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### Pharmacotherapy of Asthma

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Submitted February 9, 2007; accepted April 23, 2007; published October 15, 2007.

The pharmacotherapy of asthma is a complex and evolving topic. A detailed understanding of the pathophysiologic processes involved in the asthmatic response forms the basis for understanding the actions of drugs used to treat this condition. Likewise, a solid comprehension of the medicinal chemistry and pharmacologic properties of the numerous agents involved in the treatment of asthma is critical for rationalizing drug choices and understanding potential side effects. Asthma is addressed at several points in the PharmD curriculum at South University including in the *Pathophysiology* (quarter 2), *Integrated Sequence III* (quarter 6), and *Critical Care* (quarter 9) courses. Various teaching strategies are employed throughout, along with weekly case-based recitations. The content presented here includes a synopsis of the pathophysiology and pharmacology from our *Integrated Sequence III* block on inflammatory diseases and asthma. A short review of pertinent pathophysiology is followed by a detailed presentation on the various classes of asthma drugs which includes their chemistry, mechanism of action, pharmacokinetics, toxicity, and interactions. This presentation is designed to prepare students for asthma therapeutics, which follows next in the schedule. The complexities of asthma pharmacotherapy are stressed along with current controversies and future drug development.

**Keywords:** asthma, pharmacotherapy, pathophysiology, pharmacotherapy

## INTRODUCTION

Asthma is a chronic disease of the airways that is characterized by exacerbations of significant bronchospasm and marked airway inflammation. In the United States alone there are nearly 20 million individuals who have been diagnosed with asthma and approximately half are children. According to reports from the Centers for Disease Control (CDC), the incidence of asthma and asthma-related mortality and morbidity in the US increased significantly during the period from 1980-1998.<sup>1</sup> During this time, the number of work and school days lost to asthma-related events rose by 50%.<sup>1</sup> The yearly cost of asthma on the US healthcare system in 1990 was estimated at 6.2 billion dollars.<sup>2</sup> By 2000 the estimated cost had doubled.<sup>3</sup> While the overall costs of emergency room visits and hospitalizations for asthma patients appears to have decreased somewhat in recent years, the cost of medications for the treatment of asthma has increased significantly. As future practitioners, it is important that PharmD students not only understand the

pathophysiology and therapeutics of asthma but also have an appreciation for the personal, medical, and economic burden of asthma on society.

In the PharmD program at South University, students are exposed to the disease of asthma at several points in the curriculum. Several hours of detail on the pathogenesis and pathophysiology of asthma are presented to students in quarter 2 during *Pathophysiology 2* (first-professional year) contained in this manuscript is presented to students in the *Integrated Sequence 3* (quarter 6) where students are taught the medicinal chemistry and pharmacology of asthma drugs followed closely by asthma therapeutics. The *Integrated Sequence (IS)* begins in quarter 2 in the first-professional year of the programs and runs through quarter 9 (third-professional year). Each *IS* module focuses on diseases related to a particular organ system and contains material on the medicinal chemistry, pharmacology, and therapeutics of drugs used in those disease states. The particular lectures represented here are mainly focused on the pharmacology of asthma drugs. Selected areas of asthma pharmacotherapy such as status asthmaticus are reinforced and expanded upon in the *Integrated Sequence VI* when students are exposed to critical care topics. The medicinal chemistry, pharmacology, and therapeutics of key classes of drugs used to treat asthma, such as adrenergic agonists and corticosteroids,

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are likewise reinforced at several other points in the curriculum, namely, when material is presented on inflammation (quarter 3), the autonomic nervous system (quarter 4), and immunosuppression (quarter 9).

## INSTRUCTIONAL METHODS

From 2004-2007, a number of different instructional strategies were used to convey information on asthma pharmacotherapy to students, with emphasis on making the presentation interesting and interactive. A significant portion of the basic information regarding asthma pathophysiology, and drug pharmacology and medicinal chemistry was delivered to students using PowerPoint presentations. Although students were given the presentations before coming to class, an effort was made to keep these presentations in outline form with many pieces of information left intentionally blank in the presentation for students to fill in from the class presentation or from their assigned readings. The missing information was usually no more than a simple bullet point so that students did not become preoccupied copying information from the slides. Also embedded within the presentation were numerous questions related to a particular aspect of asthma that students could discuss and answer as part of our group discussion during class time. Review questions were also embedded in the presentation that required students to apply information they had learned in recent presentations to the current material.

Case studies were a significant component of the classroom presentation both in the pathophysiology and pharmacology classes the author teaches on asthma. In *Pathophysiology* (quarter 2), the in-class case studies tended to focus more on the disease state and its manifestations since students had not yet received detailed information about drugs. However, since the pathophysiology lays the groundwork for pharmacology and therapeutics, the rationale for using certain classes of drugs for treating asthma was stressed without going into great detail on the specific drugs. The in-class case studies in pharmacology *Integrated Sequence III*, (quarter 6) were more complex and could cover the pathophysiology, pharmacology, and medicinal chemistry of asthma drugs. Case-based questions related to asthma also regularly appeared on examinations throughout *Pathophysiology* and the *Integrated Sequence*.

Within the *Integrated Sequence* block at South University, there was a built-in 3-hour weekly recitation that could be used for formal case study. During this recitation, students were broken into small groups of 6-8 students. Each group was led by a faculty member who served mainly as the facilitator. In groups, students received a detailed case study that they were expected to work on for 1 to 1½ hours. During this time, the student groups work

independently of the facilitator. The group was expected to develop and prioritize a problem list for their patient, generate a list of additional data needed, assess the problems they have identified, and develop a plan for addressing those problems. In the second half of the recitation, the facilitator led the discussion of the case and questioned the students regarding their assessment of the case. Each facilitator received a detailed "case key" that contained major points within the case that students from each group should have addressed. Case keys provided a high degree of consistency between groups and eliminated the requirement that facilitators be content experts. Included in these case keys were a clear set of objectives for that session along with major points that students and facilitators needed to cover during their discussion of the specific case. Students were graded individually on their answers to the facilitator's questions as well as on the case-write up they submit at the end of the session. Each facilitator received an itemized grade sheet for his/her group that awarded points to individual students based on: (1) their ability to define pertinent problems and issues with the patient; (2) how well they integrated and synthesized information presented within the case; (3) their ability to report information in a clear, concise manner; (4) the students ability to work effectively within the group; and (5) the completeness of their final written patient care plan. Final recitation grades were reviewed by the course coordinators to ensure a level of consistency.

