Chronic Obstructive Pulmonary Disease

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Learning Objectives

1. Recommend interventions based on the risk factors, status, and progression of chronic obstructive pulmonary disease (COPD).
2. Develop and justify optimal therapy based on the current understanding of the pathophysiology of COPD and available clinical evidence.
3. Develop a pharmacotherapy care plan for exacerbations and progressive symptoms of COPD.
4. Design appropriate quality indicators for treatment of COPD.
5. Devise a pharmacotherapy care plan for tobacco cessation.

Introduction

Although largely preventable, mortality rates and health care costs of chronic obstructive pulmonary disease (COPD) are increasing. Prevention and management are hindered by the limited knowledge of its pathophysiology and the lack of therapies specifically targeting COPD. The disease is often overlooked and misdiagnosed. Treatment algorithms for COPD are often confused with those for asthma. Clinically useful outcome measures and improved assessment tools are needed. In addition, comorbid conditions and extrapulmonary effects of COPD may increase mortality.

Pathophysiology

Definition

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) defines COPD as: "A preventable and treatable disease with some significant extrapulmonary effects that may contribute to the severity in individual patients. Its pulmonary component is characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lung to noxious particles or gases." A revised definition emphasizes that COPD is preventable and stresses the importance of tobacco avoidance. A correct, early diagnosis should promote aggressive tobacco cessation strategies to slow COPD progression. Although COPD is not reversible, treatment may lessen its impact on quality of life. This definition also reflects the growing appreciation for potential extrapulmonary manifestations in advanced COPD.

Epidemiology and Risk Factors

Based on 2003 data from the National Center for Health Statistics, COPD is the fourth leading cause of death in the United States. In perspective, COPD causes only 5% (126,000) of all deaths annually and is well behind cardiovascular diseases, cerebrovascular diseases, and cancers. Between 1980 and 2003, deaths from these conditions declined, but the percentage of COPD deaths almost doubled. By 2030, COPD is projected to become the third leading cause of death.

The prevalence of COPD is now almost equal in men and women. The annual number of deaths increased more than 300% in women during the past 15 years and now exceeds that of men. The increasing prevalence and deaths in women are possibly caused by a relative increase in tobacco use and lower smoking cessation rates in women than in men. Deaths from COPD are still more common in white people, but COPD is the eighth most common cause of death in African American men.

In the United States, cigarette smoking remains the most important COPD risk factor, but pipe and cigar smoking also increase the risk. In a 1977 study using moderate airflow obstruction as a criterion, only 13% to 15% of people who smoke were found to develop COPD. Newer data show that most people with a significant smoking history will develop measurable airway obstruction. Air pollution and occupational exposures to dusts and chemicals are also significant risk factors and may be additive to the effects of smoking. These exposures may also explain the development of COPD in those without significant tobacco histories. Because COPD is not reversible, tobacco use prevention

Abbreviations in This Chapter

BODE	Body mass index, airflow obstruction, dyspnea, and exercise capacity
COPD	Chronic obstructive pulmonary disease
DL_{CO}	Diffusion capacity of carbon monoxide
$FEF_{25–75\%}$	Forced expiratory flow rate between 25% and 75% of forced vital capacity
FEV_1	Forced expiratory volume at 1 second
FVC	Forced vital capacity
GOLD	Global Initiative for Chronic Obstructive Lung Disease
MMRC	Modified Medical Research Council
NFκβ	Nuclear factor-κβ
TNFα	Tumor necrosis factor-α

and cessation are significant public health issues. Tobacco cessation is the only intervention that slows the loss of lung function.

Diagnosis and Clinical Presentation

Based on recent National Health and Nutrition Examination Survey data, COPD is significantly underdiagnosed in the United States. Up to 25% of men who smoke have symptoms consistent with airway obstruction. Of these, 44% do not have a respiratory diagnosis. The underdiagnosis of COPD may be because of the insidious onset of symptoms and the relatively complex diagnostic process. Individuals older than 40 years and at risk of COPD should be screened for symptoms. In the presence of progressive, persistent dyspnea, chronic cough, or chronic sputum production, COPD should be suspected, and these individuals should be referred for spirometry. Although expense and time may be barriers to performing spirometry, confirmatory testing is recommended because symptoms do not correlate to the presence or the severity of airflow obstruction. Spirometry can also exclude other conditions that may masquerade as COPD, including heart failure, restrictive lung disease, tuberculosis, and lung cancer. According to the GOLD guidelines, symptoms plus a postbronchodilator forced expiratory volume at 1 second (FEV_1) to forced vital capacity (FVC) ratio of less than 70% is consistent with the diagnosis of COPD. In adults older than 70 years, using a ratio of less than 65% has been recommended because the FEV_1/FVC ratio normally declines with advancing age.

Differentiating COPD from asthma is a common diagnostic problem. Chronic cough, either productive or nonproductive; episodes of wheezing; and shortness of breath with exercise are common to both diseases. In both, upper respiratory infections, worsening air quality, or temperature/humidity changes can trigger symptoms. In general, COPD more often develops after the age of 40, and patients often have a 20 pack-year history or more of tobacco use. Symptoms are slowly progressive and do not have the same day-to-day variation as asthma. Exacerbations occur in both disorders but may take longer, perhaps weeks, to resolve in patients with COPD. Unlike asthma, the postbronchodilator FEV_1 is often not fully reversible to greater than 80% of predicted in COPD. Perhaps because of the insidious onset of symptoms, people with COPD often have an FEV_1 of less than 50% of predicted at diagnosis. Obstruction of the smaller airways, abnormal gas exchange, and elevated residual volume are more consistent with COPD. Obstruction of the smaller airways is indicated by a forced expiratory flow rate between 25% and 75% of FVC ($FEF_{25–75\%}$) of less than 80% of predicted. Abnormal gas exchange is detected by a diffusion capacity of carbon monoxide (DL_{CO}) that is less than 80% of predicted. A residual volume that is more than 100% of predicted is considered elevated. Finally, signs of chronic hypoxemia such as cor pulmonale are more common in COPD.

In 10% to 15% of patients, asthma and COPD may be concurrent conditions. Both may be present at the time of diagnosis, or an individual with a history of asthma and tobacco use may later develop COPD. Eosinophilia, elevated immunoglobulin E levels, seasonal variation of symptoms, nocturnal awakenings, worsening symptoms in response to allergens such as mold or pollen, or a personal/family history of atopy such as eczema or allergic rhinitis may signal concurrent asthma. The therapeutic implications of coexisting asthma and COPD will be discussed later.

Table 1-1. MMRC Dyspnea Questionnaire for Assessing the Severity of Breathlessness

Questions	Score
I get breathless only with strenuous exercise	0
I get short of breath when hurrying on the level or walking up a slight hill	1
I walk slower than people of the same age do on the level because of breathlessness, or I have to stop for breath when walking on my own pace on the level	2
I stop for breath after walking about 100 m or after a few minutes on the level	3
I am too breathless to leave the house, or I am breathless when dressing or undressing	4

MMRC = Modified Medical Research Council.
Adapted from Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. 2006:34. Available at *www.goldcopd.com/Guidelineitems.asp?11=2&12=1&intld=989*. Accessed January 10, 2008.

