Take a Deep Breath: A Review of Medications Used for Asthma and COPD

Release Date: 05/01/2012
Expiration Date: 05/01/2015

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TARGET AUDIENCE:

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Program Overview:

To provide pharmacists, pharmacy technicians, and nurses with an understanding of current prevention and treatment strategies for asthma and COPD.

OBJECTIVES:

After completing this program, pharmacists and nurses will be able to:

- Outline the epidemiology and pathophysiology of asthma and COPD
- Identify the clinical similarities and differences between asthma and COPD
- Describe the pharmacological treatments for asthma to include mechanisms of action and side effects
- Describe the pharmacological treatments for COPD to include mechanisms of action and side effects
Take a Deep Breath: A Review of Medications Used for Asthma and COPD

For most of us, taking a deep breath is a way to relax or calm down. But for those with asthma and chronic obstructive pulmonary disease, taking a deep breath is often terrifying, and sometimes impossible. Fortunately there are a plethora of medications that can be used to help these patients breathe a little easier.

Epidemiology

Asthma is extremely common, and the incidence is increasing. According to the Centers for Disease Control and Prevention (CDC), one in 12 people in the U.S. (about 25 million or 8% of the population) had asthma in 2009. Certain groups are hit harder. About 10% of children had asthma in 2009. About 11% of blacks of all ages and about 17% of black children had asthma in 2009. Further, the asthma rate among black children increased by almost 50% from 2001 to 2009. By comparison, in 2001, 7% of all people had asthma.

Asthma is also costly, in terms of lives, money, and lost production. Asthma was linked to 3447 deaths in 2007, accounting for almost 9 deaths per day. Medical expenses associated with asthma totaled $50.1 billion in 2007. Up to 59% of children and 33% of adults who had an asthma attack missed school or work due to asthma in 2008. On average, children missed 4 days of school and adults missed 5 days of work because of asthma in 2008.

Unlike asthma, which affects people of all ages, chronic obstructive pulmonary disease (COPD) only affects adults. According to the CDC, in 2007-2009, 5.1% of adults aged 18 and older (11.8 million people) had COPD. Women were more likely to have COPD than men in age groups except for those older than 75 years, when the rates were similar. The groups with the highest prevalence of COPD are Puerto Rican (6.9%) and non-Hispanic white adults (5.7%), while black adults (4.4%) and Mexican-American adults (2.6%) had lower rates. There is wide geographic disparity in prevalence, ranging from 7.5% in Kentucky, Tennessee, Alabama, and Mississippi, to 3.9% in the states along the Pacific. And overall, COPD prevalence decreased with increasing income levels.

The toll of COPD is chilling. In 2007, nearly 60,000 men and 65,000 women died from COPD. By 2008, COPD was the third leading cause of death in the U.S. It is also the leading cause of hospitalization in U.S. adults.

Pathophysiology
Both asthma and COPD are considered lower airway diseases. Though they are considered separate entities, they share enough pathophysiology that the medications used to treat them are similar and, in some cases, identical. Thus, both are considered in this monograph.

The hallmark of asthma pathophysiology is a reversible inflammatory response. The first event in the pathway is bronchoconstriction: contraction of the smooth muscle surrounding the bronchioles. This is followed by airway edema, exaggerated mucus production, and airway hyperresponsiveness. This airway inflammatory process is mediated by a variety of cytokines and chemokines released by a variety of cells including lymphocytes, eosinophils, and mast cells. These last two cell types also produce leukotrienes, which cause further bronchoconstriction.\(^5\)

This process is triggered by infections, toxins, or allergens. IgE plays a key role in this pathway, causing mast cells and basophils to degranulate, precipitating bronchospasm, as well as the release of cytokine and chemokines. Bronchodilators, such as albuterol, can relax airway smooth muscle early in the process, but to treat increased airway hyperresponsiveness and inflammation, anti-inflammatory medications are required. Over a long time and repeated attacks, airway remodeling occurs, with non-reversible structural changes that lead to permanent dysfunction.\(^5\)

Clinically, asthma results in intermittent, recurrent symptoms of airway obstruction that is reversible: cough (often the only symptom), wheezing, shortness of breath, difficulty breathing, and a feeling of chest tightness. Often, symptoms are triggered or worsen with exercise, weather changes, respiratory infections, and exposure to allergens or airway irritants (tobacco smoke).\(^5\)

