Updates in the Management of Stable Chronic Obstructive Pulmonary Disease

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This is a knowledge-based activity. See end of article for CE details.

Target Audience: Pharmacists
Faculty Disclosure: The faculty have no conflicts of interest to disclose.

Goal: To review disease characteristics and discuss updates in the management of Chronic Obstructive Pulmonary Disease (COPD).

Objectives: At the conclusion of this lesson, participants should be able to:
1. Recall treatment algorithms and common pharmacologic agents used for treatment of COPD.
2. Interpret strategies identified in the 2011 GOLD guideline update which are used to assign patients into treatment groups.
3. Given a case example, appropriately assign a patient into a treatment group and select appropriate pharmacologic and non-pharmacologic therapy.
4. List advantages and disadvantages involved in using phosphodiesterase-4 inhibitors for the management of severe COPD.

Chronic Obstructive Pulmonary Disease (COPD) is a disease of the lungs characterized by persistent airflow limitation that is not fully reversible. Medications used in the management of COPD are not curative, but the disease is treatable with proper use of available therapeutic agents and preventable by reducing exposure to risk factors. Several guideline updates and new medications for COPD management have emerged in recent years.

Brief Review of Pathophysiology and Disease State Background
Airflow limitation due to COPD is progressive and associated with abnormal inflammatory response to noxious particles or gases. The airflow limitation is caused by several disease processes including small airway disease and parenchymal destruction. Small airway disease refers to airway inflammation and subsequent remodeling, whereas parenchymal destruction refers to loss of alveolar attachment and decreased elastic recoil. Together, these processes result in mucus hypersecretion, air trapping, and ultimately airflow limitation. Each of these components may be present to varying degrees in each individual patient, and therefore each patient’s COPD symptoms and traits are somewhat unique. The term “chronic bronchitis” is often used to refer to the small airway component of COPD, and is defined in the clinical setting as presence of cough or sputum production for a duration of greater than or equal to three months for at least two consecutive years. The term “emphysema” has historically been used interchangeably with COPD, but in actuality it refers more specifically to destruction of gas exchanging surfaces of alveoli.

Patients affected by COPD often have comorbidities related to their respiratory condition. Extrapulmonary effects of COPD secondary to ongoing shortness of breath include unintentional weight loss, nutritional deficits, and skeletal muscle dysfunction. COPD patients have also been associated with a higher occurrence of myocardial infarction, angina, osteoporosis, respiratory infection, depression, diabetes, and sleep disorders. Additionally, a higher incidence of lung cancer has been found in patients with COPD, however it is not known if the two are directly linked or if it is due to common risk factors.

Prevention of COPD progression is a key component of disease state management, and the primary method of preventing progression is to reduce or eliminate exposure to risk factors. The number one risk factor associated with COPD worldwide is tobacco smoking. The effect of tobacco smoking on COPD is dose related (i.e. higher number of pack-years smoking, higher risk and severity of COPD). Additional risk factors for COPD include indoor and outdoor air pollution, and occupational exposure to dusts and chemicals. Environmental risk factors aside, several host factors can cause predisposition to COPD including abnormal lung growth and development, prior respiratory infections, and alpha-1 antitrypsin deficiency.

Respiratory dysfunction and airflow limitation is evaluated using a combination of symptom assessment and spirometry, a type of pulmonary function test (PFT) that measures volume and speed of inhalation and exhalation. Diagnosis of COPD should be considered in any individual with dyspnea, chronic cough (productive or nonproductive), and/or sputum production. Guidelines also recommend spirometry as a part of diagnosis, with a ratio of Forced Expiratory Volume in One Second (FEV1) to Forced Vital Capacity (FVC) less than 70% (FEV1/FVC < 0.7) as the diagnostic criteria. Less than 70% is the threshold
that suggests airflow limitation is not fully reversible. Spirometry is the gold standard for COPD diagnosis because it is widely accessible, easily reproducible, and relatively inexpensive.

The primary clinical guidelines utilized in COPD management are entitled Global Initiative for Chronic Obstructive Lung Disease (GOLD). The GOLD guideline is a global initiative and consists of a consensus report that is updated annually. GOLD guidelines are available at www.goldcopd.com. There were several updates included in the most recent GOLD guideline. To summarize, treatment objectives were organized into two groups: immediately relieve and reduce impact of symptoms and reduce risk of adverse events that impact health in the future. FEV₁ was deemed an unreliable marker of severity of symptoms on its own, therefore higher emphasis was placed on symptom scoring and two validated symptom scoring surveys were recommended for use in clinical practice. The term “stage” was replaced with the term “grade” when classifying COPD severity, and a new assessment system that draws together impact of patient symptoms and assessment of future risk was introduced.¹

**Symptom Scoring and Assessment**

The December 2011 GOLD Guideline update suggests a stronger emphasis on symptom scoring based on patients perception of impact on daily life activities when compared to previous years. They endorse two validated symptom scoring surveys: the Modified Medical Research Council Questionnaire for Assessing the Severity of Breathlessness (mMRC) and the COPD Assessment Test (CAT) (Refer to Figures 1 and 2). GOLD guidelines suggest that one of these two surveys is administered to each patient as a part of the diagnostic and staging process. Both of the surveys are relatively simple and short in length; however the CAT is comprehensive of various aspects of COPD while mMRC focuses more specifically on severity of breathlessness. The clinical utilization of these surveys has not yet been fully established.

