COPD 2013: An update on treatment and newly approved medications for pharmacists

Katie Campoli Meyer

Abstract

Objective: To educate pharmacists about the Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease (GOLD) guidelines for treatment of chronic obstructive pulmonary disease (COPD), newly approved medications, and recent developments since the guidelines were published.

Summary: The evidence-based GOLD guidelines provide recommendations for clinicians managing patients with COPD. These guidelines were revised most recently in 2013. Three new medications (indacaterol maleate, aclidinium bromide, and fluticasone furoate/vilanterol) have been approved in the previous 2 years. Adding to the armamentarium of medications for treating COPD is useful. Studies also have been conducted to determine which inhaled agents are preferred for use when long-acting bronchodilators are needed as mono- and combination therapy. In addition, 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors and macrolides are being studied for use in COPD. An extensive COPD pipeline consists of many oral and inhaled medications, including olodaterol and glycopyrro- nium maleate, which are in Phase III clinical trials. Medication adherence is a very important piece of COPD management. Pharmacists play an integral role in drug selection and patient education to ensure the best possible outcomes.

Conclusion: The GOLD guidelines represent the standard of care for COPD management. New drug approvals and recent research may affect practitioner choices in managing the disease. Pharmacists can improve medication adherence and selection in order to maximize therapeutic effectiveness and ensure that patients are using inhalation delivery devices optimally.

Keywords: Chronic obstructive pulmonary disease, GOLD guidelines, indacaterol maleate, aclidinium bromide, fluticasone furoate/vilanterol, adherence (medication).

Katie Campoli Meyer, PharmD, is Clinical Pharmacist, Lourdes Specialty Hospital of Southern New Jersey, Willingboro.

Correspondence: Katie Meyer, PharmD, Lourdes Specialty Hospital of Southern New Jersey, 218 A Sunset Rd., Willingboro, NJ 08046. E-mail: kmeyer@acuityhealthcare.net

Reviewer: Dennis Williams, PharmD, BCPS, AE-C, Associate Professor, School of Pharmacy, University of North Carolina, Chapel Hill

Published concurrently in Pharmacy Today and the Journal of the American Pharmacists Association (available online at www.japha.org).

Learning objectives

- Discuss appropriate medication management of stable chronic obstructive pulmonary disease (COPD) based on the 2013 revised Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease guidelines.
- Describe the mechanism of action, recommended dose, major adverse effects, drug interactions, contraindications, and place in therapy for indacaterol maleate, aclidinium bromide, and fluticasone furoate/vilanterol.
- Compare olodaterol and glycopyrro- nium maleate, which are medications in the COPD pipeline.
- Discuss recent developments in the treatment of COPD, including choice among inhaled agents, 3-hydroxy-3-methylglutaryl-coenzyme A reductase reductase inhibitors, and macrolides.
- Recognize the importance of medication adherence, barriers to adherence, and the pharmacist’s role in improving patient adherence to COPD treatment regimens.

The American Pharmacists Association is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education (CPE). The ACPE Universal Activity Number assigned to this activity by the accredited provider is 0202-0000-13-225-H01-P.

ACPE number: 0202-0000-13-225-H01-P
CPE credit: 2 hours (0.2 CEUs)
Fee: There is no fee associated with this activity for members of the American Pharmacists Association. There is a $15 fee for nonmembers.

Disclosure: Dr. Williams declares that his spouse/partner is an employee and a stock/shareholder of GlaxoSmithKline. Dr. Meyer and APhA’s education staff declare no conflicts of interest or financial interests in any product or service mentioned in this activity, including grants, employment, gifts, stock holdings, and honoraria. For complete staff disclosures, please see the APhA Accreditation Information section at www.pharmacist.com/education.
Case study
Chief complaint. J.P. is a 72-year-old man who presents to his physician’s office with worsening symptoms of shortness of breath and decreased oxygen saturation of 80%. The patient was placed in a bed, put on oxygen via nasal cannula, and given a nebulizer treatment and an intravenous steroid injection. The patient’s oxygen saturation (O₂) improved to 96% posttreatment.

History of current illness. The patient has a past medical history noteworthy for chronic obstructive pulmonary disease (COPD) secondary to a long-term smoking history. The patient quit smoking 5 years ago when he was diagnosed with COPD. He has had to use his albuterol inhaler much more frequently during the previous 3 days (at least four to five times per day). He was given a steroid taper about a month ago for a COPD exacerbation. He also has hypertension, dyslipidemia, overactive bladder, and insulin-dependent diabetes.

Allergies. The patient is allergic to clarithromycin (rash).

Current home medications. Insulin glargine 50 units s.c. twice daily, atenolol 50 mg orally daily, aspirin 81 mg orally daily, rosuvastatin 10 mg orally daily, lisinopril 5 mg orally daily, formoterol 12 µg one inhalation twice daily, furosemide 40 mg orally daily, solifenacin 10 mg orally daily, and albuterol 90 µg one inhalation every 4 hours as needed for wheezing.

Social history. The patient lives at home with his wife. He has a smoking history of 50 pack-years but stopped smoking 5 years ago. J.P. also worked in a steel mill. He has no history of alcohol or any other recreational drugs.

Vital signs. Blood pressure 171/74 mm Hg, heart rate 109 bpm, respiratory rate 30 breaths per minute, O₂ saturation 80% recovered to 96%, temperature 98.6°F, and forced expiratory volume in 1 second (FEV₁) 40%.

Chronic obstructive pulmonary disease (COPD) affects an estimated 14.8 million individuals worldwide, with an estimated 12 million cases currently undiagnosed. COPD is a leading cause of morbidity and mortality worldwide, resulting in an increasing social and economic burden. It is the third leading cause of death in the United States. COPD costs an estimated $29.5 billion directly and $20.4 billion in indirect costs annually. COPD is most prevalent in men, smokers, and individuals older than 40 years.