Likewise, COPD is the end result of a chronic inflammatory process, usually triggered by cigarette smoke or other inhaled pollutants (wood smoke or occupational smoke exposure). Patients with COPD have increased inflammatory markers, such as cytokines and proteases, and increased inflammatory cells in the lungs, such as neutrophils, macrophages, T-lymphocytes, eosinophils, and mast cells. A protease-antiprotease imbalance and the production of reactive oxygen species triggered by smoking are other mechanisms leading to lung damage in COPD.\(^6\)

The end result in COPD is permanent lung damage. Clinically, COPD is divided into chronic bronchitis and emphysema. In chronic bronchitis, the lungs have thickened bronchial walls with luminal narrowing, and mucous plugging or mucopurulent debris within the airways. Sometimes a chronic inflammatory infiltrate is also present. In emphysema, the alveolar walls are destroyed, resulting in enlarged airspaces distal to the terminal bronchioles. Progressive destruction can cause impairment of lung function.\(^6\)

Because the symptoms and spirometer readings can be similar for asthma and COPD, the diagnoses are sometimes confused. Asthmatics generally develop symptoms at a younger age, are less likely to be smokers, and experience symptoms intermittently and with more variability, as evidenced by their daily peak flow measurements. COPD patients, on the
other hand, tend to be older at onset of disease, have chronic productive cough, have more persistent dyspnea and other symptoms, and have less consistent response to medical therapy, such as inhaled corticosteroids and bronchodilators.\textsuperscript{7}

**Bronchodilators**

*Case #1: Luis is a 10 year-old boy who was recently diagnosed with asthma. His pediatrician has prescribed a few medicines, including an albuterol inhaler. His mother asks you, the retail pharmacist, what are the main side effects of the albuterol? And can he get “addicted” to his inhaler?*

**Short-acting beta agonists**

For asthma, the medications are often divided into quick-relief medications (known as “rescue” medications) for use in relieving acute exacerbations, and long-term control or preventive medications (known as “controllers) aimed at preventing the inflammatory cascade. Patients who experience symptoms relatively infrequently may only have a rescue medicine, but most asthmatics should be considered for controller medication. For COPD, there is no such distinction between controller and rescue medicines, as the disease is more persistent than asthma.

The standard rescue medication in asthma and a cornerstone of treatment in COPD is the short-acting beta\textsubscript{2} agonist (SABA), such as albuterol, levalbuterol, pirbuterol and metaproterenol. Albuterol is prepared as a racemic mixture of R(-) and S(+) stereoisomers, while levalbuterol is the stereospecific preparation of the R(-) isomer.\textsuperscript{8} The chemical structures of albuterol, pirbuterol, and metaproterenol are shown below.

![Chemical structures](image1.png)  
**Albuterol**  
**Pirbuterol**
The SABAs work by increasing cellular levels of cyclic AMP, which relaxes the smooth muscle of bronchioles, causing bronchodilation and reversing bronchoconstriction. Higher c-AMP levels also inhibit the release of mediators of immediate hypersensitivity from inflammatory cells, especially mast cells. Their peak effect is seen within 15 to 30 minutes and wears off within 4 to 6 hours.

The choice of which SABA to use is an individual one, and often based on factors such as patient preference, cost, insurance coverage, and preferred administration device, as they each have similar efficacy and side effect profiles. Levalbuterol is marketed as having the same efficacy as albuterol but with fewer side effects, though studies have not conclusively shown this to be true.

Adverse effects of the SABAs include tachycardia, tremulousness, and irritability. Prolonged use or high doses can lead to hyperkalemia. Excessive or frequent use of SABAs (>2 days/week) is associated with an increased risk of hospitalization and death, though the exact relationship is unclear.

For the special case of exercise-induced asthma, SABAs are the treatment of choice. Exercise-induced asthma is a bronchospastic event that usually occurs only when performing vigorous exercise, such as long-distance running, or extremely aerobic exercise, such as basketball or soccer.

Oral SABAs are available, but are rarely used due to their side effects and lower efficacy than inhaled SABAs. They do have a limited role, however, in those older patients who cannot use inhalers.

The SABAs are all inhalational, delivered via a nebulizer, a metered dose inhaler (MDI), or in a breath-activated metered dose inhaler (“autohaler”). The trade names for albuterol include ProAir HFA®, Proventil®, Proventil HFA®, Ventolin HFA® (all MDIs) and Accuneb® (for nebulizer). The trade names for levalbuterol are Xopenex® (for neb) and Xopenex HFA®. The trade names for pirbuterol are Maxair® and Exirel® (both MDIs) and Maxair Autohaler®. The trade name for metaproterenol is Alupent® (MDI).
You can now answer Luis’ mother’s questions: the albuterol may make him a little jittery and make his heart race, and he might be a little more active than usual, but these side effects will wear off quickly. No, he cannot get “addicted” to the medicine, but she should be aware if he is using it too much, as it may be a sign that his asthma is out of control and he needs further evaluation and treatment by his pediatrician.

