2019

A Review of Asthma Treatments: Monoclonal Antibody, Corticosteroid, Leukotriene Modifier, and Bronchodilator

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One sentence summary: Asthma affects three hundred million people around the world; understanding the different types of treatment can help individuals hinder their daily conflicts with asthma.

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Abstract: Medical research has created multitudes of medications to help control the symptoms of asthma. Asthmas effects the respiratory system in different ways, creating unique challenges to researchers and doctors alike to create or a manage the symptoms of asthma. Identifying the common treatment methods and understanding their effect on the human physiology can aid in treating patients. The goal of this review is to identify the common medications used to treat asthma, how these medications work on the human's physiology, as well as bring to light a new upcoming medication with greater asthma control. As asthma research continues, the need for more advanced treatment options can decrease the symptoms of asthma.

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Introduction:

Asthma is classified as a chronic inflammatory lung disorder associated with airway obstruction and hyper-responsiveness (1). Asthma is the most common chronic illness in children and affects children worldwide, yet also affects people of all ages (2). Asthma can impact the quality of life on more than just the individual, but the family as a whole. It is common for families to have issues with missing school, work, sleep, and daily activities (3). The diversity of physiological symptoms asthma obstructs on the body implicates many different modes of treatment used for its management.

What is asthma:

As mentioned above, asthma is often characterized by airway inflammation and airway narrowing, resulting in wheezing, dyspnea, and coughing (4). These symptoms are often reoccurring while also determining the severity and treatment options for asthma (26). This chronic inflammation is associated with proinflammatory cells like mast cells, lymphocytes, eosinophils, and detached airway epithelial cells. Long term inflammation will damage airways and initiate airway remodeling resulting in fibrosis under the basement membrane, hypertrophy of smooth muscle, and submucosal gland hyperplasia. Ultimately causing irreversible airflow limitation and hyperresponsiveness of the airway (4). These symptoms cause episodes of wheezing, breathlessness, and chest tightness that are associated with airflow obstruction that spontaneously reverses on its own or with treatment (26). These symptoms often appear from

stimuli such as cold air or exercise (29). Traditionally, asthma has been categorized in two forms: allergic, and non-allergic (intrinsic) as illustrated in fig. 1. (29). The two differ in many ways but are more similar than dissimilar. Both elicit different responses from the immune system yet have similar symptoms. Allergic asthma is expressed in both adults and children, which also coincides with allergies sensitizations with the presence of IgE, and proteins associated with animal dander, spores, pollen, peanuts, or dust mites (29). The progression from allergic sensitization accompanies eczema is followed by allergic rhinitis and then commonly progresses to asthma. Non-allergic often doesn't develop until later in life, does not have IgE reactivity in serum, nor adaptive immune system involvement from type 2 helper T-cells (29). The division between just allergic and non-allergic is an over simplification, as research uncovers different phenotypes that each have a distinctive pathophysiology and defined as an endotype. These endotypes can be different in many factors such as: risk, age of onset, medicinal responses and prognosis, and genetic susceptibility (29, 5).

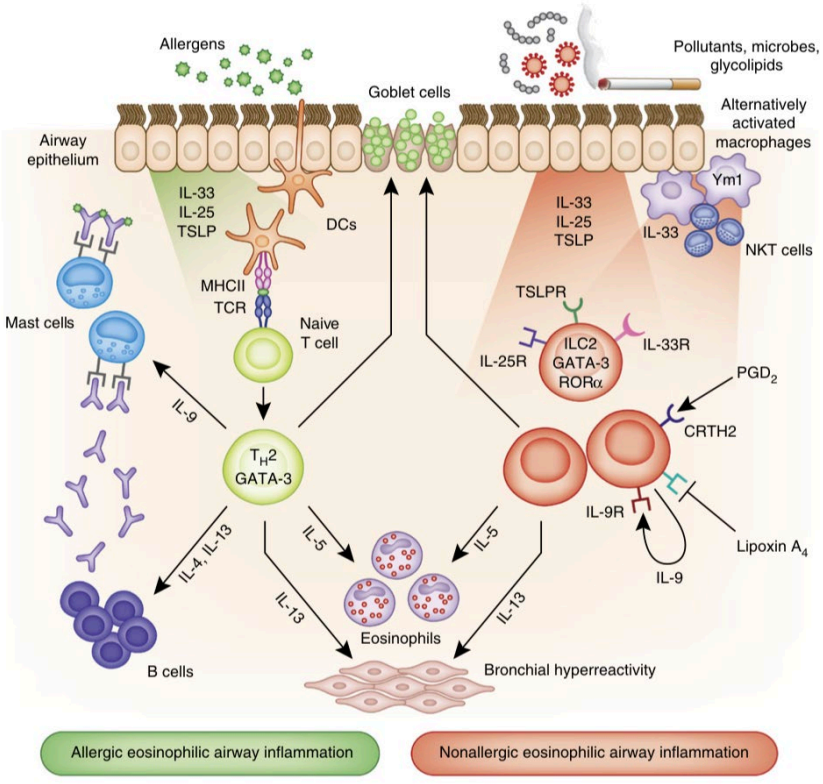

Figure 1. Example downstream effects leading to the pathophysiology of asthma caused by allergens and non-allergens.