Throughout classes a number of various review techniques were used such as "mind-mapping" exercises. In a mind-mapping exercise a central concept such as "asthmatic response" is written in a center box on the blackboard, the students were encouraged to call out any factors related to the asthmatic response. These related factors were then written on the board around the central concept and associations and further details were fleshed out for each. Arrows and connectors were used to relate the various components that contributed to the asthmatic response in an orderly and logical fashion. A second exercise involved the use of crossword puzzles that contained definitions of pertinent terminology or drug mechanisms that students could fill out.

Student knowledge of the subject matter related to asthma was assessed in several ways. Comprehensive two-hour examinations were given that included questions on the pathophysiology, medicinal chemistry, pharmacology and therapeutics of asthma and asthma drugs. Exams often contained integrated case-based questions that required students to apply their knowledge of asthma to various aspects of the disease and its treatment. During the 3-hour recitation session students were also given detailed grades on their participation and answers to case

study questions. A portion of the student grade from recitation also came from the submission of their formal case write-up. In-class quizzes were also frequently used to gauge student comprehension of subject matter while homework assignments were used to reinforce their understanding and application of the material. Finally, a capstone examination is administered to students in their final year which contains questions related to the pathophysiology, pharmacology, medicinal chemistry and therapeutics of asthma and asthma drugs. The effectiveness of the course materials and instructors was assessed through detailed course evaluations conducted during the last week of regular classes. These evaluations addressed the overall effectiveness of the class organization and instructors as well as the extent to which the course addressed the educational outcomes listed in the syllabus. In addition, we have conducted formal focus groups with students from the Integrated Sequence block to assess various parameters of the course. Peer evaluations are also used at South University to gauge and improve teaching effectiveness.

### Course Content

**Asthma Pathophysiology.** Exacerbations of bronchial asthma present with 2 key features: episodic airway obstruction and marked airway inflammation. While the exact etiology of asthma is still unknown, it is clearly multifactorial involving possible genetic predisposition(s) coupled with exposure to certain environmental triggers (Figure 1). Asthma triggers may be divided into 2 categories: “inflammatory triggers” and “bronchospastic” triggers. While all asthma patients do not respond equally to the same asthma triggers, most patients do experience 2 clear phases of the asthmatic response when exposed to a particular trigger, the “early” phase and the “late” phase. The “early” phase of the asthma response usually occurs 10-30 minutes following exposure to an asthma trigger and involves the release of inflammatory mediators from IgE-coated mast cells throughout the respiratory passages (Figure 2). These

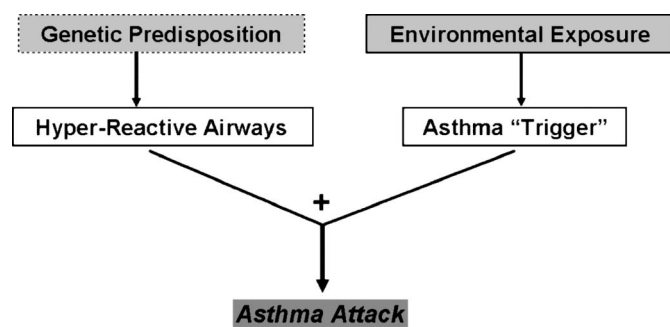


Figure 1. The etiology of asthma.

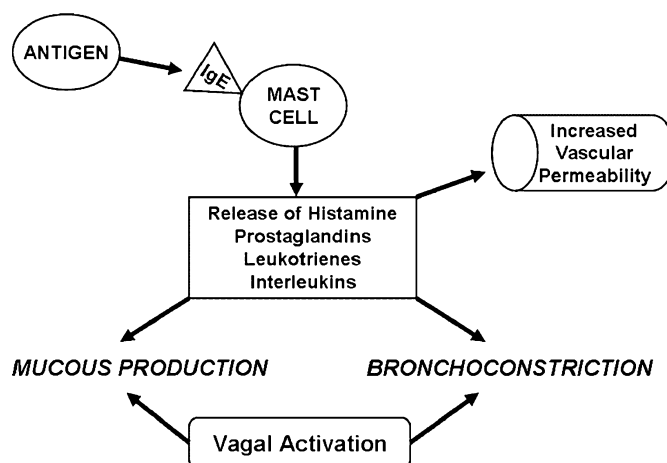


Figure 2. Components of the early phase of asthma.

inflammatory mediators include histamine, prostaglandins, leukotrienes, and interleukins. These mediators induce bronchospasm and increase permeability of the airways to antigen. Vascular permeability and mucus secretion is also increased. Abnormal activation of the parasympathetic nervous system also seems to occur during the early phase of the asthmatic response. Activation of vagal nerves in the airway constricts bronchial smooth muscle and increases secretions from mucous-producing cells.<sup>4</sup>

Toward the end of the early phase of asthmatic response (3-8 hours), airway inflammation becomes more prominent.<sup>5</sup> Neutrophils, attracted by chemotaxis to the area of inflamed airway, leave the more permeable blood vessel and enter the respiratory tissues. Neutrophils are joined by other inflammatory immune cells such as basophils, and eosinophils that escalate the inflammatory response by releasing their own inflammatory mediators. T-lymphocytes may also play an important role in the asthmatic response since a particular subset of T-lymphocytes (T<sub>H</sub>2) responds to environmental allergens by releasing cytokines that are involved in the formation of IgE-producing plasma cells.<sup>6</sup> This heightened period of inflammation constitutes the “late” phase of asthma response and can last for hours to days (Figure 3). The heightened airway inflammation that occurs during the late phase of asthma leads to marked airway edema, impaired mucociliary function, and further impaired movement of airflow. If severe or prolonged, the inflammation associated with asthma can damage respiratory epithelium and lead to a pathologic remodeling of the airways.<sup>7</sup>

