MTM essentials for COPD management: Part 1

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Abstract
Chronic obstructive pulmonary disease (COPD) is a common worldwide cause of mortality. This condition is a burden on the patient, healthcare systems, and the economy. Proper pharmacologic treatment for COPD has been shown to reduce exacerbations and improve a patient’s symptoms. Pharmacists can play an important role in ensuring the appropriate care of patients with COPD, which should help to alleviate the burden of this disease on patients and the healthcare system.

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Welcome to the CPE series, Medication Therapy Management for the Patient with Respiratory Disease, which was designed for pharmacists who take care of patients with respiratory disease. Beginning in April 2015 and continuing through December 2015, pharmacists can earn up to 18 hours of CPE credit with 9 monthly knowledge-based activities from the University of Connecticut School of Pharmacy and Drug Topics.

This series kicked off in April with MTM essentials for asthma management—Part 1, covering the pathophysiology of asthma, clinical presentations of asthma, assessment methods, and nonpharmacologic management options. In May the second part of MTM essentials for asthma management included the step-care approach of management and pharmacologic options for adults and children. This month and next, the focus shifts to MTM essentials for chronic obstructive pulmonary disease (COPD) management. The August CE activity is a primer on inhalers and nebulizers. In September, pharmacists have the opportunity to learn about allergic rhinitis management. In October, the CE activity covers MTM essentials for cold, flu, and sinusitis management. The November CE activity includes drug-induced pulmonary disease recognition and management and idiopathic pulmonary fibrosis. The series concludes in December with a focus on MTM essentials for cough management.

The series also offers application-based and practice-based activities in 2016.

Background
Chronic obstructive pulmonary disease (COPD) is a preventable and treatable respiratory disease characterized by increased airway inflammation and an incompletely reversible obstruction of airflow. Symptoms are both persistent and progressive and may worsen during acute episodes of exacerbations. Exacerbations result in decreases in functional status and quality of life and increases in healthcare expenditure and mortality. COPD is currently the third leading cause of death in the United States and worldwide. Yearly direct costs of COPD in the United States are estimated to be close to $30 billion (with another $20 billion in indirect costs), with exacerbations responsible for the greatest proportion of total burden. Because of these factors, COPD care has been one of the targets of healthcare improvement and reform. As with congestive heart failure, hospitals will be penalized for excessive 30-day readmissions for COPD in an attempt to reduce costs and improve quality of care.

As efforts are made to improve care, pharmacists can play a role in hospital and community settings to assure quality care and thereby reduce associated morbidity, mortality, and healthcare expenditure. To do this, it is essential for pharmacists to have an adequate understanding of all aspects of COPD, including its pathophysiology, prevention, and management, as well as how this condition differs from another common chronic respiratory disorder, asthma.

Pathophysiology of COPD
Although all of the causes and mechanisms responsible for the development of COPD have yet to be fully elucidated, the general picture is clear. In the vast majority of cases, COPD is a result of chronic exposure of the airways to noxious particles. These noxious particles may come from a number of different sources, including air pollution (both indoor and outdoor) and occupational exposure, but for most patients, the primary cause of COPD is smoking. It is estimated that 80% to 90% of all patients with COPD have a smoking history. However, it is also estimated that approximately 20% of smokers will develop COPD. For these reasons, the body’s response to exposure and genetic predispositions for COPD have been of interest in research regarding potential preventive and treatment strategies.

Pathologically, changes can be seen throughout the respiratory system in patients with COPD. These changes can involve the airways, the lung parenchyma (areas of the lung involved with gas exchange), and the pulmonary vasculature. The type, extent, and distribution of these changes vary from person to person but have been historically categorized into two major groups or presentations of COPD: emphysema and chronic bronchitis.

Emphysema
Emphysema refers to the remodeling of the terminal airways, in particular the alveoli. These air sacs are small elastic structures that provide a large surface area for gas exchange. In emphysema, these alveoli become damaged in two ways. First, they lose their elasticity and can no longer stretch and return easily to their original size and shape during inhalation and exhalation. This prevents air from being fully exhaled. As a result, emphysematous lungs become hyperinflated. The second type of damage that happens in emphysema is the breakdown of the alveolar structure. As a result of this breakdown, the total surface area of the lung available for gas exchange is reduced. The combination of these two changes results in “air trapping” and incomplete gas exchange in a lung that is structurally weaker. Patients with emphysema experience shortness of breath as a result.

Chronic bronchitis and small airway disease
Unlike emphysema, which is defined by physical changes in the alveolar structure of the lungs, chronic bronchitis is defined by a clinical description of symptoms: the presence of cough and excess sputum production for at least three months per year for two consecutive years. This excess sputum and cough are a result of an increase in size of mucus glands and the number of goblet cells (cells that are responsible for secreting the main components of mucus) in response to continued injury by noxious particles.