Table 1-2. Variables and Point Values Used in the BODE Index

Variable	BODE Score			
	0	1	2	3
Body mass index: body weight (in kg)/height^2 (in meters)	> 21	≤ 21	—	—
Airway obstruction: forced expiratory volume at 1 second (as percentage of predicted)	> 65	50–65	35–49	< 35
Dyspnea: Modified Medical Research Council dyspnea questionnaire score (see Table 1-1)	0 or 1	2	3	4
Exercise capacity: 6-minute walk test distance (meters)	≥ 350	250–349	150–249	≤ 149

BODE = body mass index, airflow obstruction, dyspnea, and exercise capacity.
Adapted from Celli BR, Cote CG, Marin JM, Casanova C, Montes de Oca M, Mendez RA, et al. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. N Engl J Med 2004;350:1005–12.

The severity of COPD is classified based on the postbronchodilator FEV_1. Stage I or mild COPD is defined by a postbronchodilator FEV_1 value of 80% or more of predicted; stage II or moderate COPD is 50% to 79%; stage III or severe is 30% to 49%; and stage IV or very severe is less than 30% of predicted. Use of the postbronchodilator values indicates that the obstruction is not fully reversible. Recent GOLD guidelines removed references to two earlier terms. Stage 0 or at risk was defined as the presence of symptoms with normal spirometry and was originally added in 2001 to encourage early detection. Early detection remains important, but evidence is insufficient that those in stage 0 will later develop COPD. The term *reversible COPD,* defined as greater than 15% and a 200-mL change in FEV_1 after bronchodilators, was also deleted. The designation *reversible* was not useful because it did not correlate to therapeutic response.

Pharmacists should understand the diagnostic process and be able to interpret basic pulmonary function tests. Pharmacists can prompt the early diagnosis of COPD by asking people at risk of developing COPD about the presence of symptoms and encouraging the use of spirometry testing in symptomatic individuals. Once identified, pharmacists can be instrumental in limiting COPD progression by facilitating smoking cessation. In addition, pharmacists can decrease the misdiagnosis of COPD by encouraging confirmatory spirometry in people who are receiving therapy for presumed COPD. Another commonly encountered problem is the presence of multiple diagnoses, including COPD, asthma, and reactive airway disease, within the same medical record. Pharmacists should prompt a clarification of diagnosis (or concurrent diagnoses) to choose the correct maintenance drugs. Finally, pharmacists should be able to categorize the severity of COPD. The severity of COPD has therapeutic implications, including the indication for inhaled corticosteroids and antibiotic selection to treat exacerbations.

Prognosis

The long-term prognosis for patients with severe COPD is poor. Progressive dyspnea decreases productivity and can cause severe disability. As FEV_1 declines, muscle wasting and complications of hypoxia appear. Hypoxic complications include polycythemia, with a hematocrit of greater than 55%; pulmonary hypertension, indicated by a pulmonary systolic pressure of more than 25 mm Hg; and cor pulmonale, indicated by a right ventricular hypertrophy or signs and symptoms of right-sided heart failure. Exacerbations become more frequent and severe as the FEV_1 declines and are responsible for 50% to 75% of COPD-related health care expenditures.

Increased age and the rate of decline of the FEV_1 are two accurate predictors of mortality. With smoking cessation, the rate of decline of FEV_1 often returns to that of nonsmokers, which is about 30 mL/year. Sometimes, the FEV_1 may continue to decline at an accelerated rate of more than 50 mL/year even after cessation. Repeated spirometry every few years is important to detect this accelerated decline. There is an inverse relationship between dyspnea and survival. Dyspnea can be monitored over time by the Borg dyspnea scale, with values ranging from 0 (none at all) to 10 (maximal) dyspnea. The Modified Medical Research Council (MMRC) dyspnea questionnaire is also used (Table 1-1). Individuals with scores of 2, 3, and 4 have, respectively, a 5-year mortality of 2, 8, and 61 times that of an individual with a score of 1. A body mass index of less than 21 kg/m^2 or a weight loss of more than 10% in 6 months is also associated with increased mortality. A weight gain of 2 kg in 8 weeks may improve survival.

Exercise capacity, as measured by the 6-minute walk test, can also predict mortality. In one study, the 1-year mortality rate was close to 90% if the individual was unable to walk 100 m. Changes in exercise capacity are sensitive in predicting mortality, because declines in 6-minute walk test distance may occur without a change in FEV_1. Polycythemia is more common, but a normocytic, normochromic anemia with hemoglobin less than 13 g/dL occurs in 10% to 15% of people with COPD. Anemia correlates to higher dyspnea scores and lower 6-minute walk test distances. Three-year survival rates are 24% in patients with a hematocrit of less than 35% compared with 70% in patients with polycythemia. The body mass index, airflow obstruction, dyspnea, and exercise capacity (BODE) index in Table 1-2 may better predict disease progression and risk of mortality than the FEV_1 alone. Each 1-point increase in the BODE score correlates to a 30% increase in the 5-year mortality rate and a 62% increase in mortality from respiratory causes. Individuals with BODE scores of 7–10 were shown to have a 5-year mortality rate of 80%. Use of the BODE index has been suggested instead of FEV_1 to stage COPD severity.

In addition to its pulmonary effects, COPD may be an independent risk factor for osteoporosis and death from atherosclerosis-related complications, such as coronary artery disease. The mechanism for the increased

cardiovascular risk is unknown, but one hypothesis involves systemic inflammation and elevation of C-reactive protein concentrations. Although the exact percentages are unknown, the risk of diabetes, sleep disorders, glaucoma, and mood disorders such as depression and anxiety also appear to be increased.

Pathophysiology

An imbalance between destructive proteases and protective antiproteases has long been recognized as a potential mechanism for COPD. Cigarette smoke inactivates α_1-antitrypsin and impairs other antiproteases, including secretory leukoprotease inhibitor, elafin, and a tissue inhibitor of matrix metalloproteinases. Secretory leukoprotease inhibitor may also have antimicrobial and anti-inflammatory effects by down-regulating tumor necrosis factor-α (TNFα). Increased amounts of proteases, such as matrix metalloproteinases and neutrophil elastase, destroy alveoli and collagen. Neutrophil elastase also increases mucus secretion by goblet cells, induces expression of interleukin-8, and may increase susceptibility to gram-negative infections. The protease-antiprotease theory explains some clinical manifestations, including the loss of lung elasticity, the airway obstruction caused by mucus and airway collapse, and the increased incidence of respiratory infections. Antiproteases and protease inhibitors have shown promise in animal models, but α_1-antitrypsin is only useful in genetic disorders involving this antiprotease.

An emerging theory is an imbalance of oxidative and antioxidant activity referred to as oxidative stress. Cigarette smoke and tar contain high concentrations of reactive oxidants. Air pollution contains oxidants such as ozone, nitrogen dioxide, and diesel particulates. Superoxide, hydroxyl radicals, and isoprostanes are additional oxidative mediators produced by the body. The lung's antioxidant defense system of mucin, glutathione, catalases, superoxide dismutases, and ascorbic acid is overwhelmed by the added external oxidants. The resulting oxidative stress directly damages lung cells and elastin. Increasing the activity of nuclear factor-κβ (NFκβ) causes indirect damage by increasing the production of inflammatory cytokines and the apoptosis of epithelial cells.Oxidative stress also impairs the function of antiproteases, interferes with elastin synthesis and repair, and increases mucus secretion. Some oxidants such as isoprostanes are also potent direct bronchoconstrictors. Oxidative stress is linked to muscle weakness, fatigue, and muscle wasting present in severe COPD. Reduced dietary intake of ascorbic acid in some epidemiologic studies is related to a decline in lung function.