**Long-acting beta agonists**

*Case #2: Mrs. Rosenblatt is a 73 year-old woman with a long history of smoking and COPD. She has used albuterol for years, but her internist just switched her to Serevent®, and she’s upset. She wants to know if this is better for her than her old reliable inhaler. And she heard something on the news about people dying using Serevent®, and she’s worried.*

The long-acting beta$_2$ agonists (LABAs) are currently approved for treatment of asthma or COPD. These are formoterol, arformoterol, and salmeterol. Arformoterol is the active (R,R)-enantiomer of formoterol. The chemical structure of formoterol and salmeterol are shown below.$^{13,14}$

![Formoterol](image1.png) ![Salmeterol](image2.png)

There is another LABA that is indicated for use only for COPD patients: indacaterol. The chemical structure of indacaterol is shown below.$^{15}$
All LABAs exert the same mechanism of action as the SABAs, but their duration of action is at least 12 hours. Formoterol, arformoterol, and salmeterol are all twice-daily medications, but indacaterol is a once-daily medication. LABAs are not meant for monotherapy in asthma, but are often used in combination with inhaled corticosteroids.\textsuperscript{12}

For COPD, LABAs can be used as monotherapy, and in fact, LABAs are preferred when patients have persistent symptoms and require daily use of SABAs.\textsuperscript{16} Some advocate that indacaterol has an advantage over the other LABAs because of its once a day dosing, which is assumed to help with adherence. One major study showed that poor adherence with inhaled medications among COPD patients doubled their risk for death from COPD.\textsuperscript{17} Clearly, any medication that can improve adherence is the preferred choice.

As with SABAs, there is an association with LABAs and increased asthma deaths.\textsuperscript{18} However, this association has not been seen with LABAs and COPD patients. Regardless, any product containing a LABA now has a black-box warning from the Food and Drug Administration (FDA).

Side effects from LABAs are similar to SABAs. All trade names come as dry powder inhalers (DPIs), except for Perforomist. The trade names for formoterol are Foradil\textsuperscript{®} and Perforomist\textsuperscript{®} (nebulizer solution). The trade name for arformoterol is Brovana\textsuperscript{®}. The trade name for salmeterol is Serevent\textsuperscript{®}. The trade name for indacaterol is Arcapta\textsuperscript{®} Neohaler\textsuperscript{®}.

You can safely reassure Mrs. Rosenblatt that Serevent\textsuperscript{®} is actually better and safer for her than using her old albuterol inhaler so many times. And the increased risk of using the LABA is only for those people with asthma, not COPD.

**Anticholinergics**

Ipratropium and tiotropium are the two anticholinergics used for asthma and COPD. The chemical structures for these two compounds are shown below.\textsuperscript{19,20}
Both drugs inhibit muscarinic cholinergic receptors and reduce vagal tone in the airways, thus accomplishing bronchodilation. Tiotropium is a long-acting, 24-hour medicine, taken once daily.

Ipratropium is used for both asthma and COPD, but tiotropium is indicated only for COPD. Ipratropium is usually used in combination with inhaled albuterol for mild and moderate acute exacerbations of asthma, but is not indicated for the inpatient treatment of asthma. It is also approved for maintenance therapy of COPD. Tiotropium is approved for both maintenance therapy and to prevent exacerbations of COPD. Common side effects for both include dry mouth and blurred vision, but rarer, more serious side effects include bladder neck obstruction, worsening signs and symptoms of narrow-angle glaucoma, and prostatic hyperplasia.

One initial meta-analysis of anticholinergics and COPD suggested an increased risk of major cardiovascular-related events and death. However, a large, 4-year, randomized, prospective study, entitled Understanding the Potential Long-Term Impacts on Function with Tiotropium (UPLIFT), demonstrated no association between use of tiotropium and cardiovascular events or death.

The trade name for ipratropium is Atrovent®, and it comes in an MDI. The trade name for tiotropium is Spiriva® Handihaler®, which is a DPI.