COPD is characterized by progressive inflammation that causes modification and narrowing of pulmonary airways, leading to development of chronic airflow limitation. Damage to the parenchyma of the lungs also occurs. Chronic inflammation causes changes in small airways and lung parenchyma that lead to decreased lung recoil and an inability of the airways to remain open during expiration. The inflammatory process is initiated by macrophages and epithelial cells in response to noxious stimuli such as cigarette smoke or environmental toxins. Following repeated exposure, a variety of chemicals including but not limited to tumor necrosis factor (TNF), interleukin 8, and leukotriene B4 are activated. These cytokines and chemoattractants bring more inflammatory cells into the lungs, which release a variety of chemicals that cause irreversible damage to the lung tissues.

Symptoms of COPD include progressive dyspnea that is persistent and worsens with exercise, chronic cough, and sputum production. Diagnosis of COPD is considered in patients who present with these symptoms plus have a history of exposure to irritants (e.g., tobacco smoke, occupational chemicals) or a family history of COPD. Postbronchodilator spirometry confirms a suspected diagnosis if the patient’s forced expiratory volume in 1 second (FEV₁) divided by forced vital capacity (FVC) is less than 70%. The Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease (GOLD) guidelines classify COPD severity in patients into four grades upon diagnosis (Table 1). Patients are further classified into four groups that incorporate patient-specific symptoms based on exacerbation rate and validated questionnaires regarding symptom severity and frequency (Table 2). The patient group classification aides in determining a preferred treatment regimen.

1. Based on J.P.’s history, in which GOLD group would he be classified?
   a. A
   b. B
   c. C
   d. D

Treatmet of stable COPD
The goals of pharmacologic treatment are to reduce symptoms, reduce the frequency and severity of exacerbations, and improve exercise tolerance and health status. All patients who smoke should be provided help quitting in order to improve the natural history of COPD. Smoking cessation programs with nicotine replacement therapy and/or pharmacologic therapy should be initiated as soon as possible in order to delay the progression of COPD. All patients with COPD also should be offered the pneumococcal polysaccharide vaccine. An annual influenza vaccine is indicated for all patients, independent of age, to reduce their risk of complications from infection.

The GOLD guidelines for pharmacological management recommend a stepwise approach to treatment based on patient classification. All patients should be prescribed a rescue inhaler (short-acting beta agonist or beta agonist/anti-cholinergic combination). Treatment of patients in group A consists of a short-acting bronchodilator used only as needed for symptomatic relief. These patients have few symptoms and a low exacerbation risk. Long-acting bronchodilators are recommended as the agent of choice for patients in group D.

<table>
<thead>
<tr>
<th>Table 1. Classification of severity of airflow limitation in COPD (based on postbronchodilator FEV₁)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOLD 1</td>
</tr>
<tr>
<td>GOLD 2</td>
</tr>
<tr>
<td>GOLD 3</td>
</tr>
<tr>
<td>GOLD 4</td>
</tr>
</tbody>
</table>

Abbreviations used: COPD, chronic obstructive pulmonary disease; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; GOLD, Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease. All patients FEV₁/FVC <70%. Reprinted with permission from the Global Initiative for Chronic Obstructive Lung Disease.
B. These patients have increased symptoms and can benefit from continuous therapy. Group C patients should be treated with both an inhaled corticosteroid and bronchodilator because of their high exacerbation rate. Last, group D patients also should be started on combination therapy, but if it fails, a third drug can be added to improve symptoms.2 Individualizing agent choice based on patient-specific factors is important. Research currently is being done to evaluate which drug class is superior and whether adding medications currently marketed for indications other than COPD can help decrease the exacerbation rate.

**Bronchodilators**

Bronchodilators increase airflow by altering smooth muscle tone. Those indicated for treatment include anticholinergics and beta-2 agonists.

**Anticholinergics**

Anticholinergics bind to muscarinic receptors and block the action of acetylcholine, which reduces bronchomotor tone leading to bronchodilation. They are generally a safe drug class when inhaled, with dry mouth being the most common adverse effect.2 Systemic anticholinergics being used for different indications, such as oxybutynin, should be used with caution because of the increased potential for anticholinergic adverse effects. Three inhaled anticholinergic agents are commercially available. Ipratropium bromide is a short-acting anticholinergic agent available in both a metered inhaler and nebulized solution. A typical nebulized dose is 0.5 mg inhaled every 6 to 8 hours, consistent with its duration of action.2 Tiotropium bromide is a long-acting anticholinergic that is available in a dry powder inhaler. Tiotropium is dosed 18 µg daily and has a 24-hour duration of action. Tiotropium may be challenging to use for patients who have difficulty with dexterity as it requires them to take a capsule out of a packet and load the device before inhaling.7 Aclidinium bromide is the newest anticholinergic and will be discussed in further detail later.

**Beta-2 agonists**

Beta-2 agonists relax bronchial smooth muscles by stimulating beta-2-adrenergic receptors. Common adverse effects associated with this class include tremor, tachycardia, and cardiac rhythm disturbance.2 Patients should be educated not to exceed their prescribed dose, as the majority of adverse effects occur with overuse. The most common drug classes that interact with beta-2 agonists include diuretics, steroids, tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), and systemic beta blockers. A recently published study of 76,661 patients with COPD found a significant increase in the rate of severe cardiac dysrhythmias with new use of short-acting beta-2 agonists. The retrospective study did not assess patient-specific factors such as underlying cardiac disease and duration of use of the beta agonist; thus, further research is warranted.8 Mortality risk increases when beta-2 agonists are used alone for the treatment of asthma, but this association has not been found in COPD.2,9,10 Commerically available beta-2 agonists are summarized in Table 3.