When these noxious particles contact epithelial cells in the respiratory tract, a nonspecific inflammatory response is triggered.
As part of this process, cytokines (such as tumor necrosis factor-α and interleukin-1 and 8) attract members of the innate immune system, including macrophages, neutrophils, and dendritic cells. A release of proteolytic enzymes and reactive oxygen species results in further damage to the airways. With prolonged exposure, the damage may become permanent and inflammation may remain even after years of smoking cessation.6

Chronic bronchitis contributes narrowing of the airways and increased mucus secretion to the COPD pathology. This increased resistance (obstruction) to the flow of air results in greater effort required to breathe. Increased mucus not only worsens what little space is open in the airways but also leads to a characteristic, long-standing cough.

Although these two presentations of COPD are easily isolated by their respective definitions, the clinical picture is not so clear. Patients frequently have a combination of emphysema and chronic bronchitis, with relative contributions that vary from person to person. This respiratory state results in the three characteristic symptoms of COPD: progressive shortness of breath, chronic cough, and excessive sputum production that may vary from day to day.2 As a result, the terms of and distinction between “emphysema” and “bronchitis” are being de-emphasized and are not included in the current definition used by the global initiative for chronic obstructive lung disease guidelines.

**Genetic differences**

Genetic factors may predispose a patient to the development of COPD upon exposure to noxious particles or even in the absence of such exposure. The most well-understood example of these genetic factors involves alpha-1 antitrypsin deficiency.2 Alpha-1 antitrypsin is a protease inhibitor that is naturally produced in the liver and has a variety of functions. Patients with a deficiency of alpha-1 antitrypsin present with shortness of breath, wheezing, and exercise intolerance, with some patients eventually developing emphysema.8

**COPD versus asthma**

**Pathophysiology**

Asthma is a condition in which the lungs become hyper-responsive to irritating stimuli. As a result, a patient with asthma experiences shortness of breath and wheezing due to bronchoconstriction, inflammation, and increased mucus production. These attacks are recurrent but can be avoided or reduced in frequency and severity with adequate treatment. In COPD, the primary and defining characteristic is the existence of incomplete reversibility of airflow obstruction. This is a key distinction between COPD and asthma. With adequate treatment, a patient with asthma may have normal lung function between periods of symptoms. In COPD, this is not the case. There is a baseline loss of function, and so despite adequate treatment, patients with COPD will have some degree of constant airflow limitation. This clinical presentation correlates with findings seen in chest imaging. In patients with asthma, a chest X-ray will generally appear normal. In patients with COPD, structural changes, such as hyperinflation, can be seen.5 Refer to Table 1 for a comparison of features associated with asthma and COPD.5 11

**Presentation**

Asthma and COPD also differ in terms of when they present. Asthma may present at any age, but the onset is most common in childhood. Patients with COPD, on the other hand, are generally aged at least 40 years at disease onset.8 This highlights the chronic and progressive nature of COPD as well as the potential for early interventions (eg, smoking cessation) aimed at preventing the development or progression of COPD.

Management of Asthma and COPD

In terms of management, many of the core therapies used in asthma and COPD are quite similar. For both disease states, short-acting beta-2 agonists (SABAs), long-acting beta-2 agonists (LABAs), and inhaled corticosteroids (ICSs) may be used. However, the efficacy, point of initiation, and place in therapy for these agents may be different in patients with COPD and those with asthma.24 For example, patients with COPD and those with chronic asthma may both use inhaled LABAs and ICSs as part of their daily medication regimen. For the patient with COPD, the LABA would likely be added first, without the use of an ICS. In the patient with asthma, the reverse is true. In asthma, ICSs are generally used earlier in the course of treatment, and a LABA may or may not eventually be added. In fact, patients with asthma should not use a LABA
without an ICS, as the use of a LABA alone has been shown to increase mortality because of airway spasticity (a factor seen more often in asthma than in COPD). For a patient with COPD, however, the use of a LABA without an ICS is common in cases involving moderately severe symptoms. This is a key distinction in treatment strategies between these disease states. The GOLD guidelines recommend the addition of an ICS in patients with severe to very severe COPD with frequent exacerbations that are not adequately controlled by long-acting bronchodilators. The use of ICS is recommended in combination with LABAs, not as monotherapy for management of COPD. The guidelines for asthma diagnosis and treatment, the Expert panel report-3, support ICS as a cornerstone of therapy once asthma becomes persistent to manage long-term control of the disease beginning with mild presentations of severity.

Another broad distinction in therapy comes with the use of inhaled long-acting anticholinergics. In patients with COPD, a long-acting anticholinergic may be one of the first bronchodilators added to a regimen. However, inhaled long-acting anticholinergics are not listed in the Expert panel report-3 stepwise treatment algorithm for asthma management. That being said, long-acting anticholinergics may still have a role in asthma management for patients who cannot tolerate standard therapy.

Asthma and COPD?

Although hyperresponsiveness is more commonly associated with asthma, this characteristic can be present in cases of COPD as well; some degree of hyperresponsiveness is seen in approximately 60% of patients with COPD.

Research and clinical experience have shown that there are patients who do not clearly fit into the categories of either “asthma” or “COPD.” Although certain aspects of one disease may predominate, a prevalence rate of overlap ranging from 15% to 55% has been reported. While the prevalence of concurrently diagnosed asthma and COPD in a single patient is at the lower end of this range (15%-20%), this is still a significant subset of patients deserving further attention. In these patients, symptoms and outcomes tend to be worse and patients tend to have a more rapid decline in function versus patients with either condition alone.

