dropping less than 90%.

PATHOPHYSIOLOGY:

Asthma is characterized by fluctuating airways obstruction, with diurnal variation and nocturnal exacerbations. This manifests as the triad of wheeze, cough and breathlessness. These symptoms are due to a combination of constriction of bronchial smooth muscle, oedema of the mucosa lining the small

bronchi, and plugging of the bronchial lumen with viscous mucus and inflammatory cell. Asthma is broadly categorized into non-allergic and allergic, but there is considerable overlap. In allergic asthma, which is usually of early onset, extrinsic allergens

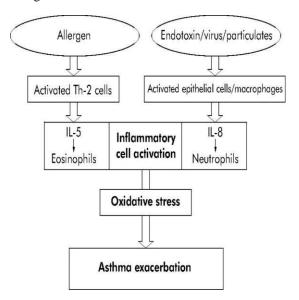


Figure 1

produce a type I allergic reaction in atopic subjects. Type I reactions are triggered via reaginicantibodies (Ige) on the surface of mast cells and other immune cells, especially activated effector lymphocytes, which release cytokines that recruit eosinophils and promote further Ige synthesis and sensitivity. Patients with non-allergic (late-onset) asthma do not appear to be sensitive to any single well-defined antigen, although infection (usually viral) often precipitates an attack. Inflammatory mediators implicated in asthma include histamine. several leukotrienes (LTC4/D4 and E4) 5hydroxytryptamine (serotonin), prostaglandin D2, platelet-activating factor (PAF), neuropeptides and tachykinins. Increased parasympathetic tone due to local and centrally mediated stimuli also promotes bronchoconstriction. (8)

TREATMENT:

- Goals of Treatment: Goals for chronic asthma management include:
- **✓** Reducing impairment:
- ✓ (1) prevent chronic and troublesome symptoms (example; coughing or breathlessness in the daytime, at night, or after exertion).
- ✓ (2) require infrequent use (≤2 days/week) of inhaled short-acting β2 -agonist for quick

- relief of symptoms (not including prevention of exercise-induced bronchospasm [EIB]).
- ✓ (3) maintain (near-) normal pulmonary function.
- ✓ (4) maintain normal activity levels (including exercise and attendance at workor school).
- ✓ (5) meet patients' and families' expectations and satisfaction with care. (9)
- ✓ Reducing risk:
- √ (1) prevent recurrent exacerbations and minimize need for emergencydepartment visits or hospitalizations.
- ✓ (2) prevent loss of lung function; for children, prevent reduced lung growth.
- ✓ (3) minimal or no adverse effects of therapy. (10)
 - For acute severe asthma, treatment goals are
 - (1) correct significant hypoxemia.
 - 2) rapidly reverse airway obstruction (within minutes).
 - (3) reduce likelihood of recurrence of severe airflow obstruction.
 - (4) develop a written action plan in case of future exacerbation. (11)

PATIENTS COUNSILING:

Patient counselling deals with providing information to the patients regarding their medications in simple layman's language. It may be defined as providing medication information orally or in written form to the patients or to their representative.

Self-monitoring of treatment is essential in asthma:

Similar to any chronic disease, the success of asthma management depends on how much the patient, on his/her own, is able to take care of his/her own health. The patient should know the indications for the use of short-acting bronchodilators during an attack, strategies to prevent the occurrence of an attack, etc.⁽¹²⁾

I. Counselling regarding disease:

The patients should be told that the disease will not spread to their neighbours and will not affect the children. It will also not spread through eating in the same plates, using the same utensils, etc. If medications are taken properly, the progression of the disease can be prevented and hence the outcomes may be better and they will be symptom free.

II. Counselling regarding medication:

The counselling regarding medication depends upon the type of medications. Some ofthe essential points to be counselled are discussed below.