**Corticosteroids**

Inhaled corticosteroids exert anti-inflammatory effects by binding to glucocorticoid receptors. Corticosteroids improve symptoms and reduce the frequency of exacerbations in COPD but do not modify the occurrence of long-term decline

---

**Table 2. Summary of GOLD COPD assessment2**

<table>
<thead>
<tr>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
<th>Group D</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOLD 1 or GOLD 2</td>
<td>GOLD 1 or GOLD 2</td>
<td>GOLD 3 or GOLD 4</td>
<td>GOLD 3 or GOLD 4</td>
</tr>
<tr>
<td>0–1 exacerbation/year</td>
<td>0–1 exacerbation/year</td>
<td>≥2 exacerbations/year</td>
<td>≥2 exacerbations/year</td>
</tr>
<tr>
<td>Low level of symptoms</td>
<td>High level of symptoms</td>
<td>Low level of symptoms</td>
<td>High level of symptoms</td>
</tr>
</tbody>
</table>

**Table 3. Summary of beta-2 agonists used in the treatment of COPD2,20**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Formulations</th>
<th>Dosage</th>
<th>Duration of action (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short acting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levalbuterol</td>
<td>MDI, neb</td>
<td>0.63–1.25 mg every 4–6 h as needed</td>
<td>6–8</td>
</tr>
<tr>
<td>Albuterol</td>
<td>MDI, neb</td>
<td>2.5 mg every 4–6 h as needed</td>
<td>4–6</td>
</tr>
<tr>
<td>Pirbuterol</td>
<td>MDI</td>
<td>400 µg every 4–6 h as needed</td>
<td>4–6</td>
</tr>
<tr>
<td>Long acting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arformoterol</td>
<td>Neb</td>
<td>15 µg every 12 h</td>
<td>12</td>
</tr>
<tr>
<td>Formoterol</td>
<td>DPI, neb</td>
<td>12–20 µg every 12 h</td>
<td>12</td>
</tr>
<tr>
<td>Salmeterol</td>
<td>DPI</td>
<td>50 µg every 12 h</td>
<td>12</td>
</tr>
<tr>
<td>Indacaterola</td>
<td>DPI</td>
<td>75 µg daily</td>
<td>24</td>
</tr>
</tbody>
</table>

**Abbreviations used:** DPI, dry powder inhaler; MDI, metered-dose inhaler; neb, nebulizer solution. Aclidinium bromide discussed in further detail.
in pulmonary function or the rate of mortality. When used in combination with beta-2 agonists, inhaled corticosteroids are more effective in reducing exacerbations and improving lung function compared with corticosteroids alone.2,11

The adverse effects commonly associated with corticosteroids include oral candidiasis, hoarse voice, skin bruising, pneumonia, and decreased bone mineral density. All of the inhaled corticosteroids are cytochrome P450 (CYP)3A4 substrates; therefore, caution is advised when adding medications that will induce or inhibit this class. Patients with high exacerbation risk and severe symptoms benefit from corticosteroid addition.2 Several formulations of corticosteroids are commercially available, both alone and in combination with beta-2 agonists (Table 4).

### Table 4. Summary of inhaled corticosteroids used in treatment of COPD

<table>
<thead>
<tr>
<th>Drug</th>
<th>Formulations</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Single agent</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Budesonide</td>
<td>MDI</td>
<td>Max 200 µg/day divided b.i.d.</td>
</tr>
<tr>
<td>Budesonide/ formoterol</td>
<td>MDI</td>
<td>Max 640 µg/day divided b.i.d.</td>
</tr>
<tr>
<td>Beclomethasone</td>
<td>DPI, neb</td>
<td>Max 1,440 µg/day divided b.i.d.</td>
</tr>
<tr>
<td>Fluticasone</td>
<td>DPI</td>
<td>Max 440 µg/day divided once daily to b.i.d.</td>
</tr>
<tr>
<td>Mometasone</td>
<td>MDI</td>
<td>Max 1,000 µg/day divided b.i.d.</td>
</tr>
<tr>
<td>Mometasone/ formoterol</td>
<td>MDI</td>
<td>Max 800 µg/20 µg/day divided b.i.d.</td>
</tr>
<tr>
<td>Formoterol</td>
<td>MDI</td>
<td>Max 1,000 µg/100 µg/day divided b.i.d.</td>
</tr>
<tr>
<td>Ciclesonide</td>
<td>DPI</td>
<td>Max 440 µg/day divided once daily to b.i.d.</td>
</tr>
<tr>
<td>Budesonide/fomoterol</td>
<td>DPI</td>
<td>Max 1,000 µg/day divided once daily to b.i.d.</td>
</tr>
</tbody>
</table>

### Combination agent

<table>
<thead>
<tr>
<th>Drug</th>
<th>Formulations</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Budesonide</td>
<td>DPI</td>
<td>Max 640 µg/20 µg/day divided b.i.d.</td>
</tr>
<tr>
<td>Budesonide/ formoterol</td>
<td>MDI</td>
<td>Max 640 µg/18 µg/day divided b.i.d.</td>
</tr>
<tr>
<td>Ciclesonide</td>
<td>DPI</td>
<td>Max 440 µg/day divided once daily to b.i.d.</td>
</tr>
<tr>
<td>Fluticasone</td>
<td>DPI</td>
<td>Max 440 µg/day divided once daily to b.i.d.</td>
</tr>
<tr>
<td>Fluticasone/ salmeterol</td>
<td>DPI</td>
<td>Max 440 µg/day divided once daily to b.i.d.</td>
</tr>
<tr>
<td>Fluticasone/ flunisolide</td>
<td>DPI</td>
<td>Max 440 µg/day divided once daily to b.i.d.</td>
</tr>
</tbody>
</table>

Abbreviations used: DPI, dry powder inhaler; MDI, metered-dose inhaler; neb, nebulizer solution.

Other agents

Two additional drugs are alternatives for use in COPD when it is not adequately controlled with standard therapy or when appropriate based on patient-specific factors. Roflumilast is a phosphodiesterase-4 inhibitor that exerts its action by increasing intracellular cyclic adenosine monophosphate, leading to reduced inflammation. It is indicated specifically in patients with chronic bronchitis who have severe COPD with a history of exacerbations. Roflumilast is an oral medication dosed at 500 µg by mouth daily. Because it is absorbed systemically, roflumilast has an extensive adverse effect profile compared with inhaled agents. The most common adverse effects associated with use include nausea, abdominal pain, diarrhea, sleep disturbances, reduced appetite, and headache. These adverse effects may lessen over time with continued treatment. Roflumilast should be used in caution in patients with depression because of an increased frequency of anxiety, depression, and sleep disorders when using the drug. Patients who are taking roflumilast should have their weight monitored regularly, as it has been implicated in causing substantial weight loss.2,12

Ongoing long-term studies will further evaluate safety and the risk versus benefit of use.13 Because of safety concerns and limited clinically significant efficacy data, roflumilast should be reserved for patients who have severe COPD with chronic bronchitis that is inadequately controlled by inhaled bronchodilators.2,14 Other phosphodiesterase inhibitors currently in the pipeline include an inhaled version in Phase II trials.15