### TABLE 2

**RECOMMENDED USE OF SHORT-ACTING BRONCHODILATORS BY PATIENT GROUP**

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Short-acting beta-2 agonists (SABA)</th>
<th>Mechanism of Action: Stimulates beta-2 receptors resulting in relaxation of bronchial smooth muscle</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOLD treatment strategy for patient groups</td>
<td>Primary therapy</td>
<td>Alternative therapy option</td>
</tr>
<tr>
<td>Group A: SAMA</td>
<td>Group A: SAMA</td>
<td>Groups B, C, and D: SAMA or SABA + SAMA</td>
</tr>
<tr>
<td>Generic</td>
<td>Brand</td>
<td>Strengths of dosage forms</td>
</tr>
<tr>
<td>Albuterol</td>
<td>Ventolin HFA, Proventil HFA, ProAir HFA, ProAir RespClick</td>
<td>Inhalers: 90 mcg/actuation Neb: 0.63 mg/3 mL, 2.5 mg/3 mL</td>
</tr>
<tr>
<td>Levalbuterol</td>
<td>Xopenex HFA, Xopenex (neb)</td>
<td>Inhaler: 45 mcg/actuation Neb: 0.63 mg/3 mL, 1.25 mg/3 mL</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Short-acting muscarinic receptor antagonists (SAMA)</th>
<th>Mechanism of Action: Block the effects of acetylcholine on muscarinic receptors resulting in relaxation of bronchial smooth muscle</th>
</tr>
</thead>
<tbody>
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<td>Primary therapy</td>
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</tr>
<tr>
<td>Ipratropium</td>
<td>Atrovent HFA</td>
<td>Inhalers: 17 mcg/actuation Neb: 0.02%, 2.5 mL</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Combination product: (SABA + SAMA)</th>
<th>Mechanism of Action: Stimulation of beta-2 receptors resulting in relaxation of bronchial smooth muscle + Block the effects of acetylcholine on muscarinic receptors resulting in relaxation of bronchial smooth muscle</th>
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<td>Groups B, C and D: (SABA + SAMA)</td>
<td></td>
</tr>
<tr>
<td>Generic</td>
<td>Brand</td>
<td>Strengths of Dosage forms</td>
</tr>
<tr>
<td>Ipratropium/albuterol</td>
<td>Combinvent, Combinvent Respimat, DuoNeb</td>
<td>Inhaler: Combinvent: 18 mcg/90 mcg per actuation Combinvent Respimat: 20 mcg/100 mcg per inhalation Neb: DuoNeb: 0.5 mg/2.5 mg per 3 mL</td>
</tr>
</tbody>
</table>

Abbreviations: Neb, nebulizer

Source: Ref 2, 46-55
**Assessment tools for COPD**

The GOLD guidelines recommend tools for diagnosis, disease staging, and disease management. These tools are used to classify COPD cases into categories. For each category, there are recommended treatment strategies.

**Spirometry**

A diagnosis of COPD should be considered for any patient demonstrating progressive or persistent dyspnea, chronic cough, or sputum production with a history of exposure to noxious particulates (eg, cigarette smoke), a family history of COPD, or any combination of these factors. However, the updated 2015 GOLD guidelines state that spirometry is required for a confident diagnosis of COPD. Patients who undergo spirometry first receive a dose of a bronchodilator, which will alleviate any reversible bronchoconstriction. Spirometry is then performed to assess the severity of obstruction of airflow by measuring the ratio of forced expiratory volume in one second to the forced vital capacity (FEV1/FVC). A diagnosis of COPD is confirmed when FEV1/FVC is less than 0.7. The FEV1 obtained from this test also stratifies cases into grades of severity: GOLD 1, mild airflow limitation with an FEV1 ≥80% of predicted value; GOLD 2, moderate airflow limitation with an FEV1 between 50% and 79% of predicted value; GOLD 3, severe airflow limitation with an FEV1 between 30% and 49% of predicted value; and GOLD 4, very severe airflow limitation with an FEV1 less than 30% of predicted value. Spirometry also provides some of the information required to identify the best treatment strategy for each patient. FEV1 alone is a poor indicator of symptoms and disease burden for an individual patient; the patient’s current symptoms, exacerbation risk, and comorbidities must also be considered.³

**Symptom questionnaires**

Three surveys are simple enough to be commonly used to assess a patient’s symptoms. The modified British Medical Research Council Questionnaire (mMRC) assesses a patient’s reported degree of breathlessness in relation to level of activity. The higher the mMRC grade (mMRC grade zero to grade four), the more easily a patient experiences shortness of breath. The COPD assessment test (CAT) is an eight-question survey on a six-point scale that is used to assess symptoms and the effect of the disease on quality of life. The CAT is a quick and easy assessment that can be completed during an office visit. Scores range from zero to 40, with higher scores indicating a greater effect of COPD on a patient’s health status. The COPD control questionnaire (CCQ) is a two-minute, 10-question patient survey of a patient’s symptoms over the previous week that is used to assess control of the disease. All of these tools can quickly measure the symptomatic burden of COPD on the patient, but these tools alone do not direct practitioners to a treatment strategy.

