COPD 2009: An update for pharmacists
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Abstract

Objective: To update pharmacists on recent research and emerging information related to the management of chronic obstructive pulmonary disease (COPD).

Data sources: Recently published articles listed in Medline and resources on various government, proprietary, and pharmaceutical manufacturer websites, identified using search terms such as chronic obstructive pulmonary disease, COPD, smoking cessation, and pneumonia and the names of specific drugs and drugs classes, as well as bibliographies of gathered articles.

Summary: COPD affects as many as 24 million Americans and is an increasingly important cause of morbidity and mortality in the United States. Although COPD cannot be cured, adherence to current evidence-based guidelines and optimal use of available therapies can help to control patients’ symptoms, slow the progression of the disease, and improve health-related quality of life. Background information about COPD and key recommendations of current international guidelines are reviewed. Recent developments related to COPD management are discussed, including use of the novel H1N1 vaccine, smoking cessation strategies, and selection and safety of drug therapy options. Possible roles for pharmacists in increasing the appropriate use of spirometry are described. Emerging treatment options are previewed, including ultra-long–acting beta2-agonists, novel long-acting inhaled anticholinergics, and phosphodiesterase-4 enzyme inhibitors.

Conclusion: New advances continue to contribute to our understanding of optimal management of patients with COPD. Pharmacists who keep abreast of these developments can make substantial contributions to patient care and treatment outcomes.

Keywords: Chronic obstructive pulmonary disease, anticholinergic agents, corticosteroids, nicotine replacement therapy, phosphodiesterase inhibitors, vaccines.


Learning objectives
At the conclusion of this program, the pharmacist will be able to:

- Summarize current evidence-based treatment strategies for chronic obstructive pulmonary disease (COPD).
- Discuss recent news and research findings that may influence the management of patients with COPD.
- Describe ways in which pharmacists might help to improve the management of patients with COPD.
- Identify new and emerging treatment options for COPD.

ACPE Activity Type: Knowledge-Based
Chronic obstructive pulmonary disease (COPD) is an increasingly important cause of morbidity and mortality in the United States. An estimated 12 million Americans had a diagnosis of COPD in 2006, but data from the National Center for Health Statistics suggest that the true prevalence is closer to 24 million (nearly 14% of the population). COPD was the underlying cause of approximately 126,000 deaths in 2005, making it the fourth leading cause of death after heart disease, cancer, and stroke. The age-standardized death rate for COPD more than doubled from 1970 to 2002, even as the rates for heart disease, cancer, and stroke were decreasing. COPD accounted for 636,000 hospitalizations in 2004 and more than 15.4 million physician office visits in 2003. The total economic burden of COPD in 2007 was estimated to be $42.6 billion, with direct medical costs accounting for $26.7 billion.

Despite rapidly rising rates of illness, disability, and death due to COPD, the condition remains largely underidentified, underdiagnosed, and undertreated. The primary care providers who treat the majority of patients with COPD may lack awareness and understanding of current evidence-based guidelines. Primary care providers also may harbor considerable pessimism about the value of COPD treatments. Awareness of COPD among at-risk individuals and even among patients already diagnosed with the condition remains distressingly low.

Although COPD cannot be cured, optimal use of currently available therapies can help to control patients' symptoms, slow the progression of the disease, and improve health-related quality of life. Given the unique access pharmacists have to both primary care providers and patients, pharmacists are well positioned to intervene to improve COPD outcomes. To do so, however, pharmacists must have a thorough understanding of current evidence-based guidelines, emerging research data, and new treatment options.

Objective
This article reviews the management of COPD and summarizes recent developments of greatest relevance to pharmacists.

About COPD
Current international guidelines, including those published by the American Thoracic Society/European Respiratory Society (ATS/ERS) and the Global Initiative for Chronic Obstructive Lung Disease (GOLD), define COPD as a preventable and treatable disease characterized by airflow limitation that is not fully reversible and usually is progressive. The airflow limitation is associated with an abnormal inflammatory response of the lungs to inhaled noxious particles or gases. COPD develops as chronic inflammation leads to structural changes and narrowing of the small airways.

In the United States, active and passive tobacco smoke—primarily from cigarette smoking—constitute by far the most important risk factor for COPD. However, many clinicians and patients have heard the often-quoted statistic that only 15% of smokers develop clinically significant COPD and thus underestimate the impact of smoking. In fact, studies using spirometry suggest that 50% or more of smokers will develop COPD and that all smokers are likely at risk.

Although COPD is primarily a pulmonary disease, it also produces important systemic effects that may worsen a patient's prognosis, independent of pulmonary function. These effects include nutrition abnormalities, weight loss, skeletal muscle weakness, and systemic inflammation. COPD is associated with a number of well-recognized comorbidities: the risks of bone fractures, chronic anemia, coronary heart disease, depression, diabetes, glaucoma, osteoporosis, respiratory infection (e.g., pneumonia), and sleep disorders all are increased in patients with COPD. More patients with COPD (including severe disease) are believed to die from acute cardiac events than from respiratory failure. Having COPD also increases a person's risk of developing lung cancer.