Causes of Asthma:

Asthma is a multifactorial disease associated with many different variables that contribute to its severity or phenotype (5). Although there is not a definitive cause that leads to the inflammatory process, research has shown that genetics has a large interplay in its development (26). During the course of development for children, environmental exposures also have a large role due their developing immune system (26). A number of studies have shown the prevalence of asthma increases in adults and children due to smoking or exposure to tobacco smoke (27). Air pollutants such as ozone and particulate matter show decrease in lung function, exacerbation triggering, and increasing rates of hospital stays may be linked to initial asthma development (27). More research is uncovering the causation of obesity and diet's role in the development of asthma. Increasing evidence is relating body mass to the prevalence and incidence of asthma in both children and adults. These same studies and demonstrating that weight loss tends to improve lung function and relieve some symptoms of asthma (27). Studies are also conducted to determine what foods in the diet may lead to asthma yet lack clear evidence or associations (27).

Exposure to microbial substances or infections, especially early in life, may lead to increased risk of developing asthma (5, 27).

Diagnosing Asthma:

Diagnosing asthma is an arbitrary process that does not have a clear measurement test to determine asthma (16). Asthma in children is often presented as being wheezy, although wheezy may mean an obstruction has occurred, but asthma may be contributed to other variables as well (16). Clinicians are held responsible for determining if these episodic symptoms are contributed to asthma (26). Spirometry is often used to asses airflow obstruction and to measure peak flow. Other physical examinations look to find indications of asthma from upper respiratory tract,

abnormal chest sounds form breathing, as well as skin abnormalities (26). Extensive work up for determining that asthma is the underlying cause of symptoms is important, due to other health issues resulting in the physical symptoms instead of asthma (26). Underlying issues such as vocal cord dysfunction, obstructive sleep apnea, and allergic bronchopulmonary aspergillosis may coexist or mimic the symptoms of asthma (26). Once asthma is determined as the cause of symptoms, the clinicians main aim is to maintain the control over the asthma symptoms; yet each patient may respond differently to such treatments (26,16). Differences in asthma severity also complicates diagnosis, as well as different responses in sensitivity to diagnostic tests such as response to bronchodilators or corticosteroids (28). Recent advancements have allowed more accurate diagnosis in regard to measuring exhaled nitric oxide and sputum analysis to identify airway inflammation (28). Other tests such as x-rays, pulmonary function studies for COPD, lung restrictive defect tests, and inspiratory flow tests may be conducted to exclude other underlying issues (26).

Methods:

This review was written with the help of Academic Search Premier, and EBSCOHost for aiding in relevant articles. Hilton M. Briggs library also aided in use of interlibrary loans of material previously inaccessible. Keywords searched in seeking articles included: asthma, asthma treatments, diagnosing asthma, asthma causations, monoclonal antibodies, corticosteroids, leukotriene modifiers, and bronchodilators.

Asthma Treatments:

Due to asthma's multiple routes of inflammation within the respiratory tract has required the development of multiple classes of treatment. Many of these treatments have been proven to be more efficient at treating certain phenotypes of asthma over others, where as other classes are

shown to prevent symptoms for different amounts of time. Each class of drug discussed has different modes of action against asthmas inflammatory response. The classes of drugs discussed in this review include monoclonal antibodies, corticosteroids, leukotriene modifiers, and bronchodilators.

Monoclonal Antibody:

Omalizumab is a monoclonal antibody that binds and inactivates IgE by binding to the FcεRI receptor on mast cells or basophils. As seen on fig. 1, binding of omalizumab to these receptors results in a reduced inflammatory response by inactivating effector cells release of leukotrienes and interleukins. Omalizumab was originally developed for patients six years or older dealing with severe persistent allergic asthma (9, 36). Omalizumab is also found effective for patients with multiple exacerbations, despite daily uses of corticosteroids or long activating beta2-agonist.

A study conducted by Hutyrova on the effects of omalizumab with 310 patients enrolled in a twelve-month study showed a significant reduction in the need of corticosteroids for asthma exacerbations compared to the start of treatment. The prescribed dosage of corticosteroids was reduced by an average of 15% compared to their