**The Pharmacology of Asthma Drugs.** The rational for asthma pharmacotherapy centers on 2 main areas: reversal or prevention of bronchial smooth muscle constriction and reversal or prevention of airway inflammation. Table 1 provides an overview of current drugs used for the treatment of asthma. Early medical descriptions of asthma

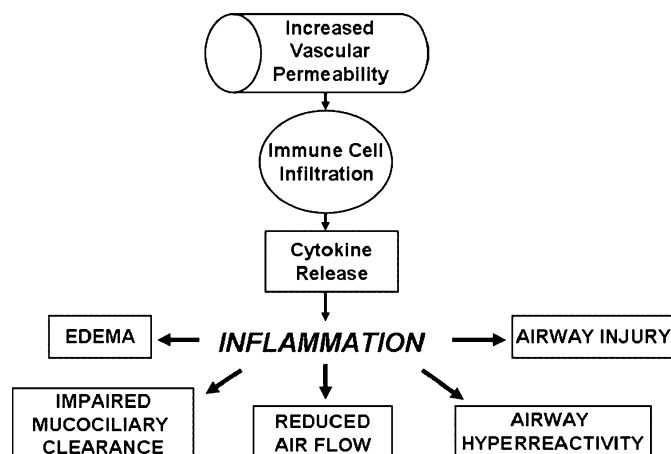


Figure 3. Components of the late phase of asthma.

and asthma treatment first appear in the literature in the mid to late 19th century. While our understanding of asthma pathogenesis has expanded greatly in recent decades, our clinical approach to its treatment has changed very little in the past quarter century. In the early 1900s, anticholinergic agents were the mainstays of asthma pharmacotherapy. Atropine- and belladonna-containing compounds were injected, formulated as inhaled powders or even incorporated into belladonna-containing “asthma cigarettes.” While “coffee” was cited as a poten-

tial treatment for asthma in a 1914 medical text, it was not until the early 1940s that the methylxanthines (theophylline, aminophylline) were first cited as being effective for the treatment of asthma when administered intravenously.<sup>8</sup>

One of our current mainstays for asthma pharmacotherapy, adrenergic agonists, were first given in the early 1900s to asthma patients as adrenal extracts.<sup>9</sup> The use of crude extracts was soon followed by the parenteral administration of epinephrine. Oral and inhaled adrenergic agonists such as epinephrine, isoproterenol, and ephedrine remained the mainstay of asthma pharmacotherapy until the specific subtypes of  $\beta$  receptors were identified in the late 1960s. The obvious drawback to these early agents was their lack of receptor specificity, which leads to a number of serious side effects through  $\beta_1$  and even  $\alpha$  receptor activation. Specific inhaled  $\beta_2$  agonists then became agents of choice for the treatment of asthma. Their main drawback was a relatively short duration of action, a limitation that has been addressed with the recent advent of highly lipid-soluble, long-acting inhaled agents like salmeterol with extended durations of action.

Specific  $\beta_2$  agonists exert their beneficial effects through relaxation of bronchial smooth muscle (Figure 4). These agents bind to G-protein-linked cell surface

Table 1. Overview of Current Asthma Drugs

Drug	Mechanism of Action	Uses	Potential Adverse Effects
$\beta_2$ Agonists (albuterol, salmeterol)	Relaxation of bronchial smooth muscle	Long-acting inhaled forms for moderate to severe asthma	Skeletal muscle tremor, tachycardia, tolerance?
Corticosteroids (beclomethasone, budesonide)	Broad antiinflammatory actions	Mild, moderate persistent asthma by inhaler  Orally for severe asthma	Cough, oral candidiasis, Systemic effects: growth suppression, adrenal suppression, osteoporosis
Methylxanthines (theophylline)	Relaxation of bronchial smooth muscle, effects on eosinophils & T-cells, $\uparrow$ mucociliary clearance	Secondary choice in mild to moderate persistent asthma	Dose-dependent cardiac stimulation, CNS stimulation, gastric upset, weak diuresis
Cromolyn, Nedocromil	Inhibit release of inflammatory mediators	Mild persistent asthma	Cough, dryness, unpleasant taste. Rare dermatitis and myositis
Leukotriene Modifiers (zafirlukast, montelukast)	Antagonize the actions of the leukotrienes in the airways	Secondary choice in mild to moderate persistent asthma	Minor G.I complaints, headache, nausea
Muscarinic Antagonists (ipratropium)	Muscarinic blockade in airways	Acute treatment of severe exacerbations with a $\beta_2$ agonist	Anticholinergic effects
Monoclonal Antibodies (omalizumab)	Block IgE binding to mast cells	Patients with refractory severe asthma with IgE-mediated sensitivity	Injection site reactions drug antibodies increased malignancies?