**Theophylline**

Theophylline is a potent bronchodilator that is one of the oldest drugs in the armamentarium against asthma and COPD. The chemical structure of theophylline is shown below.
Theophylline

Theophylline is a methylxanthine that increases c-AMP and causes bronchodilation. It also has some mild anti-inflammatory effects due to its action as a non-selective phosphodiesterase inhibitor (this will be further discussed in the section on anti-inflammatories). It has fallen out of favor over the past few decades due to its narrow therapeutic index, dangerous side effects, and the advent of newer, safer bronchodilators. It is currently a third-tier option for COPD maintenance and is not recommended in treatment of COPD exacerbations. Currently, it has a very limited role in asthma, and is not advocated for maintenance therapy in asthma.\textsuperscript{12,16,24}

Theophylline’s side effects include tachycardia, nausea, vomiting, disturbed pulmonary function, and sleep problems. Overdose can lead to arrhythmias, seizures, and even death.\textsuperscript{7}

Trade names include Theo-Dur\textsuperscript{®} (capsules), Uniphyll\textsuperscript{®} (sustained-release tablets), Theo-24\textsuperscript{®} (timed-release capsules), Theochron\textsuperscript{®} (sustained-release tablets), Elixophyllin\textsuperscript{®} (oral elixir), Theophylline\textsuperscript{®} (oral solution and extended-release tablets). Many other multi-ingredient medications containing theophylline are available, usually without a prescription, such as Primatene\textsuperscript{®} Dual Action and Glyceryl T\textsuperscript{®}.

\section*{Anti-Inflammatories}

\section*{Inhaled Corticosteroids}

\textit{Luis was also given a prescription for Flovent\textsuperscript{®}, which his mother understands is a steroid. She asks you if this is safe for her child, because everyone knows that steroids are dangerous.}

In the last few decades, our understanding of asthma as a primarily inflammatory process has led to a greater reliance on anti-inflammatory medications, especially inhaled corticosteroids. The National Heart Lung and Blood Institute first published Guidelines for the Diagnosis and Management of Asthma in 1991. The report was updated in 1997.
and again in 2007. These guidelines were instrumental in convincing clinicians to utilize inhaled corticosteroids (ICS) as a first-line option in the maintenance therapy of persistent asthma.\textsuperscript{25}

Both oral and inhaled corticosteroids induce production of annexin-1 (or lipocortin-1), which inhibits production of inflammatory agents such as prostaglandins, thromboxanes, and leukotrienes. Corticosteroids also inhibit the activity of phospholipase A2-\(\alpha\) activity. Finally, they also suppress cyclooxygenase 2 (COX-2). These anti-inflammatory actions have multiple effects in the airways, including inhibiting inflammatory cells, accelerating eosinophil apoptosis, reducing the number of mast cells, inhibiting cytokine expression, and decreasing mucus production.\textsuperscript{26}

While these effects are generally immediate, there is a lag time of several hours before the corticosteroids produce a clinical response. For this reason, a single dose of corticosteroids is most effective against the late asthmatic response, not the early response. However, prolonged treatment with ICS can be effective in reducing even the early response to an allergen challenge in a dose-dependent manner. Furthermore, corticosteroids can increase the number of beta\(_2\) receptors in a time- and dose-dependent manner, which explains why some combination medicines of steroids and LABAs provide a synergistic effect.\textsuperscript{26} With daily administration, some effects from ICS may be seen within 1 to 2 weeks, though the full anti-inflammatory effects may not be noticed for 4 weeks.\textsuperscript{12}

Though potent in their effects, oral corticosteroids also have potent side effects. However, when taken as an inhaled preparation, these effects are greatly reduced, though not eliminated. Minor adverse effects include thrush, hoarseness, reflex cough, and bronchospasm. Patients can reduce these effects by using a valved holding chamber (also known as a “spacer” device) with the MDIs, slowing the rate of inhalation, and rinsing the mouth with water after inhalation.\textsuperscript{12}

The more worrisome side effect of ICS is a decrease in the rate of linear growth in children, a large segment of the asthmatic population. Multiple studies have demonstrated a deceleration in linear growth, but this is usually seen in the first few months of treatment, is usually small, and is not progressive.\textsuperscript{27} This deceleration usually does not affect final adult height.\textsuperscript{28} And ICSs have not been found to decrease bone mineral density, cause cataracts, cause hypertension, or have any of the other more serious effects seen with long-term oral steroid use.