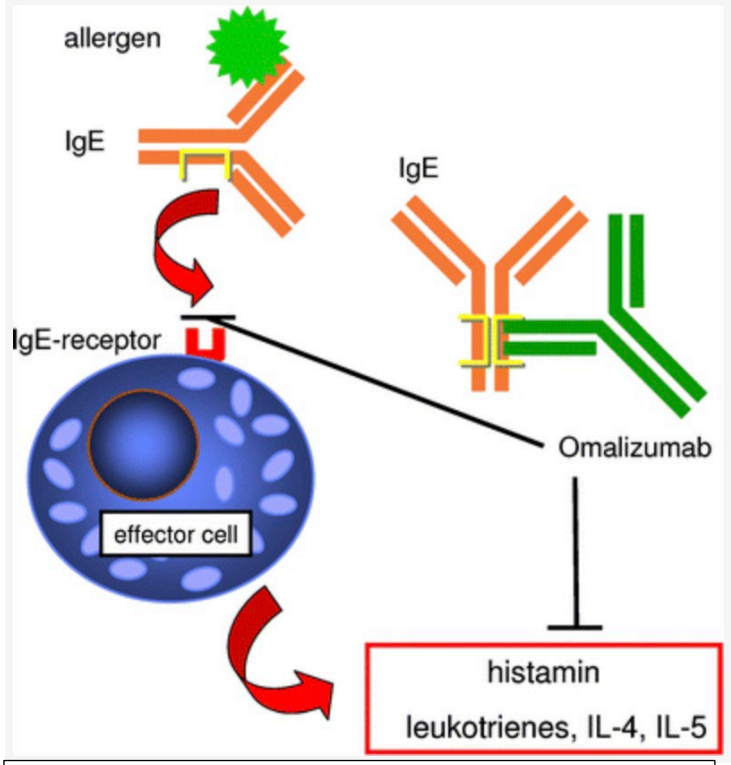

Figure 1. Omalizumab's mode of action taken during an allergen response (36).

baseline averages. Prescribed omalizumab results in an improvement in asthma control, reduction in asthma exacerbations, reduced asthma hospitalizations, and reduced dosage of corticosteroids.

Omalizumab also had effects on patients with allergic rhinitis, atopic dermatitis, and food allergies. In the case of allergic rhinitis, symptoms disappeared in 18.7% and improved in 63.5% of individuals. Individuals with atopic dermatitis experienced resolved symptoms, 5.8% of individuals, and improvement in 46.3% of individuals. Individuals experiencing food allergens gained complete remission in 39.7% and improvement in 27.6% of the studies participants. Indicating omalizumab's capability of reducing overall inflammation responses due to allergies and not just asthmas.

An observational study implemented in Canada revealed similar outcomes to that of Hutyrova. Omalizumab is part of the Canadian asthma protocol, this study aimed to understand the efficacy and safety in its treatment in patients with moderate to severe asthma, as well as the corticosteroid sparing effect of treatment.

Documented patients from the study were prescribed oral corticosteroids (OCS) for daily use or as needed. The majority of these individuals used OCS periodically for exacerbations, while 25% had used them for daily management for their asthma. The mean total OCS dose pre-study was calculated as 2301.5 mg. Completion of the study revealed significant reduction in the prescribed OCS dosage was reduced to a mean total of 1130.0 mg post study. This dosage equated to a 50% reduction in annual OCS dosage as well as enabling 70.8% of patients to either stop or reduce dosage by 40% or more. Asthma control was also found improved with the treatment of omalizumab.

Reduced needs of corticosteroids have many potential benefits to the individuals relying on them to reduce their daily asthma symptoms. Individuals were able to reduce their corticosteroid usage as well as decrease in their potential side effects such as: increased infection risk, hypertension, cataracts, bone density, and diabetes. Canadian study indicates individuals were seen to have an increased life benefit that enabled better self-control of their asthma with omalizumab, as well as aiding in potential health risks associated with corticosteroid usage.

Side effects found tend to be relatively minor with the prescribing of omalizumab. The most common side effects being headache, nausea, fatigue, weight gain, and paresthesia. Only 3.5% of patients in Hutyrova's study discontinued therapy, with no serious side effects (9). In comparison with the benefits of omalizumab, the benefits greatly out-weight the potential side effects.

Corticosteroids:

Inhaled corticosteroids are the first line treatment options for persistent asthma. Corticosteroids work by suppressing the inflammation in the airways of the lungs by binding to the glucocorticoid receptor, repressing inflammatory genes, and reverses histone acetylation. Glucocorticoids have also been found to regulate genes associated with the epithelial barrier and airway remodeling (8, 34). These processes are displayed in fig. 3. An action taken by some corticosteroids is to upregulate the transcription of anti-inflammatory genes such as lipocortin, protease inhibitor, and plasmin activator inhibitors (34). Many corticosteroids work to

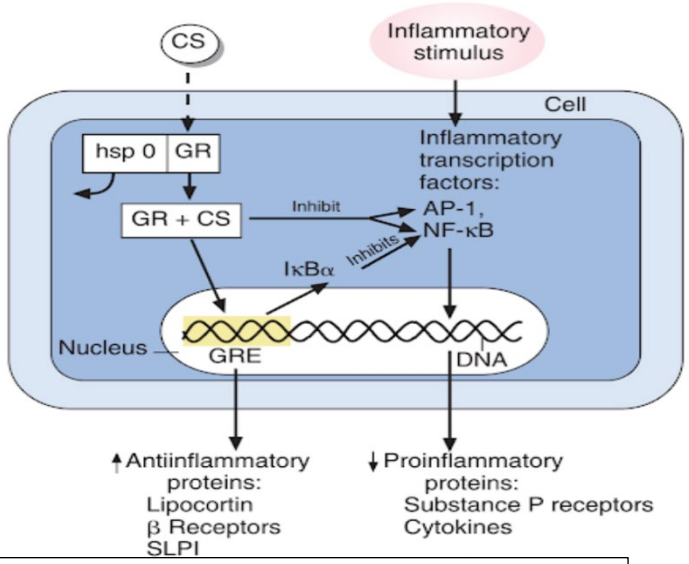

Figure 3. Illustrates the mode of action corticosteroids use on cells of the airway during asthma inflammation.

suppress activator protein 1 (AP1) and nuclear factor-kB (NF-kB) that initiate transcription of inflammatory genes. NF-kB regulates genes for many cytokines seen in asthma responses such as interleukins; chemokines; tumor necrosis factor-α (TNF-α); nitric oxide synthase; and adhesion molecules. Another action is an upregulated expression of NF-kB inhibitors known as nuclear factor protein (IkBα) (34).