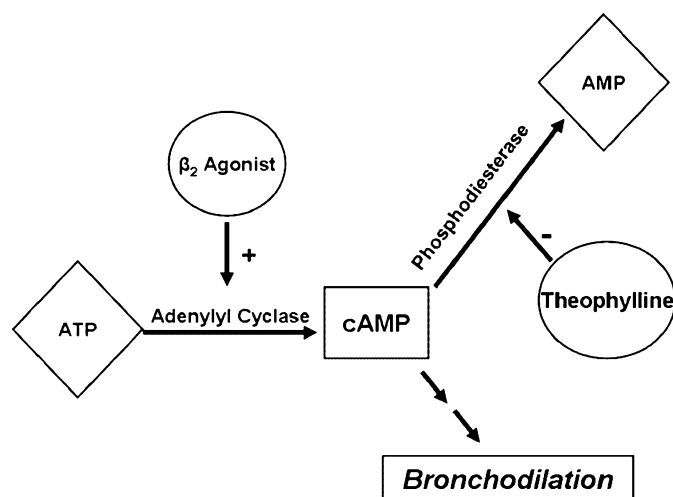


Figure 4. Cellular actions of  $\beta_2$  agonists and theophylline.

receptors in the airways. Activation of  $\beta_2$  receptors leads to the activation of adenylate cyclase and subsequent generation of cyclic AMP (cAMP). Increased levels of cAMP in turn activate protein kinase A which induces calcium extrusion and sequestration and thus smooth muscle relaxation.

Adverse effects of short term use of specific  $\beta_2$  agonists are relatively minor and infrequent due to their high specificity and topical delivery. The potential for adverse effects is greater when these agents are used orally and may include muscle tremors and cramps, cardiac effects and metabolic changes. There has also been significant concern recently regarding the potential safety of long-acting inhaled beta agonists such as salmeterol. In 2005, the Food and Drug Administration (FDA) issued a stern public health advisory warning patients and health care providers that “these medicines may increase the chance of severe asthma episodes, and death when those episodes occur” ([www.fda.gov/cder/drug/advisory/LABA.htm](http://www.fda.gov/cder/drug/advisory/LABA.htm)). This warning came about as a result of data from the Salmeterol Multi-Center Research Trial (SMART) that showed patients (especially African Americans) taking this medication were at a significantly higher risk of severe asthma attacks and death than patients taking a placebo.<sup>10</sup> However, while these finding are of concern, long-acting beta

agonists remain an important treatment option in patients with asthma when used correctly and monitored carefully.

Another concern that has been raised with the chronic use of  $\beta_2$  receptor agonists is the potential for  $\beta$  adrenergic receptor desensitization and down regulation. Beta-2 adrenergic receptors in bronchial smooth muscle seem to be somewhat resistant to desensitization, while those on mast cells and lymphocytes appear more susceptible to this phenomenon.<sup>11</sup> This finding may in part explain the lack of significant antiinflammatory effect with these agents. Although clinical studies have reported the degree of efficacy lost to these 2 processes is not clinically significant, there may be some loss of the bronchoprotective effects of  $\beta_2$  agonists in patients presented with an antigen challenge. Potential pharmacogenomic variations in  $\beta$ -adrenergic receptors may also affect patient responsiveness and will be discussed later under the “Pharmacogenomics and Patient Response” section. Table 2 lists some of the more commonly used  $\beta_2$  agonists for treatment of asthma.

Recognition of the beneficial effects of the antiinflammatory actions of corticosteroids in asthma patients were first documented in the medical literature in the 1940s for intramuscular ACTH and cortisone.<sup>12</sup> The first inhaled corticosteroid came into use about a decade later and they have remained mainstays till the current day. Early inhaled corticosteroids, however, had high levels of systemic absorption and thus a significant potential for systemic side effects. Newer agents like beclomethasone and budesonide were designed specifically to have less systemic absorption. Corticosteroids exert multiple antiinflammatory actions including inhibition of inflammatory cytokine release and reduced activity of inflammatory immune cells. Corticosteroids also interact with specific receptors in tissues to regulate expression of corticosteroid-responsive genes. Several inhibitor proteins such as annexins and lipocortins are generated in response to corticosteroid receptor binding, which appear to inhibit the release of the arachidonic acid substrate from membrane lipids. Though highly efficacious at blocking the inflammatory phase of asthma, their potential long-term side effects limit their oral use. Side effects of oral corticosteroid uses may include endocrine suppression,

Table 2. Inhaled  $\beta_2$  Agonists Commonly used for the Treatment of Asthma

Drug	Duration of Effect	Characteristics
Metaproterenol	3-6 hours	Less $\beta$ selectivity, more cardiac effects
Terbutaline	3-6 hours	Parenteral form available for status asthmaticus
Albuterol	3-4 hours	Available in an oral form but greater risk for adverse effects
Formoterol	up to 12 hours	Highly lipophilic, high affinity for $\beta_2$ receptors
Salmeterol	12 hours or more	Highly lipophilic, 50x greater specificity for $\beta_2$ receptors than albuterol

increased risk of infections, osteoporosis, osteonecrosis, cataract formation, fluid and electrolyte imbalances and impaired growth and development in children.

Administration of corticosteroids by inhalation can greatly reduce the potential for serious side effects. The newer corticosteroids have very low bioavailability due to extensive first-pass metabolism and are well-suited for inhalation use. However, even these agents have some potential for adverse localized and systemic effects such as respiratory infections, suppression of endocrine (hypothalamic/pituitary/adrenal) function, and decreased bone mineral density in females.<sup>13</sup> The potential growth-suppressing effects of corticosteroids in children may also be of significant concern even when these agents are given by inhalation.

Table 3 lists some of the most commonly used corticosteroids for the treatment of asthma. Recently developed combination agents such as Advair, combined a fixed amount of salmeterol and fluticasone in a convenient dosage form. An important consideration for corticosteroid use in asthma is the fact that they do not directly cause bronchial smooth muscle relaxation but rather reduce the frequency and severity of asthma attacks. Thus, patients still need to have access to a quick acting  $\beta_2$  bronchodilator to treat the acute bronchospastic phase of asthma.

As far back as the 1830s strong coffee and tea were reported to have beneficial effects on asthma symptoms due to the presence of the active xanthines caffeine (from coffee) and theophylline (from tea). Aminophylline was

widely used throughout the 1930s and 1940s for its bronchodilator effect. Long-acting oral formulations of theophylline are still currently used (albeit as third-line agents) for the treatment of asthma. There are several proposed mechanisms for the beneficial effect of theophylline in asthma. The first involves its ability to inhibit cyclic nucleotide phosphodiesterases which in turn inhibits the degradation of cyclic AMP and cyclic GMP (Figure 4). Increased levels of these second messengers in turn lead to bronchodilation (similar to  $\beta_2$  agonists) as well as decreased release of inflammatory mediators from mast cells. Theophylline is a relatively non-selective inhibitor of phosphodiesterases and it is this lack of specificity that may contribute to some of the adverse effects that are observed with theophylline use.

