

COPD 2009: An update for pharmacists

Karen J. Tietze and Cynthia Knapp Dlugosz

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 drug 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.

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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.¹ 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).^{2,3} 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.^{2,4} 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.⁵ COPD accounted for 636,000 hospitalizations in 2004 and more than 15.4 million physician office visits in 2003.⁶ The total economic burden of COPD in 2007 was estimated to be \$42.6 billion, with direct medical costs accounting for \$26.7 billion.⁶

Despite rapidly rising rates of illness, disability, and death due to COPD, the condition remains largely underidentified, underdiagnosed, and undertreated.^{3,7} The primary care providers who treat the majority of patients with COPD may lack awareness and understanding of current evidence-based guidelines.⁸⁻¹¹ Primary care providers also may harbor considerable pessimism about the value of COPD treatments.¹¹ Awareness of COPD among at-risk individuals and even among patients already diagnosed with the condition remains distressingly low.^{12,13}

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.^{10,14} 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.^{15,16} The airflow limitation is associated with an abnormal inflammatory response of the lungs to inhaled noxious particles or gasses.^{15,16} COPD develops as chronic inflammation leads to structural changes and narrowing of the small airways.¹⁶

In the United States, active and passive tobacco smoke—primarily from cigarette smoking—constitute by far the most important risk factor for COPD.^{15,16} 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.^{3,15,17} In fact, studies using spirometry suggest that 50% or more of smokers will develop COPD and that all smokers are likely at risk.^{3,18}

Although COPD is primarily a pulmonary disease, it also produces important systemic effects that may worsen a patient's prognosis, independent of pulmonary function.^{15,16} These effects include nutrition abnormalities, weight loss, skeletal muscle weakness, and systemic inflammation.¹⁵⁻¹⁷ 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.^{15-17,19} More patients with COPD (including severe disease) are believed to die from acute cardiac events than from respiratory failure.^{14,17} Having COPD also increases a person's risk of developing lung cancer.¹⁶

Clinical presentation and diagnosis

The clinical presentation of COPD is characterized by the following symptoms^{15,16}:

- 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.¹⁶ Thus, current guidelines recommend considering a

At a Glance

Synopsis: Although chronic obstructive pulmonary disease (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. Given their access to both primary care providers and patients, pharmacists have a unique opportunity to intervene in ways that can improve COPD outcomes.

Analysis: *Smoking cessation, immunizations, inhaled bronchodilators, and inhaled corticosteroids are key components of a comprehensive treatment strategy, with medications added in a stepwise manner for worsening disease severity. The status of several medications provided in chlorofluorocarbon metered-dose inhalers remains unclear, despite an impending deadline for removal of their "essential use" designation. Increasing evidence confirms an increased risk of pneumonia among patients treated with inhaled corticosteroids; the cardiovascular safety of anticholinergic agents is less clear, although recent evidence supports the safety of tiotropium. Among the new treatment options expected to be available soon for COPD are ultra-long-acting beta₂-agonists, novel long-acting inhaled anticholinergics, phosphodiesterase-4 enzyme inhibitors, new fixed drug combinations, and new inhaler technology.*

Table 1. Spirometric classification of chronic obstructive pulmonary disease severity^a

Severity	GOLD stage ^b	FEV ₁ /FVC	FEV ₁ % predicted
Mild	I	<0.7	≥80
Moderate	II	<0.7	≥50 and <80
Severe	III	<0.7	≥30 and <50
Very severe	IV	<0.7	<30 or <50 plus chronic respiratory failure

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

^aBased on postbronchodilator FEV₁.

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

Source: References 15 and 16.

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.^{9,22,23}

The natural history of COPD is marked by exacerbations that cause abrupt deteriorations in patients' health-related quality of life and worsen disease prognosis.^{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

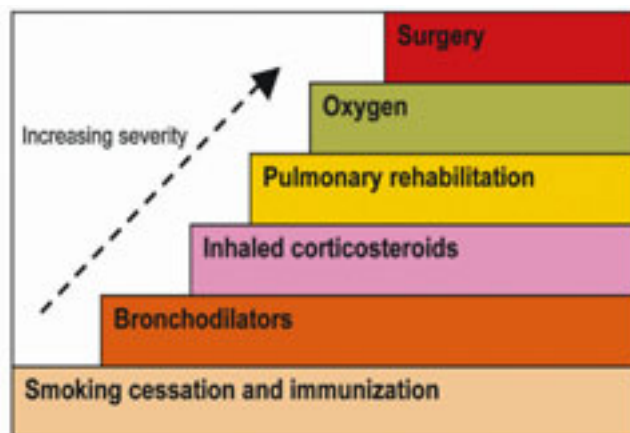


Figure 1. Stepwise approach to COPD therapy

Abbreviation used: COPD, chronic obstructive pulmonary disease.