Corticosteroids are often administered by two main types, inhaled corticosteroids (ICS) and long-acting B-agonist (LABA) in combination. They are administered via dry powdered inhalers (DPI) or pressurized metered-dose inhalers (pMDIs). The patient preferred choice is inhaled corticosteroid and long acting B-agonist combination (11). Both methods of drug delivery have limitations, such as particle size, flow rate, and loss of dose through exhalation. Today, there are several different types of devices and delivery methods that are currently usable for corticosteroid administration, making it hard to determine which method is appropriate for different asthma responses.

Corticosteroid use was found to have a reduction in daily exacerbations, as well as a reduced need for Montelukast and bronchodilator use (33). This study by Guilbert followed a large group of toddlers through two years of fluticasone used twice daily. Exacerbations were found to be significantly reduced in toddlers using fluticasone during the study. Guilbert's study continued follow ups on these toddlers a year post treatment of fluticasone and discovered exacerbation and symptoms resurfaced after stopping fluticasone use. Guilbert was able to determine that corticosteroid therapy is not a disease modifying treatment for asthma symptoms (33).

A Japanese study conducted by Masato and Kyuya aimed to determine which device should be used for patients with specific asthma characteristics such as drug benefits, side

effects, and patient preferences. The study utilized two different delivery methods, DPIs and pMDIs, that delivered the same amount of salmeterol/fluticasone preparation combination (SFC). The drug of choice known as (Adoair) is available in both types, Adoair DPI (Diskus) and Adoair pMDI (Aerosol) and was administered in the same dosage.

It was found that patients preferred to use pMDI 44%, while 29.4% preferred to use the DPI. This was most likely correlated due to patients referring hoarseness, throat irritation, and throat discomfort as a major side effect of DPI. Masato's study indicates aerosol as the preferred method amongst patients, as well as the method most likely to be used. Masato's study illustrated that prescribing pMDI may be preferred but may be limited to patients with different severities of asthma (11).

Leukotriene modifiers:

Leukotriene modifiers are recommended for patients with moderate to severe persistent asthma. They work by reducing bronchoconstriction and have anti-inflammatory effects (8). Leukotriene modifiers are grouped into two categories: cysteinyl LT1 receptor antagonists and 5-lipooxygenase pathway inhibitors. These classes of drugs target cysteinyl leukotrienes (cysLTs) as well as other leukotrienes (LTA4, LTB4, LTC4, LTD4 and LTE4) which are created through 5-lipoxygenase pathway and expressed during many types of activated inflammatory cells during allergic airway inflammation. Each leukotriene may be expressed more some individuals than others which may induce different pathophysiological responses patient to patient (12).

The 5-lipooxygenase pathways results in the creation of the LT classes: LTA4, LTB4, LTC4, LTD4, and LTE4. The pathway is normally limited to the myeloid cells: neutrophils, eosinophils, monocytes/macrophages, mast cells and B lymphocytes. LTs LTC4, LTD4, and LTE4 are generally produced in alveolar macrophages, eosinophil epithelial cells and vascular endothelial cells in the airways and the lungs. The creation of these proteins act upon the LT receptors present on cell membranes. As seen on fig. 4 below, LTB4 activates LT B-receptor (BLT), CysLT activates CysLT receptors 1 and 2 which are G-protein coupled proteins expressed in monocytes, macrophages, eosinophils, basophils, mast cells T cells, smooth muscle cells and vascular endothelial cells. The activated CysLTs are the most potent airway constrictor muscles known. CysLT also acts with granulocyte macrophage colony stimulating factor, known as Interleukin - 5, to cause growth of progenitor cells. CysLTs also illicit the proliferation of lung fibroblasts leading to progressive loss of lung function in chronic asthma. CysLT receptor antagonism also affects the anti-remodeling effects in the airways, and inhibitory effects on airway structural cells that remodeling airway inflammation in asthma patients. LTB4 is the strong chemotactic inflammatory seen in asthma exacerbations in patients with severe asthma (13).