Clinical presentation and diagnosis
The clinical presentation of COPD is characterized by the following symptoms:
- Chronic cough that may be intermittent and unproductive.
- Production of small quantities of tenacious, mucoid sputum.
- Progressive dyspnea that may become persistent and usually is worse with exercise.

Chronic cough and sputum production may be present for many years before airflow limitation develops; conversely, considerable airflow limitation may precede the development of symptoms. Thus, current guidelines recommend considering a
Clinical diagnosis of COPD for any person older than 40 years who presents with any of the hallmark symptoms, a history of exposure to COPD risk factors, or both.15,16

COPD contrasts with asthma, which is associated with reversible airflow limitation.17 However, patients may have coexisting COPD and asthma, characterized by considerable airflow limitation and a large response to bronchodilators.15 COPD also is commonly misdiagnosed as asthma.7,18

Both the ATS/ERS and GOLD guidelines specify spirometry for diagnosing and staging COPD, monitoring progression of the disease, and guiding treatment decisions.8,15,16 Spirometry is a pulmonary function test that measures airflow: the specific measurements of interest for COPD are forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV₁).15,16 To determine FVC, the patient inhales maximally to total lung capacity, then exhales as rapidly and forcefully as possible into the spirometer.17 FEV₁ is the volume of air exhaled during the first second of that maneuver.16,17 The presence of airflow limitation that is not fully reversible is confirmed by the presence of an FEV₁ less than 80% predicted and an FEV₁/FVC ratio of less than 0.7 after administration of a short-acting bronchodilator.15–17,20

Spirometry results are used to categorize patients with COPD into one of four stages of disease severity (Table 1).15,16 COPD may be diagnosed at any stage, and diagnosis in the advanced stages of the disease is not unusual.16,21 In community studies, approximately 50% of patients of newly diagnosed patients had moderate severity (GOLD stage II) COPD.9,12,23

The natural history of COPD is marked by exacerbations that cause abrupt deteriorations in patients’ health-related quality of life and worsen disease progression.15,16,24 As defined in the ATS/ERS and GOLD guidelines, exacerbations involve an acute change in the patient’s baseline symptoms (especially increased breathlessness) that is beyond normal day-to-day variability and may be sufficient to warrant a change in usual medication.15,16 Exacerbations range in severity from mild (typically managed by the patient at home by increasing the dose or frequency of medications) to severe (usually requiring hospitalization with possible ventilatory support).15,25 The more than 1 million Americans who seek care for exacerbations in emergency departments each year have considerably higher risk for mortality in the ensuing 6 months.24

### Treatment strategies

The goals of therapy for COPD are multifold and include the following15–17:

- Symptom relief
- Prevention of disease progression
- Prevention and treatment of exacerbations and COPD-related complications
- Improvement in exercise tolerance and health status
- Reduction in mortality

These goals are addressed by adding pharmacologic and non-pharmacologic treatments (e.g., pulmonary rehabilitation, surgical procedures) in a stepwise manner to limit the effect of deteriorating lung function (Figure 1).9,16

**Smoking cessation.** Smoking cessation is considered the most important intervention for managing COPD.3,9 It is the only proven way to slow the accelerated loss of lung function that characterizes COPD and thereby prevent or delay the development of airflow limitation.15–17 Although smoking cessation is most beneficial in the earliest stages of the disease, stopping smoking at any stage—even after considerable airflow limitation is present—can result in some improvement in lung function, reduce disease progression, and increase survival.15–17,26 A recent cohort study of nearly 24,000 U.S. veterans who were current or past smokers found that ex-smokers had a substantially reduced risk of COPD exacerbations after adjusting for age, comorbidity, markers of COPD severity, and socioeconomic sta-

<table>
<thead>
<tr>
<th>Severity</th>
<th>GOLD stage⁸</th>
<th>FEV₁/FVC</th>
<th>FEV₁ % predicted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>I</td>
<td>&lt;0.7</td>
<td>≥80</td>
</tr>
<tr>
<td>Moderate</td>
<td>II</td>
<td>&lt;0.7</td>
<td>≥50 and &lt;80</td>
</tr>
<tr>
<td>Severe</td>
<td>III</td>
<td>&lt;0.7</td>
<td>≥30 and &lt;50</td>
</tr>
<tr>
<td>Very severe</td>
<td>IV</td>
<td>&lt;0.7</td>
<td>&lt;30 or &lt;50 plus chronic respiratory failure</td>
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</tbody>
</table>

Abbreviations used: FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease.

Stage classification used by the Global Initiative for Chronic Obstructive Lung Disease.

Source: References 15 and 16.
tus; the magnitude of risk reduction increased with increasing duration of smoking abstinence. 