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 2. Inhaled medications used commonly in the treatment of chronic obstructive pulmonary disease^a

Drug name	Brand name(s)	Delivery device(s)
Bronchodilators		
Short-acting beta₂-agonists		
Albuterol	ProAir Proventil Ventolin	HFA metered-dose inhaler
Levalbuterol	Xopenex	HFA metered-dose inhaler
Pirbuterol	Maxair	CFC metered-dose inhaler (breath-actuated)
Short-acting anticholinergic		
Ipratropium	Atrovent	HFA metered-dose inhaler
Combination short-acting beta₂-agonist/ short-acting anticholinergic		
Albuterol/ipratropium	Combivent	CFC metered-dose inhaler
Long-acting beta₂-agonists		
Formoterol	Foradil	Dry powder inhaler (Aerolizer)
Salmeterol	Serevent	Dry powder inhaler (Diskus)
Arformoterol	Brovana	Inhalation solution
Long-acting anticholinergic		
Tiotropium	Spiriva	Dry powder inhaler (HandiHaler)
Corticosteroids		
Beclomethasone dipropionate	Qvar	HFA metered-dose inhaler
Budesonide	Pulmicort	Dry powder inhaler (Flexhaler)
Fluticasone	Flovent	Dry powder inhaler (Diskus) HFA metered-dose inhaler
Triamcinolone	Azmacort	CFC metered-dose inhaler
Combination corticosteroid/long-acting beta₂-agonist		
Budesonide/formoterol	Symbicort	HFA metered-dose inhaler
Fluticasone/salmeterol	Advair	Dry powder inhaler (Diskus) HFA metered-dose inhaler

Abbreviations used: CFC, chlorofluorocarbon; HFA, hydrofluoroalkane.

^aDoes not include medications administered by nebulizer.

tus; the magnitude of risk reduction increased with increasing duration of smoking abstinence.²⁷

Immunizations. Approximately 80% of COPD exacerbations are caused by viral or bacterial respiratory infections.¹⁴⁻¹⁶ Thus, immunization with influenza and pneumococcal vaccines is considered a key prophylactic strategy.^{15,16,24} 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.^{28,29} (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.²⁹)

Pharmacologic therapy. To date, no medication has been shown to alter the rate of decline in lung function in patients with COPD.^{8,9,15,16} Pharmacologic therapy is directed primarily at preventing or decreasing symptoms (especially dyspnea) by reducing airway smooth muscle tone or reducing inflammation.^{9,17} Unlike in asthma, stepping down therapy after symptom

control has been achieved is not usually possible.¹⁶

Inhaled therapy is preferred in COPD.^{15,16} 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.^{9,10,24} Simplifying the dosage regimen by reducing the frequency of dosing and number of individual products is considered of paramount importance to improving adherence.^{9,10,30}

Bronchodilators. Inhaled bronchodilators are the cornerstone of COPD therapy.^{8,9} They are used both for as-needed “rescue” use and on a chronic basis.^{16,17} In COPD, dyspnea occurs primarily with exertion or other increased respiratory demands, rather than in response to acute bronchospasm as occurs in asthma.¹⁷ Accordingly, preventing episodes of dyspnea as much as possible with regular maintenance therapy is more appropriate than treating episodes when they occur.¹⁷

Bronchodilator therapy for COPD includes beta₂-agonists and anticholinergics in short- and long-acting formulations

(Table 2).^{9,15,16} These agents produce small but important improvements in lung emptying through airway smooth muscle relaxation.^{15,25} Patients generally experience a reduction in perceived breathlessness and improved exercise tolerance, even if the improvement in resting spirometry is modest.^{15,17}

Bronchodilator therapy is typically initiated with a single agent.¹⁷ 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.^{8,17} 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.^{9,16,31,32} 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.^{8,17} Combination therapy with agents from different classes can achieve better results while limiting adverse effects.^{8,16,17}

In the stepwise approach to therapy, all patients with COPD should have a short-acting bronchodilator available to use as needed for intermittent symptoms.^{15,16} 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.^{31,33} Ipratropium has the advantage of a longer duration of effect (up to 9 hours for ipratropium vs. 4 to 6 hours for beta₂-agonists).^{31,33} 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.^{15,16,34} The currently available long-acting beta₂-agonists (Table 2) have a duration of effect of 12 hours or more and are administered twice daily.⁹ 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 who may take weeks or months to improve after maintenance therapy is initiated; therefore, lack of an immediate response does not necessarily indicate treatment failure.⁸