**Exacerbation risk**

GOLD spirometric grades provide population-based estimates for exacerbation risk (the risk of exacerbation increases with increasing airway obstruction). GOLD levels 3 and 4 indicate a high risk of exacerbation. However, for an individual, these grades do not provide a good estimate of future exacerbation risk. For a specific patient, his or her personal exacerbation history is an important prognostic marker for future exacerbation risk. A single hospitalization for an exacerbation in the previous year or a patient history of two or more exacerbations in the previous year indicates a high risk of future exacerbations.

**The Combined COPD Assessment**

The Combined COPD Assessment pulls together an individual’s GOLD grade, symptom assessment, and exacerbation risk to define a patient group and treatment strategy for that individual. To use the tool, the results from the patient’s CAT or mMRC are used to identify whether the patient’s COPD is best categorized by the boxes on the right or left of the tool. Boxes on the left indicate a CAT score of less than 10 or an mMRC grade of zero to one. Boxes on the right indicate a CAT score of 10 or higher or an mMRC grade of two or higher and are associated with more severe symptoms. A patient’s risk of exacerbations identifies whether the patient’s COPD is best categorized by the upper or lower boxes on the tool. The upper box is associated with a high risk of exacerbations, and the lower box is associated with a lower risk.

To use this tool, clinicians should use the worst score of either the mMRC or CAT surveys to place the patient in the left or right column of the grid, and then use the worst of either the exacerbation history or the airflow limitation stage to place the patient in the top or bottom row. The quadrant in which the identified row and column intersect represents a patient group (A, B, C, or D) and an appropriate therapy strategy.

For a specific patient, his or her personal exacerbation history is an important prognostic marker for future exacerbation risk.

**Comorbidity assessment**

Patients with COPD commonly have other comorbidities. This may be because most patients with COPD are older and therefore at increased risk of other diseases, or because the risk factors leading to COPD also lead to other pathologies and diseases. Comorbidities must be recognized and carefully managed to avoid the worsening of symptoms and health status, which in turn may worsen exercise intolerance, making COPD management more difficult. For example, anxiety can lead to shortness of breath, thus initiating an episode of breathlessness that can in turn worsen feelings of anxiety. To ensure symptom control, both disease states must be carefully managed to avoid one precipitating symptoms of the other. Depression is a common comorbidity among COPD patients and must be carefully considered when initiating therapy with a phosphodiesterase-4 inhibitor.

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**Pause & Ponder**

**What role could pharmacists play in preventing COPD?**
**Medical management of COPD**

The goals of treatment for patients with COPD include reductions in symptoms, disease progression, and risks of exacerbation and mortality and improvements in exercise tolerance and health status.²

**Bronchodilators**

Bronchodilators are the primary therapy for COPD management. The inhaled route of administration is preferred, as this delivers the medication directly to the lungs for maximal effect and with minimal side effects. Beta-agonists and inhaled anticholinergics are both classified as bronchodilators because they open up the airways of the lungs, resulting in an increase in FEV1. Beta-agonists bind and stimulate the beta-2 adrenergic receptor of the lungs, resulting in an increase in relaxation of smooth muscle and a reduction in bronchoconstriction. SABAs may be used for bronchodilation as scheduled or on an as-needed basis. The use of LABAs allows for prolonged symptom relief with fewer doses of medication. Patients taking LABAs have demonstrated improvements in FEV1 and breathlessness and a reduction in exacerbations but no reduction in disease progression or mortality.²¹²⁷ LABAs and SABAs may be prescribed together. However, adverse effects are dose related, so the use of high-dose, as-needed SABAs in addition to scheduled LABAs is not supported by the guidelines. Adverse effects of beta-agonist medications may include palpitations, tachycardia, and tremor.² When these agents are used in combination with