Immunizations. Approximately 80% of COPD exacerbations are caused by viral or bacterial respiratory infections. Thus, immunization with influenza and pneumococcal vaccines is considered a key prophylactic strategy. The Centers for Disease Control and Prevention (CDC) recommends annual immunization with the trivalent inactivated influenza vaccine and one or two doses of pneumococcal vaccine for all patients with chronic pulmonary disease, including COPD. (Patients 65 years of age or older should receive a second dose of pneumococcal vaccine if they were younger than 65 years at the time of primary vaccination and the vaccine was administered 5 or more years previously.)

Pharmacologic therapy. To date, no medication has been shown to alter the rate of decline in lung function in patients with COPD. Pharmacologic therapy is directed primarily at preventing or decreasing symptoms (especially dyspnea) by reducing airway smooth muscle tone or reducing inflammation. Unlike in asthma, stepping down therapy after symptom control has been achieved is not usually possible. Inhaled therapy is preferred in COPD. One consequence of this preference is that medication regimens for patients with COPD are particularly vulnerable to adherence problems because they may require the use of multiple inhalers with different instructions for use and different inhalation techniques, often at different times of the day. Simplifying the dosage regimen by reducing the frequency of dosing and number of individual products is considered of paramount importance to improving adherence.

### Table 2. Inhaled medications used commonly in the treatment of chronic obstructive pulmonary disease

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Brand name(s)</th>
<th>Delivery device(s)</th>
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</thead>
<tbody>
<tr>
<td><strong>Bronchodilators</strong></td>
<td></td>
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<tr>
<td><strong>Short-acting beta₂-agonists</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albuterol</td>
<td>ProAir, Proventil, Ventolin</td>
<td>HFA metered-dose inhaler</td>
</tr>
<tr>
<td>Levalbuterol</td>
<td>Xopenex</td>
<td>HFA metered-dose inhaler</td>
</tr>
<tr>
<td>Pirbuterol</td>
<td>Maxair</td>
<td>CFC metered-dose inhaler (breath-actuated)</td>
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<tr>
<td><strong>Short-acting anticholinergic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ipratropium</td>
<td>Atrovent</td>
<td>HFA metered-dose inhaler</td>
</tr>
<tr>
<td><strong>Combination short-acting beta₂-agonist/short-acting anticholinergic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albuterol/ipratropium</td>
<td>Combivent</td>
<td>CFC metered-dose inhaler</td>
</tr>
<tr>
<td><strong>Long-acting beta₂-agonists</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Formoterol</td>
<td>Foradil</td>
<td>Dry powder inhaler (Aerolizer)</td>
</tr>
<tr>
<td>Salmeterol</td>
<td>Serevent</td>
<td>Dry powder inhaler (Diskus)</td>
</tr>
<tr>
<td>Arformoterol</td>
<td>Brovana</td>
<td>Inhalation solution</td>
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<tr>
<td><strong>Long-acting anticholinergic</strong></td>
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<tr>
<td>Tiotropium</td>
<td>Spiriva</td>
<td>Dry powder inhaler (HandiHaler)</td>
</tr>
<tr>
<td><strong>Corticosteroids</strong></td>
<td></td>
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<tr>
<td>Beclomethasone dipropionate</td>
<td>Qvar</td>
<td>HFA metered-dose inhaler</td>
</tr>
<tr>
<td>Budesonide</td>
<td>Pulmicort</td>
<td>Dry powder inhaler (Flexhaler)</td>
</tr>
<tr>
<td>Fluticasone</td>
<td>Flovent</td>
<td>Dry powder inhaler (Diskus)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HFA metered-dose inhaler</td>
</tr>
<tr>
<td>Triamcinolone</td>
<td>Azmacort</td>
<td>CFC metered-dose inhaler</td>
</tr>
<tr>
<td><strong>Combination corticosteroid/long-acting beta₂-agonist</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Budesonide/formoterol</td>
<td>Symbicort</td>
<td>HFA metered-dose inhaler</td>
</tr>
<tr>
<td>Fluticasone/salmeterol</td>
<td>Advair</td>
<td>Dry powder inhaler (Diskus)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HFA metered-dose inhaler</td>
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</tbody>
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Abbreviations used: CFC, chlorofluorocarbon; HFA, hydrofluoroalkane.
- Does not include medications administered by nebulizer.
Bronchodilator therapy is typically initiated with a single agent. If the patient’s symptoms are not controlled adequately, a second bronchodilator from a different class may be added rather than increasing the dose of the initial agent. Beta₂-agonists and anticholinergics produce airway smooth muscle relaxation through different pathways; using a beta₂-agonist in combination with an anticholinergic has an additive effect, providing greater efficacy compared with either agent alone.

Also, the rate of adverse effects with bronchodilators—primarily tremor and palpitations with beta₂-agonists and dry mouth with anticholinergics—increases progressively with increasing doses. Combination therapy with agents from different classes can achieve better results while limiting adverse effects.