There are a multitude of ICSs, and choosing one over another is usually a matter of clinician preference, delivery method, patient preference, and cost, rather than efficacy. One recent review examined the available studies and found no difference between equipotent doses of ICSs in their ability to control asthma symptoms, prevent exacerbations, reduce the need for additional medication, or in their incidence of adverse events.\textsuperscript{26} Often, following an exacerbation, providers will prescribe a higher dose of ICS, then “step down” treatment to a lower dose of ICS as the patient improves and stabilizes. Because of the delayed start of action, when starting daily ICS therapy, some effects may
be seen within 1 to 2 weeks, though the full anti-inflammatory effects may not be noticed for 4 weeks. Likewise, some of the beneficial effects will be seen for a few weeks after stopping ICSs.12

Questions like those of Luis’s mother are quite common. You can reassure her that serious side effects are not seen with inhaled corticosteroids, unlike oral steroids. ICSs are safe, though his growth will need to be monitored, and he should rinse and spit after taking the medication. In fact, you can tell her that ICSs are associated with a lower risk of death from asthma.12

For COPD patients, ICSs are not recommended as a monotherapy, but should be used in a combination with bronchodilators, usually LABAs or anticholinergics. Of the multiple studies demonstrating efficacy of this combination, the largest is the TORCH study (Towards a Revolution in COPD Health), involving 6112 patients in a multicenter, double-blind, placebo controlled, randomized clinical trial. Investigators demonstrated that combination inhaled fluticasone/salmeterol provided patients with a statistically significant improvement in health status, reduction in frequency of exacerbations, and improved post-bronchodilator forced expiratory volume in 1 second (FEV₁, a common pulmonary function test used in asthma), compared to placebo or the individual components alone. There was also a decrease in the risk of all-cause mortality over the 3-year study period, but this was not statistically significant.29

In addition, triple therapy has also been used in COPD. In separate studies, investigators found that fluticasone/salmeterol/tiotropium was better than fluticasone/salmeterol or tiotropium/salmeterol in improving bronchodilation, use of rescue medicine, lung function, quality of life, and hospitalization rates in patients with moderate to severe COPD.30,31

Some studies have shown an increase in pneumonia in COPD patients using ICSs. But one meta-analysis of 7 large, randomized controlled trials showed that budesonide treatment for 12 months did not increase the risk of pneumonia in patients with COPD.32

There are a large number of brands of ICSs, some of which are Aerobid® and Aerobid-M® (flunisolide), Alvesco® (ciclesonide), Asmanex® (mometasone), Azmacort® (triamcinolone), Beclovent®, Qvar®, and Vanceril® (all beclomethasone), Flovent® (fluticasone), and Pulmicort® (budesonide). Most of these come as MDIs, with the Asmanex® as a “twisthaler,” and the Pulmicort® as an MDI and respules for the nebulizer.

**Systemic Corticosteroids**

Systemic corticosteroids (SCSs) are given orally, intravenously, or intramuscularly. They are used to relieve moderate to severe exacerbations of both asthma and COPD. The oral agents used most commonly are prednisone and prednisolone. Prednisone is a synthetic glucocorticoid derived from cortisone that is biologically inert and converted to prednisolone in the liver. Methylprednisolone is the most commonly used intravenous
agent. The chemical structures of prednisone and methylprednisolone are shown below.\(^{33,34}\)

![Chemical structures of prednisone and methylprednisolone](image)

For asthma, steroids improve airway responsiveness to SABAs, improve lung function, and decrease the risk of relapse from an acute exacerbation. Hospitalized patients treated with SCSs have shorter lengths of stay and are less likely to relapse in the first 3 months after discharge.\(^{35}\) Providers usually prescribe SCSs in short “bursts” of 3-10 days, which also helps to decrease the side effects. However, patients who use SCSs frequently (daily or \(>2\) “bursts” per year) may have poorly controlled asthma, and may have more serious side effects, such as mild adrenal suppression. For inpatient and outpatient use, oral steroids seem to be equivalent in efficacy to intravenous steroids.\(^{12,35}\)

As with asthma, corticosteroid use in COPD is reserved for limited periods to treat acute exacerbations. Short courses of SCSs increase the time to subsequent exacerbation, decrease the rate of treatment failure, short hospital stays, and improve hypoxemia and pulmonary function testing.\(^{24}\) Oral steroids are as efficacious as intravenous steroids for most patients.\(^{36}\) However, intravenous steroids are the best choice for those patients with poor intestinal absorption or comorbid conditions that prevent safe oral intake (e.g. decreased mental status, vomiting).\(^{24}\)

There are a multitude of trade names for SCSs. Trade names for prednisone include Deltasone\(^{®}\), Sterapred\(^{®}\), Sterapred DS\(^{®}\), and Orasone\(^{®}\). Trade names for prednisolone include Orapred\(^{®}\), Orapred\(^{®}\) ODT, Prelone\(^{®}\), Pediapred\(^{®}\), and Millipred\(^{®}\). Trade names for methylprednisolone include Solu-Medrol\(^{®}\), Medrol\(^{®}\), and Medrol\(^{®}\) DosePak\(^{®}\). Dexamethasone is another SCS that is not used as frequently for asthma or COPD, and it is sold under the trade names of Decadron\(^{®}\), Dexak\(^{®}\) Taperpak, Dexamethasone Intensol\(^{®}\).