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 in the previous 3 years.^{15,16}) In these patients, inhaled corticosteroids have been shown to cause a modest improvement in airflow and reduce both the frequency and severity of exacerbations through undetermined mechanisms.^{16,17}

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.^{32,35} A recent cohort analysis by Lee et al.³⁶ 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.^{9,34,37,38} 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).^{15,34,37}

COPD news and updates

The pace of research into the causes and treatment of COPD makes a comprehensive review of all of the latest information nearly impossible. The goal of this section is to provide an overview of new developments that may be of greatest use to pharmacists.

Immunization

Following the emergence of novel H1N1 influenza in March and April 2009 and its recent designation as a global pandemic, the U.S. government worked closely with manufacturers to expedite the availability of a targeted vaccine.^{39,40} Four influenza A (H1N1) 2009 monovalent vaccines—three injectable vaccines and one intranasal vaccine—were licensed for use in September 2009.⁴¹ Recommendations from the CDC's Advisory Committee on Immunization Practices included COPD patients younger than 65 years among the priority groups that should be targeted as an initial focus of vaccination efforts.⁴² Patients 65 years or older also should consider vaccination after vaccine supply and demand among younger age groups is met.⁴²

Evidence from clinical trials of the vaccines support a single dose of novel H1N1 vaccine in adults.⁴¹ Although administering seasonal influenza vaccine and the novel H1N1 vaccine on the same day is possible, all patients (especially those older than 65 years) were encouraged to receive the 2009 seasonal influenza vaccine as soon as it became available.⁴²

Smoking cessation

According to the latest data from CDC, an estimated 43.4 million Americans (one in five adults) are current cigarette smokers.⁴³ Of these, 77.8% (33.8 million) smoke every day and 22.2% (9.6 million) smoke some days.⁴³

Interest in smoking cessation remains high. The CDC data indicate that 39.8% (13.4 million) of the 33.8 million everyday smokers had stopped smoking for more than 1 day during the preceding 12 months because they were trying to quit.⁴³ Unfortunately, no behavioral or pharmacologic treatment is used in about two-thirds of these attempts, and most untreated smok-



Figure 2. Depiction of lung age

Abbreviation used: FEV₁, forced expiratory volume in 1 second.
Source: Reproduced from reference 50 with permission from BMJ Publishing Group Ltd. Figure adapted from: Fletcher C, Peto R. The natural history of chronic airflow obstruction. *BMJ*. 1977;1(6077):1645-8.

ers end up relapsing within the first 8 days after quitting.^{43,44} 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.^{16,45,46}

Several recent studies add to the growing body of knowledge about the effectiveness of various smoking cessation strategies. Etter et al.⁴⁷ conducted an open randomized trial of 314 daily smokers to test whether starting nicotine polacrifex 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 biochemically verified evidence of smoking abstinence. The authors concluded that the “cut down to quit” strategy was no more effective than starting treatment on the quit date.

Individuals who smoke tend to perceive lung cancer as the main and only hazard of smoking.^{3,13} New attention is being paid to the concept of “lung age” as a strategy for encouraging smoking cessation. A patient’s lung age is equivalent to the age of the average healthy individual who has the same FEV₁ as the patient.⁴⁸⁻⁵⁰ For example, a 52-year-old smoker with an FEV₁ that

is 25% below normal has an FEV₁ similar to that predicted for a 75-year-old nonsmoker (Figure 2); hence, the smoker has a lung age of 75 years.³ A 60-year-old smoker with an FEV₁ that is 50% of normal has a lung age of nearly 100 years.³ Lung age can be calculated from formulas developed by Morris and Temple⁴⁸ (men: lung age = [2.87 × height (in inches)] – [31.25 × observed FEV₁ (liters)] – 39.375; women: lung age = [3.56 × height (in inches)] – [40 × observed FEV₁ (liters)] – 77.28), but many spirometers in current use are able to generate a patient’s lung age automatically.⁵⁰ Parkes et al.⁵⁰ tested the hypothesis that telling smokers their lung age would lead to successful smoking cessation, especially in those with the most damage. A total of 561 current smokers 35 years or older were recruited to undergo 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.²¹ 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).^{3,11,24,51} 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.^{7,15,16,18,51}

Advances in technology have made creating portable spirometers that are small, reliable, accurate, affordable, and easy to use possible.²⁴ As a result, interest in moving spirometric testing out of the realm of pulmonary specialists and into the primary care arena is increasing.^{7,24} Two recent reports explored the feasibility of pharmacist involvement in spirometry.