A second proposed mechanism action of theophylline in asthma centers around its ability to antagonize adenosine receptors in the airways.<sup>14</sup> When administered to isolated airway tissues, adenosine induces both contraction of smooth muscle and release of inflammatory mediators from mast cells. Thus, antagonism of adenosine receptors by theophylline may prevent both of these adverse events in asthma. While the methylxanthines are inexpensive drugs for treating asthma, one of their major drawbacks is their potential toxicity. The methylxanthines exert mild central nervous system (CNS) stimulant effects at low doses but can cause significant nervousness and insomnia in sensitive individuals. At high doses they can cause marked CNS stimulation, tremors, and even convulsions. The cardiovascular effects of methylxanthines are also significant and may include tachycardia, increased cardiac output and, of greatest concern with high blood levels, cardiac arrhythmia and sudden death. Several agents with high specificity for the phosphodiesterase isoform found in the airways (PDE4) have been studied in asthma but the results thus far have been disappointing due to significant gastrointestinal (GI) side effects and toxicity of these agents.<sup>15</sup> One agent, roflumilast (Daxas, Altana Pharmaceuticals), appears to have less adverse effects than other similar agents under development and is currently undergoing clinical trials to determine its efficacy/usefulness in the treatment of chronic obstructive pulmonary disease (COPD) and asthma.<sup>16</sup>

Numerous anticholinergic compounds derived from plant alkaloids (*Datura stramonium*) have been used for 200 years for the treatment of asthma symptoms. Although atropine, the major active anticholinergic compound in plant alkaloids, was first isolated in 1833, it was not until the late 1800s that its bronchodilator properties were first utilized for asthma. Anticholinergic agents exert a bronchodilator effect through blockade of muscarinic receptors in the airways. Blocking cholinergic

Table 3. Commonly used Corticosteroids for the Treatment of Asthma

For Inhalation Use	Potential Adverse Effects
Beclomethasone	■ Cough
Budesonide	■ Dysphonia
Fluticasone	■ Hoarseness
Flunisolide	■ Oral candidiasis
Triamcinolone	■ Systemic effects at high doses
For Systemic Use	Potential Adverse Systemic Effects
Methylprednisone	■ Growth suppression
Prednisolone	■ Adrenal suppression
Prednisone	■ Osteoporosis
	■ Peptic ulcers
	■ Myopathy
	■ Fluid & electrolyte imbalance
	■ Hypertension
	■ Cushing's syndrome

activity likewise blocks the increase in mucous secretion that occurs in response to vagal activation. The major limiting factor to the use of atropine was its potential for CNS penetration and cardiac effects. In an effort to limit systemic bioavailability, a quarternary ammonium antimuscarinic agent, ipratropium bromide, was developed in the 1970s as an inhalation agent with limited systemic absorption and CNS penetration. The potency of ipratropium as a bronchodilator is generally lower than that of  $\beta_2$  agonists and the bronchodilator response of patients to ipratropium also shows greater variability than does the response to  $\beta_2$  agonists. There is research to suggest a significant amount of pharmacogenomic variation in the parasympathetic nervous systems (and airway receptors) of different individuals, a finding that may help explain the varying efficacy of anticholinergic drugs in asthma patients.<sup>17</sup> The most common side effects reported with inhaled ipratropium use are cough, dry mouth, and throat irritation. A new, long duration selective antimuscarinic agent, tiotropium, has just been approved for use in treatment of chronic obstructive pulmonary disease (COPD); however, research on the use of this agent for treatment of bronchial asthma has not shown it to be superior to current agents.

Extracts from the plant *Ammi vinaga* were used by herbalists for many years as treatments for asthma. The active agent *khellin* has been shown to have properties that were useful in asthma. The first synthetic analogues of khellin were developed in the early 1960s as cromolyn sodium (disodium cromoglycate) and later nedocromil sodium. Both of these agents are very insoluble salts that are administered by inhaler.

The mechanism of action for these agents remains incompletely understood. It is likely they exert multiple effects including inhibition of mast cell release, altered parasympathetic response, altered leukocyte function, and suppression of leukocyte chemotaxis. The major use of these agents is to prevent asthma attacks in patients with mild to moderate asthma. These agents block bronchoconstriction that is induced by exercise and allergens. Nedocromil is generally more effective at relieving asthma symptoms than cromolyn and may reduce the amount of inhaled steroids used in certain asthmatic patients.<sup>18</sup> While the efficacy of these agents in treating asthma appears to be less than the  $\beta_2$  agonists and inhaled corticosteroids, both drugs have excellent track records of safety and few side effects due to their limited solubility.

The first class of asthma drugs to be targeted to a specific component of the asthmatic response were the leukotriene pathway inhibitors. A substance originally called the slow reacting substances of anaphylaxis (SRS-A) was found to play a key role in a number of inflammatory

processes including those associated with the asthmatic response. This substance was later identified as the leukotrienes.<sup>19</sup> It is now known that several leukotrienes, such as  $LTB_4$ ,  $LTC_4$  and  $LTD_4$ , mediate a number of the responses seen during an asthma attack including bronchoconstriction, edema, excess mucous secretion, and bronchial hyperreactivity. Studies have shown  $LTD_4$  to be nearly 100 times more potent than histamine in causing bronchoconstriction.<sup>20</sup> Two strategies have been employed to block the actions of the leukotrienes in the airways (Figure 5). The first involves direct inhibition of the enzyme 5-lipoxygenase, which is responsible for the synthesis of leukotrienes (zileuton). The second involves direct blockade of leukotriene receptors in the airways (zafirlukast and montelukast; "lukast" = leukotriene antagonist).