The third proposed mechanism involves inflammation. In contrast with asthma, the predominant inflammatory cell lines are neutrophils, macrophages ($CD68^+$), and T lymphocytes ($CD8^+$ more than $CD4^+$). Higher concentrations of these cells in lung tissue correspond to a lower FEV_1 and greater COPD severity. The exact sequence and mechanism for the inflammatory cell changes are unknown, but the increase in $CD8^+$ cells occurs early. Cytokines, such as granulocyte macrophage colony-stimulating factor, leukotriene B_4, and TNFα, may cause chemotaxis of neutrophils and macrophages. The $CD8^+$ cells may cause apoptosis of epithelial cells by producing TNFα and may play a role in the bacterial colonization of lungs. Impaired phagocytosis by macrophages may be another mechanism for bacterial colonization. Cigarette smoke activates transcription factors such as NFκβ in neutrophils and macrophages to increase production of elastases, oxidants, and inflammatory mediators including interleukin-8. This activation of transcription factors does not always resolve with tobacco cessation and may explain the continued accelerated decline in lung function in some patients. During exacerbations and as COPD worsens, eosinophil concentrations increase but usually remain less than neutrophil or macrophage concentrations. Destruction of epithelial cells and cilia impairs mucociliary clearance. Epithelial cells have a protective role by producing defensins, which have antimicrobial effects, antiproteases, and antioxidants. Cigarette smoke impairs these protective effects and stimulates epithelial cells to produce oxidants and inflammatory mediators such as interleukin-8 and TNFα. Increased production of transforming growth factor-β may be the cause of small airway fibrosis and obstruction.

The contrasting pathophysiology of asthma and COPD may explain the differing response to drugs and respective treatment algorithms. Bronchoconstriction plays a small role in COPD and explains the very modest impact of inhalation β-agonist and anticholinergic agents on FEV_1, symptoms, quality of life, and prognosis. No pathophysiologic basis exists for using currently available leukotriene inhibitors that affect cysteinyl leukotrienes derived from mast cells. Eosinophils are more sensitive to the effects of corticosteroids than neutrophils or macrophages. Therefore, there is a significant clinical response to corticosteroids only in more severe cases of COPD or during exacerbations.

Emerging knowledge of the pathophysiology of COPD has not yet been translated into disease-specific therapies. Outcomes may improve as newer, more effective agents become available. Inhibitors of TNFα and TNFα-converting enzyme are under development and in early clinical trials. Transforming growth factor-β or NFκβ might be a useful target for developing specific drugs for COPD. Without better therapies, prevention strategies such as smoking cessation/prevention, improved air quality, and limiting occupational exposures are essential for lowering the public health impact of COPD and improving patient outcomes.

Monitoring Achievement of Therapeutic Goals and Outcomes

The GOLD guidelines list the optimal goals as relief of symptoms, prevention of COPD progression, prevention and treatment of exacerbations, improved exercise tolerance and health status, and decreased mortality. Preventing and correcting extrapulmonary manifestations and complications of COPD such as anemia are also goals. Translating these prevention/control goals into clinical practice is challenging. Until recently, the only surrogate markers for the risk of COPD-related mortality were increased age and FEV_1, which are not significantly modified by available therapy. Useful tools to measure symptom level and document clinical improvement are limited. The BODE score is an improvement in measuring COPD prognosis because it incorporates multiple disease aspects. Available drugs such as inhaled bronchodilators may improve individual aspects of the BODE scale (e.g., the 6-minute walk test). Unfortunately, prospective trials have

not shown any drugs to have a clinically significant impact on COPD progression or mortality. The commonly used research tool for measuring quality of life in COPD is St. George's Respiratory Questionnaire; however, because it has more than 50 questions, this questionnaire is not practical for clinical use. The MMRC questionnaire is less sensitive in detecting significant changes in function but is clinically useful because it is short and documents the progression of dyspnea. Because the incidence of exacerbations is typically between zero and three per year, it is difficult to document change in the exacerbation rate of a specific individual.

Quality Patient Care

GOLD Guidelines

The primary role of drug therapy is to minimize symptoms and preserve functional status by means of a step-up approach of gradually adding drugs as pulmonary function declines. For mild or uncommon symptoms, a short-acting inhaled β_2-agonist or anticholinergic agent as needed is adequate. There is no documented benefit to using levalbuterol over older agents such as albuterol or ipratropium. Long-acting inhaled bronchodilators, including formoterol, salmeterol, and tiotropium, are more effective and convenient as the incidence and severity of symptoms increase. Combination therapy with an inhaled anticholinergic agent and a β_2-agonist is useful when monotherapy is no longer adequate to control symptoms and maintain activity levels. Clinically significant tolerance to bronchodilators does not appear to occur. Because of the modest benefit in decreasing symptom severity and incidence of exacerbations, moderate- to high-dose inhaled corticosteroids are recommended when the FEV_1 declines to less than 50% of predicted and with frequent exacerbations such as three or more in the past 3 years. In severe COPD, long-term oxygen therapy is often indicated to maintain the oxygen saturation above 90%. In patients with hypoxia, continuous oxygen therapy for more than 15 hours per day can decrease mortality rates by one-half.

If drugs have been maximized, surgery may improve some symptoms, functional capacity, and quality of life. A bullectomy may improve hemoptysis, infection, or chest pain if there are large, localized bullae. Eligibility criteria include an FEV_1 of more than 40%, a large residual volume, and a nearly normal DL_{CO}. Surgery for lung volume reduction decreases hyperinflation and the patient's labor to breathe. Selection criteria are controversial but include individuals younger than 75 years who are nonsmoking, lack surgical comorbid conditions, and have an FEV_1 of less than 45% of predicted and a residual volume exceeding 150% of predicted.

Sustained-release theophylline can be effective but is rarely indicated in place of inhaled bronchodilators because of its high potential for drug interactions and dose-related toxicities. Oral corticosteroids are no longer in the treatment algorithm for stable COPD. Potential toxicities of oral maintenance therapy with corticosteroids (e.g., myopathy, glaucoma, osteoporosis) likely outweigh the potential benefit of symptom improvement. In addition, because 10-day to 14-day courses of oral therapy have not been found to reliably predict the response to long-term inhaled corticosteroid therapy, oral corticosteroids are no longer recommended for this purpose.

Exacerbations of COPD are identified by acute increases in baseline dyspnea, cough, and sputum or by the presence of sputum purulence. Exacerbations are managed primarily with inhaled bronchodilators, systemic corticosteroids, and antibiotics. Short-acting inhaled β_2-agonists are usually recommended to improve dyspnea, although ipratropium can be added if maintenance therapy was an inhaled β_2-agonist. Nebulized bronchodilator therapy is not necessarily more beneficial than delivery by a metered-dose inhaler plus holding chamber. Systemic corticosteroids shorten recovery time, decrease hospital length of stay, and improve lung function and hypoxia, especially if the baseline FEV_1 is less than 50%. Oral prednisone regimens of 30–40 mg per day for 7–10 days are usually adequate. There is no documented benefit to longer or tapering corticosteroid regimens. Parenteral corticosteroid therapy is not necessary unless impaired absorption is suspected.

Antibiotics are indicated for exacerbations when all three cardinal symptoms of increased dyspnea, sputum volume, and sputum purulence are present. Antibiotics are also indicated when two cardinal symptoms are present if one of the symptoms is increased sputum purulence or exacerbations requiring mechanical ventilation. The recommended empiric antibiotic regimens, listed in Table 1-3, are based on the most likely causative organisms and generally are given for 3–7 days. Sputum cultures and sensitivity studies are only recommended if the exacerbation does not respond to empiric therapy.