**Mast Cell Stabilizers**
Cromolyn sodium and nedocromil sodium are two agents that are used for maintenance treatment of asthma only, and not for COPD or for acute asthma treatment. They are considered mast cell stabilizers, though their mechanism of action is slightly different. Cromolyn is the first generation drug, and it prevents the activation and degranulation of mast cells by stabilizing their membranes. Nedocromil does that, too, but it also prevents the release of chemotactic and inflammatory mediators by neutrophils, eosinophils, monocytes, and alveolar macrophages. The chemical structure of these two medicines are shown below.

Cromolyn sodium and nedocromil prevent both the early- and late-phase response to inhaled allergens. They are less effective than ICSs, so they are used as alternative medications for long-term control in patients who have mild persistent asthma. They can also be used to prevent exercise-induced asthma.

Side effects are minimal for both agents, and usually consist of minor complaints such as unpleasant taste or sore throat. Multiple studies have demonstrated that the adverse effects in trials of cromolyn and nedocromil are usually no different from that of placebo.

The trade name for cromolyn sodium is Intal® (MDI). The trade name for nedocromil is Tilade® (MDI).

**Phosphodiesterase 4 Inhibitors**

*Mrs. Rosenblatt is still worried about the Serevent® she got. She read something in a magazine about a new “wonder drug” for COPD called Daliresp®, and she likes it because it’s a pill, not an inhaler. Why didn’t her doctor give her this medicine instead of that Serevent®?*
Phosphodiesterase 4 (PDE4) inhibitors are a class of medicines that hold a lot of promise for treatment of asthma and COPD. Currently, there are two PDE4 inhibitors approved by the FDA for COPD treatment: roflumilast and cilomilast. Their chemical structures are shown below.  

![Roflumilast](image1.png) ![Cilomilast](image2.png)

Phosphodiesterases are a group of enzymes that degrade the phosphodiester bonds of cAMP and cyclic guanosine monophosphate (cGMP). Phosphodiesterases participate in many processes, including inflammation, cognition, apoptosis, and ion channel function. PDE inhibitors, therefore, help to increase cAMP and CGMP levels, which helps relax airway smooth muscle and leads to bronchodilation. But PDEs also have anti-inflammatory effects, and PDE4 actions are especially noted in the lung.

Studies with the selective PDE4 inhibitor cilomilast showed not only improvement in pulmonary function tests, suggesting a bronchodilatory effect, but also decreased inflammatory cells in the airway. And several studies of roflumilast showed improvement in pulmonary function, an increased quality of life, and reduced frequency of COPD exacerbations.

Interestingly, theophylline is a non-selective PDE inhibitor, which is why investigators now feel that theophylline has some anti-inflammatory properties in addition to its bronchodilatory effects.

However, the side effects of both agents may limit their clinical use. Roflumilast has been associated with intractable diarrhea, acute pancreatitis, weight loss, psychiatric symptoms, and significantly more prostate, lung, and colorectal cancers than placebo. And cilomilast has been associated with nausea and vomiting.

The trade name for roflumilast is Daliresp® (tablets). The trade name for cilomilast is Ariflo® (tablets).
You can reassure Mrs. Rosenblatt that inhaled corticosteroids are actually much better for her COPD than the PDE4 inhibitors: the ICSs are more effective, and the PDE4 inhibitors come with many unpleasant side effects.

**Leukotriene Modifiers**

Leukotrienes are inflammatory mediators that contribute to eosinophil infiltration of asthmatic airways. Leukotriene modifiers are anti-inflammatory agents that interfere with the production or activity of leukotrienes. They are approved for use in asthma, but are not currently approved for use in COPD. There are two classes of leukotriene modifiers. The first class is the cysteinyll leukotriene receptor antagonists (LTRAs): montelukast and zafirlukast. The other class is the lipoxygenase inhibitors, which inhibit leukotriene synthesis: zileuton. The chemical structure for these compounds are shown below.

Montelukast

Zafirlukast

Zileuton
In clinical trials, the leukotriene modifiers have shown efficacy compared to placebo in improving daytime and nighttime asthma symptoms, increasing the number of days without symptoms, and reducing the number of asthma exacerbations. However, the effects were minimal, which is why leukotriene modifiers are alternative, not preferred, therapy for those with mild persistent asthma. ICSs are still the preferred preventive therapy. But for those who do not achieve good control with ICSs, leukotriene modifiers can be used as an “add-on” therapy.12,51

Side effects of leukotriene modifiers include elevation of liver enzymes and rare cases of liver toxicity. These are more severe when using zileuton. Therefore, providers need to monitor liver function tests when using zileuton.2

The trade name for montelukast is Singulair® (tablets). The trade name for zafirlukast is Accolate® (tablets). The trade name for zileuton is Zyflo® (tablets).