**TABLE 3**

**PHARMACOLOGIC MANAGEMENT STRATEGIES WITH LONG-ACTING BRONCHODILATORS BY PATIENT GROUP**

<table>
<thead>
<tr>
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<th>Long-acting beta-2 agonists (LABA)</th>
</tr>
</thead>
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<td>Mechanism of Action</td>
<td>Stimulates beta-2 receptors resulting in relaxation of bronchial smooth muscle</td>
</tr>
<tr>
<td>GOLD treatment strategy for patient groups</td>
<td></td>
</tr>
<tr>
<td>Primary therapy</td>
<td>Alternative therapy option</td>
</tr>
<tr>
<td>Group B: LABA</td>
<td>Group A: LABA</td>
</tr>
<tr>
<td>Group C: LABA + LAMA</td>
<td>Group B: LABA + LAMA</td>
</tr>
<tr>
<td>Group D: ICS + LABA or ICS + LABA + LAMA</td>
<td>Group C: LABA + LAMA or LABA + PDE4 inhibitor</td>
</tr>
<tr>
<td>Generic</td>
<td>Brand</td>
</tr>
<tr>
<td>Formoterol</td>
<td>Foradil Aerosolizer, Perforomist</td>
</tr>
<tr>
<td>Arformoterol</td>
<td>Brovana</td>
</tr>
<tr>
<td>Indacaterol</td>
<td>Arcapta Neohaler</td>
</tr>
<tr>
<td>Salmeterol</td>
<td>Serevent Diskus</td>
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</tbody>
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</tr>
<tr>
<td>Generic</td>
<td>Brand</td>
</tr>
<tr>
<td>Tiotropium</td>
<td>Spiriva HandiHaler, Spiriva Respimat</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Aclidinium</td>
<td>Tudorza</td>
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<tr>
<td>Umeclidinium</td>
<td>Incruse Ellipta</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Combination product: (LABA + LAMA)</th>
</tr>
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<tbody>
<tr>
<td>Mechanism of Action</td>
<td>Stimulation of beta-2 receptors resulting in relaxation of bronchial smooth muscle + Block the effects of acetylcholine on muscarinic receptors resulting in relaxation of bronchial smooth muscle</td>
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<td>GOLD treatment strategy for patient groups</td>
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<td>Primary therapy</td>
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<td>Group D: (LABA + LAMA) + ICS</td>
<td>Groups B, C and D: (LABA + LAMA)</td>
</tr>
<tr>
<td>Generic</td>
<td>Brand</td>
</tr>
<tr>
<td>Umeclidinium / vilanterol</td>
<td>Anoro Ellipta</td>
</tr>
</tbody>
</table>

Abbreviations: ICS, inhaled corticosteroids; LABA, long-acting beta-2 agonists; LAMA, long-acting muscarinic receptor antagonists; Neb, nebulizer

Source: Ref 2, 58-66
Corticosteroids
ICSs exert an anti-inflammatory effect on the airways by decreasing the formation, release, and activity of inflammatory mediators. The use of ICSs reduces exacerbations and modestly slows the progression of symptoms when these agents are administered as part of a combination regimen; ICSs should not be used as monotherapy for COPD. Adverse effects of ICSs are dependent on the dose and administration technique. Common adverse effects are hoarseness of voice and oral thrush. Oral thrush is more likely to occur if the patient does not rinse his or her mouth after administration of the medication. However, information about the long-term adverse effects associated with the use of ICSs in patients with COPD patients is lacking. Systemic oral corticosteroid therapy is generally reserved for treatment of exacerbations because of the significant adverse effects associated with long-term systemic corticosteroid exposure.

The combination of a bronchodilator plus an ICS is a common management strategy for patients with moderate to severe COPD. However, one study observed up to 75% of patients with COPD were prescribed an ICS. Many of these patients received a combination of ICS and LABAs as the initial strategy for COPD management. While an ICS is an effective strategy for reducing exacerbations, this treatment is not without associated harm, as well. The risk of pneumonia and fracture increases with the addition of regular use of an ICS to bronchodilator therapy. Patients groups administered ICS therapy in two separate trials demonstrated twice the rates of pneumonia compared to groups not exposed to ICS therapy. Although an analysis of risk factors associated with pneumonia in ICS users is similar to the known risk factors for pneumonia, proper timing of ICS initiation is prudent to maximize benefit and minimize risk associated with this therapy option for patients with COPD.

If patients are not adequately controlled on single bronchodilator therapy plus an ICS, triple therapy with a beta-agonist, an anticholinergic agent, and an ICS may improve lung function and quality of life. Triple therapy is more commonly prescribed for patients with refractory COPD and is used despite a lack of strongly supportive evidence. Further study of the use of triple therapy for the management of refractory COPD is necessary. Patients with refractory symptoms should also be assessed for adherence concerns, smoking cessation, and proper inhaler technique. An upcoming article in this continuing education series will address proper inhaler technique for the variety of available products on the market.

Cough is a protective mechanism that allows the body to clear the lungs of debris.

Other medications
Phosphodiesterase-4 inhibitors block the breakdown of cyclic AMP via phosphodiesterase-4 inhibition, which in turn reduces inflammation in the respiratory tract. The phosphodiesterase-4 inhibitor roflumilast is FDA approved for the reduction of exacerbations in patients with COPD associated with chronic bronchitis and a history of exacerbations. No dosage adjustments are recommended for elderly patients or for patients with renal impairment; however, strong inhibition of CYP3A4 or 1A2 enzymes can increase levels of roflumilast. The drug is contraindicated in patients with moderate to severe liver impairment (Child-Pugh class B or C). Adverse effects of this medication are significant but generally reversible with discontinuation of the drug and may be reduced over time with continued treatment. These adverse effects may include nausea, poor appetite, abdominal pain, diarrhea, sleep disturbances, and headache. Weight loss associated with this medication can be significant, which is problematic in patients with late-stage COPD for whom nutritional status is a key concern. Roflumilast has also been associated with adverse psychiatric reactions. In trials, patients taking roflumilast experienced higher rates of anxiety and depres-
sion. This drug should therefore be used with caution in patients with pre-existing anxiety and depression.33