Oral or intravenous theophylline can be considered for treatment of severe exacerbations if there has been an inadequate response to short-acting inhaled bronchodilators; however, theophylline has not been shown to add a clear benefit over combination inhaled bronchodilators. In addition, the macrolide or quinolone antibiotics often used to treat COPD exacerbations can decrease the clearance of theophylline. Acute or worsening cor pulmonale can occur during exacerbations, also decreasing theophylline clearance. Before initiating theophylline therapy, the patient-specific risk of toxicity versus the potential benefit should be carefully considered.

Supportive therapy is important during severe COPD exacerbations to minimize mortality and length of hospital stay. Supplemental oxygen is provided to maintain the oxygen saturation greater than 90%. Appropriate fluid intake is important to avoid dehydration and lessen the risk of developing cor pulmonale. An adequate nutritional status should also be maintained. Hospitalized patients, especially those with polycythemia or requiring mechanical ventilation, are at increased risk of developing deep venous thrombosis and should receive appropriate prophylactic therapy.

Therapeutic Issues

Selection of Initial Maintenance Bronchodilator Therapy

The GOLD guidelines recommend either a long-acting inhaled β_2-agonist or an anticholinergic agent as first-line maintenance therapy. Both classes are well tolerated when administered by inhalation. The risk of significant toxicities, such as arrhythmias with inhaled β_2-agonists or worsening urinary retention in men receiving inhaled

Table 1-3. Stratification of Patients and Antibiotic Selection for COPD Exacerbations

Group and Definition	Common Microorganisms	Treatment Options
Group A (mild exacerbation) At least two of three cardinal symptoms are present: • Increased dyspnea • Increased sputum volume • Increased sputum purulence Patient with no comorbid diseases • Baseline $FEV_1 \geq 50\%$ of predicted • < 3 exacerbations/year • No antibiotics in past 3 months	*Haemophilus influenzae, Streptococcus pneumoniae, Moraxella catarrhalis, Chlamydia pneumonia,* viruses	Oral options: amoxicillin, ampicillin, penicillin, trimethoprim/sulfamethoxazole, tetracycline Alternatives: amoxicillin/clavulanic acid, azithromycin, clarithromycin, second- or third-generation cephalosporin[a] Parenteral therapy usually not necessary
Group B (moderate exacerbation) At least two cardinal symptoms plus one of the following is present: • Comorbid diseases • Baseline $FEV_1 < 50\%$ predicted • > 3 exacerbations/year • Taken antibiotics in past 3 months	Group A microorganisms plus β-lactamase–producing penicillin-resistant *S. pneumoniae, Enterobacteriaceae*	Oral options: amoxicillin/clavulanic acid Alternatives: levofloxacin, moxifloxacin, or gemifloxacin Parenteral therapy: ampicillin/sulbactam, second- or third-generation cephalosporin, levofloxacin, or moxifloxacin
Group C (severe exacerbation) At least two cardinal symptoms plus one of the following is present: • Recent hospitalization • Common use of antibiotics (four courses in past year) • Prior isolation or colonization of *P. aeruginosa*	Group B microorganisms plus *Pseudomonas aeruginosa*	Oral options: ciprofloxacin and levofloxacin[b] Parenteral therapy: ciprofloxacin, levofloxacin,[b] β-lactam with *P. aeruginosa* activity

[a]Telithromycin is also listed, but the U.S. Food and Drug Administration removed the indication for treatment of COPD exacerbations because of reports of severe liver injury.
[b]High-dose levofloxacin (750 mg).
COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume at 1 second.
Adapted from Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. 2006. Available at *www.goldcopd.com/Guidelineitem.asp?l1=2&l2=1&intId=989*. Accessed January 10, 2008.

anticholinergic agents, is minimal. Long-acting inhaled bronchodilators are preferred to short-acting agents because of improved exercise capacity, dyspnea, and quality-of-life scores. Once-daily or twice-daily administration of long-acting bronchodilators is also more convenient. Unit-of-use prices for long-acting agents are generally higher than for short-acting agents. Short-acting agents may be appropriate if symptoms are controlled with low to moderate daily doses. However, at higher doses (e.g., 15 puffs per day of albuterol or 20 puffs per day of ipratropium), the monthly cost differential between short- and long-acting agents may significantly decrease. In addition, as the number of puffs per day increases, the adherence to short-acting agents may decrease. Not all formularies include long-acting agents because of their cost. Pharmacists need to advocate for the use of long-acting agents when these agents may improve symptoms or adherence.

When choosing a specific long-acting inhaled bronchodilator, salmeterol, formoterol, and tiotropium all significantly improve symptom scores. A 6-month study indicated that tiotropium decreased the percentage of individuals having exacerbations by 5% compared with placebo, which was statistically significant. There are no data to document a difference in adherence among the long-acting inhaled agents. There are some differences between the current delivery devices for these agents, which may affect individual preferences or their ability to use the devices correctly. Patients with poor manual dexterity may find it difficult to open and place individual capsules into the tiotropium and formoterol devices. Some patients may have trouble seeing the numbers on the salmeterol device, or the taste of a drug may not be acceptable. Based on the small improvement in exacerbations, there is slightly stronger patient-oriented evidence to support the use of tiotropium. Until there are comparative data clearly documenting a superior benefit from monotherapy with a specific agent, the choice of an initial inhalation bronchodilator should be based primarily on institutional factors, including acquisition costs and local formularies, as well as patient-specific factors, such as the ability to use a particular delivery device.

Formoterol is now available in a twice-daily nebulized formulation. Arformoterol is a new long-acting inhalation β_2-agonist requiring twice-daily administration by a nebulizer. Indacaterol is another long-acting β_2-agonist in Phase III trials that is administered once daily. The less frequent administration of these agents may not be a significant advantage, because many of these patients will likely have severe COPD requiring concurrent nebulized ipratropium administration every 4–6 hours. The additional cost of these newer nebulized agents may outweigh their convenience.

Combination Bronchodilator Therapy vs. Monotherapy

Theoretically, the effect of two long-acting inhaled bronchodilators with differing mechanisms should be additive. As symptoms increase with worsening lung function, the GOLD guidelines recommend combination therapy. This recommendation is based on studies with small populations using single doses or short-term therapy for 3–14 days. These limited data suggest that a combination of salmeterol and tiotropium or formoterol and tiotropium can result in a 70-mL to 150-mL improvement in FEV_1. Studies evaluating patient-oriented outcomes such as improved quality of life would justify the significant increase in cost. Because of individual patient response to therapy, the effect of combination therapy should be carefully evaluated in clinical practice. Without symptomatic improvement, the second inhaled bronchodilator should be discontinued rather than committing the individual to expensive, long-term therapy.

Some formularies may promote the combination product containing inhaled ipratropium plus albuterol instead of long-acting inhaled bronchodilators because of the cost. Again, at higher daily doses, the cost savings of the short-acting combination product likely diminishes. The higher cost of combined long-acting inhaled bronchodilator therapy should be weighed against the potential for improved symptom control and adherence. Also, the short-acting combination product contains ozone-depleting substances. If the U.S. Food and Drug Administration proposal to remove the essential-use designation for the ipratropium plus albuterol combination is approved, there may be a gap in availability until a revised product becomes obtainable.