Castillo et al.⁵² 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 screening 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 Zaiken⁵³ 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.⁸ At least three recent reviews recommend tiotropium as the initial agent for long-acting bronchodilator maintenance therapy.^{8,34,54} When tiotropium is used, a short-acting beta₂-agonist (not ipratropium, alone or in combination) is preferred for as-needed use.^{8,34} A long-acting beta₂-agonist would be added to the treatment regimen when tiotropium monotherapy failed to control the patient's symptoms sufficiently.

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, 2008.⁵⁵ 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, 2009.⁵⁶ 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.⁵⁷ 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).⁵⁸ 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.⁵⁹ 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.⁶⁰ reported a 34% increased risk of pneumonia with no increase in all-cause mortality, while Singh et al.⁶¹ 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).⁶² 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.⁶³ 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.⁶⁴ 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.⁶⁵ 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.⁶⁶ 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.⁶⁷ Rodrigo et al.⁶⁸ 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.⁶⁹ 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.⁷⁰ 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.^{30,71} 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 2009.⁷² 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.⁷² Another agent, carmoterol, is in Phase II trials.⁷⁰ Ultra-long-acting beta₂-agonists are expected to be available as monotherapy and in fixed combinations with long-acting anticholinergics or corticosteroids.^{9,30,71}

Novel long-acting inhaled anticholinergics

In the lung, activation of muscarinic receptors by acetylcholine causes bronchoconstriction (primarily through M₃ receptors present on airway smooth muscle) and mucus secretion (through both M₁ and M₃ receptors).^{9,17} M₂ receptors also are present in the lung; activation of these receptors provides a feedback function, inhibiting further release of acetylcholine and presumably mitigating bronchoconstriction.^{9,17} Inhaled anticholinergic agents work by competing with acetylcholine at muscarinic receptors.^{9,17,73} Thus, the ideal anticholinergic for COPD would inhibit M₁ and M₃ receptors preferentially.⁹

Ipratropium is a nonselective muscarinic antagonist that inhibits all three receptor subtypes in the lung.^{9,17} 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.^{9,17} Slow dissociation from M₁ and M₃ receptors also is responsible for the prolonged duration of action seen with tiotropium.^{9,17}

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 2011.⁷⁴ 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.^{9,30} 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.^{9,30} Glycopyrrolate is expected to be available as monotherapy and in combination with the ultra-long-acting beta₂-agonist indacaterol.⁷⁴

Acclidinium bromide also is in Phase III clinical trials.⁷⁵ It is being developed for administration via a novel, breath-actuated, multidose dry powder inhaler (Genuair).^{75,76} In Phase II trials, acclidinium 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.^{9,30,76} Acclidinium appears to be well tolerated, with an incidence of adverse effects generally comparable with placebo and no evidence of treatment-associated tachyphylaxis.⁷⁶

Phosphodiesterase-4 enzyme inhibitors

The pathophysiology of COPD is marked by both pulmonary and systemic inflammation.⁷⁷ 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.^{71,77} Selective PDE-4 enzyme inhibitors represent a possible new class of medications for treating COPD, with the ability to decrease pulmonary inflammation.^{71,77}

Roflumilast (Daxas) currently is undergoing review by FDA and is poised to become the first PDE-4 enzyme inhibitor to reach the marketplace.⁷⁸ 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.⁷⁹) 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.^{71,77,78} 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.^{80,81} 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.⁷⁷

The development of oral PDE-4 enzyme inhibitors has been hindered by dose-limiting gastrointestinal adverse events, par-

ticularly 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.⁷⁷

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 traditional 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.^{9,30,84} 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.

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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

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.

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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 was 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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Shortcuts that don't save time

Error-prone abbreviations may save time for the writer, but they do not for the dispenser. Nearly everyone in health care uses shortcuts such as abbreviations and symbols in an effort to conserve time when handwriting or typing words, phrases, or units of measure.

Some of these shortcuts can be very time consuming for the person on the receiving end, however. The telephone calls and reference material checks made in order to clarify these shortcuts may pose a greater potential for error than if the statement were initially written out in full. It's not until medical abbreviations, symbols, or nonstandard dose designations lead to patient harm that action is taken to prevent future misunderstandings.

For a complete list of error-prone abbreviations, symbols, and dose designations, see www.ismp.org/Tools/error-proneabbreviations.pdf

Q1D or QID?