Methylxanthines are thought to inhibit phosphodiesterase enzymes, resulting in bronchodilation. Theophylline is the only currently available oral dosage formulation. Theophylline, the most commonly used agent in this class, can reduce the occurrence of exacerbations in patients with COPD. With theophylline, drug levels should be maintained between 8 and 12 mcg/mL. CYP 1A2 inhibitors and inducers can affect the metabolism and alter plasma levels of theophylline. Cigarette

### TABLE 4
**RECOMMENDED USE OF ICS PLUS LAMA, LABA, PDE4 INHIBITOR BY PATIENT GROUP**

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Inhaled corticosteroids (ICS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanism of Action</td>
<td>Anti-inflammatory and immunosuppressive effects</td>
</tr>
</tbody>
</table>

#### GOLD treatment strategy for patient groups

<table>
<thead>
<tr>
<th>Group C: ICS + LAMA or ICS + LABA</th>
<th>Group D: ICS + LABA + LAMA or ICS + LAMA + PDE4 inhibitor</th>
</tr>
</thead>
</table>

<table>
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<tr>
<th>Generic</th>
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<td>beclomethasone</td>
<td>QVAR</td>
<td>Inhaler: 50 mcg/inhalation, 100 mcg/inhalation</td>
</tr>
<tr>
<td>budesonide</td>
<td>Entocort EC, Uceris, Pulmicort Flexhaler, Pulmicort Respules</td>
<td>24-hour Extended Release: Entocort EC: 3 mg capsule, Uceris: 9 mg tablet Neb: Pulmicort: 0.25 mg/2 mL, 0.5 mg/mL and 1 mg/2 mL budesonide: 0.25 mg/2 mL, 0.5 mg/mL and 1 mg/2 mL Inhaler: Pulmicort Flexhaler: 90 mcg/actuation</td>
</tr>
<tr>
<td>fluticasone</td>
<td>Flovent Diskus, Flovent HFA, Arnuity Ellipta</td>
<td>Inhalers: Arnuity Ellipta: 100 mcg/actuation, 200 mcg/actuation Flovent HFA: 44 mcg/actuation, 110 mcg/actuation, 220 mcg/actuation Flovent Diskus: 50 mcg/dose 100 mcg/dose 250 mcg/dose</td>
</tr>
</tbody>
</table>

#### GOLD treatment strategy for patient groups

<table>
<thead>
<tr>
<th>Group D: (ICS + LABA)</th>
<th>Group D: (ICS +LABA) + LAMA (ICS + LABA) + PDE4 inhibitor</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Generic</th>
<th>Brand</th>
<th>Strengths of Dosage forms</th>
</tr>
</thead>
<tbody>
<tr>
<td>budesonide / formoterol</td>
<td>Symbicort</td>
<td>Inhaler: 80 mcg/4.5 mcg per actuation, 160 mcg/4.5 mcg per actuation</td>
</tr>
<tr>
<td>fluticasone / salmeterol</td>
<td>Advair</td>
<td>Inhaler: HFA: 45 mcg/21 mcg per actuation, 115 mcg/21 mcg per actuation, 500/50 per actuation Diskus: 100 mcg/50 mcg per dose, 250 mcg/50 mcg per dose, 500 mcg/50 mcg per dose</td>
</tr>
<tr>
<td>fluticasone / vilanterol</td>
<td>Breo Ellipta</td>
<td>Inhaler: 100 mcg/25 mcg per inhalation</td>
</tr>
<tr>
<td>formoterol / mometasone</td>
<td>Dulera</td>
<td>Inhaler: 100 mcg/5 mcg per actuation, 200 mcg/5 mcg per actuation</td>
</tr>
</tbody>
</table>

**Abbreviations:** ICS, inhaled corticosteroids; LABA, long-acting beta-2 agonists; LAMA, long-acting muscarinic receptor antagonists; PDE4, phosphodiesterase-4

Source: Ref 2, 71-82
smoke is a CYP 1A2 inducer and can decrease plasma theophylline levels. Smoking cessation removes the induction to this enzyme and can also alter theophylline levels as a patient quits smoking. Common dose-related adverse effects include headache, nausea, insomnia, and heartburn. Arrhythmias and seizures are potential serious dose-related adverse events. Methylxanthines are not the preferred therapy for COPD management because of their limited beneficial effect, potential for toxicity, and multiple drug interactions.

Because thick secretions can be very problematic in patients with COPD, particularly in those with chronic bronchitis, mucolytics would seem to have great potential as a treatment option. However, studies have provided conflicting evidence regarding the use of mucolytics in patients with COPD. The GOLD guidelines, which were recently updated in 2015 do not recommend the use of mucoactive medications as a common treatment for COPD. However, the PEACE trial studied the use of carbocysteine versus placebo in 354 Chinese patients over one year. Patients in the carbocysteine group had a lower rate of exacerbations than those in the placebo group. The authors concluded that mucolytics still hold potential for the treatment of COPD and that carbocysteine should be considered an option for exacerbation prevention in Chinese patients. The GOLD guidelines do state that some patients with viscous sputum may achieve some benefit with mucolytics. More research is needed to better define the patient population who would reap the most benefit from this therapy.