New Data Regarding the Role of Inhaled Corticosteroids

Interpretations of studies published before 1999 evaluating the benefit of inhaled corticosteroids were confounded by the inclusion of subjects with asthma. The outcomes studied were primarily limited to FEV_1. Studies from 2000 to 2003 limited subjects to those with COPD and were continued for 1–3 years. Results indicated that inhaled corticosteroids could modestly improve FEV_1 by 25–50 mL and decrease exacerbations by less than one per year. Of importance, benefits were limited to subjects with a lower FEV_1. These data support the current GOLD recommendation for inhaled corticosteroids in patients who have an FEV_1 of less than 50% of predicted with three or more exacerbations in the previous 3 years.

Recent studies further identify the patients who are likely to benefit from inhaled corticosteroids with or without a long-acting inhaled β_2-agonist and have evaluated the impact on outcomes such as mortality, hospitalization rates, and severity of exacerbation rates. A recent meta-analysis using data from the 2000–2003 trials indicates that inhaled corticosteroids can lower all-cause mortality by 27%. A subgroup analysis revealed that the mortality benefit was primarily in subjects with GOLD stage 3 and 4 COPD. Another trial evaluated whether the initial benefit of inhaled fluticasone plus salmeterol on FEV_1 would be maintained for up to 1 year if the fluticasone component were discontinued. Results indicated that in the salmeterol group, the FEV_1 was about 4% or 50 mL lower, and the dyspnea score increased slightly (by 0.17 on a 0–4 scale). Continuing fluticasone decreased the incidence of mild COPD exacerbations by less than one per year. Another trial compared the combination of inhaled fluticasone plus salmeterol with inhaled fluticasone, inhaled salmeterol, or placebo for 3 years in more than 6000 patients with an FEV_1 of less than 60% predicted. There was no difference in the primary end point of death from any cause. However, subjects receiving combination therapy had 0.34, 0.06, and 0.18 fewer exacerbations requiring corticosteroids per year compared with the placebo, fluticasone, and salmeterol groups, respectively. The number needed to treat to prevent one exacerbation per year was 4 relative to placebo. However, significantly more patients in the combination group developed pneumonia than in the placebo or salmeterol groups (19.6%, 12.3%, and 13.3%, respectively). The very modest decrease in exacerbations supports the use of an inhaled corticosteroid and salmeterol for individuals with an FEV_1 of less than 60% of predicted even without a history of frequent exacerbations.

There are few pharmacoeconomic data for COPD treatment. A recent study evaluated the cost-effectiveness of withdrawing fluticasone for 6 months. The results indicated that continuing fluticasone significantly increased annual drug costs by $396, but these costs were partially offset by $292 in cost savings related to exacerbations and hospitalizations.

Recent data indicate that in patients with an FEV_1 lower than 60% of predicted, inhaled corticosteroids can modestly decrease exacerbation rates by less than one per year. Additional benefit may occur with the combination of an inhaled corticosteroid and a long-acting β_2-agonist. These results are consistent with the current understanding of the pathophysiology of COPD because inhaled corticosteroids do not provide benefit in mild COPD when inflammatory cells less responsive to corticosteroids predominate. Even with further identification of the optimal candidates, inhaled corticosteroids are likely to provide only a modest clinical and pharmacoeconomic benefit. Because of costs and likely lifelong therapy, inhaled corticosteroid use should be limited to cases with a reasonable chance of a benefit, such as those with severe COPD or frequent exacerbations.

Treatment of Concurrent COPD and Asthma

There are no currently available data evaluating therapeutic options with concurrent COPD and asthma, but it would be logical to overlap the two disease algorithms. For example, in the individual with moderate asthma who develops COPD after years of tobacco use, the addition of ipratropium to an inhaled corticosteroid plus a long-acting β_2-agonist combination could be recommended for symptom management. If concurrent asthma and COPD are identified at the time of diagnosis, a trial of an inhaled corticosteroid should be considered even if the baseline FEV_1 is greater than 50% of predicted. An inhaled corticosteroid in a patient with concurrent asthma would be expected to have a greater effect on FEV_1 and symptoms than on an individual with COPD alone. However, the inhaled corticosteroid should be discontinued if a benefit is not documented.

Table 1-4. Common Drug-Related Issues in COPD

Stable COPD	
Drugs	Poor drug delivery (device instruction and device selection for physical impairments)
	Non-adherence to multiple and frequently dosed drugs or oxygen
	Not stepping up therapy based on symptoms, quality of life, or functional level
	Under- or overprescribing of inhaled corticosteroids based on lung function
	Access to and cost of multiple, expensive inhalers or nebulized drugs
Monitoring	Not confirming initial diagnosis with spirometry
	Not monitoring/documenting progression with spirometry or oxygen saturation
	Not monitoring/documenting response to drugs
Health maintenance	Poor nutritional status
	Inadequate control of comorbid conditions such as hypertension, osteoporosis, and anxiety
	Inadequate resources, training, or counseling for tobacco cessation
	Underprescribing of influenza and pneumococcal vaccines
	Underuse of or inadequate resources for pulmonary rehabilitation
Psychosocial	Lack of social support to maintain daily activities/social isolation
	Lack of transportation to follow-up or rehabilitation visits
	Lack of decisions or documentation regarding end-of-life issues such as advanced directives
Acute exacerbations	
Drugs	Over- or underuse of antibiotics and corticosteroids based on indications
	Unnecessary or prolonged use of broad-spectrum or parenteral antibiotics
	Overuse of theophylline or mucolytics
	Unnecessary use of high-dose, prolonged, or tapering corticosteroid regimens
	Not performing drug reconciliation or smoking interventions on admission and discharge
Monitoring	Not performing postexacerbation/hospitalization follow-up
	Unnecessary sputum cultures
	Not monitoring acute toxicities of corticosteroids (e.g., glucose levels)
	Not monitoring or preventing acute complications (e.g., cor pulmonale, deep venous thrombosis, stress ulcers, dehydration, malnutrition)
	Documenting continued need for or tapering of oxygen therapy

COPD = chronic obstructive pulmonary disease.

Nondrug Therapy and Health Maintenance

Because of the relatively insignificant impact of drugs on the preservation of lung function and the progressive nature of symptoms, health maintenance is a high priority for all patients with COPD. An annual influenza vaccination is a level A recommendation by the GOLD guidelines. Administration of a single dose of pneumococcal vaccine is a level B recommendation for individuals older than 65 years or with an FEV_1 of less than 40% predicted. Pharmacists should encourage the regular monitoring of blood pressure and cholesterol concentrations to minimize cardiovascular risk. In addition, they should educate patients about the importance of calcium supplementation and bone mineral density screening to prevent osteoporosis. Pharmacists can also refer patients to dietitians to assist in maintaining weight, lowering cholesterol concentrations, and decreasing sodium intake in patients with cor pulmonale.

Pulmonary Rehabilitation Programs

All individuals with COPD can benefit from exercise training to limit deconditioning, muscle wasting, and right ventricular dysfunction, which can impair activity and functioning. Exercise training programs consist of a minimum of 20 visits for 3–7 weeks, but usually, three sessions per week occur for 20 weeks. Ideally, upper and lower limb exercises and both strength and endurance training are included. More comprehensive pulmonary rehabilitation programs also address nutritional and psychosocial issues and are especially recommended for those with moderate COPD. Self-management components include breathing strategies, end-of-life decision-making, adherence to exercise and drugs, and tobacco cessation. Pulmonary rehabilitation can improve the duration of exercise by 87% and the 6-minute walk test distance by 81 m. The MMRC dyspnea score can decrease by about 1.8 points, and the number of exacerbations can decrease by about 50%. Mood, muscle wasting, and 2-year survival can also improve. The programs have been shown to be cost-effective by decreasing the incidence of hospitalization and length of hospital stay. Benefits can be retained for up to 2 years and potentially longer if exercises are continued at home.