In the stepwise approach to therapy, all patients with COPD should have a short-acting bronchodilator available to use as needed for intermittent symptoms. Beta₂-agonists are considered to be better suited for as-needed use because they have a more rapid onset of action than the short-acting anticholinergic agent ipratropium. Ipratropium has the advantage of a longer duration of effect (up to 9 hours for ipratropium vs. 4 to 6 hours for beta₂-agonists). A fixed combination of albuterol and ipratropium is available commercially in a single inhaler.

Regular maintenance therapy with one or more long-acting bronchodilators is added (Figure 1) for COPD of at least moderate severity, when a patient’s symptoms are poorly controlled, or when as-needed use of short-acting bronchodilators exceeds one canister per month. The currently available long-acting beta₂-agonists (Table 2) have a duration of effect of 12 hours or more and are administered twice daily. The long-acting anticholinergic agent tiotropium has a duration of action of more than 24 hours and can be administered once daily. No fixed combinations of long-acting bronchodilators in a single inhaler are available at this time. Of important note, some patients are slow responders to bronchodilators and tiotropium is available commercially in a single inhaler.

Corticosteroids. Inhaled corticosteroids (Table 2) are added to bronchodilator therapy for patients with severe COPD (post-bronchodilator FEV₁ < 50% predicted) who experience repeated exacerbations. The GOLD guidelines use the example of three exacerbations through undetermined mechanisms. In these patients, inhaled corticosteroids have been shown to cause a modest improvement in airway and reduce both the frequency and severity of exacerbations through undetermined mechanisms.

So-called “triple therapy” with a long-acting beta₂-agonist, a long-acting anticholinergic, and an inhaled corticosteroid is possible and has been shown to provide improvements in lung function and health-related quality of life, as well as a reduction in severe exacerbations. A recent cohort analysis by Lee et al. of more than 42,000 patients in the Department of Veterans Affairs (VA) health system with a diagnosis of COPD found that triple therapy was associated with a 40% reduction in risk of all-cause mortality, a 16% reduction in risk of exacerbations, and a 22% reduction in risk of COPD-related hospitalizations compared with a regimen that did not include tiotropium.

Products combining a long-acting beta₂-agonist and a corticosteroid in a single inhaler are available (Table 2), but no fixed combinations of a long-acting anticholinergic and a corticosteroid are marketed currently. No single inhaler combines agents from all three classes.

Pharmacists should be aware that the use of inhaled corticosteroids in COPD is a topic of ongoing debate and controversy, despite the current guideline recommendations. Opponents argue that the benefits of therapy do not outweigh potential risks, particularly in patients with less severe disease. These risks include possible adverse events such as osteoporosis, skeletal muscle myopathy, glaucoma, and cataracts, as well as an increased risk of pneumonia (see COPD news and updates).
ers end up relapsing within the first 8 days after quitting. Pharmacists are among the health professionals singled out in the GOLD guidelines as key to the delivery of smoking cessation messages and interventions; pharmacists who seek to provide smoking cessation services should consult the most recent guidelines and recommendations from the U.S. Public Health Service and the U.S. Preventive Services Task Force.

Several recent studies add to the growing body of knowledge about the effectiveness of various smoking cessation strategies. Etter et al. conducted an open randomized trial of 314 daily smokers to test whether starting nicotine polacrilex gum treatment 4 weeks before the quit date (precessation treatment group) improved smoking abstinence rates compared with starting treatment on the quit date (usual care group). Participants in the precessation treatment group were advised to decrease their cigarette smoking by one-half before quitting. Smoking cessation rates were similar in both groups on all follow-up surveys; for example, at 8 weeks after the target quit date, self-reported 4-week abstinence rates were 41.6% in the precessation treatment group and 44.4% in the usual care group. At 1 year after the target quit date, 20.8% of participants in the precessation treatment group and 19.4% in the usual care group had undergone spirometry initially and at 12 months. Spirometry results were reported to participants in the intervention group in terms of lung age; participants in the control group received their results as raw FEV₁ scores. The verified smoking cessation rate at 12 months was more than twice as high for participants in the intervention group (13.6%) as for participants in the control group (6.4%). This represented a significant absolute reduction of 7.2% in the smoking rate. The number needed to treat for the intervention to achieve one additional sustained quitter was 14.

**Spirometry**

A 2008 statement from the U.S. Preventive Services Task Force recommends against the screening of asymptomatic adults for COPD using spirometry. Nonetheless, a growing consensus exists that spirometry is vastly underused for detecting COPD in at-risk patients and confirming the diagnosis, especially in primary care settings (where the majority of care for COPD is provided). Underuse is blamed in part on the tendency of both primary care providers and patients to discount chronic cough and sputum production as expected and inevitable consequences of smoking.

Advances in technology have made creating portable spirometers that are small, reliable, accurate, affordable, and easy to use possible. As a result, interest in moving spirometric testing out of the realm of pulmonary specialists and into the primary care arena is increasing. Two recent reports explored the feasibility of pharmacist involvement in spirometry.