- 1. Beta 2 agonists (salbutamol, salmeterol and bambuterol): These drugs are available as metered-dose inhalers (MDIs), dry powder inhalers (DPIs) oral liquids and tablets. The patients should be advised not to take salbutamol if they had an allergic reaction to it and should call their doctors if they notice any allergic reaction, tightness of problems, chest. breathing irregular heartbeat, seizure and tremor. Patients should be advised to take the missed dose as soon as possible. If a patient remembers the missed dose when it is almost time for the next dose, he/she should take the next dose and skip the missed dose.
- 2. **Xanthine alkaloids (Theophylline):** It is available as tablets or injections. The patients should not change the dose without doctor's advice and should inform their doctor if they have any cardiac or lung problems. The tablets which are to be swallowed whole should not be chewed and crushed. The patient should call their doctor if they develop nausea, vomiting, sleeping disturbances, seizure or uneven heartbeats.
- 3. Anticholinergics (Ipratropium bromide):
 This drug is available as an MDI. The patients should be advised not to use the medicine if they have had an allergic reactionto this drug or to atropine, peanuts or soyabean. It is not beneficial during an asthma attack. The patient may develop anticholinergic side effects like dryness of mouth and reduced secretions. The patient should be advised to inform the doctor if he/she has blurred vision, dry mouth, dry throat, cough and nervousness.
- Corticosteroids (prednisolone, budesonide, fluticasone, beclomethasone): These drugs are available as MDIs, DPIs or as an oral form (Prednisolone). The patient should be advised not to take any of these if he/she has had an allergic reaction to it. Patients should not use more medicine than instructed and should be advised to rinse their mouth with water after inhalation. The patient should inform the doctor if she is pregnant and about any type of infection, especially of the lung. The patient should inform the doctor if he/she develops allergy, tightness of chest, headache, dizziness, nausea or vomiting. Upon longterm use, they may cause elevation in blood glucose (mainly with oral therapy), and hence the patient should be advised regular follow-ups.

- 5. Mast cell stabilizers (sodium cromoglycate): It is available as an MDI. The patient should not use it if he/she has had allergic reaction to it. This medicine should not be used during an acute asthma attack. The patient should inform the doctor if he/she is taking other medicines, i.e., herbal, over-the-counter medicines, etc. The patient shouldinform the doctor if he/she has heart, kidney or liver disease. The patient should call the doctor if his/her symptoms are worsening.
- Leukotriene-receptor antagonists leukotriene-synthesis inhibitors: The main drugs of this class are Montelukast, Zafirlukast and Zileuton. The patient should not use these medicines if he/she has had an allergic reaction to these drugs. The patients should not take more medicine than what their doctor has advised. If the patient misses a dose or forgets to take his/her medicine, he/she should take it as soon as possible. If it is almost time for the next dose, he/she should skip the missed dose. These medicines will not stop a severe asthma attack after it has started. The doctor may give him/her a medicine to inhale that will work quickly for a severe attack. The doctor should be called right away if asthma is getting worse or any serious side effects are experienced.
- Anti-Ig E therapy (omalizumab): The patient should not use this medicine if he/she has had an allergic reaction to omalizumab or hamster protein. As it is an injection, a nurse or some other trained health professional will give this medicine. This medicine needs to be given on a fixed schedule. Patients should ensure that they keep all appointments. This medicine will not stop an asthma attack that has already started. The doctor may prescribe another medicine for the patient to use in case of an acute asthmaattack. If the other medicine does not work as well, the patient should inform his/her doctor right away. The doctor should be called right away if the patient notices any allergic reaction, fever, sore throat or cough. Some of the key points to be taken into consideration while counselling about some commonly used drugs is listed. (13)

III. Counselling on inhalation techniques:

Asthma is a disease of the respiratory tract, where the patient will be benefited by the inhaled medication. So, the choice of suitable inhalation device is crucial in the management of asthma. Counselling

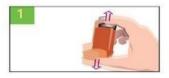
- regarding the proper use of inhalation device is discussed below.
- 1. Metered-dose inhaler (MDI): The MDIs offer many advantages over the conventional methods of administering drugs in asthma. The major advantage of inhalation therapy is the direct delivery of medications in much smaller effective doses compared to systemic routes, thus reducing side effects. There are several guidelines that explain thecorrect use of inhalers. The National Asthma Education and Prevention Program (NAEPP) criteria mention that the following ten points should be followed by the patients while using an inhaler
- a) Shake vigorously
- b) Remove cap

- c) Hold upright
- d) Breathe out gently, not fully
- e) Start breathing in slowly and deeply
- f) Actuate during inspiration
- g) Continue slow inhalation
- h) No aerosol loss is visible
- i) Hold breath for 10 s
- j) The next dose after 1 min

Steps 5-8 is vital where hand-lung coordination is required It is found that most of the patientsdo not use MDIs correctly. After proper technique, only 10% of the drug reaches the airway, with 80% deposition in oropharynx. The pharmacist before dispensing an inhaler should thoroughly explain its use.⁽¹⁴⁾

Figure 2

How to use your metered-dose inhaler (MDI):