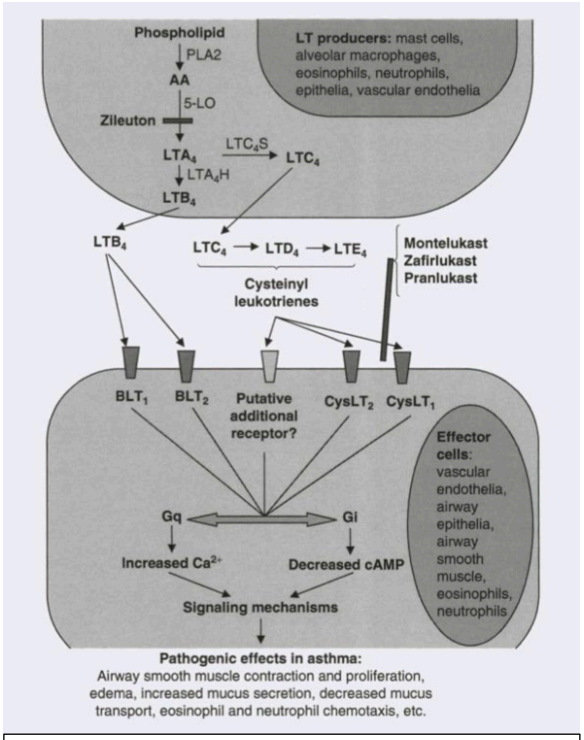

Figure 4. Illustrates the mode of action of Montelukast, Zafirlukast, Pranlukast, and Zileuton (13).

LT modifiers used in clinical practice for asthma treatment are seen on table 1. This table includes two different groups including leukotriene receptor antagonists (LTRA): pranlukast,

Table 1. Lists Montelukast, Pranlukast, Zafirlukast, and Zileuton; commonly used Leukotriene modifiers in the treatment of asthma (15).

Drug	Montelukast	Pranlukast	Zafirlukast	Zileuton
Target	CysLT1 receptor	CysLT1 receptor	CysLT1 receptor	5-LO inhibition
Dosing	Adults: 10 mg Children 6–14 y: 5 mg Children 2–5 y: 4 mg	Adults: 225 mg bid	Children ≥12 y and adults: 20 mg bid Children 5–11 y: 10 mg	Adults and children 12 y and older: 600 mg qid
Half-life	2.7–7 h	3–9 h	10 h	2.5 h
Indications	In asthma and allergic rhinitis; as controller therapy in children with mild persistent asthma; particularly effective in exercise-induced asthma, ASA, allergen-induced asthma; as add-on therapy with ICS	In asthma and allergic rhinitis; mostly effective in exercise-induced asthma, ASA, allergen-induced asthma; as add-on therapy with ICS	In asthma; particularly effective in exercise-induced asthma, ASA, allergen-induced asthma; as add-on therapy with ICS	In asthma, particularly effective in exercise-induced asthma and ASA

5-LO = 5-lipooxygenase; **ASA** = aspirin-sensitive asthma; **bid** = twice daily; **CysLT1** = cysteinyl leukotriene 1; **ICS** = inhaled corticosteroids; **qid** = four times daily.

zafirlukast, and Montelukast and a second group being a LT biosynthesis inhibitor zileuton. The modes of action of these drugs are shown on fig. 4. Montelukast, pranlukast, and zafirlukast work by inhibiting the binding of cysteinyl leukotrienes, LTC4, LTD4, and LTE4 from binding to the CysLT1 receptor of many airway effector cells. Zileuton, a LT biosynthesis inhibitor, works by blocking the 5-lipooxygenase pathway, as illustrated in fig. 4. Zileuton's blocking mechanism prevents the production of LTA4, LTB4, and LTC4 that initially bind to effecter cell receptors and produce the physiological symptoms presented in asthma.

Montelukast studies reveal exacerbations reduced to half 50% along with a reduction of 24% in B2 agonist use. Montelukast studies revealed that children proved to adhere better with the oral does than inhaled corticosteroid. Parents found Montelukast favorable in terms of ease of use due easy administration and taste in the use of children (15).

Pranlukast has a mixture of results from different studies (32,15). Pranlukast's mode of action is shown in fig. 4. Study done by Morita determined pranlukast was only associated with reduced asthma exacerbations in one to five-year-olds. Older age groups experienced no

significant reduction in exacerbations during the trial (32). The differences in age groups is difficult to explain yet may have to do with the number of viral infections occurring in the younger age groups (32).

Zafirlukast has been a heavily studied drug in its effects as an asthma preventer. Zafirlukast has been shown to greatly improve asthma symptoms with regards to fewer nighttime interruptions, reduced daytime symptoms, and less albuterol use in adults. Children also experience a benefit of Zafirlukast use, with improvements at lower ranged dosages. These benefits included larger expiratory flow rates in the morning (28%) and evening (41%), fewer rescue medications, fewer night awakenings, and 28% reduced B2 agonist use. Quality of life was determined to be improved by 18% (15).

Zileuton inhibits 5-lipooxygenase, it is then thought that the complex forms with the enzymes iron molecule in the active site. This follows the inhibition of the neutrophil production of LTA4, LTB4, and LTC4 with an efficiency of 80% (14). This allows long term control of asthma and may prevent exacerbation with the help of prednisone treatment. Zilueton is also the only known drug that can confirmed efficacy in preventing airway obstruction induced by aspirin allergens and NSAIDS.

Analysis has shown that CysLT receptor antagonist are generally less effective than inhaled glucocorticoids, but there remains a large gap between effectiveness amongst individual patients with asthma. There is no known regimen that will determine which individual will respond better to which treatment. Additional treatment with glucocorticoids and CysLt receptor antagonists shown an improved asthma control with a lowered dosage use of glucocorticoids (12).