Castillo et al. investigated whether pharmacists who had attended a 4-day spirometry training course would be able to appropriately identify at-risk patients of 13 urban community pharmacies in Barcelona, Spain, and supervise high-quality spirometric maneuvers. Pharmacists approached patients who appeared to be older than 40 years to determine their smoking status and gauge their interest in study participation, then administered a GOLD scoring questionnaire to 161 qualified patients who agreed to participate. A total of 96 high-risk participants performed prebronchodilator spirometry in the pharmacy; 21 participants with an FEV₁-to-FVC ratio less than 0.7 were referred to a local hospital for follow-up. The spirometric curves obtained in the pharmacy were deemed to be of acceptable quality overall, with 70% rated as acceptable by the spirometer software and 73% rated as acceptable by a lung function expert.

Mann and Zaiken described a pharmacist-driven spirometry and medication program in a multispecialty medical group...
practice center with 19 locations in the greater Boston area. Through chart review, the pharmacist identified 87 patients with a diagnosis of COPD, chronic bronchitis, or emphysema who were being cared for by primary care providers. The pharmacist recommended spirometry testing for 80 of those patients; 60 of the recommendations (75%) were accepted by the primary care providers, and 29 of the patients actually were tested during the study period. Based on the results of those tests, the pharmacist made recommendations to add or change inhaled medications in 14 patients, most commonly to add a long-acting anticholinergic agent.

Pharmacotherapy

Choice of initial agent for long-acting bronchodilator maintenance therapy. None of the current international COPD guidelines provide specific recommendations regarding drugs of choice in any of the therapeutic categories. A number of recent publications have sought to provide guidelines that are relevant to clinical practice. Several guidelines provide specific recommendations regarding drugs of choice in any of the therapeutic categories. A number of recent publications have sought to provide guidelines that are relevant to clinical practice. Several guidelines provide specific recommendations regarding drugs of choice in any of the therapeutic categories.

Status of remaining chlorofluorocarbon metered-dose inhalers. The FDA regulation banning the marketing of single-agent albuterol metered-dose inhalers containing chlorofluorocarbons (CFCs) took effect on December 31, 2008. Three CFC-containing products used for treating COPD were not affected by this ban: Combivent (ipratropium bromide and albuterol sulfate), Azmacort (triamcinolone), and Maxair Autohaler (containing pirbuterol acetate). The proposed date for removing the “essential use” designation of these products is December 31, 2009. Comments about this proposed rule were due to FDA by August 10, 2007; the Agency had not issued a final rule as of September 2009.

Clinical trials of Combivent Respimat—ipratropium bromide and salbutamol inhalation spray combination administered by the novel Respimat Soft Mist Inhaler (see EMERGING TREATMENT OPTIONS)—have been completed, but Boehringer Ingelheim Pharmaceuticals has not announced when that product might be available. The manufacturer of the Maxair Autohaler (Graceway Pharmaceuticals, LLC) has stated that it is developing a new, CFC-free pirbuterol metered-dose inhaler, with the goal of having the product available by 2015 (with sufficient CFC stocks to produce the Maxair Autohaler through that time). Little information is available about the pending availability of Azmacort in a CFC-free inhaler.

Safety issues. Ongoing concerns exist regarding the risk of cardiovascular events with inhaled anticholinergics and the risk of pneumonia with inhaled corticosteroids used in patients with COPD. A number of recent publications have sought to provide the last word on each of these issues.

The possibility that treatment with inhaled corticosteroids might increase patients’ risk of pneumonia was first raised in the Towards a Revolution in COPD Health (TORCH) trial—a randomized controlled trial that compared the combination of salmeterol and fluticasone propionate with each of the components alone and with placebo in more than 6,000 patients during a 3-year period. In that trial, the probability of having pneumonia as an adverse event was significantly greater among patients receiving any study medication containing fluticasone propionate. The increase in pneumonia did not appear to represent an increase in the number of deaths, however. Two subsequent meta-analyses also reported a significantly increased risk of pneumonia with inhaled corticosteroid use in COPD. Drummond et al. reported a 34% increased risk of pneumonia with no increase in all-cause mortality, while Singh et al. reported a 60% increased risk of pneumonia without a significantly increased risk of pneumonia-related death.

A more recent post hoc analysis of the TORCH trial has confirmed a greater rate of pneumonia among patients treated with fluticasone propionate plus salmeterol (88 per 1,000 treatment years) or fluticasone propionate alone (84 per 1,000 treatment years) compared with salmeterol or placebo (52 per 1,000 treatment years for each). No increase in pneumonia deaths occurred among patients who received combination therapy, but results were inconclusive for patients treated with fluticasone propionate alone. The authors underscored the importance of remaining vigilant for the possible development of pneumonia and implementing early and appropriate therapy.

In contrast, a recent meta-analysis by Sin et al. showed no increased risk of pneumonia during 12 months of treatment with budesonide. The meta-analysis included data from seven large clinical trials and 7,042 patients, 3,801 of whom were treated with budesonide. In speculating about the reasons for these discordant results, the authors cited their access to patient-level data (which gave them the ability to assess or adjust for potential confounders) and pointed out that previous meta-analyses were heavily weighted with studies of fluticasone.