Antitussives have also been considered for the treatment of patients with COPD. However, cough is a protective mechanism that allows the body to clear the lungs of debris. Stifling this mechanism inhibits the body’s ability to clear noxious particles from the lungs. The regular use of antitussives for the management of COPD is therefore not recommended.

Oxygen therapy is indicated when a patient has multiple confirmed instances of low blood oxygen levels over a period of weeks of stable disease, PaO2 <55 mmHg or SaO2 ≤88% or PaO2 between 55 and 60 mmHg or SaO2 of 88% with evidence of pulmonary hypertension, peripheral edema suggestive of congestive heart failure, or polycythemia (hematocrit >55%). Oxygen therapy increases survival in patients with resting hypoxemia, but its chronic use is not supported in ambulatory patients without chronic hypoxemia at rest. The use of oxygen therapy in patients with more moderate disease has not demonstrated a survival benefit.

Data regarding the prophylactic use of antibiotics in patients with COPD are conflicting, and the long-term consequences of antibiotic exposure on adverse effects, resistance patterns, and exacerbation management have not been defined. The prophylactic use of antibiotics is not currently supported in patients with COPD.

### Patient groups

Patients in group A have a low risk of exacerbation and few symptoms. The GOLD guidelines recommend a short-acting bronchodilator, either a beta-agonist or anticholinergic medication, used as needed for control of symptoms. Alternatively, a combination of short-acting bronchodilators or a long-acting bronchodilator may be used. There is little evidence supporting a treatment strategy for patients with mild COPD and a FEV1 >80%. However, the recommendations are based on the known beneficial effect of bronchodilators on breathlessness. Refer to Table 2 for product information and recommended use of SABAs by patient group. Similar to patients in group A, patients in group B have a low risk of exacerbation. However, group B patients have more severe symptoms than group A patients and may experience better control and convenience with a long-acting bronchodilator than with an as-needed short-acting bronchodilator.

For many patients, the most dramatic benefit comes from smoking cessation.

Either an inhaled beta-agonist or anticholinergic therapy is an acceptable choice for these patients. The guidelines do not support one class over the other as initial bronchodilator therapy for COPD. An alternative therapy, recommended by the guidelines, includes combination therapy with both classes of long-acting bronchodilators, LABA plus long-acting muscarinic antagonist (LAMA). Other options for bronchodilation include short-acting bronchodilators and theophylline, a xanthine derivative. See Table 3 for pharmacologic management strategies with long-acting bronchodilators by patient group.

Group C patients demonstrate few symptoms. Recommendations for these patients are not well defined. The guidelines do not recommend the use of mucolytics in Group C patients.
of life in patients with COPD and an FEV1 less than 60 percent.67-70 These patients can initially be treated with a combination of an ICS and LABA bronchodilator therapy or with an inhaled long-acting anticholinergic. There is evidence to support both strategies as first-line options in this patient population, but there is a paucity of data comparing the two strategies to clarify which may be best initial choice. Long-acting bronchodilators reduce exacerbation risk. Therefore, they are a sound clinical option despite a lack of long-term benefit on COPD and health status. The GOLD guidelines base the alternative recommendation of a corticosteroid in combination with an anticholinergic not on evidence but on the soundness of the therapeutic rationale. An alternative combination of LABA and LAMA inhalers without an ICS is a potential strategy, which may maximize bronchodilation via different mechanisms while minimizing the adverse effects of long-term ICS. Short-acting bronchodilators and theophylline are alternative strategies to consider in this patient population if long-acting bronchodilator therapy is not possible. Patients in group C may also benefit from adjunctive therapy with a phosphodiesterase-4 inhibitor in combination with long-acting bronchodilator therapy. Refer to Table 4 for product information.7,71,82

Group D patients have a high risk of exacerbation and a heavy burden of symptoms. A combination of an ICS and a LABA or a long-acting anticholinergic is recommended as initial therapy. However, because these patients have the most symptoms and are at the highest risk of exacerbation, an alternative primary strategy commonly employed in practice is combination therapy with an ICS plus long-acting inhaled bronchodilators, a beta-agonist, and an anticholinergic. A phosphodiesterase-4 inhibitor is a possible add-on therapy for this patient population.

Monitoring therapy

A yearly spirometry test is recommended for patients with COPD to identify any decline in lung function. Patients should also monitor their symptoms to be on guard for exacerbations that would require changes in therapy. Patients should recognize changes in breathlessness, exercise tolerance, cough, sputum production, requirements for as-needed medications, and frequency of exacerbations. Patient assessment tools such as the CAT or mMRC can be used to determine changes to the patient’s symptoms and health status, and this information can be used to guide changes in therapy.

Conclusion

COPD is a complex chronic disease that involves aspects of other chronic respiratory disorders, including bronchitis, emphysema, and asthma. Knowledge about the pathophysiology of the disease and about the patient’s degree of airflow obstruction, burden of symptoms, risk of exacerbation, and comorbidities is necessary for the proper management of COPD. Pharmacists are well positioned to facilitate implementation of an appropriate treatment strategy, assist patients with trending symptoms, and monitor for adverse effects to help assure the best patient outcomes.