Normally, LTRA's are taken without much difficulty, however, some adverse effects may occur. These affects normally range from headache, abdomen pain, rashes, nausea, arthralgia, tremors, depression, and suicidal thinking. However, LTRA's improved pulmonary function and increased baseline forced expiratory volume, as well as increased peak expiratory flow. This questionnaire held at the end up the trial concluded that individuals experienced an increased quality of life with reduced asthma exacerbations. This has led to the favorability of LTRA as an alternative first-line treatment for mild asthma in children (12).

Bronchodilators:

Bronchodilators, a commonly used treatment for asthma, act as predictors of future lung function. Poor bronchodilator response (BDR) has been researched to show poor asthma control and is used to identify individuals at risk of poor asthma outcomes (17). Bronchodilators work as beta$_2$-agonists, or adrenergic agonists, that relax the smooth muscle of the airway, helps to increase muco-ciliary clearance, reduce mediator releasing from mast cells and basophils, and can decrease the permeability of the lung's vasculature (21).

beta$_2$-agonists therapy can be utilized via aerosol or inhaled methods and has been comparable to oral methods. These methods have also shown to have reduced side effects compared to oral medications. Most beta$_2$-agosnists have limited durations, normally four to six hours and considered short acting, some lasting more than twelve hours and classified as longer acting. Longer acting beta$_2$-agosnists are used for allergen-induced asthmatic response or histamine-induced responses (21). Whereas shorter acting beta$_2$-agonists are the leading therapy choice for acute exacerbations and exercise induced asthma. Short acting beta$_2$-agosnists are often used as a

regularly scheduled control over asthma, yet as been proven to decrease the control of asthma and should be kept to a minimum.

Beta-adrenoreceptors exist in activated or inactivated forms, activation requires the association of the alpha subunit of a G-protein and guanosine triphosphate (GTP). Cyclic adenosine monophosphate (cAMP) is produced from ATP, reduces the affinity of the alpha subunit to the receptor, and induces smooth muscle cell relaxation. The mechanism of smooth muscle cell relation from cAMP is not completely understood yet is thought to result from the activation of protein kinase A and phosphorylation of proteins involved in muscle tone control. Little evidence has shown cAMP to inhibit the cells intracellular stores of calcium and preventing the airway smooth muscle from relaxing (22). $Beta_2$-antagonits bind with high affinity for the inactivated form of beta-adrenoreceptor and moves the equilibrium away from the activated form (22).

Salbutamol, also known as albuterol, is a very common bronchodilator. Salbutamol works by selecting binding to and activating beta2 adrenergic receptors and the surface of cells. This elicits an inflammatory response primarily seen on CD4 cells, but also on leukocytes with beta2 receptors, such as macrophages, monocytes, Langerhans cells. Binding of beta2 receptor agonist inhibits inflammatory gene expression of IL2 and interferon gamma (23). Salbutamol increases PEF up to 90% after inhalation yet returns to nearly baseline after only six hours. Indicating it has a very short duration as expected with beta2 antagonists (24).

Salmeterol, also known as Serevent, is used a longer acting bronchodilator as compared to salbutamol (24). Salmeterol's smooth muscle relaxation of the airway is accompanied by a slow onset yet long duration. The long duration is attributed to Salmeterol binding to the $Beta_2$-adrenoreceptors active site, as well as binding to a saligenin moiety of a different site (30).

Salmeterol has been proven to increase peak expiratory flow, as well as increased FEV and airway responsiveness when compared to that of placebos in study (25). Salmeterol has a more prolonged peak flow when compared to salbutamol by several hours, making it a longer acting medication (24).

Anticholinergics, such as ipratropium bromide, act by reducing intrinsic vagal tone in the lung's airways upon inhalation working to block post-ganglionic efferent pathways. Their effects in controlling asthma symptoms are similar to that of beta$_2$-agonists and are normally prescribed together (31). Anticholinergics target M1, M2, and M3 muscarinic receptors responsible for binding acetylcholine (38).