A greater disparity is seen in the findings regarding cardiovascular safety of anticholinergic agents. A 2008 systematic review and meta-analysis by Singh et al. of 17 randomized controlled trials enrolling more than 14,000 patients concluded that inhaled anticholinergics are associated with a significantly increased risk of cardiovascular death, myocardial infarction, or stroke among patients with COPD. The findings of a cohort study by Ogale et al. were consistent with that conclusion. Among more than 82,000 patients in the VA health system with a new diagnosis of COPD, use of an inhaled anticholinergic (mostly ipratropium) within the previous 6 months was associated with a 40% increase in the risk of cardiovascular events. In contrast, a reduction in cardiac adverse events was associated with tiotropium (versus placebo) in the 4-year Understanding Potential Long-Term Impacts on Function with Tiotropium (UPLIFT) trial. A subsequent analysis that combined the UPLIFT results with those of all other tiotropium placebo-controlled trials of at least 4 weeks’ duration representing more than 19,000 patients with COPD found that the incidence rates for all-cause mortality, cardiovascular mortality, and a composite cardiovascular endpoint (encompassing cardiac death, nonfatal myocardial infarction, and nonfatal stroke) were lower for patients treated with tiotropium than for patients who received...
placebo. Rodrigo et al. performed a systematic review with meta-analysis using data from 19 randomized controlled trials with more than 18,000 participants; the results showed that tiotropium did not significantly increase the risk of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke compared with salmeterol or placebo. As Hilleman et al. pointed out in another recent systematic review, the question of cardiovascular safety of anticholinergic agents in patients with COPD may not be answered definitively until adequately powered randomized controlled trials with adjudication of cardiovascular events are conducted.

**Emerging treatment options**

An awareness of gaps in available treatment options, coupled with growing research interest in the cell and molecular biology of COPD, have led to an explosion of drug development activity. A search of the Pharmaceutical Research and Manufacturers of America new medications database lists 35 drugs or drug combinations that are in Phase I, II, or III clinical trials or undergoing FDA review for use in COPD. A comprehensive exploration of all emerging therapies is beyond the scope of this article; this section focuses on some of the agents in late-stage development.

**Ultra-long–acting beta₂-agonists**

Because existing long-acting beta₂-agonists require twice-daily dosing, the debut of ultra-long–acting beta₂-agonists with a duration of action of 24 hours or longer—allowing for once-daily dosing—is eagerly anticipated. Indacaterol (QAB149) appears to be closest to commercial availability; a new drug application (NDA) was filed in December 2008, and initial results from three multinational pivotal Phase III trials that included more than 3,800 patients with moderate to severe COPD were reported in May 2009. In those studies, indacaterol demonstrated “clinically relevant” improvements in lung function (improvement in FEV₁ > 120 mL more than placebo) within 5 minutes of the first dose. Another agent, carmoterol, is in Phase II trials. Ultra-long–acting beta₂-agonists are expected to be available as monotherapy and in fixed combinations with long-acting anticholinergics or corticosteroids.

**Novel long-acting inhaled anticholinergics**

In the lung, activation of muscarinic receptors by acetylcholine causes bronchoconstriction (primarily through M₁ receptors present on airway smooth muscle) and mucus secretion (through both M₁ and M₂ receptors). M₁ receptors also are present in the lung: activation of these receptors provides a feedback function, inhibiting further release of acetylcholine and presumably mitigating bronchoconstriction. Inhaled anticholinergic agents work by competing with acetylcholine at muscarinic receptors. Thus, the ideal anticholinergic for COPD would inhibit M₁ and M₂ receptors preferentially.

Ipratropium is a nonselective muscarinic antagonist that inhibits all three receptor subtypes in the lung. Tiotropium also binds to all three subtypes but displays relative selectivity because it dissociates much faster from M₂ receptors than from M₁ or M₃ receptors. Slow dissociation from M₁ and M₃ receptors also is responsible for the prolonged duration of action seen with tiotropium.

The search for novel long-acting inhaled anticholinergics centers on agents that will have a high affinity for M₁ and M₃ receptors and cause few or no adverse effects (especially systemic adverse effects). Glycopyrrolate (also known as glycopyrronium bromide or NVA237) is in Phase III trials with an expected NDA filing in 2011. Data from earlier phases of development have shown glycopyrrolate to have a rapid onset of effect and long duration of action (up to 32 hours), with efficacy similar to that of tiotropium. It also appears to have a favorable safety profile, notable for a lack of dry mouth and a significantly lower effect on cardiovascular parameters than tiotropium. Glycopyrrolate is expected to be available as monotherapy and in combination with the ultra-long–acting beta₂-agonist indacaterol.