For the mMRC test, scores range from zero to four, with zero being minimal symptoms and four being severe symptoms. CAT test scores range from zero to forty, with zero being minimal symptoms and forty being severe symptoms. These symptom scores are used as part of the algorithm for placing the individual into a treatment group and selecting appropriate therapy.²

**Determining COPD Grade**

In addition to obtaining a symptom score, the guidelines also suggest placing the patient into a “grade” category (Refer to Table 1). The grade is based on the results of spirometry, specifically the percent of predicted FEV₁.¹

**Using Symptom Score and COPD Grade to Determine Treatment Group**

Both the symptom score and COPD Grade are used to determine treatment group. In addition, the number of COPD exacerbations the individual has experienced in the previous twelve months is also considered (Refer to Figure 3).¹

The symptom scoring surveys are listed along the bottom axis. Based on the patients symptom score, the severity of symptoms can be determined. Subsequently, along the vertical axis, the GOLD Grade is used to specify “low” or “high” risk. If the patient has had two or more COPD exacerbations in the past year, that automatically places them in the “higher risk” category.¹

**COPD Maintenance and Treatment**

The first step in COPD treatment is reduction of exposure to risk factors, specifically tobacco cessation when applicable. Smoking is associated with a greater rate of airflow decline and increased mortality associated with COPD. Tobacco cessation has been shown to be the most successful and cost effective method of preventing disease progression, and is an area where pharmacists can serve an important role.

It is also imperative that COPD patients receive appropriate vaccination with annual trivalent influenza vaccine as well as pneumococcal vaccine to reduce risk of respiratory infection.

An important education point for patients with regard to COPD is that none of the existing medications have been shown to modify the long-term decline in lung function, therefore pharmacotherapy is used to decrease symptoms, complications, or both. Goals of therapy for COPD are to prevent disease progression, relieve symptoms, improve exercise tolerance, improve health status, prevent and treat exacerbations and complications, reduce mortality, and minimize adverse effects of treatment. Along with elimination or minimization of risk factors, pharmacologic therapy is warranted for patients in all treatment groups. After the appropriate treatment group is determined, pharmacologic therapy can be individualized for the patient.¹

**Group A**

It is suggested that patients who are included in treatment Group A (low risk, less symptoms) initiate treatment with a short-acting bronchodilator such as a short-acting beta agonist or short-acting anticholinergic. Short-acting bronchodilators are used for acute relief of intermittent symptoms (“rescue medication”). Short-acting bronchodilators increase FEV₁ by altering airway smooth muscle tone, widening airways, and improving emptying of the lungs. If symptom relief is not sufficient with one short-acting bronchodilator, a combination of both can be used to maximize the bronchodilation effect through two different mechanisms. Combination products may also be helpful in challenging adherence situations.¹

The most common short-acting beta agonist is albuterol (via inhaler or nebulization) which has a short onset of action (less than five minutes) and relatively short duration of action (less than four hours). Adverse effects such as tachycardia, tremor, insomnia and headache are predictable and dose
dependent. Trade names for albuterol inhalers include Proair® and Ventolin®. Ipratropium (Atrovent®) is the most common short-acting anticholinergic (via inhaler or nebulization). Ipratropium has an onset of action of approximately fifteen minutes and duration of action about six to eight hours. It is generally well tolerated with adverse effects including dry mouth and metallic taste.

Combination products of short-acting beta agonist plus short-acting anticholinergic include Combivent® inhaler, and Duoneb® solution for nebulization. Traditional Combivent® inhalers are currently being transitioned to Combivent Respimat® inhalers, which are propellant-free. Traditional aerosolized Combivent® will only be available for a limited time, and will be completely phased out by the end of 2013. The Food and Drug Administration has ordered this change under the Clean Air Act and it is consistent with the changes that have taken place with other inhalers containing Chlorofluorocarbon (CFC) based on the Montreal Protocol, intended to help protect the ozone layer. While most CFC inhalers have already made the transition, Combivent® was granted an extension to accommodate the challenges in converting a medication with more than one ingredient.