Leukotriene receptor antagonists are highly specific for the CysLT1 receptor, which is activated by  $LTC_4$ ,  $LTD_4$ , and  $LTE_4$ . Activation of the CysLT1 receptor mediates smooth muscle constriction, immune cell (eosinophil) infiltration, and vascular changes that lead to edema. Leukotriene synthesis inhibitors such as zileuton are potent inhibitors of the enzyme 5-lipoxygenase and thus prevent formation of all leukotrienes including  $LTB_4$ , whose actions are not blocked by the CysLT1 receptor antagonists.  $LTB_4$  acts as a potent chemotactic agent that appears to be involved in leukocyte infiltration of the airways.

Adverse effects for the leukotriene receptor antagonists are low. A small percentage of patients taking these agents have developed a systemic vasculitis that is similar to Churg-Strauss syndrome. However, it is unclear in these if the condition was caused directly by the leukotriene

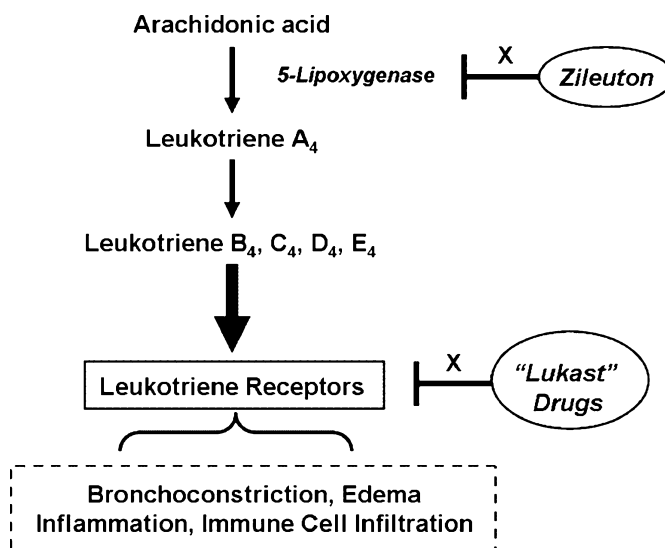


Figure 5. Role of leukotrienes in asthma.



receptor antagonist or was an underlying condition previously suppressed by corticosteroids the patients may have been taking.<sup>21</sup>

Leukotriene antagonists block the ability of aspirin (and only aspirin) to induce bronchoconstriction in 5%-10% of asthma patients. An interesting finding that may support the theory that aspirin-induced asthma is caused by a shifting of arachidonic acid metabolism away from prostaglandins and toward the leukotrienes.

Studies on the efficacy of leukotriene inhibitors in asthma patients have shown them to be significantly less effective (and significantly more expensive) than inhaled corticosteroids.<sup>22</sup> These agents are currently most useful for prophylaxis of mild asthma or as add-on agents to inhaled  $\beta$ -agonists and corticosteroids. An advantage to the use of leukotriene antagonists is the fact that they may be given orally.

Another approach to the treatment of asthma involves the targeting of IgE, the main immunoglobulin involved in the binding and degranulation of mast cells. A “humanized” recombinant monoclonal antibody against IgE (omalizumab (Xolair)) was the first approved for the treatment of asthma. Humanizing monoclonal antibodies is a process by which a mouse antibody has most of its amino acids genetically replaced with human amino acids to reduce its potential antigenicity. Omalizumab is designed to bind the *Fc* receptor on IgE, the same receptor that IgE uses to bind to mast cell FC epsilon receptor I (FC $\epsilon$ RI) (Figure 6). Thus omalizumab is essentially an antibody against an antibody. Omalizumab binds free IgE with high affinity but does not interact with any IgE that is already bound to mast cells and thus will not induce mast cell degranulation even if IgE is already present on mast cells. FC $\epsilon$ RI is also found on the surface of a number of other immune cells such as basophils, lymphocytes, monocytes, and eosinophils. Inhibition of IgE binding to these cells might also contribute to the effects of omalizumab.

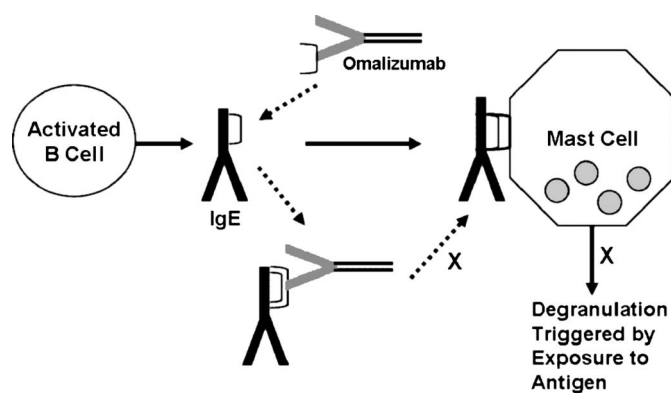


Figure 6. Actions of omalizumab in asthma.

One drawback to the use of monoclonal antibodies as therapeutic agents is the fact that they must be administered by injection. The adverse effects of omalizumab reported in controlled trials up to this point have been relatively minor and include mainly injection site reactions. Less than 1% of patients receiving omalizumab developed antibodies against the drug (antibodies against an antibody designed to bind an antibody). One source of potential concern with the use of omalizumab was the finding that asthma patients taking this drug had a higher frequency of malignancies than did asthma patients taking other agents.<sup>23</sup> More long term studies on malignancy rates with omalizumab use are clearly needed, particularly in patients who may be at a higher risk for malignancies. A second concern with the use of omalizumab is the potential risk of anaphylactic reaction following injection. This potentially dangerous reaction mandates that the drug be administered in the physician's office so the patient might be monitored after injection. Finally, the cost of therapy with this agent might make it prohibitive for many patients. Omalizumab is clinically indicated for treating moderate to severe asthma in patients 12 years and older. Studies report that omalizumab can decrease the amount of inhaled steroids used by allergic asthma patients while reducing the severity and frequency of asthma attacks.<sup>24</sup> Due to its antagonism of IgE, omalizumab appears to be most efficacious in clear antigen-induced asthma and has also been shown effective in treating allergic rhinitis and food allergies.