Aclidinium bromide also is in Phase III clinical trials. It is being developed for administration via a novel, breath-actuated, multidose dry powder inhaler (Genuair). In Phase II trials, aclidinium demonstrated anticholinergic activity comparable with that of tiotropium and ipratropium but with a more rapid onset of effect than tiotropium (as soon as 15 minutes) and a duration of action of at least 24 hours. Aclidinium appears to be well tolerated, with an incidence of adverse effects generally comparable with placebo and no evidence of treatment-associated tachyphylaxis.

**Phosphodiesterase-4 enzyme inhibitors**

The pathophysiology of COPD is marked by both pulmonary and systemic inflammation. Phosphodiesterase-4 (PDE-4) is expressed in a variety of inflammatory cells that are believed to play an important role in COPD, including the pulmonary neutrophils that increase in number as COPD worsens. Selective PDE-4 enzyme inhibitors represent a possible new class of medications for treating COPD, with the ability to decrease pulmonary inflammation.

Roflumilast (Daxas) currently is undergoing review by FDA and is poised to become the first PDE-4 enzyme inhibitor to reach the marketplace. In contrast with most other drugs used to treat COPD, roflumilast is administered orally. (Delivery of PDE-4 enzyme inhibitors by inhalation has been ineffective.) In early Phase III clinical trials that enrolled patients with moderate to very severe COPD, once-daily administration of roflumilast produced a significant improvement in FEV₁, compared with placebo, as well as a positive trend toward decreased exacerbations. In more recent and larger Phase III trials, roflumilast was found to consistently improve lung function in patients with moderate to severe COPD who were already being treated with salmeterol or tiotropium and to improve lung function and reduce the frequency of exacerbations in patients with bronchitic symptoms and severe airflow limitation. Roflumilast also appears to have important anti-inflammatory effects outside the lungs, which potentially could have a positive impact on COPD comorbidities such as cardiovascular disease.

The development of oral PDE-4 enzyme inhibitors has been hindered by dose-limiting gastrointestinal adverse events, par-
particularly nausea, vomiting, and abdominal pain.71 Roflumilast appears to be well tolerated by patients with COPD, with a low rate of gastrointestinal adverse events that decreases with continued treatment.72

On the horizon

Pharmacists are likely to see a profusion of new combination products for treating COPD (in addition to the possible combinations already mentioned), as well as new devices for delivering medications.9,30,71,73 For example, a fixed-dose combination of mometasone furoate plus formoterol fumarate is undergoing review by FDA for maintenance treatment of asthma, and Phase III clinical trials for its use in patients with COPD are under way.82 The novel Respimat Soft Mist Inhaler is approved for use in the European Union and is expected to become available in the United States initially as an alternative delivery system for tiotropium. Respimat is a propellant-free metered-dose liquid inhaler; actuation of a dose-release button on the inhaler produces an aerosol cloud that contains a higher fraction of fine particles, moves more slowly, and has a more prolonged duration than the aerosol cloud produced by a traditionally pressurized metered-dose inhaler.83 This combination of characteristics (1) simplifies coordination between actuation and inhalation and (2) produces high lung deposition and low oropharyngeal deposition.83

One novel approach to drug development that has the potential to revolutionize pharmacotherapy for COPD involves covalently linking an M3 receptor antagonist to a beta2-agonist in a single dimer molecule.84 Several so-called M3 antagonist beta2-agonist bronchodilators are in the early stages of clinical development.30

Drugs that currently are used in treating other conditions may find a role in treating COPD. Evidence suggests that statins may have a beneficial effect on various COPD outcomes, including number of exacerbations, pulmonary function, and mortality through anti-inflammatory and immunomodulatory mechanisms outside of their usual lipid-lowering effects.85 A recent single-blind non-placebo-controlled trial showed that daily treatment with lansoprazole 15 mg significantly reduced the risk of exacerbations among 100 ex-smokers with COPD.86 COPD is influenced by multiple genetic factors and environmental factors.15,16 Information is beginning to emerge about the genes involved or potentially involved in the pathogenesis of COPD. This information may reveal roles for new treatments such as protease inhibitors and inflammatory mediator inhibitors.87 In the future, classification of COPD according to pathogenesis may make developing individualized therapeutic strategies possible.87

Summary

The pace of research on the causes, prevention, and treatment of COPD remains brisk, and options for patient management continue to expand. Armed with a thorough understanding of current evidence-based treatment guidelines and familiarity with recent developments that affect patient management, pharmacists can seize their unique opportunity to intervene with primary care providers and patients in ways that can improve COPD outcomes.

References


Assessment Questions

**Instructions:** The assessment test for this activity must be taken online; please see “CPE processing” below for further instructions. There is only one correct answer to each question. This CPE will be available at www.pharmacist.com no later than November 30, 2009.

1. Among leading causes of death in the United States, chronic obstructive pulmonary disease (COPD) currently ranks
   a. Third.
   b. Fourth.
   c. Seventh.
   d. Twelfth.

2. In the United States, the most important risk factor for COPD is
   a. Biomass fuels.
   b. Cigarette smoking.
   c. Occupational dusts.
   d. Outdoor air pollution.