It is important for pharmacists to become familiarized with the differences between traditional Combivent® inhalers and Combivent Respimat® as patients may need assistance in learning to use their new device. The Respimat® device must first be prepared by removing the clear base and recording the discard date (3 months from date of cartridge insertion) on the device. A new cartridge should be inserted into the device, piercing a hole so that medication can be released. The clear base is then replaced and should not be removed again for the entire duration that the inhaler is used. It needs to be primed by holding the inhaler upright and turning the clear base in the direction of the white arrows. The orange cap is flipped open and a dose is released by pressing the dose-release button. After a spray is visible, the device is ready for use. It is important to note that Respimat® inhalers contain 120 doses compared to 200 doses in the traditional inhalers. However, only one puff is required per dose compared to two puffs via the traditional inhaler. There is no need to shake the device prior to inhaling a puff of medication. Patients may notice that the spray does not feel as powerful as a puff from the traditional CFC inhaler. The device contains a dose counter and displays a “red zone” when there is a one week supply of medication remaining.

Theophylline is the most commonly used methylxanthine and is mentioned in the guideline as an alternative therapy for treatment of COPD. Use of this agent, however, has fallen out of favor due to serious adverse effects, variable metabolism, drug interactions, and need for therapeutic monitoring.

**Group B**
A long-acting bronchodilator should be added for patients who are included in treatment Group B (low risk, more symptoms). Regular use of long-acting bronchodilators (“controller medication”) for patients with chronic symptoms is more effective and convenient for patients, as it reduces the need for repeated use of short-acting agents. Long-acting agents are not effective during acute episodes of shortness of breath. As with short-acting bronchodilators, mechanisms of action of different types of agents can be combined to maximize bronchodilation effect.

Long-acting beta agonists relax airway smooth muscle tissue by stimulating beta-2 adrenergic receptors. The onset of action is between five and twenty minutes and the duration is generally twelve hours. The most commonly used long-acting beta agonists include formoterol (Foradil®), salmeterol (Serevent®), and arformoterol (Brovana®). Indacaterol (Arcapta Neohaler®) is the newest addition to this class, and is unique in that its duration of action is approximately twenty-four hours, therefore dosed once daily. It is delivered via inhaler device that punctures a medication-containing capsule prior to inhalation. Adverse effects of long-acting beta agonists are similar to those of short-acting beta agonists. There is no evidence that the boxed warning for increased asthma-related deaths with use of long-acting beta agonists applies to the COPD population.

Long-acting anticholinergics block acetylcholine’s effect on muscarinic receptors. The typical onset of action is fifteen minutes and duration is twenty-four hours. There is currently only one long-acting anticholinergic available (tiotropium, Spiriva®). Similar to indacaterol, it is delivered via inhaler device that punctures a medication-containing capsule prior to inhalation. Adverse effects of long-acting anticholinergics are similar to those of short-acting anticholinergics. Use of concomitant long and short acting anticholinergics is not recommended due to increased risk of systemic anticholinergic adverse effects.

**Group C**
According to GOLD guidelines, when patients progress into treatment Group C (high risk, less symptoms), an inhaled corticosteroid should be added to their regimen. Inhaled corticosteroids reduce the frequency of COPD exacerbations and may decrease the rate of decline in lung function, but do not improve COPD-related mortality.

Commonly used inhaled corticosteroids include mometasone (Asmanex Twinthaler®), fluticasone (Flovent®), and budesonide (Pulmicort Flexhaler®). They are dosed twice daily and are commonly utilized as part of a combination product with a long-acting beta agonist. Patients should be counseled to rinse their mouth after each use in an effort to reduce risk of developing oral candidiasis infection. With higher doses of inhaled corticosteroid use, increased risk of osteoporosis and pneumonia have been observed. Combination inhaled corticosteroid plus long-acting beta agonist include budesonide/formoterol (Symbicort®), mometasone/formoterol...
of exacerbations by 15% and 18% in two 12-month trials. Additionally, number of exacerbations per patient-year was 1.1 versus 1.3 (placebo) in one trial and 1.2 versus 1.5 (placebo) in another clinical trial. The patient population that received the most benefit from use of roflumilast were patients with severe COPD associated with chronic bronchitis, at least one exacerbation in the previous year, and at least a 20 pack-year history of smoking. It should be noted that in clinical studies that showed reduction in COPD exacerbations, use of an inhaled corticosteroid was prohibited.6

There are some important adverse effects to consider prior to initiating therapy with roflumilast. Common adverse effects observed in clinical studies include diarrhea (9.5%), weight decrease (7.5%), nausea (4.7%), headache (4.4%), back pain (3.2%), insomnia (2.4%), dizziness (2.1%), and abdominal pain (12%). In addition, several psychiatric effects were observed in clinical studies including one completed suicide and two suicide attempts in roflumilast groups versus one instance of suicidal ideation in placebo groups. Among all eight trials, 5.9% of patients treated with roflumilast reported some degree of adverse psychiatric reactions versus 3.3% in placebo groups. Given the occurrence of psychiatric adverse effects, roflumilast should be used with caution in patients with a history of mental health disorders.7,9

Roflumilast use is contraindicated in patients with moderate to severe liver impairment (Childs-Pugh class B or C). No dosage adjustments are required for patients with renal impairment.5

For a summary of treatment recommendations for treatment groups A through D, refer to Table 2.