**New Drugs for Asthma Pharmacotherapy.** Significant advances in our overall understanding of asthma pathogenesis on a molecular and immunologic level should greatly increase the number of available targets for asthma pharmacotherapy in the near future. One key component of chronic asthma that needs to be addressed with new therapies is the prevention or reversal of airway remodeling. The pathological changes that occur in patients with chronic asthma are generally irreversible and signal a poor long-term prognosis when they occur.

Agents currently used for asthma might also be reformulated or modified to enhance their pharmacokinetics and thus improve efficacy and reduce potential side effects. For example, currently used inhaled steroids still have some degree of systemic absorption at high doses, which can lead to significant adverse effects. The development of so called synthetic “soft” steroids has been an active area of research. These synthetic steroids may take the form of inactive ester prodrugs that are converted to their active form in the airways. One such agent, ciclesonide (Alvesco) received preliminary FDA approval in 2003 and is still undergoing extensive clinical testing.<sup>25</sup>

Early results indicate that systemic bioavailability of this agent was negligible and that it did not suppress cortisol secretion.<sup>26</sup> Despite the proven efficacy of corticosteroids in treating asthma, long-term studies with these agents have shown that they may not completely prevent the adverse effects of airway remodeling that are observed with chronic asthma.<sup>27</sup> A better understanding of the processes involved in asthma-related airway remodeling must be a priority. One substance, endothelin, has been shown to induce smooth muscle proliferation and fibrosis in the airways and may be a potential target for prevention of asthma-induced remodeling in the future.

New agents and targets for the treatment of asthma are currently under investigation. Novel bronchodilator compounds such as vasoactive intestinal peptide (VIP), atrial natriuretic peptide (ANP), and prostaglandin E analogs are undergoing investigation.<sup>28</sup> Despite some promising success, the main draw of using peptides as therapeutic agents, their instability, still needs to be overcome.

Selective adenosine receptor ( $A_{2B}$  subtype) antagonists are also potential drugs of interest in asthma since activation of this receptor has been shown to stimulate mast cell release. Conversely, activation of adenosine receptor subtype  $A_{2A}$  has inhibitory effects on leukocyte activity and agonists of this specific receptor are under investigation as well.<sup>29</sup> While promising adenosine receptor targets have been identified in mast cells and immune cells, the challenge remains to develop agents that are highly specific for a particular adenosine receptor subtype. Research is currently ongoing in this area.

Cytokines such as interleukins (IL) and tumor necrosis factor alpha (TNF- $\alpha$ ) have been the subject of intensive recent investigation in a number of inflammatory human conditions such as inflammatory bowel disease and rheumatoid arthritis.<sup>30</sup> The role of these substances in asthma has likewise been intensively investigated in recent years.<sup>31</sup> Interleukins such as IL-5 appear to mediate the inflammatory response of eosinophils in animal models of asthma. However, an experimental monoclonal antibody against IL-5 (mepolizumab, GlaxoSmithKline) did not show efficacy in human asthma trials, pointing to a questionable role of this pathway in human asthma. Antagonism of 2 related cytokines, IL-4 and IL-13, have shown more promising effects on asthma in early trials.<sup>32</sup> Interleukin-4 is involved in the production of IgE while IL-13 appears to mediate a number of key asthma features in animal models including airway fibrosis, mucous secretion, and eosinophil activity. However, in recent large-scale studies, IL-4 antagonists did not show great efficacy in humans.<sup>33</sup> Clinical trials of IL-13 antagonists are ongoing.

Another key cytokine TNF- $\alpha$  appears to play a key role in several inflammatory conditions such as Crohn's disease and rheumatoid arthritis.<sup>30</sup> Currently, there is little data on the use of approved TNF- $\alpha$  blockers such as infliximab in the treatment of asthma. Several reports on the benefits of TNF- $\alpha$  blockade in asthma patients have been retrospective, while other preliminary studies designed specifically to investigate the effects of TNF- $\alpha$  blockade, although somewhat positive, have included very small numbers of patients.<sup>30</sup> A main concern of TNF- $\alpha$  blockade remains the possible increased risk of malignancies given the proposed role of this cytokine in tumor surveillance.

Chemotactic cytokine called "chemokines" are also substances of interest in asthma. Through interaction with cell surface chemokine receptors (CCR), these substances (eg, eotaxin) mobilize a number of immune cells such as eosinophils and lymphocytes that are involved in the allergic asthmatic response. A number of potent and highly specific small molecule CCR antagonists are under development (eg, SB-328437 from Glaxo-SmithKline and RO116-9132/238 from Roche). Several of these (eg, GSK 766994) have entered early clinical trials.<sup>34,35</sup> Given the wealth of new therapeutic targets currently under investigation, the next decade holds great promise for the development of new and effective asthma drugs, particularly in the area of preventing the detrimental long-term effects of airway remodeling.