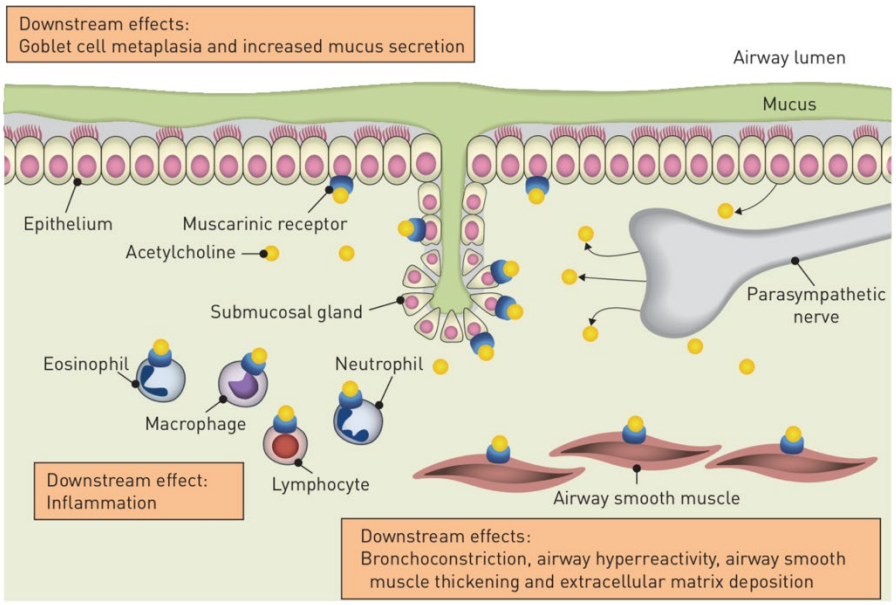

Figure 5. Summary of acetylcholine's effect in the pathophysiology of asthma. Binding of acetylcholine to the muscarinic receptors triggers the downstream effects of asthma (35).

Acetylcholine is the primary neurotransmitter in the airway, binding to the epithelial cells, smooth muscle cells and submucosal glands within the airway. As seen in fig. 5, binding of the muscarinic receptors leads to a downstream effect of airway symptoms such as: Broncho restriction, airway hyperreactivity, smooth muscle thickening, and extracellular matrix deposition (35). The combination of anticholinergics and beta$_2$-agosnists has been established to have greater bronchodilation than each agent alone (31). Anticholinergics often have a delayed

reaction time after administering or overall reduced effect yet can have a more positive effect if taken with a $beta_2$-agosnist (21).

A longer acting anticholinergic tiotropium bromide has been shown to increase lung function, asthma control, and decrease exacerbations. Studies have shown tiotropium bromide to be well tolerated and safe. Studies have shown to have increased FEV_1 by 102 mL, as well as decreasing the number of exacerbations compared to those on placebos (18).

Conclusion:

In conclusion, there is a wide variety of treatments to control the symptoms of asthma. The clinician's role is vital in ensuring the proper medications are administered to better aid the patient in their fight over asthma. This emphasizes the need for continued research into the process of development as well as the prevention of asthma and its symptoms. Today's use of monoclonal antibodies, corticosteroids, leukotriene modifiers, and bronchodilators have increased the daily living of individuals affected by asthma. Each class of medication has its function in controlling different phenotypes of asthma and therefore limits itself to asthmas broad spectrum of inflammation. Asthma research has provided victims symptom relief that specifically targets their inflammation, allergic or non-allergic. Clinicians are able to determine the best treatment plans for individuals centered around their physiologic disruptions attributed form asthma. This has enabled individuals to receive treatment that not only works to control their symptoms, but also allows them to take their medication at their level of comfort and need.

Implications:

This review exemplifies the diversity of asthma control methods as well as the multitude of physiological pathways asthma uses to inflict symptoms onto the human body. This review also illustrates how certain medications are used to control such symptoms. Research into

asthma's diverse physiological pathways utilized to induce symptoms demands the development of specific medications for better asthma management and control.

Limitations:

Asthma elicits a multitude of effects on the human body, this review was limited to the most common methods used to treat asthma. This review is also limited towards the development of asthma, as its development can largely be multifactorial. Treating each patient may require more than the described medications as mentioned above.

Future Research:

Future asthma research has many avenues to continue its understanding of asthma. Different medications that have greater control over asthma as well as reduced side effects would make large strides towards improving daily conflicts confronted with its victims. Many medications are aimed at the control of symptoms, as well as prevention of exacerbations caused by asthma. Research into preventing the overall cause of symptoms while preventing asthma symptoms from ultimately occurring is greatly needed. Once these are discovered, the overall prevention of asthma can occur.

References:

1 C. Francisco, Effects of physical exercise training on nocturnal symptoms in asthma: Systematic review. *PLoS ONE*. 1(18) (2018).

2 M. Harvey, Evidence-Based Asthma Control Assessments in Pediatric Care. *Pediatric Nursing*. 44(4):163-168 (2018).

3 V. Marsh, Asthma in children. *Practice Nurse*. *47*(8): 22–26 (2017).

4. S. Yanagisawa, Definition and diagnosis of asthma–COPD overlap (ACO). *Allergology International*. 67(2):172-178 (2018).

5. M. Edwards, The microbiology of asthma. *Nature Reviews Microbiology*. 10(7):459-471 (2012).

6 C. Loureiro, Omalizumab for Severe Asthma: Beyond Allergic Asthma. *BioMed Research International*. 1(10) (2018).

7 A. Arabkhazaeli, Patterns of topical corticosteroids prescriptions in children with asthma. *Pediatric Dermatology*. 35(3):378-383 (2018).

8 N. Farzan, Pharmacogenomics of inhaled corticosteroids and leukotriene modifiers: a systematic review. *Clinical & Experimental Allergy*, 47(2):271-293 (2017).

9 B. Hutyrová, The effect of omalizumab treatment on severe allergic asthma and allergic comorbidities: Real-life experience from the Czech Anti-IgE Registry. *Postępy Dermatologii I Alergologii.. 35*(5): 510-515 (2018).

10 M. Bhutani, Real world effect of omalizumab add on therapy for patients with moderate to severe allergic asthma: The ASTERIX Observational study. *PLoS ONE*, *12*(8): 1–13 (2017).