Theophylline is a xanthine derivative. The exact mechanism of action of this class is unknown. Animal studies suggest that it exhibits similar properties to a phosphodiesterase inhibitor. A limited amount of data support use of theophylline in COPD. The current data only support use of the slow-release preparations. The pharmacokinetics of theophylline vary widely among patients. Certain diseases, including hepatic disease, severe COPD, heart failure, and cigarette smoking, require factor adjustment when estimating a patient’s clearance. Theophylline is metabolized via the CYP system, and therefore it has a wide array of drug interactions. Cimetidine, ciprofloxacin, diltiazem, erythromycin, propranolol, and verapamil are just a few of the medications that require close monitoring and factor adjustment when considering theophylline dose. It also has many adverse effects, including headaches, insomnia, nausea, heartburn, and more serious adverse effects, such as grand mal convulsions and fatal atrial and ventricular dysrhythmias. Because of its within-subject variation in metabolism, treatment recommendations include measuring serum theophylline concentrations at least every 24 hours in acutely ill patients and at 6- to 12-month intervals in patients receiving long-term therapy. The target therapeutic concentration is 5 to 15 mg/L.15 Theophylline is not recommended for use in COPD unless other bronchodilators are unavailable or unaffordable.2

### Treatment of COPD exacerbations

A COPD exacerbation is defined as a patient presenting with an acute change of symptoms deviating from their daily norm that leads to a change in medication.2,16 Several factors can precipitate a COPD exacerbation, including bacterial or viral infections, air pollution, and other unknown causes. Treatment goals are to improve the current exacerbation and prevent recurrent exacerbations. Short-acting beta-2 agonists are the bronchodilator of choice during an exacer-
bation. Short-acting anticholinergics may be added as well. Use of short-course systemic corticosteroids, such as prednisolone for 10 to 14 days, also has been shown to improve lung function and reduce recovery time. Antibiotics should be reserved for patients who show clinical signs of bacterial infection (e.g., increased dyspnea, sputum volume, sputum purulence), unless the patient requires mechanical ventilation. Studies have shown that a mortality benefit may exist in ventilated patients.2,7

Newly approved drugs for managing COPD

Aclidinium bromide

Aclidinium is a long-acting anticholinergic that was approved for use in July 2012. It is indicated for the long-term maintenance treatment of COPD. The drug is available in a multidose dry powder inhaler that does not require loading a capsule. This may offer an advantage over tiotropium for selected patients. Aclidinium’s recommended dosage is 400 µg (one puff) inhaled twice daily.

The effectiveness of aclidinium for COPD patients was demonstrated in three placebo-controlled studies in patients with an FEV₁ of at least 30% and less than 80% predicted and FEV₁/FVC less than 70%. The primary endpoint was an improvement in bronchodilation as measured by an increase in FEV₁ at 12 weeks compared with placebo. All three studies resulted in statistically significantly greater bronchodilation at 12 weeks. Data comparing aclidinium and tiotropium are limited.

The adverse reactions most commonly implicated with aclidinium include headache, cough, and nasopharyngitis. Possibility of immediate hypersensitivity reaction is an important, uncommon adverse reaction. Aclidinium has a similar chemical structure to that of atropine; thus, caution is advised in patients with a history of hypersensitivity. Aclidinium also should be used in caution in patients with severe hypersensitivity to milk proteins. Aclidinium should be discontinued if hypersensitivity reactions occur, and alternative therapies should be considered. Aclidinium also may worsen narrow-angle glaucoma, so caution should be used in this population.

Information regarding drug interactions with aclidinium is limited to the potential for interaction with anticholinergic medications used concomitantly. Aclidinium is not metabolized via the CYP metabolic pathway. Only 0.1% of an aclidinium dose is excreted in the urine, making it a potentially safe option in patients with renal insufficiency. No dosage adjustment is needed in this population.

Aclidinium is the second long-acting anticholinergic approved for use in COPD in the United States. Although it does not have the extensive data support of tiotropium, it may be an appropriate option in patients who have difficulties using tiotropium because of its delivery mechanism. Compared with tiotropium, a disadvantage of aclidinium is that it must be used twice daily, which may lead to decreased regimen adherence. Although trials have been completed, no studies have been published regarding use of aclidinium in combination with formoterol.19

Indacaterol maleate

Indacaterol is a long-acting beta-2 agonist indicated for long-term maintenance bronchodilator treatment of patients with COPD. Indacaterol’s main advantage compared with other drugs in its class is its convenient once-daily dosage regimen. Indacaterol is available in a 75-µg hard capsule that must be removed from a blister packet and loaded into a dry powder inhaler before inspiration. The recommended dose of indacaterol is 75 µg inhaled once daily, at the same time each day.20

The effectiveness of indacaterol was demonstrated in several placebo controlled studies that analyzed patients with an FEV₁ of at least 30% but less than 80% predicted normal and FEV₁/FVC less than 70%. The primary endpoint was an improvement of bronchodilation, as assessed by an improvement of FEV₁ after 12 weeks of treatment. Indacaterol also was compared with tiotropium, but only at doses of 150 to 600 µg per day. At increased dosage, indacaterol was at least as effective as tiotropium and appeared to be more effective than formoterol and salmeterol; however these studies were not conducted with the FDA-approved 75-µg dose. The higher dosages also were implicated with increased frequency of cardiovascular and cerebrovascular adverse events.21–23

The most common adverse reactions associated with indacaterol are cough, oropharyngeal pain, nasopharyngitis, headache, and nausea. Immediate hypersensitivity reactions, hypokalemia, and hyperglycemia also are of concern. Like other beta-2 agonists, indacaterol can cause increases in heart rate or blood pressure and prolong the QT interval; therefore, it should be used in caution in patients with cardiovascular disease (CVD).20

Indacaterol should not be used in acutely deteriorating COPD or for relief of acute symptoms. Indacaterol should be used in caution in patients with convulsive disorders, thyrotoxicosis, or those who are sensitive to sympathomimetic drugs. Indacaterol is Pregnancy Category C and therefore should be used in pregnant women only when the benefit outweighs the potential risk to the fetus.20