Anti-IgE

Omalizumab is a monoclonal anti-IgE antibody used for maintenance therapy in asthma. This antibody prevents binding of IgE to high-affinity receptors on basophils and mast cells. It is reserved for patients 12 years of age and older who have sensitivity to relevant allergens (e.g. dust mite, cockroach, cat, or dog) and have severe persistent asthma that is not well controlled with high dose ICSs and LABAs. Omalizumab is administered subcutaneously in the physician’s office. The most significant side effect is anaphylaxis, so providers using this need to be prepared for that possibility.12,25 One study comparing omalizumab to placebo showed significant improvements in asthma control, but only in patients with poorly controlled asthma.52

The trade name for omalizumab is Xolair®.

Combination Medications

Luis’s mother comes back to the pharmacy a few months later and is complaining that her son’s medicine was changed again. She reports that they stopped the inhaled steroid and put him on Advair®. She knows there are two medicines in this inhaler. She asks you if that seems like too much medicine for a little boy.

Medications that combine two or more of the agents already discussed are quite common in treating both asthma and COPD. There are a multitude of combinations, including cromolyn/albuterol, and ipratropium/albuterol. But the most common combination is a LABA with an ICS. For asthmatics, LABAs are the preferred adjunctive therapy to be added to ICSs for those who do not achieve good control with medium dose ICSs alone.12

One of the first studies of this combination investigated the efficacy of fluticasone/salmeterol compared to fluticasone alone. Patients treated with the
combination therapy had greater improvement in FEV$_1$, asthma symptom score, and percent of days with no asthma symptoms compared to those treated with monotherapy.$^{53}$ More recent studies have supported these findings, and have shown the benefits of combination therapy over monotherapy with ICS in preventing severe exacerbations of asthma, even in high-risk populations.$^{54}$

The use of combination medications has even become so commonplace that it has spawned an entire approach to treating asthma. The Single Inhaler Maintenance and Reliever Therapy (SMART) uses the ICS/LABA inhaler in a novel way. Traditionally, an asthmatic used an ICS/LABA combination for maintenance therapy, and then used a SABA inhaler as a rescue medicine when needed. In the SMART approach, the asthmatic uses only one ICS/LABA inhaler for both maintenance and as a rescue medicine. The rationale is that the higher ICS use at the time of increased symptoms improves outcomes by reducing exacerbation risk.$^{55}$ The most recent evaluation of SMART care versus guideline-driven usual care showed that use of budesonide/formoterol therapy in a SMART model over 12 months produced a lower total ICS dose and increased peak flow volumes.$^{56}$

You can confidently answer Luis’s mother by stating that the combination medicine is not too much for him, and may actually decrease his total steroid intake and keep him form having so many exacerbations. You can tell her it’s the SMART thing to do.

For COPD patients, the combinations used are even greater in number. In addition to the usual ICS/LABA combinations$^{57}$, a combination of tiotropium with ICS and LABA was compared to the ICS/LABA therapy. Use of the triple therapy was associated with a decreased risk of mortality, COPD exacerbations, and COPD hospitalizations.$^{58}$ Unlike the other combinations mentioned, there is currently no single inhaler that combines tiotropium, an ICS, and a LABA.

There are many combination inhalers, some of the most popular of which are Intal® (cromolyn and albuterol), Combivent® (ipratropium and albuterol), Advair® (fluticasone and salmeterol), and Symbicort® (budesonide and formoterol, the original SMART combination).

Other Therapies

Antihistamines

Because of their immunomodulating effects, antihistamines have been tried as treatments for asthma and COPD. However, studies are lacking that demonstrate antihistamines’ clinical benefits. One review of 14 studies of antihistamines in allergic rhinitis and comorbid asthma concluded that antihistamines may have a beneficial effect on asthma, but that further studies are needed.$^{59}$ In COPD patients, cetirizine was shown to have some beneficial effects, though not clinically significant.$^{60}$ Perhaps with discovery of additional histamine receptors and the development of next generation antihistamines, the
promise of these drugs will be realized, but they presently are not considered effective in treating asthma or COPD.