11 M. Muraki, Which inhaled corticosteroid and long-acting β-agonist combination is better in patients with moderate-to-severe asthma, a dry powder inhaler or a pressurized metered-dose inhaler? *Drug Delivery*, 24(1):1395-1400 (2017).

12 P. Montuschi, Leukotriene modifiers for asthma treatment. *Clinical & Experimental Allergy*, 40(12):1732-1741 (2010).

13 C. Dumitru ,Role of Leukotriene Receptor Antagonists in the Management of Pediatric Asthma. *Pediatric Drugs*, 14(5):317-330 (2012).

14 K. McGill, Zileuton. *Lancet*, 348(9026):519-524 (1996).

15 L. García-Marcos L, Benefit-Risk Assessment of Anti-leukotrienes in the Management of Asthma. *Drug Safety*, 26(7):483-518 (2003.

16 J. Wever-Hess, Prognostic characteristics of asthma diagnosis in early childhood in clinical practice. *Acta Paediatrica*, 88(8):827-834 (1999).

17 S. Carlson, Self-reported racial/ethnic discrimination and bronchodilator response in African American youth with asthma. *PLoS ONE*, 12(6):1-13 (2017).

18 G. Rodrigo, Efficacy and safety of tiotropium in school-age children with moderate-to-severe symptomatic asthma: A systematic review. *Pediatric Allergy & Immunology*, 28(6):573-578 (2017).

19 J. Su, Feasibility of Deploying Inhaler Sensors to Identify the Impacts of Environmental Triggers and Built Environment Factors on Asthma Short-Acting Bronchodilator Use. *Environmental Health Perspectives*, 125(2):254-261 (2017).

20 M. Pollock, Inhaled short-acting bronchodilators for managing emergency childhood asthma: an overview of reviews. *Allergy*, 72(2):183-200 (2017).

21 'Establish Medication Plans for Chronic Management'. *Clinical & Experimental Allergy*, 22:28–39 (1992).

22 M. Johnson, Beta$_2$-adrenoreceptors: mechanisms of action of beta$_2$-agonists. *Pediatric Respiratory Reviews*, 2(1):57-62 (2001).

23 H. Uzkeser, Anti-Inflammatory and Antinociceptive Effects of Salbutamol on Acute and Chronic Models of Inflammation in Rats: Involvement of an Antioxidant Mechanism. *Mediators of Inflammation*. 1(10) (2012).

24 A. Ullman, Salmeterol, a new long acting inhaled Beta2 adrenoceptor agonist: comparison with salbutamol in adult asthmatic patients. *Thorax*, 43(9). (1988).

25 R. Simons, A comparison of beclomethasone, salmeterol, and placebo in children with asthma. *The New England Journal of Medicine,* (337): 1659-1665. (1997).

26 Expert panel report t3 (EPR-3): guidelines for the diagnosis and management of asthma-summary report (2007).

27 E. Waltraud, The asthma epidemic. *The New England Journal of Medicine*, 355(21): 2226-2235. (2006).

28 A. Smith, Diagnosing Asthma Comparisons between exhaled nitric oxide measurements and conventional tests. *ATS Journals,* 169(4). 2004.

29 B. Lambrecht, The immunology of asthma. *Nature Immunology,* 16(1): 45-46. (2015).

30 M. Cazzola, Clinical pharmacokinetics of salmeterol. *Clinical pharmacokinetics*, 41(1). (2002).

31 J. Donohue, Efficacy and safety of ipratropium bromide/albuterol compared with albuterol in patients with moderate-to-severe asthma: a randomized controlled trial. *BMC pulmonary Medicine,* (2016).

32 Y. Morita, Pranlukast reduces asthma exacerbations during autumn especially in 1-5- year-old boys. *Asia Pac Allergy*, 7(1): 10-18. (2017).

33 T. Guilbert, Long-term inhaled corticosteroids in preschool children at thigh risk for asthma. *The new England journal of medicine*, 354: 1985-1997 (2006).

34 D. Gardenhire, Rau's Respiratory Care Pharmacology-E-Book. Elsevier Health Sciences, (2015).

35 R. Gosens, The mode of action of anticholinergics in asthma. *Eur Respiir J,* (52) (2018).

36 M. Volkmar, Omalizumab: Anti-IgE therapy in allergy. *Current allergy and asthma reports* 11(2): 101-106. (2011).

Acknowledgements:
The author of this review would like to thank Dr. Tylor Johnson for his time in reviewing this paper and all of his corrections, suggestions, and help. The author would additionally like to thank Dr. Greg Heiberger and fellow peers for their support.

Funding:
The author did not receive any funding for this work

Competing interests:
The author declares no competing interest.

Data and materials availability:
All data is available in the main text or supplementary materials.

Appendix A
Citations for "A Review of Asthma Treatments: Monoclonal Antibody, Corticosteroid, Leukotriene Modifier, and Bronchodilator" were cited in AMA format.

Appendix B
The external reviewer for this review was Dr. Tylor Johnson a microbiologist for the FDA. His help was greatly needed in making the corrections required for this paper. Dr. Johnson was exceptionally keen at determining which areas of this review required more attention.