The references are available online at www.drugtopics.com/cpe.

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TEST QUESTIONS

1. Which of the following contributes to the destruction of alveoli seen in COPD?
   a. Asthma  
   b. Bronchitis  
   c. Dyspnea  
   d. Emphysema

2. Which intervention provides the most benefit by altering the progression of COPD?
   a. Smoking cessation  
   b. Management of anxiety  
   c. Initiation of an antitussive medication  
   d. Switching from a SABA to a LABA for chronic management of COPD

3. Which of the following contributes most toward the excessive production of mucus in COPD?
   a. Asthma  
   b. Bronchitis  
   c. Dyspnea  
   d. Emphysema

4. A patient with possible COPD presents with an FEV1/FVC <0.70 and an FEV1 ≥30% but <50% of predicted value. According to the GOLD spirometric classification of COPD, what stage of COPD does this patient present?
   a. Grade 1: Mild  
   b. Grade 2: Moderate  
   c. Grade 3: Severe  
   d. Grade 4: Very severe

5. According to the GOLD guidelines, which of the following would be the recommended treatment(s) for a patient with grade 2 (moderate) COPD?
   a. Short-acting bronchodilator only (when needed)  
   b. Short-acting bronchodilator and yearly influenza vaccination  
   c. Short-acting bronchodilator (when needed), yearly influenza vaccination, one or more long-acting bronchodilators (when needed)  
   d. Short-acting bronchodilator (when needed), yearly influenza vaccination, one or more long-acting bronchodilators (when needed), rehabilitation

6. A patient comes into your pharmacy with a prescription for Pulmicort inhaler. Which of the following counseling points should you convey to this patient?
   a. “Pulmicort is an inhaled corticosteroid not to be used in conjunction with any other inhalers used for COPD.”  
   b. “Common side effects seen with Pulmicort include shortness of breath and vision changes.”  
   c. “Pulmicort is a metered-dose inhaler.”  
   d. “Oral thrush is common with Pulmicort, so it is advised that you rinse your mouth after each use.”

7. A patient experiencing refractory COPD disease is a candidate for:
   a. Triple therapy: tiotropium, salmeterol, and fluticasone  
   b. Assessment of inhaler technique to ensure maximum benefit of medications  
   c. Pulmonary rehabilitation  
   d. All of the above

8. Which of the following assessment tools is used to identify a treatment group for a patient?
   a. mMRC  
   b. COPD control questionnaire  
   c. Combined COPD Assessment  
   d. Exacerbation assessment scale

9. Which of the following medications may result in significant weight loss in patients with COPD?
   a. Levalbuterol  
   b. Roflumilast  
   c. Prednisolone  
   d. Tiotropium

10. A long-acting bronchodilator is not a recommended first-line therapy for which patient group?
   a. Patient group A  
   b. Patient group B  
   c. Patient group C  
   d. Patient group D

11. A phosphodiesterase-4 inhibitor is an appropriate choice for a patient with COPD who has a significant bronchitis component and which of the following?
   a. A history of exacerbations that places the patient at high risk of future exacerbations  
   b. GOLD spirometric classification of one or two  
   c. An mMRC score of zero to one  
   d. A CAT score of ten or higher

12. Your patient reports experiencing occasional tremor in association with the use of her medication. Which of the following medications is most likely associated with this adverse effect?
   a. Albuterol  
   b. Tiotropium  
   c. Roflumilast  
   d. Budesonide

13. If a patient taking an ICS does not regularly rinse his or her mouth after administration of the drug, which of the following adverse effects is likely to occur?
   a. Dental cavities  
   b. Canker sores  
   c. Oral thrush  
   d. Cold sores

14. Your patient has decreased renal function, benign prostatic hyperplasia, and asthma. Which of the following is the best initial selection for COPD treatment?
   a. An ICS  
   b. An inhaled beta-agonist bronchodilator  
   c. An oral methylxanthine bronchodilator  
   d. An inhaled anticholinergic bronchodilator

15. Which of the following is an appropriate treatment consideration for all patients with COPD?
   a. Smoking cessation  
   b. A regular exercise regimen  
   c. Yearly influenza vaccination  
   d. All of the above

16. Chronic therapy with which of the following is appropriate when objective markers of hypoxia have been observed in a resting patient?
   a. Pulmonary rehabilitation  
   b. Oral bronchodilator therapy  
   c. ICS therapy  
   d. Chronic supplemental oxygen therapy

17. The best COPD treatment strategy for a specific patient considers which of the following?
   a. Baseline FEV1  
   b. Symptoms of breathlessness  
   c. History and risk of exacerbations  
   d. All of the above

18. True or false: There is strong evidence to support the use of prophylactic antibiotics in patients with severe COPD.
   a. True  
   b. False

19. Which patient assessment tool focuses on the effect that COPD has on a patient’s quality of life?
   a. mMRC  
   b. CAT  
   c. CCQ  
   d. Combined COPD Assessment

20. It is important to manage which of the following disease states to maintain adequate control of COPD symptoms?
   a. Anxiety  
   b. Diabetes  
   c. Osteoporosis  
   d. Atrial fibrillation
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