Drug interactions with indacaterol include concomitant use with other adrenergic drugs that may potentiate its sympathomimetic effect. Xanthine derivatives, steroids, or non–potassium-sparing diuretics may increase the chances of hypokalemia and electrocardiogram changes. MAOIs,
The use of indacaterol should be reserved for patients who have difficulties with adherence and would benefit from a once-daily long-acting beta-2 agonist. A trial comparing indacaterol plus tiotropium versus tiotropium alone evaluated 2,276 patients with moderate to severe COPD in a double-blind, 12-week study looking at the area under the curve of FEV1 from 5 minutes to 8 hours postdose at week 12. A statistically significant improvement in FEV1 was found with the addition of indacaterol to tiotropium; however, the study did not assess risk of COPD exacerbation. Further robust studies are needed to determine the clinical use of indacaterol plus tiotropium.

Newly approved device

In October 2011, Boehringer Ingelheim gained approval for their first in class Respimat Soft Mist Inhaler. This multiple-dose device is a propellant-free inhaler that uses liquid formulations of drug similar to those in nebulizers. The device uses the energy of a compressed spring to generate aerosol at a slower rate than that of an MDI, resulting in increased lung deposition in COPD patients with poor inhaler technique. The device was approved for administration of ipratropium/albuterol under the name Combivent Respimat and became available in mid-2012. Studies also have shown non-inferiority when comparing tiotropium delivered via the Respimat device with its currently approved HandiHaler.

Patients taking Combivent Respimat should be educated on the proper technique for assembly of the device. A drug cartridge must be inserted into the device, and after this is done, the inhaler should be given an expiration date of 3 months. The inhaler also needs to be primed before first use, which may be difficult for some patients to understand. Community pharmacists should ensure that patients understand the proper process for priming before dispensing the Combivent Respimat inhaler.

Fluticasone furoate/vilanterol

Fluticasone furoate/vilanterol is a combination product that gained approval in May 2013 for long-term maintenance of airflow obstruction and reduction of exacerbations in COPD. The product combines the already-marketed inhaled corticosteroid fluticasone with a newly approved long-acting beta-2 agonist, vilanterol. The product is delivered in a newly patented dry powder inhaler device that when inhaled once daily, delivers 100 µg fluticasone and 25 µg vilanterol.

Clinical trials showed a statistically significant decrease in exacerbation rate when fluticasone/vilanterol was compared with vilanterol alone in 7,700 patients with an FEV1 less than 70% and at least one documented COPD exacerbation in the year before study enrollment. Nasopharyngitis was the most frequently reported adverse effect in clinical trials. Studies also showed an increased fracture rate (2.2%) and increased chance of pneumonia (3%) when the combination product was compared with vilanterol alone.

Fluticasone/vilanterol will be available for distribution in the third quarter of 2013, according to GlaxoSmithKline. It will be the only inhaled corticosteroid/beta agonist combination dosed once daily. This new medication will most likely be used in patients with group C or D COPD who have difficulty with adherence or prefer a once-daily treatment option. Larger-scale studies with vilanterol alone and in combination with tiotropium may be warranted and allow for greater use of the drug within the COPD population.

6. If J.P. needs addition of a long-acting beta-2 agonist, which medication is indicated?
   a. Ciclesonide
   b. Beclomethasone dipropionate
   c. Levalbuterol
   d. Indacaterol

7. If J.P. has difficulty with adherence, which treatment may be a better option for him?
   a. Levalbuterol
   b. Indacaterol
   c. Fluticasone furoate/vilanterol
   d. Theophylline

COPD pipeline

An extensive pipeline of chemical entities is currently being investigated for use in COPD. Agents are being developed to target specific receptors of cytokines involved in the inflammatory process associated with COPD with the goal of reversing the course itself. Olodaterol, glycopyrronium, and umeclidinium/vilanterol are nearing FDA approval.

Olodaterol

In January 2013, an FDA advisory committee recommended approval of Boehringer Ingelheim’s olodaterol based on Phase III trials. Olodaterol is a long-acting beta-2 agonist administered via the Respimat device. Based on 10 Phase III studies, the advisory committee recommended approval of a dose of 5 µg inhaled once daily gain. Nasopharyngitis, dizziness, rash, and arthralgia were the adverse effects most commonly associated with treatment. Patients were not excluded from trials if they had a history of CVD, and no detrimental effects were observed in this population. Clinical trials comparing olodaterol in combination with tiotropium to olodaterol alone are currently ongoing. Information has not been released regarding olodaterol’s approval or release.
Glycopyrronium bromide
In October 2012, Novartis gained approval in Europe for glycopyrronium bromide, a long-acting muscarinic antagonist for treating moderate to severe COPD. The manufacturer plans to seek approval in the United States for both mono- and combination therapy with indacaterol. Glycopyrronium is another long-acting anticholinergic agent and is comparable with tiotropium. A series of Glycopyrronium Bromide in Chronic Obstructive Pulmonary Disease Airways (GLOW) studies have assessed glycopyrronium versus placebo and tiotropium.31,32 The GLOW 2 study assessed improvement in FEV₁ at 52 weeks and found a statistically significant improvement compared with placebo but not with tiotropium.32 The dose most commonly tested in clinical trials is 50 µg inhaled once daily, though studies are being conducted with 100 and 200 µg doses. Similar to currently approved anticholinergic agents, glycopyrronium appears to be well tolerated. Studies of glycopyrronium alone and in combination with indacaterol versus placebo and active comparators are ongoing.33

Umeclidinium/vilanterol
In September 2013, the Pulmonary-Allergy Drugs Advisory Committee to FDA recommended approval of GlaxoSmithKline’s umeclidinium/vilanterol for long-term, once-daily maintenance treatment of airflow obstruction in patients with COPD based on Phase III trials.34 Umeclidinium/vilanterol is a combination of a newly developed long-acting muscarinic antagonist and an already-marketed long-acting beta-2 agonist. The advisory committee recommended that the 62.5/25 µg inhaled once-daily dose gain approval. Adverse effects most frequently reported in clinical studies were headache, nasopharyngitis, cough, upper respiratory tract infection, and back pain. Because of an imbalance in the number of nonfatal myocardial infarctions compared with placebo in some studies, the panel recommended conducting postmarket studies to further analyze safety.35 Umeclidinium/vilanterol has potential to be a useful modality in treating moderate to severe COPD because of its once-daily dosing regimen. It also is the first combination of a long-acting antimuscarinic and beta-2 agonist, which are commonly used together in various stages of COPD treatment.