Some abbreviations used to indicate the frequency of drug administration can be problematic. A computerized prescription for "penicillin VK 500 mg Q1D X 7D" led a pharmacy technician to type a label as the directions implied: "Take 1 tab p.o. daily for 7 days." A pharmacist subsequently realized that penicillin for this patient was supposed to be taken four times a day, not once a day. The physician had mistyped "Q1D" (q one day) instead of "QID" in the computerized order entry system.

It is also not uncommon for nonstandard dose designations to lead to errors. Although it wasn't a factor in this case, the abbreviation "D" for day in "7D" can also cause problems if it is misunderstood as "7 doses."

Legibility matters

Even when a prescriber has legible handwriting, the use of the abbrevia-

tion "q.d." or "qd" has led to errors. For example, the loop of a cursive "q" that comes up between the "q" and the "d" (see Figure 1) or a period after the "q" can look like an "i," causing some to read the notation as "qid."

The use of the abbreviation "q.o.d." (every other day) has also caused problems because it has been misinterpreted as "q.d." (every day) or "q.i.d." (four times daily) if the "o" is poorly written. In the prescription in Figure 2, digoxin was intended to be dosed qod, but the dispenser initially misinterpreted the instructions as "qid" because of the way the "o" was written. In order to prevent confusion, write out the directions "daily" and "every other day" instead of using abbreviations that can be subject to misinterpretation.

Would you believe that the letter "q" could look like the number "5"? Just look at the handwritten order in Figure

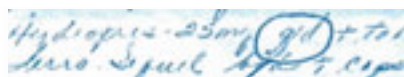


Figure 1

3. The physician had prescribed Levoxy (levothyroxine—King) "1 tab po q day," but the "q" was misread as a "5," and the medication was subsequently dispensed with directions to take "1 tab 5 days each week."

In this case, the patient was familiar with the proper dosing frequency and recognized the mistake immediately. Although the pharmacist misinterpreted "q" as "5," the error could have been avoided if the pharmacist had not assumed that the physician intended to write "each week" on the prescription.

Write it out

"AD" is sometimes used as an abbreviation for right ear (aura dexter). One problem with this abbreviation is that

a handwritten lowercase "a" can easily look like an "o." Thus, a patient might risk getting an otic medication in the right eye (OD or oculus dexter) instead of the right ear.

In one case, a physician ordered "Auralgan (antipyrine, benzocaine, glycerin) two drops AD" for a patient in the emergency department, but the nurse administered the drops into the patient's right eye. When the error was discovered, the eye was flushed and the patient suffered no permanent harm. Using "AS" for left ear or "AU" for each ear might cause similar problems. "AD" has also been misread as "PO" or as "QD" (if the tail of the handwritten lowercase "a" looks like a "q").



Figure 2

Another type of error related to the abbreviation "AD" has surfaced recently. Tired of writing out "as directed" when transcribing prescriptions received by telephone, one pharmacist began to abbreviate that term as "AD." Later, a pharmacy technician misinterpreted the directions for an oral liquid prescription

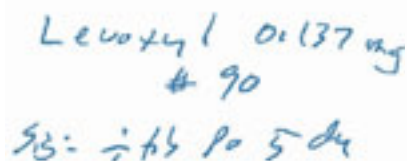
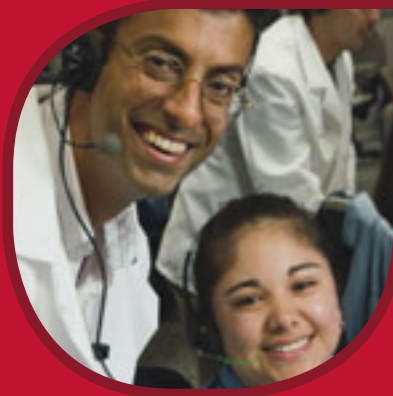


Figure 3

transcribed as "5 mL TID AD" and typed the directions as "one teaspoonful three times a day in right ear." "AD" would be a good abbreviation to avoid in general. The best practice is to write out all directions for left and right ear and eye.

—Institute for Safe Medication Practices

The reports described in this column were received through the ISMP Medication Errors Reporting Program (MERP). Errors, close calls, or hazardous conditions may be reported on the Institute for Safe Medication Practices (www.ismp.org) website or communicated directly to ISMP by calling 800-FAIL-SAF (800-324-5723) or e-mailing ismpinfo@ismp.org. The topics in this column are covered in greater detail in *Medication Errors, 2nd edition*, written by ISMP President Michael R. Cohen, BPharm, MS, ScD. The book may be purchased from APHA at www.pharmacist.com or by calling 800-878-0729.



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Use as directed.

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