Several issues prevent patients from receiving timely referrals or successfully completing pulmonary rehabilitation programs. The perceived cost and a misconception that these programs are only for patients with end-stage COPD decrease referrals for those who would potentially benefit. A delay in referring until severe COPD develops is potentially costly in terms of impaired functional status, lower quality of life, and higher health care expenditures. In addition, those with severe COPD may find it physically challenging to complete the program and therefore not achieve maximal

Table 1-5. Examples of Indicators to Document Quality of Management of Stable COPD

All individuals with COPD	
Drugs	Short-acting inhalation bronchodilator prescribed as needed for symptoms
Monitoring	Spirometry at diagnosis and every 2–3 years to document severity/progression Monitoring of symptoms and functioning (e.g., Modified Medical Research Council dyspnea score, missed workdays) documented yearly
Vaccinations	Annual influenza vaccination One-time pneumonococcal vaccination if older than 65 years
Education	Provided at diagnosis and at least every year Initial instruction regarding device technique and rechecked every 6–12 months
Tobacco	Current tobacco status documented at each visit (includes cigars and smokeless tobacco) Patients who smoke receive brief interventions at each visit Those actively attempting cessation receive or are referred to intensive interventions Drugs prescribed and continued only for those actively attempting cessation Number of quit attempts per patient per year
Individuals with moderate to severe COPD (in addition to the above)	Advanced directives and preferences for end-of-life care (checked yearly) Completion of pulmonary rehabilitation program (optimally completed for all with moderate COPD) Pneumococcal vaccination (one time) if forced expiratory volume at 1 second is less than 40% of predicted or patient is older than 65 years Adherence to drugs and oxygen therapy checked at each visit Monitoring: ability to complete activities of daily living, incidence of exacerbations, and oxygen saturation (goal = 90% to 92%) (checked at each visit)

COPD = chronic obstructive pulmonary disease.

benefit. Patient barriers include motivation, transportation, finances, and time. Pharmacists have a role in promoting timely referrals by educating both patients and practitioners about the indications for and value of completing pulmonary rehabilitation programs. Pharmacists can also be members of the multidisciplinary pulmonary rehabilitation team.

Tobacco Abstinence and Cessation

The decline in initiation of tobacco use in recent years is thought to be because of the rising cost of cigarettes and the effect of public service announcements funded by tobacco settlement funds. More recently, this decline has slowed, and the concern is now that more adolescents will use tobacco. Pharmacists working with children and adolescents should be aware that most regular tobacco use begins by age 18, but experimentation begins as early as age 9. It is important to regularly deliver the message to avoid tobacco by age 5 years. More information is needed about how to tailor an effective abstinence message to children and adolescents.

The 2000 National Institute of Health and GOLD guidelines stress the five A's. These include *asking* all patients about tobacco use. Those using tobacco should receive brief, frequent interventions, including *advice* to quit, *assessment* of their willingness to quit, *assistance* with cessation, and *arrangement* for follow-up.

Effective tobacco counseling is tailored. Brief interventions to those not yet interested in quitting should focus on identifying personal motivators and removing roadblocks to quitting. Health care providers often focus primarily on the long-term cardiovascular and cancer-related benefits of cessation, but these are often not important motivators. Other reasons to quit such as tooth loss, erectile dysfunction, wrinkles, effects of secondary smoke on their family, or being a positive role model for their children should be explored. Personal roadblocks should be identified and removed by dealing with stress or triggers for tobacco use such as coffee, living with others who smoke, or concerns about weight gain. Repetition is a key to the success of brief interventions. Motivating factors and roadblocks should be discussed often by multiple providers. All pharmacists with patient contact should provide brief interventions.

Intensive interventions should involve individualized behavioral modification and problem-solving strategies. A successful quit attempt requires an individualized plan, and most patients will need assistance dealing with specific triggers to tobacco use, enlisting social support, and managing nicotine withdrawal symptoms. Those who have recently quit are at significant risk of relapse, so it is important to screen for relapses and encourage abstinence. Clinicians should acknowledge success and assist with solving any problems or barriers to abstinence. Individuals can usually identify the cause of a relapse, but they often need assistance with developing an effective plan. Any pharmacist who has ongoing relationships with patients is in an excellent position to provide intensive interventions. The local American Lung Association or the American Cancer Society affiliates are great resources for patients who require intensive interventions or for pharmacists who are interested in developing skills to provide intensive interventions.

The National Institutes of Health guidelines recommend that all individuals attempting tobacco cessation be offered pharmacotherapy. This recommendation has been criticized as potentially biased, because key authors of the guidelines were also involved in major studies involving pharmacological therapy. The concern is whether the positive data on behavioral modification alone were given adequate weight. The recommended first-line agents include nicotine gum; nicotine patch, inhaler, or spray; and bupropion. A recent meta-analysis assessed 70 placebo-controlled trials. At 1 year, use of the nicotine patch and gum increased cessation by 70% over placebo. Bupropion also was shown to be twice as effective as placebo. A comprehensive discussion of general indications, dosing, and adverse effects of tobacco cessation therapies is included in the Substance Use Disorders chapter in Book 3.

The choice of a nicotine replacement product, bupropion, or a combination is patient-specific. The Fagerstrom questionnaire can be used to identify those at higher risk of nicotine withdrawal symptoms. For example, positive responses to the questions relating to difficulty in abstaining from smoking where it is prohibited or continuing to smoke while ill may indicate physical dependence. A Fagerstrom score of 7 points or more identifies a significant risk of developing withdrawal symptoms. Other hints of potential nicotine dependence include withdrawal symptoms with a prior quit attempt or smoking despite a serious disorder that is worsened by smoking (e.g., COPD). Nicotine products can prevent withdrawal symptoms. The gum and lozenge can delay weight gain as long as patients are using the product. The nicotine gum can worsen temporomandibular joint dysfunction and loosen dental fillings or inlays. The inhaler, gum, and lozenge can potentially worsen gastroesophageal reflux symptoms in up to 18% of patients. The nicotine inhaler and nasal spray should be avoided in individuals with COPD because of the risk of bronchospasm. People with concurrent unstable angina, serious arrhythmias, or a myocardial infarction within the past 2 weeks should not use nicotine replacement products.

Bupropion inhibits norepinephrine and dopamine reuptake. Bupropion can also delay weight gain. The immediate-release product is not recommended for tobacco cessation because of a lack of data. Sustained-release bupropion is started at 150 mg once daily for 3 days and then increased to twice daily. A quit date is set for 1 week after initiating bupropion. Individuals with a history of an eating disorder, seizures, or alcohol abuse should avoid bupropion because it can lower the seizure threshold. Bupropion, at these doses, can safely be combined with selective serotonin reuptake inhibitors in individuals with concurrent mood disorders.