1. Shake the inhaler well before use (3 or 4 times)



2. Remove the inhaler cap



3. Breathe out completely and slowly



4. Bring the inhaler to your mouth. Place it in your mouth between your teeth and close your mouth around it



5. Start to breathe in slowly evenly and deeply; press down on the inhaler one time (start to breathe in, then press); and continue to breathe in slowly until you have taken a full breath



6. Remove the inhaler from your mouth, and hold your breath for 10 seconds (or as long as you can). Then breathe out

- 2. **Metered-dose inhaler with spacer:** Use of spacer with metered-dose inhaler allows greater evaporation of the propellant, reducing particle size and velocity, which reduces the oropharynx deposition and potentially increases lung deposition. Spacers overcome the problem of hand-lung coordination encountered while using MDI alone. It is beneficial in elderly patients and few patients (with rheumatoid arthritis, parkinsonism,etc.) who cannot coordinate the actuation and inhaling procedure of the inhaler properly. (15)
- 3. **Dry powder inhaler**: The dry powder inhalers (DPIs) are propellant free and are designed for easier use. The dry powder inhaler has the advantage over MDI that no hand-lung coordination is required and it also can be easily used by children, elderly and arthritic patients. For the proper use of the dry powder inhaler following steps are recommended.

Step 1: Insert a rota cap, transparent end first, into the raised square hole of the DPI Step 2: Rotate the base of the DPI in order to separate the two halves of the rota cap Step 3: Breathe in as deeply as you can

Step 4: Hold your breath for 10 sStep 5: Breathe out slowly

Step 6: After each use, pull the two halves of the DPI apart and throw away the loosecapsules Step 7: Reassemble the DPI

Step 8: Repeat the above steps if more than one rota cap is prescribed .⁽¹⁵⁾

4. **Nebulizer:** Nebulizer is the device which changes liquid medicine into fi ne droplets (in aerosol or mist form) that are inhaled through a mouthpiece or mask. These are very useful in children under 2 years of age, patients with severe attacks of asthma unable to produce sufficient inspiratory effort and those lacking the coordination to use the MDI. But the disadvantages are that they are costly and also run-on electricity and so are notbeneficial to the patients living in the rural area where electricity may be lacking. (16)

COMPLICATION

1. Low blood oxygen:

A wide range of serious clinical complications are found to be associated with asthma that primarily includes low supply of blood to lungs resulting in comparatively very low blood oxygen level and very high carbon dioxide

levels. And, if the O2 levels dangerously fall below critical limit than the patients have to be shifted on ventilators to avert any casualty. (17)

2. Poor quality of life:

Since asthma is a respiratory complication, it is found that people suffering from it led an inactive and low life. It affects the ability to exercise; restricting oneself to light physical activities and to stay away from any recreational activities. Also, people are found to underperform due to psychological pressure resulting from anxiety, stress and depression. Fatigue and days away from school & work are also quite commonly observed in asthmatics.⁽¹⁸⁾

3. Respiratory issues:

Lung infection causing pneumonia, collapse of lungs or a part of it and respiratory failure are the severe clinical complications that are reported in addition to wide range of other respiratory problems. (19) Acute respiratory failure in which the bronchial tubes of person suffering from asthma are completely blocked calling for an emergency.

4. Status Asthmaticus:

Status asthmaticus is an acute complication of asthma in which the sufferer fails to respond to initial treatment with bronchodilators. Sometimes it can become severe and cause bronchospasms and inflammation of the airway, making breathing extremely difficult. It can sometimes lead to respiratory failure. (20)

ROLE OF ANTIHISTAMINES IN ALLERGY INDUCED ASTHMA DEFINITION

Antihistamines can play a crucial role in managing allergic asthma. Allergic asthma, also known as atopic or allergy-induced asthma, is triggered by exposure to an allergen. This exposure sets off an overreaction of the immune system, during which the body releases a chemical called histamine. (21)

Allergy Induced Asthma.



When your airways become extra sensitive to some allergens, you end up developing allergic asthma. immune system reacts to these allergens and tightens up the muscles around your airways. This leads to the inflammation of the airways and causes excessive build-up of thick mucus in your airways in the long term. The symptoms of both allergic and non-allergic asthma are usually the same and include wheezing, coughing, quick breathing and chest congestion. You are more likely to develop allergic asthma if you have hay fever or have a family history of allergies.(22)

Causes of Allergy Induced Asthma

As mentioned, an exposure to certain allergens will lead to the development of allergy induced asthma. Some of these allergens are so small, which can be breathed into the lungs, such as dust mite faeces, windblown pollen from grasses, animal dander, mould, spores, and cockroach faeces.