**Pharmacogenomics and Patient Response to Therapy.** Genetic variability from patient to patient may complicate asthma pharmacotherapy. Polymorphisms in drug metabolizing enzymes (CYP450's for example) can significantly alter the half-life and thus potential effectiveness and toxicity of certain asthma drugs. The actual targets of asthma drug therapy may likewise be affected by genetic variability. At least 17 single nucleotide polymorphism have been documented for the  $\beta_2$ -adrenergic receptor, some of which may lead to reduced drug binding affinity and altered downregulation responses.<sup>36</sup> A study by Israel demonstrated that patients who were homozygous for arginine at codon 16 of their  $\beta_2$  adrenoreceptors showed a greater decline in lung function following chronic albuterol use than patients who were homozygous for glycine at the same codon.<sup>37</sup> A recent study by Hawkins reported a total of 49 polymorphisms in the  $\beta_2$ -adrenergic receptor.<sup>38</sup> A number of these polymorphisms showed significant inter-ethnic variation that may be associated with differences in response to  $\beta$ -agonists amongst different ethnic groups. Genetic variations in other asthma targets such as phosphodiesterase, 6-lipoxygenase, and muscarinic receptors, have likewise been documented.<sup>36</sup> Polymorphisms for lipoxygenase

(in the ALOX5 gene core promoter) in particular may reduce efficacy of agents directed against this target.<sup>39</sup> The effect of genetic variability on a patients' response to steroids is also of interest since polymorphisms in cytokine genes (IL-4 for example) can alter B-lymphocyte activity and the subsequent expression of IgE.<sup>40</sup> As our understanding of human genetic variation advances, new findings may significantly impact the development of new asthma drugs with respect to their pharmacodynamic and pharmacokinetic parameters.

## ASSESSMENT

The student course evaluations related to the Integrated Sequence in which this topic was taught were consistently positive. In the course evaluation 97.7% and 100% of the students surveyed either agreed or strongly agreed that the course content was intellectually challenging and built understanding of key concepts and principles, respectively. Likewise all of the students surveyed agreed or strongly agreed that the lectures and recitations addressed the educational outcomes defined in the syllabus for this topic. Performance on examinations (exam averages in the low 80s) and case write-ups related to asthma pharmacotherapy were likewise very good (average 83 out of 100). Formal and informal student feedback on the case studies, review exercises, and presentation format was consistently positive. Numerous student comments on the course evaluations stated that the inclusion of case studies and recitations significantly enhanced their understanding of key topics and enhanced the integrations of pharmacology, medicinal chemistry and therapeutics content.

## DISCUSSION

While the future holds great promise for the treatment of asthma, our current pharmacotherapy still centers

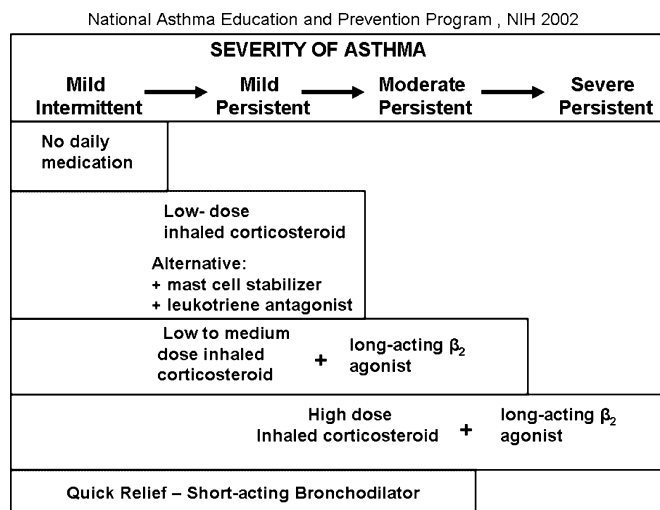


Figure 7. Current asthma treatment guidelines in children above 5 years of age and adults.

around 2 main classes of drugs:  $\beta_2$  agonists and corticosteroids (see Figure 7 and Table 4). According to current guidelines, patient who suffer from mild persistent asthma (approximately one fourth of all asthma patients) receive an inhaled  $\beta_2$  agonist for immediate relief of bronchospastic symptoms and daily inhaled corticosteroids to reduce airway inflammation and decrease the severity and incidence of attacks. However, according to recent findings from the multicenter Improving Asthma Control (IMPACT) trial, a significant number of these patients were able to achieve adequate relief of symptoms by using inhaled corticosteroids only during periods of exacerbation.<sup>41</sup> Daily use of budesonide or zafirlukast in patient with mild persistent asthma did not significantly improve peak expiratory flow over patients who used these agents as needed for worsening symptoms. The authors concluded that while this approach was viable, longer and larger studies were needed to validate it. An updated Ex-

Table 4. Degrees of Asthma Severity

Severity	Clinical Features	Nocturnal Features
Mild Intermittent	<ul style="list-style-type: none"> <li>Symptoms occur two times per week or less</li> </ul>	<ul style="list-style-type: none"> <li>Nocturnal awakenings two times or fewer in a month</li> </ul>
Mild Persistent	<ul style="list-style-type: none"> <li>Exacerbations are brief</li> <li>Symptoms occur more than two times per week</li> <li>Exacerbations may affect activity</li> </ul>	<ul style="list-style-type: none"> <li>Nocturnal awakenings occur more than two time in a month</li> </ul>
Moderate Persistent	<ul style="list-style-type: none"> <li>Symptoms occur daily</li> </ul>	<ul style="list-style-type: none"> <li>Nocturnal awakenings more than one time per week</li> </ul>
Severe Persistent	<ul style="list-style-type: none"> <li>Exacerbations may last for days</li> <li>Continual symptoms</li> <li>Frequent exacerbations that limit physical activity</li> </ul>	<ul style="list-style-type: none"> <li>Frequent nocturnal awakenings</li> </ul>

pert Panel 3 report is due out shortly from the National Heart Lung and Blood Institute at the National Institutes of Health that may further revise current guidelines for the treatment of asthma.

## CONCLUSION

Rapid advances in molecular biotechnology and extensive ongoing drug research and development will likely have significant impact on how we treat asthma in the near future. The current reality still presents a complex and evolving picture of asthma pharmacotherapy. It is crucial for students of pharmacy to have a comprehensive understanding of the many drug options available to patients with asthma. Knowledge of the acute and chronic pathophysiologic features of asthma is also essential since it provides students with the rationale for drug effects and choices. Practicing pharmacists likewise need to keep current with ongoing drug research and development in order to provide the best level of future care to their patients who suffer from this often debilitating and potentially fatal disease.

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