Varenicline is an $\alpha_4\beta_2$ nicotinic acetylcholine receptor partial agonist-antagonist released after the 2000 guidelines were published. By acting as a partial agonist, varenicline releases dopamine to reduce tobacco cravings. As a partial antagonist, varenicline blocks nicotine from binding to its receptor and decreases the pleasurable effects of smoking. The usual oral starting dosage is 0.5 mg once daily for 3 days and then twice daily for the remainder of the first week, followed by 1 mg twice daily. No dosage adjustment is necessary for mild to moderate renal disease. Those with severe renal disease should not receive more than 0.5 mg twice daily. With hemodialysis, the maximal recommended dose is 0.5 mg once daily. A quit date is set for 1 week after starting varenicline. Varenicline is typically continued for 12 weeks but may be used for up to 24 weeks if needed. Varenicline appears to be well tolerated. Adverse effects include vivid dreams and transient nausea that can be lessened by taking with food. However, a recent U.S. Food and Drug Administration advisory notice warns of reports of suicidal ideation, erratic behavior, and drowsiness in patients taking varenicline. Patients should be counseled to report mood or behavior changes after starting varenicline.

Data from clinical trials favor varenicline over both placebo and bupropion at 12 months. At 1 year, 23% of individuals receiving varenicline were continuously abstinent compared with 10.3% in the placebo group and 14.6% in the sustained-release bupropion group**.** The initial efficacy data on varenicline are promising, but varenicline may be less effective in usual practice, which typically includes patients who are less motivated and have comorbid conditions. In addition, behavioral support is not as available.

Combination therapy with a long- and short-acting nicotine product can be recommended for those who smoke more than 2 packs per day, have a high degree of physical dependence, or have found other monotherapies unsuccessful. The 1-year quit rate for bupropion combined with the nicotine patch was not found to be better than for bupropion alone in a recent randomized controlled trial. Clonidine and nortriptyline are second-line options typically reserved for instances when other treatments fail, when they are not tolerated, or when contraindications to first-line drugs exist. Auricular acupuncture or auriculotherapy for smoking cessation is often expensive, and 1-year abstinence data are needed before acupuncture can be recommended. A Phase III trial was due to begin in 2007 for CYT-002-NicQb, a vaccine to induce antibodies to nicotine. Pharmacogenomic investigations are exploring whether dopamine$_4$ receptor or serotonin transporter genes can identify patients more likely to respond to bupropion or nicotine replacement therapies.

Pharmacists have an important role in preventing COPD by aggressively promoting tobacco avoidance and in limiting COPD progression by facilitating tobacco cessation. Patients need assistance to optimally select and use drugs based on their personal preferences, potential for adverse effects, comorbid conditions, and financial limitations. Many patients also need assistance in developing a comprehensive behavioral modification plan and remaining motivated.

Issues Potentially Diminishing Efficiency and Effectiveness

Drug-related issues and examples of quality indicators for the management of COPD are listed in Tables 1-4 and 1-5. The focus of interventions by the pharmacist shifts as the severity of COPD increases. For those with mild COPD, interventions promoting an early diagnosis, limiting COPD progression, managing comorbid conditions, and minimizing the impact of symptoms on quality of life are important. Special attention should be directed toward evaluating the individual's ability to use a given drug delivery device. Dyspnea or arthritis can make hand-lung coordination difficult even in mild COPD, so metered-dose inhalers plus holding chambers or dry powder devices are routinely necessary. The dry powder devices for tiotropium

and formoterol require some manual dexterity to place and puncture the capsule. Drug delivery by metered-dose or dry powder inhalers is often compromised by insufficient breath holding or negative inspiratory force. In these instances, nebulized delivery can be recommended. Because 50% to 75% of the health-related costs of COPD are caused by exacerbations, optimizing therapy and avoiding/shortening hospitalizations for exacerbations are essential for minimizing health costs. As COPD progresses, maintaining functional status and addressing psychosocial issues such as anxiety and depression become increasingly important.

Conclusion

As a worsening public health problem, COPD will consume more health care resources and cause increasing morbidity and mortality. Pharmacists are in an excellent position to prevent the development and progression of COPD through promoting tobacco abstinence and cessation. To increase the early, correct diagnosis of COPD, pulmonary function testing should be advocated for at-risk patients who have symptoms. Pharmacotherapy issues range from drug selection to optimal drug delivery, appropriate monitoring, and optimal management of concurrent cardiovascular risk factors. Individuals with COPD require significant education about respiratory drugs and devices and behavioral modification for tobacco cessation. By optimizing drug therapy and implementing quality improvement programs, pharmacists can improve the quality of care for COPD. In the future, new disease-specific therapies may interfere with the underlying pathophysiology of COPD and result in improved patient outcomes.

Annotated Bibliography

1. Barnes PJ. Mediators of chronic obstructive pulmonary disease. Pharmacol Rev 2004;56:515–48. Available at *www.aspetjournals.org/.* Accessed February 11, 2008.

   This is a comprehensive article describing the current understanding of the pathophysiology of COPD. The article describes in depth the roles of various inflammatory cells, growth factors, proteases, and oxidative stress in the pathogenesis of COPD. Unfortunately, the improved understanding of the pathophysiology of COPD has not yet translated into effective agents to prevent or treat the progression and exacerbations of COPD. This article describes the pathophysiologic differences between asthma and COPD, which explains why COPD does not respond as well as asthma to current therapy. Understanding the differences can help justify the importance of performing the appropriate diagnostic studies to differentiate these two conditions. This will also help clinicians persuasively recommend options for treatment. This article identifies several novel therapies that are currently under development.

2. Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. 2007. Available at *www.goldcopd.com/Guidelineitem.asp?l1=2&l2=1&intId=989.* Accessed February 11, 2008.

   The GOLD guidelines are a collaborative effort between the National Heart, Lung, and Blood Institute and the World Health Organization. The main objectives are to increase worldwide awareness of COPD and to create a consensus document regarding prevention, diagnosis, and treatment. The guidelines are summarized into four components: assess and monitor disease, reduce risk factors, manage stable COPD, and manage exacerbations. The pathophysiology of COPD and recommendations for implementing these guidelines into primary care are discussed.

   Unlike the European Respiratory Society/American Thoracic Society or the National Institute for Clinical Medicine guidelines, the GOLD guidelines are updated yearly. The Executive and Science Committees' membership is international, with members from North and South America, Japan, and Europe, and includes leading researchers in COPD. In addition, the guidelines are evidence based, with each major therapeutic recommendation assigned an evidence level of A–D. The GOLD guidelines are both comprehensive and concise and are an essential reference for health care professionals who manage patients or perform quality assurance in COPD. Some specialty topics are discussed in more detail in other COPD guidelines referenced below. The GOLD guidelines are accessible at *www.goldcopd.com* and can be downloaded as PDF files. The 2007 guidelines do not have any significant changes in recommendations for either chronic COPD or its acute exacerbation.

3. Celli BR, MacNee W, Agusti A, Anzueto A, Berg B, Buest AS, et al. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. Eur Respir J 2004;23:932–46.

   Pharmacists who care for those with COPD should be aware of this joint statement because the pulmonologists and respiratory therapists with whom they collaborate are likely familiar with it. This publication outlines a joint updated version of the position papers published by the American Thoracic Society and the European Respiratory Society in 1995. The reference is the summary, but a more detailed discussion is available at *www.thoracic.org/sections/copd/resources/copddoc.pdf.* The publication on the Internet is intended to provide a mechanism for more timely updates.

   The COPD task force for this joint document is composed of members from the American Thoracic Society and the European Respiratory Society. Members from this task force will be on the Executive Committee of GOLD to encourage cohesiveness between this statement and the GOLD document. This document is consistent with the general GOLD recommendations for treatment and diagnosis. The recommendations are well referenced but are not classified based on the level of evidence. The staging for COPD severity still includes an at-risk level, which is similar to stage 0 in the earlier versions of GOLD. Specialty topics such as nutrition, surgical management, sleep, air travel, and ethical and palliative care issues are covered in this joint paper, but they are not included in the GOLD guidelines.