Bear in mind that allergens can definitely trigger an allergic reaction, but you may also have an asthma attack by being exposed to certain irritants such as air pollution, dusty rooms, cold air, tobacco smoke, perfumes, strong chemical odours, and exercise in coldair

(23) **ROLE OF ANTIHISTAMINE**

Antihistamines can play a crucial role in managing allergic asthma. Allergic asthma, also known as atopic or allergy-induced asthma, is triggered by exposure to an allergen. This exposure sets off an overreaction of the immune system, during which the body releases a chemical called histamine.

Histamine is responsible for allergic symptoms. In people with allergic asthma, histamine causes airway (bronchiole) constriction. It also causes excess mucus production. Together, these effects impede airflow to the lungs. (24)

MECHANISM OF ACTION OF ANTIHISTAMINES.

Antihistamines prevent histamine from binding to receptors that trigger symptoms in bothconditions.

• Histamine H1 -receptor antagonists bind to H1 receptors without activating them, preventing histamine binding and action.

They are effective in preventing the histamine response but not in reversing its effects after they have occurred.

• Oral antihistamines are divided into two categories: nonselective (first-generation or sedating antihistamines) and peripherally selective (second-generation or non sedating antihistamines). However, individual agents should be judged on their specific sedating effects because variation exists among agents within these categories. The sedating effect may depend on ability to cross the bloodbrain barrier. Most older antihistamines are lipid soluble and cross this barrier easily. Peripherally selective agents have little or no central or autonomic nervous system effects.

Antihistamine Uses

People primarily use antihistamines to treat or prevent nasal allergy symptoms. They're effective for seasonal and year-round allergies, as well as other causes of itching and urticaria (hives).

TREATMENT

To Treat Allergies

These medications are not a first-line treatment for allergic asthma. That's because histamine is not the only chemical involved in asthma symptoms. However, they can help to relieve asthma symptoms triggered by histamine, including:

- Inflammation
- Bronchoconstriction (narrowing of the airways)
- Excess mucus in the airways

When antihistamines are used to control allergy symptoms, there can sometimes be a slight improvement in allergic asthma.

Histamine may play a more significant role in specific subtypes of allergic asthma, but this isn't well understood. Therefore, people use antihistamines for allergy symptoms with a limited expectation for improving allergic asthma. (25)

Antihistamines are ineffective for acute asthma symptoms and should never be taken for anasthma attack

Combined Therapy for Asthma

If you have allergic asthma, your healthcare provider may recommend antihistamines incombination with other asthma medications, among them:

- Short-acting beta-agonists (SABAs), also known as rescue inhalers
- Inhaled corticosteroids to prevent symptoms
- Leukotriene modifiers to control mucus production, airway constriction, andinflammation
- Monoclonal antibody medications, such as Xolair (omalizumab)

Antihistamines and leukotriene modifiers are commonly taken as a combination therapy for allergies. However, they may have an enhanced effect in treating mild to moderate persistent asthma. (16)

People use antihistamines to treat allergy symptoms. They are not a first-line treatment for asthma, but they help relieve allergy symptoms that trigger asthma. In addition, antihistamines are sometimes combined with other medications to treat allergic asthma.

Determining Your Asthma Severity

1. Establishing a Treatment Plan

Talk to a healthcare provider about whether an antihistamine should have a place in your asthma management plan. They'll want to consider the specific symptoms you experience and how often they occur.

2. Tests

A doctor may want to do a blood or skin test to confirm you have an allergy. That way, you will know which things to avoid, if possible. They also may want to measure your lung function with spirometry. This test estimates your degree of airway constriction before and after using an inhaler. Once the tests are complete, your asthma will be classified based on severity. This classification will influence your treatment plan and the combination of medications your doctor prescribes.

3. Allergy Treatment.

The best allergy treatment is prevention. You may prevent symptoms by steering clear of the allergen involved, but this can be challenging. Among the most common allergens are things that often are hard to avoid, such as:

Pollens (from trees, grasses, weeds)
Mould
Dusts mites
Cats and Dogs
Pests (like cockroaches).

SIDE EFFECTS:

Some of the common side effects of firstgeneration antihistamines include:

Drowsiness.
Dry mouth, dry eyes.
Blurred or double vision.
Dizziness and headache.
Low blood pressure.
Mucous thickening in the airways.
Rapid heart rate.
Difficulty urinating and constipation. (21)

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