**Antibiotics**

Antibiotics have no direct role in treating asthma, though they are important for treating acute comorbid conditions, such as sinusitis and pneumonia. However, antibiotics play a much more significant role in treating COPD exacerbations. Acute COPD exacerbations are associated with a mortality rate of 10% for those admitted to the hospital, whether admitted to the ICU or not. And for patients who have an exacerbation with signs of respiratory failure, the mortality rate for 6 to 12 months after the exacerbation is between 30% and 40%. Therefore, early and aggressive treatment of COPD exacerbations is critical. Viruses and bacteria are known triggers of exacerbations, so treatment with antibiotics is urged for patients with an exacerbation. One half of patients with exacerbations have high concentrations of bacteria in their lower airway.\(^{16,24}\)

The choice of antibiotics to use depends on many factors, including patient history, local resistance patterns, and culture results of sputum or blood. However, *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis* and *Mycoplasma pneumoniae* are the most common bacteria found on culture.\(^{24}\)

Because of the anti-inflammatory properties of the macrolide antibiotics, investigators have studied using these agents as a prophylactic treatment to prevent exacerbations. One study demonstrated that daily azithromycin use for 1 year, in addition to usual treatment, decreased the frequency of COPD exacerbations and improved quality of life, but caused a decrease in hearing in some patients. Furthermore, the rate of isolation of macrolide-resistant bacteria increases with this treatment.\(^{61}\) For now, there is no role for routine use of antibiotics in prevention of COPD exacerbations.

**Statins**

Statins are another group of agents that have some immunomodulating and anti-inflammatory effects that have led some to believe they may be used to treat COPD. A recent review of nine original studies involving the effects of statin treatment in COPD demonstrated that statins decrease all-cause mortality, decrease COPD-related mortality, reduce the incidence of COPD exacerbations, and attenuate a decline in pulmonary function. Only one of these studies was a randomized clinical trial. The conclusion was that statins may reduce morbidity and mortality in COPD patients, but it is still too early to advocate for routine used of statins in this population.\(^{62}\)

**Allergy Immunotherapy**

Allergens can precipitate an asthma or COPD exacerbation, but allergen immunotherapy is recommended only for asthma patients, especially in children. The NIH guidelines urge providers to consider subcutaneous allergen immunotherapy for patients who have persistent asthma when there is clear evidence of a relationship between symptoms and
exposure to an allergen. Such therapy is usually more useful against single allergens, especially dust mites, animal dander, and pollen.

**Vaccinations**

For asthma and COPD patients, influenza is a known powerful trigger of exacerbations, pulmonary complications, and even death. Fortunately, prevention is possible with yearly influenza vaccinations, which are highly recommended for these groups of patients.\(^{25,63}\) Adults aged 19 to 64 who have COPD should be given the 23-valent pneumococcal vaccine once, and again after age 65 years if the previous vaccination was given more than 5 years earlier.\(^{63}\)

**Devices**

*Mrs. Rosenblatt suffered an exacerbation and was hospitalized. You are the pharmacist assigned to the floor she is on. The team has decided to put her on nebulized albuterol. What can you tell them about using an MDI and spacer versus nebulized albuterol?*

Effectively delivering the medicine to the patient is a chronic problem in both asthma and COPD. Most inhaled medicines come as MDIs. Most experts recommend using a valved holding chamber (VHC or “spacer”) device to help administer the medicine. These devices are recommended for all ages, not just young children. Spacers minimize the problem of poor inhalation techniques with MDIs, reduce oropharyngeal deposition, and increase lung deposition of the medicine. Spacers may increase the response to beta\(_2\) agonists. Large-volume spacers are recommended for delivering high doses of inhaled corticosteroids and may allow a lower maintenance dose to be used.\(^{64}\) Another benefit of VHCs is that they may improve care in COPD, even when compared to a nebulizer. A chart review of 259 patients admitted for severe, non-life-threatening COPD exacerbations revealed that patients missed 24.3\% of their nebulized bronchodilator doses. These doses need to be administered by respiratory therapists, who often have conflicting assignments. Using an MDI with a VHC, which can be administered by nursing staff, can decrease the number of missed doses and improve care for these patients.\(^{65}\)

As the hospital pharmacist, you can advise the medical team that just because Mrs. Rosenblatt is in the hospital, she does not have to get her bronchodilators via a nebulizer. Giving her the medicine via an MDI and VHC may help ensure that she does not miss any doses and actually improve her care.

For those asthmatic patients who are old enough to comply, using a peak flow meter may help better control their asthma. If a patient knows her baseline measurements on the peak flow meter, then she can quickly start the appropriate medicine or seek assistance when her peak flow readings start to decline significantly.\(^{25}\)
References

Note: all trade names refer to the products used for asthma or COPD, not for other uses. And trade names reflect those drugs that are available in the United States.

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