Recent developments in COPD
Tiotropium compared with long-acting beta-2 agonists
The current guidelines for patients classified in GOLD group B (i.e., those with persistent symptoms of COPD who need more than an as-needed bronchodilator) recommend use of a long-acting inhaled bronchodilator. The choice between an anticholinergic and long-acting beta-2 agonist is currently based on clinician and patient experience and preferences.

A 1-year, randomized, double-blind study compared tiotropium 18 µg daily with salmeterol 50 µg twice daily in 7,376 patients with moderate to severe COPD. The study was funded by the manufacturers of tiotropium. The primary endpoint was time to the first COPD exacerbation. Patients included in the study were at least 40 years of age, had a smoking history of 10 pack-years or more, had a diagnosis of COPD with a FEV₁ after bronchodilation of 70% or more predicted, and had at least one documented exacerbation within the previous year. Time to the first COPD exacerbation was 187 days versus 145 days with salmeterol (P < 0.001). Tiotropium also reduced the annual number of moderate to severe exacerbations (0.64 vs. 0.72, P = 0.002), and fewer deaths occurred in the tiotropium group (1.7%) than in the salmeterol group (2.1%). The incidence of adverse effects was similar in the two groups.36

A retrospective, population-based, cohort study was conducted in Ontario, Canada, and included patients 66 years or older who were diagnosed with COPD and were newly prescribed a long-acting inhaled anticholinergic or beta-2 agonist. Patients were followed for up to 5.5 years, and the primary endpoint was all-cause mortality. A total of 46,403 patients were evaluated, and mortality was higher in those initially prescribed a long-acting anticholinergic than in those initially prescribed a long-acting inhaled beta-agonist. Hospitalization rates also were higher in the anticholinergic group.37 Of note, the study was not a prospective, randomized, controlled trial.

Data are conflicting regarding which class is superior for initial treatment of COPD when a long-acting agent is needed. It is important to keep in mind patient comorbidities that exist when selecting an agent. For example, in patients with history of heart failure, tiotropium would be preferred because beta-2 agonists can oppose the benefits of beta blockers and worsen cardiac outcomes.38 In patients with renal insufficiency, beta-2 agonists would be preferred, whereas tiotropium could result in increased anticholinergic effects.39

8. What action(s) should be taken to reduce J.P.’s exacerbation risk?
   a. Add theophylline 100 mg orally b.i.d.
   b. Change formoterol to budesonide/formoterol 160 µg/4.5 µg two puffs inhaled b.i.d.
   c. Change atenolol to amlopidine 5 mg orally daily
   d. Both b and c are correct.

9. Which adverse effect may occur with the addition of the above medication?
   a. Pneumonia
   b. Reduced appetite
   c. Headache
   d. Seizures

Beta-2 agonist/steroid combination selection
A recent large-scale, retrospective, observational study in 5,468 patients with moderate to severe COPD compared budesonide/formoterol with fluticasone/salmeterol for up to 11 years. The study compared the ability of the two different combinations to prevent COPD exacerbations. Patients who were included were matched into pairs based on similar baseline characteristics. Exacerbation rates were found to be
0.8 and 1.09 per patient-year in the budesonide/formoterol and fluticasone/salmeterol treatment groups, respectively. These rates corresponded to a 26.6% lower exacerbation rate in the budesonide/formoterol group ($P < 0.0001$) and a number needed to treat with budesonide/formoterol to prevent one exacerbation per year of 3.4. The study also reported that the yearly rate of COPD-related hospitalizations also was significantly lower in the budesonide/formoterol group (29.1% reduction, $P < 0.0001$). The number needed to treat to prevent one hospitalization per patient-year was 16. Oral steroid use, antibiotic use, and addition of tiotropium also were significantly higher in the fluticasone/salmeterol group ($P < 0.0001$). Differences in the frequency of adverse effects were not reported.\(^\text{40}\)

No randomized double-blind trials have compared budesonide/formoterol with fluticasone/salmeterol. A previous retrospective 1-year study reported a 15% reduction in COPD exacerbations with budesonide/formoterol compared with fluticasone/salmeterol (nonsignificant).\(^\text{41}\) The PATHOS study was a long-term, robust study in a large number of patients and may have real-world implications. The publication stated that patients who switched treatment during the course of chart review had a higher yearly exacerbation rate but did not show the supporting data. Recommending budesonide/formoterol over fluticasone/salmeterol for initial combination therapy in patients with moderate to severe COPD is reasonable. More data are needed to assess whether switching from one combination to the other would be of benefit.

**HMG-CoA reductase inhibitors in COPD**

3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins) are indicated for the reduction of serum cholesterol. Interest in the anti-inflammatory pleotropic effects of statins has been longstanding. In addition to their cardiovascular benefit, evidence shows that statins have strong immune-modulating effects in pulmonary circulation. Statins are known to reduce neutrophil influx in the lung and inhibit the expression of many inflammatory mediators, such as C-reactive protein, TNF-alpha, and various cytokines, which are inversely related to FEV\(_1\). This inhibition may delay inflammatory-mediated lung deterioration in COPD.\(^\text{42}\) Several retrospective observational studies have displayed beneficial effects of statin use for a number of different COPD outcomes, including exacerbation rate and mortality. One large retrospective case–control study in 14,316 Taiwanese patients who were hospitalized for COPD exacerbations displayed a 30% decreased risk of COPD exacerbation with statin use.\(^\text{43}\) Currently, long-term prospective trials assessing simvastatin, lovastatin, and rosuvastatin for use in COPD are in progress.\(^\text{5}\)

10. If J.P.’s physician would like to add an oral agent to reduce his COPD exacerbation rate, which medication would you recommend?