3. What percent of smokers is expected to develop COPD?
   a. 15%
   b. 25%
   c. 35%
   d. 50%

4. Which of the following statements about COPD is true?
   a. Both COPD and asthma are characterized by fully reversible airflow limitation.
   b. COPD rarely produces important systemic effects.
   c. Having COPD decreases a person’s risk of developing lung cancer.
   d. Patients with COPD are more likely to die from cardiovascular disease than from respiratory failure.

5. Which of the following is not one of the characteristic symptoms of COPD?
   a. Chronic cough
   b. Dyspnea
   c. Pleuritis
   d. Sputum production

6. The presence of airflow limitation that is not fully reversible is confirmed by a ratio of forced expiratory volume in 1 second to forced vital capacity of less than
   a. 0.4.
   b. 0.5.
   c. 0.6.
   d. 0.7.

7. Which of the following statements about COPD exacerbations is true?
   a. They are an expected part of the natural history of COPD.
   b. They have little effect on the disease prognosis.
   c. They reflect normal day-to-day variability in symptom severity.
   d. They typically do not require any change in the patient’s usual medications.

8. Which of the following is considered the most important intervention for managing COPD?
   a. Annual influenza vaccine
   b. Pneumococcal vaccine
   c. Short-acting bronchodilator therapy
   d. Smoking cessation

9. In the stepwise approach to COPD therapy, which of the following treatments is most appropriate for a patient with moderate-severity COPD?
   a. Inhaled corticosteroid
   b. Long-acting inhaled bronchodilator
   c. Oxygen
   d. Surgery

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**CPE Credit:**

To obtain 2.0 contact hours of continuing pharmacy education credit (0.2 CEUs) for “COPD 2009: An update for pharmacists,” go to www.pharmacist.com and take your test online for instant credit. CPE processing is free for APhA members and $15 for nonmembers. A Statement of Credit will be awarded for a passing grade of 70% or better. You have two opportunities to successfully complete the posttest. Pharmacists who complete this exercise successfully before November 1, 2012, can receive credit.

The American Pharmacists Association is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. The ACPE Universal Activity Number assigned to the program by the accredited provider is 202-000-09-234-H01-P.

“COPD 2009: An update for pharmacists” is a home-study continuing education activity for pharmacists developed by the American Pharmacists Association.
10. In current treatment guidelines, inhaled corticosteroids are considered appropriate for:
   a. All patients with symptomatic COPD.
   b. COPD of at least moderate severity in patients 65 years or older.
   c. Patients with severe COPD who experience repeated exacerbations.
   d. Treating acute exacerbations only.

11. Which of the following medications is not part of “triple therapy” for COPD?
   a. Inhaled corticosteroids
   b. Long-acting beta2-agonists
   c. Long-acting anticholinergics
   d. Short-acting beta2-agonists

12. Which of the following patients with COPD is considered to be a priority for immunization with the novel H1N1 vaccine?
   a. 72-year-old woman
   b. 65-year-old man
   c. 57-year-old woman
   d. Alternatives b and c are correct.

13. In a recent study, which of the following interventions was found to more than double the number of people who stopped smoking?
   a. Starting nicotine gum 4 weeks before the quit date as part of a “cut down to quit” strategy.
   b. Telling patients their risk of lung cancer in addition to their spirometry results.
   c. Translating spirometry results into “lung age.”
   d. Using cigarettes engineered to contain less nicotine.

14. In the study by Castillo et al.,52 approximately what percent of pharmacist-supervised spirometry results were rated as acceptable by a lung function expert?
   a. 25%
   b. 45%
   c. 60%
   d. 70%

15. Which of the following agents is gaining support as initial therapy when a long-acting bronchodilator is added to the treatment regimen of patients with COPD?
   a. Formoterol
   b. Ipratropium
   c. Salmeterol
   d. Tiotropium

16. Recent data confirm that inhaled corticosteroid therapy is associated with an increased risk of:
   a. Myocardial infarction.
   b. Pneumonia.
   c. Stroke.
   d. Tremor.

17. What is the anticipated advantage of ultra-long-acting beta2-agonists?
   a. Lower incidence of adverse effects
   b. Greater affinity for beta2 receptors
   c. Once-daily dosing
   d. Oral dosing

18. Which of the following agents is an investigational new long-acting anticholinergic?
   a. Aclidinium bromide
   b. Glycopyrronium bromide
   c. Mometasone
   d. Roflumilast

19. What differentiates phosphodiesterase-4 enzyme inhibitors such as roflumilast from most currently available drugs used to treat COPD?
   a. They are administered orally.
   b. They are being developed specifically for use with a novel metered-dose liquid inhaler.
   c. They have been shown to alter the rate of decline in lung function in patients with COPD.
   d. They were developed using dimer molecule technology.

20. Which of the following drug classes may have a beneficial effect in COPD, outside of the usual clinical effects?
   a. Bisphosphonates
   b. Glitazones
   c. Selective serotonin reuptake inhibitors
   d. Statins

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