Conclusion

COPD is a progressive respiratory disease that is associated with irreversible airflow limitation. Risk factor minimization is a key step in preventing onset and progression of COPD, therefore tobacco cessation should be kept as high priority in patients who smoke. Proper medication management is another important component of slowing disease progression and pharmacists can play an important role in collaboration with physicians and pulmonologists. The most recent GOLD guidelines recommended a new strategy for symptom scoring and treatment groups, which are then utilized to select appropriate medication management. Roflumilast (PDE-4 inhibitor) has been included in the most recent guideline update as a potential add-on therapy to help reduce COPD exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations.

REFERENCES


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**Figure 1. Modified Medical Research Council Questionnaire for Assessing the Severity of Breathlessness (mMRC)**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Is not troubled with breathlessness except with strenuous exercise</td>
</tr>
<tr>
<td>1</td>
<td>Is troubled by shortness of breath when hurrying on level ground or walking up a slight hill</td>
</tr>
<tr>
<td>2</td>
<td>Walks slower than people of the same age on level ground because of breathlessness, or has to stop for breath when walking at own pace on level ground</td>
</tr>
<tr>
<td>3</td>
<td>Stops for breath after walking about 100 meters or after a few minutes on level ground</td>
</tr>
<tr>
<td>4</td>
<td>Is too breathless to leave the house or is breathless when dressing or undressing</td>
</tr>
</tbody>
</table>

*Adapted from Fletcher CM, et al. BMJ 1959;2:257-266.*

**Figure 2. COPD Assessment Test (CAT)**

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Accessed from www.catastonline.org
Table 1. Classification of Severity of Airflow Limitation in COPD (Based on post-bronchodilator FEV₁) in Patients with FEV₁/FVC < 0.7

<table>
<thead>
<tr>
<th>GOLD Grade</th>
<th>Severity</th>
<th>FEV₁ Requirement</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Mild</td>
<td>FEV₁ ≥ 80% of predicted</td>
</tr>
<tr>
<td>2</td>
<td>Moderate</td>
<td>50% ≤ FEV₁ &lt; 80% of predicted</td>
</tr>
<tr>
<td>3</td>
<td>Severe</td>
<td>30% ≤ FEV₁ &lt; 50% of predicted</td>
</tr>
<tr>
<td>4</td>
<td>Very Severe</td>
<td>FEV₁ &lt; 30% of predicted</td>
</tr>
</tbody>
</table>
Table 2. Treatment recommendations based on assigned groups per 2011 GOLD Guidelines.

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>First Choice</th>
<th>Second Choice</th>
<th>Alternative Choice*</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Short-acting anticholinergic as needed</td>
<td>Long-acting anticholinergic or Long-acting β-2 agonist or Short-acting β-2 agonist and Short-acting anticholinergic</td>
<td>Theophylline</td>
</tr>
<tr>
<td></td>
<td>or Short-acting β-2 agonist as needed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>Long-acting anticholinergic or Long-acting β-2 agonist</td>
<td>Long-acting anticholinergic and Long-acting β-2 agonist</td>
<td>Short-acting β-2 agonist and/or Short-acting anticholinergic and Theophylline</td>
</tr>
<tr>
<td></td>
<td>Low risk</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>More symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>Inhaled corticosteroid + Long-acting anticholinergic</td>
<td>Long-acting anticholinergic and Long-acting β-2 agonist</td>
<td>Phosphodiesterase-4 inhibitor</td>
</tr>
<tr>
<td></td>
<td>or Inhaled corticosteroid + Long-acting β-2 agonist</td>
<td></td>
<td>Short-acting β-2 agonist and/or short-acting anticholinergic and Theophylline</td>
</tr>
<tr>
<td></td>
<td>High risk</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Less symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>Inhaled corticosteroid + Long-acting anticholinergic</td>
<td>Inhaled corticosteroid + Long-acting anticholinergic or Inhaled corticosteroid + Long-acting β-2 agonist and phosphodiesterase-4 inhibitor or Long-acting anticholinergic and Long-acting β-2 agonist or Long-acting anticholinergic and phosphodiesterase-4 inhibitor</td>
<td>Short-acting β-2 agonist and/or short-acting anticholinergic and Theophylline</td>
</tr>
<tr>
<td></td>
<td>or Inhaled corticosteroid + Long-acting β-2 agonist</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Medications in this column can be used alone or in combination with other options in the First and Second columns.