- a. Theophylline extended release 300 mg orally each morning
- b. Roflumilast 500 µg orally daily
- c. Azithromycin 250 mg orally daily
- d. Simvastatin 40 mg orally daily

**Macrolides in COPD**

Macrolide antibiotics are indicated for treatment because of their antibacterial effects. The class also has been associated with immunomodulatory and anti-inflammatory effects. Macrolides reduce mucus, sputum production, and the percentage of neutrophils in pulmonary fluid, which may decrease the amount of cytotoxic substances that cause pulmonary remodeling. Macrolides also may inhibit the release of cytokines and TNF-alpha.\(^\text{44}\)

Several small studies have yielded conflicting results regarding the use of macrolides to prevent acute COPD exacerbations. A randomized, prospective, placebo-controlled study recently was conducted to test the hypothesis that azithromycin 250 mg orally administered once daily reduces the frequency of COPD exacerbations when added to usual care. The study included 1,142 patients who were 40 years or older and had a smoking history of 10 pack-years, clinical diagnosis of COPD, and FEV\(_1\)/FVC less than 70%. Patients must have had a history of exacerbation within the previous year. Patients were excluded if they had a resting heart rate greater than 100 bpm, had a prolonged QTc interval (>450 ms), or were using medications that prolong the QTc interval.\(^\text{45}\)

The primary endpoint was time to first COPD exacerbation. Median time to first exacerbation was 266 days among patients receiving azithromycin compared with 174 days in the placebo group ($P < 0.001$). The frequency of exacerbations also was significantly decreased in the azithromycin group. An increased incidence of colonization with macrolide-resistant organisms occurred in patients receiving azithromycin, and a statistically significant increase in hearing decrements was observed compared with the placebo group.\(^\text{45}\)

A retrospective cohort from 2012 found a statistically significant increase in the risk of cardiovascular death associated with azithromycin compared with no antibiotics, amoxicillin, or ciprofloxacin.\(^\text{46}\) Patients received only 5 days of therapy in the study. Albert et al.\(^\text{46}\) did not find any significant increase in cardiovascular events in the treatment group; however, patients with cardiovascular comorbidities were excluded. Azithromycin should not be used in patients with a history of CVD for preventing exacerbation in COPD.

Azithromycin may be a viable option in patients without CVD for exacerbation prevention; however, further studies are needed to assess the frequency of hearing loss and bacterial resistance patterns. Macrolides are an important antibacterial class in the treatment of pneumonia in patients with COPD. The clinical significance of resistance to this class remains unknown.
Patient adherence
As stated by former U.S. Surgeon General C. Everett Koop, “Drugs don’t work if patients don’t take them.” Medication adherence can be difficult in COPD because of the typical age of affected patients and the mode of administration of the majority of the drugs. Studies have shown that better medication adherence is associated with a decrease in hospitalizations and improved quality of life.25 A subanalysis of the TORCH (Towards a Revolution in COPD Health) study showed that good adherence to COPD medication decreased mortality rates compared with poor adherence (26.4% vs. 11.3%).47

Studies analyzing adherence in the COPD population are limited; however, data suggest that adherence is poor. A retrospective study conducted in 2,730 veterans with COPD reported an adherence of only 19.8% in patients taking inhaled corticosteroids, 30.6% in patients taking inhaled long-acting beta agonists, and 25.6% in patients taking inhaled ipratropium. Although the study was unable to determine the exact cause of poor adherence, it did state that past adherence issues to medications in one class led to adherence issues if the drug was changed to another in the same class.48 Multiple-inhaler use also has been associated with higher rates of non-adherence compared with single-inhaler use. A combination product should be recommended whenever possible in order to improve adherence rates.

Pharmacists play a huge role in improving treatment adherence in COPD. Patients need to be taught how to use their devices, and pharmacists should ensure that patients can demonstrate proper use of devices before leaving the practice site. Studies have shown that if patients feel their inhaler is not working, adherence is more likely to be poor.9 Pharmacists can observe and improve inhalation technique, help find discounts to offset cost, and reassure patients about what to expect regarding adverse effects.

In 2010, a group of 55 community pharmacist conducted a study in 597 patients with asthma or COPD. Pharmacists interviewed and checked inhalation technique in patients at baseline, corrected any errors, and reassessed technique 4 to 6 weeks later. At baseline, 78.9% of patients made at least one mistake when using their inhaler. When the patients returned 4 to 6 weeks after they were educated, the percent was reduced to 28.3%.30 Pharmacists can have a major impact on inhaler technique after spending time with a patient just once, which can ultimately lead to improved medication adherence and quality of life.

Conclusion
COPD is a major cause of morbidity and mortality in the United States. The GOLD guidelines continue to be the standard for medication management for COPD. Aclidinium bromide, indacaterol maleate, and fluticasone furoate/vilanterol are new medications that have been approved since the guidelines were published. These drugs may be viable treatment options based on patient-specific factors in managing COPD. Research is ongoing for the use of currently approved agents such as HMG-CoA reductase inhibitors and macrolides to prevent COPD exacerbations. An extensive COPD pipeline also exists. Regardless of the treatment approach, patient adherence is a critical factor in predicting success. Pharmacists play a vital role in promoting patient adherence in order to maximize therapeutic efficacy, leading to decreased morbidity and mortality and an improved quality of life.

Answers to case study questions: 1, c; 2, c; 3, a; 4, b; 5, c; 6, d; 7, c; 8, d; 9, a; 10, b.

References
CPE assessment

Instructions: This exam must be taken online; please see “CPE information” for further instructions. The online system will present these questions in random order to help reinforce the learning opportunity. There is only one correct answer to each question.

1. A patient tells you that he has been diagnosed with GOLD group A chronic obstructive pulmonary disease. Which of the following medication classes is indicated for this stage?
   a. Inhaled long-acting anticholinergic
   b. Inhaled corticosteroid
   c. Inhaled short-acting beta-2 agonist
   d. Oral phosphodiesterase-4 inhibitor

2. The most common adverse effect associated with use of tiotropium is:
   a. Pharyngitis.
   b. Dry mouth.
   c. Decreased bone mineral density.
   d. Urinary incontinence.

3. Which of the following medications is a short-acting beta-2 agonist?
   a. Salmeterol
   b. Indacaterol
   c. Arformoterol
   d. Levalbuterol

4. A patient has been stable on salmeterol 50 µg every 12 hours and fluticasone 220 µg every 12 hours for the previous 3 months. Which of the following would you recommend?
   a. Continue the current regimen
   b. Add tiotropium 18 µg daily
   c. Decrease salmeterol to 50 µg daily
   d. Add theophylline extended release 300 mg orally daily

5. A patient comes to the pharmacy with a prescription for clarithromycin. You notify their physician to alert them about a potential interaction with which of the following?
   a. Fluticasone/salmeterol
   b. Acldinium
   c. Tiotropium
   d. Ipratropium

6. Roflumilast belongs to which of the following classes of medications?
   a. Long-acting beta-2 agonist
   b. Xanthine derivative
   c. Phosphodiesterase-4 inhibitor
   d. Corticosteroid

7. Which of the following medications would you be hesitant to recommend for patients with epilepsy?
   a. Aclidinium
   b. Theophylline extended release
   c. Fluticasone/vilanterol
   d. Ipratropium bromide and albuterol

8. Which of the following nebulizer treatment is indicated for patient who are having acute, severe dyspnea due to a COPD exacerbation?
   a. Arformoterol 15 µg
   b. Formoterol 20 µg
   c. Budesonide 0.5 mg
   d. Albuterol/ipratropium 0.5/2.5 mg

CPE information

To obtain 2.0 contact hours (0.2 CEUs) of CPE credit for this activity, you must complete the online Assessment and Evaluation. A Statement of Credit will be awarded for a passing grade of 70% or better on the Assessment. You will have two opportunities to successfully complete the CPE Assessment. Pharmacists who successfully complete this activity before October 1, 2016, can receive CPE credit. Your Statement of Credit will be available upon successful completion of the Assessment and Evaluation and will be stored in your ‘My Training’ page and on CPE Monitor for future viewing/printing.

CPE instructions:
1. Log in or create an account at pharmacist.com and select LEARN from the top of the page; select Continuing Education, then Home Study CPE to access the Library.
2. Enter the title of this article or the ACPE number to search for the article, and click on the title of the article to start the home study.
3. To receive CPE credit, select Enroll Now or Add to Cart from the left navigation and successfully complete the Assessment (with randomized questions), Learning Evaluation, and Activity Evaluation.
4. To get your Statement of Credit, click “Claim” on the right side of the page. You will need to provide your NABP e-profile ID number to obtain and print your Statement of Credit.

Live step-by-step assistance is available Monday through Friday from 8:30 am to 5:00 pm ET at APhA Member Services at 800-237-APhA (2742) or by e-mailing education@aphanet.com.
9. Aclidinium bromide should be used in caution in patients with:
   a. Depression.
   b. Glaucoma.
   c. Hypertension.
   d. Atrial fibrillation.

10. Aclidinium bromide is advantageous over tiotropium because it:
   a. Is less likely to cause hypersensitivity reactions.
   b. Has a more convenient dosing regimen.
   c. Does not require unwrapping and loading a capsule into a device.
   d. Has fewer adverse effects.

11. A patient has severe osteoarthritis and difficulty using his hands. Which of the following medications would you be least likely to recommend?
   a. Roflumilast
   b. Indacaterol
   c. Formoterol/mometasone
   d. Beclomethasone

12. A patient presents a new prescription for indacaterol 75 µg inhaled once daily. Which of the following medications in the patient’s profile would require you to notify the patient’s physician about a potential interaction?
   a. Simvastatin 80 mg
   b. Sertraline 50 mg
   c. Alprazolam 0.25 mg
   d. Carvedilol 25 mg

13. Your patient is currently taking budesonide/formoterol for managing chronic obstructive pulmonary disease. You notice that they are refilling their prescription every 60 days. To improve adherence, you recommend:
   a. Formoterol/mometasone 200 µg/10 µg inhaled b.i.d.
   b. Fluticasone/vilanterol 100 µg/25 µg inhaled daily.
   c. Ciclesonide 80 µg inhaled b.i.d.
   d. Indacaterol 75 µg inhaled daily.

14. Which of the following medications has the same mechanism of action as fluticasone/vilanterol?
   a. Formoterol/mometasone
   b. Budesonide
   c. Indacaterol
   d. Simvastatin

15. Patients taking albuterol/ipratropium (Combivent Respimat—Boehringer Ingelheim) must load a drug cartridge into the device and give the inhaler an expiration date of:
   a. 28 days.
   b. 3 months.
   c. 6 months.
   d. 1 year.

16. Glycopyrronium bromide has a similar mechanism of action to which of the following?
   a. Fluticasone
   b. Ciclesonide
   c. Aclidinium
   d. Albuterol

17. A patient who is currently managed with only a rescue inhaler presents with a chronic obstructive pulmonary disease exacerbation. Comorbidities include benign prostatic hyperplasia treated with tamsulosin and seizures. Which of the following long-acting bronchodilators would you recommend?
   a. Tiotropium 80 µg inhaled daily
   b. Formoterol 12 µg inhaled every 12 hours
   c. Fluticasone/salmeterol 250/50 µg inhaled b.i.d.
   d. Fluticasone 440 µg inhaled every 12 hours

18. Your patient continues to have chronic obstructive pulmonary disease exacerbations in spite of a current regimen of indacaterol 75 µg inhaled once daily. The physician would like to add a steroid. You recommend:
   a. Adding fluticasone 110 µg inhaled every 12 hours.
   b. Adding tiotropium 80 µg inhaled once daily.
   c. Changing to budesonide/formoterol 160/4.5 µg inhaled twice daily.
   d. Changing to fluticasone/salmeterol 250/50 µg inhaled twice daily.

19. Which of the following medications should be used in caution in patients who have chronic obstructive pulmonary disease and a history of atrial fibrillation?
   a. Azithromycin
   b. Rosuvastatin
   c. Aclidinium
   d. Ciclesonide

20. Patients with chronic obstructive pulmonary disease are less likely to adhere to their regimens if they are taking:
   a. Multiple inhalers.
   b. One inhaler twice daily.
   c. A combination product.
   d. An oral medication.