4. National Institute for Clinical Excellence (NICE). Management of chronic obstructive pulmonary disease in adults in primary and secondary care. Available at *www.nice.org.uk/nicemedia/pdf/CG012_niceguideline.pdf.* Accessed February 11, 2008.

   The 2004 British NICE guidelines are similar to the 2006 GOLD guidelines. Minor differences include performing spirometry in symptomatic individuals older than 35 years versus 40 years. They are more specific about defining repeated exacerbations as two or more exacerbations in

a 1-year period that require antibiotics or corticosteroids. These guidelines are more detailed regarding the importance of device instruction and the cleaning and use of holding devices. Pulmonary rehabilitation is recommended for all individuals who have at least grade 2 dyspnea on the MMRC questionnaire. Patients who are at risk of exacerbations are encouraged to have a self-management plan for starting systemic corticosteroids and antibiotic therapy at home. These guidelines provide indications and rationales for both long- and short-term oxygen therapies. The differentiation of asthma from COPD is discussed, and a comprehensive list of indications for referral to specialist care is provided. Review of these guidelines is expected to begin in 2008 with an update available by 2010. Pharmacists who often care for those with COPD or who are responsible for quality assurance should be aware that guidelines other than those from GOLD exist.

5. Calverley PMA, Anderson JA, Celli B, Ferguson GT, Jenkins C, Jones PW, et al. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease (TORCH). N Engl J Med 2007;356:775–89.

   This trial compared the effects of the combination of fluticasone 500 mcg plus salmeterol 50 mcg with each component alone and placebo. The primary end point at 3 years was time to death from any cause. The mean FEV_1 was 44% of predicted at baseline. The risk of death was similar between the combination and salmeterol groups, but individuals in the group receiving the combination were less likely to die than those in the fluticasone-alone group (12.6% vs. 16%; p=0.007). Participants receiving combination therapy experienced fewer exacerbations (exacerbation rate ratio = 0.75; 95% confidence interval [CI] = 0.69–0.81) and improved health status and lung function. Pneumonia developed in a significantly greater proportion of patients in the combination group versus the salmeterol and placebo groups (19.3%, 13.3%, and 12.3%, respectively).

   The number needed to prevent one exacerbation was 4, and to prevent one hospitalization, the number was 32. The GOLD 2006 update does not reflect these results. Decreased exacerbations were seen in the combination group, but frequent exacerbations were not part of the inclusion criteria. Based on these results, additional patients may benefit from the combination of a long-acting inhaled β_2-agonist and a corticosteroid, including those with an FEV_1 of less than 60% of predicted even if they do not have frequent exacerbations. Strengths include the large sample size, the trial length, and the use of mortality as an end point.

6. Aaron SD, Vandemheen KL, Fergusson D, Maltais F, Bourbeau J, Goldstein R, et al. Tiotropium in combination with placebo, salmeterol, or fluticasone-salmeterol for treatment of chronic obstructive pulmonary disease. Ann Intern Med 2007;146:545–55.

   This Canadian trial compared inhaled tiotropium, tiotropium plus salmeterol, and tiotropium plus fluticasone-salmeterol in patients with moderate to severe COPD. The primary outcome was the proportion of patients experiencing an exacerbation at 1 year. About 60% of patients overall had at least one exacerbation, which was not significantly different between the groups. With regard to secondary end points, patients in the tiotropium plus fluticasone-salmeterol group had lower rates of exacerbations requiring hospitalizations than those receiving the tiotropium. The 1-year change in St. George's Respiratory Questionnaire scores was −4.5 points for the tiotropium group, −6.3 for the tiotropium plus salmeterol group (p=0.02), and −8.6 for the tiotropium plus fluticasone-salmeterol group (p=0.01).

   The mean baseline FEV_1 of subjects was less than 50% of predicted, but only one exacerbation in the past year was required for entry into the study. The relatively short study duration and uncommon history of exacerbations required for inclusion into the study may explain the lack of improvement in the rate of exacerbations. There was a modest benefit in preventing hospitalizations and in the health-related quality-of-life scores in both combination groups. Readers are reminded to make individualized decisions regarding which patients should be given inhaled corticosteroids, and if no benefit is seen, discontinuation is appropriate.

7. Wouters EFM, Postma DS, Fokkens B, Hop WCJ, Prins J, Kuipers AF, et al. Withdrawal of fluticasone propionate from combined salmeterol/fluticasone treatment in patients with COPD causes immediate and sustained disease deterioration: a randomized controlled trial (COSMIC). Thorax 2005;60:480–7.

   This trial from the Netherlands evaluated the effects on FEV_1 1 year after the withdrawal of inhaled fluticasone. Patients with a baseline FEV_1 of 30% to 70% of predicted and at least two COPD exacerbations in the previous year received salmeterol 50 mcg plus fluticasone 500 mcg twice daily during a 3-month run-in period and then were randomized to continue the combination or salmeterol alone. The prebronchodilator FEV_1 averaged 49% of predicted in both groups. The withdrawal of fluticasone resulted in a decrease in FEV_1 of about 50 mL per year (95% CI = 0.01–0.10 L). The annual rate of moderate to severe exacerbations was not statistically significant. Mild exacerbations decreased by less than one per year in the combination group (p=0.020). The two groups were similar in terms of symptom and quality-of-life scores.

   The inclusion criteria were similar to the GOLD guidelines for inhaled corticosteroids regarding exacerbation history, but a prebronchodilator FEV_1 was used versus a postbronchodilator FEV_1, which is used to classify COPD in the GOLD guidelines. The small sample size may have precluded the authors from finding a difference in moderate to severe exacerbation rates. This study supports continuing inhaled corticosteroids for a modest effect on lung function and exacerbation rate.

8. Sin DD, Wu L, Anderson JA, Anthonisen NR, Buist AS, Burge PS, et al. Inhaled corticosteroids and mortality in chronic obstructive pulmonary disease. Thorax 2005;60:992–7.

   This study pooled data regarding all-cause mortality from seven randomized trials of inhaled corticosteroids versus placebo. All trials lasted at least 1 year. Overall, 4% of subjects died, and those in the inhaled corticosteroid group had a lower risk of mortality (hazard ratio = 0.75; 95% CI = 0.57–0.99). A subgroup analysis revealed that inhaled corticosteroids reduced mortality (adjusted hazard ratio = 0.66; 95% CI = 0.45–0.96) in subjects with GOLD stage 3 and 4 COPD, but the effect was not significant in those with GOLD stages 1 and 2. None of the trials included in this meta-analysis were designed to include mortality as an end point, but statistical significance was reached when data were pooled for analysis. Different corticosteroids were used, so the decrease in mortality appears to be a class effect.

   Patient-level data and patient-stratified data based on their FEV_1 and COPD stage were used. Baseline FEV_1 numbers were varied; nevertheless, an effect on mortality was seen. These are the first data to show the positive effect of inhaled corticosteroids on mortality in COPD. Results reinforce the GOLD guidelines reserving inhaled corticosteroid for patients with stage 3 and 4 COPD. Unfortunately, the authors

did not describe how they performed their initial search, what statistical methodology was used to identify trials, or how the trials were critiqued for inclusion.

9. Nichols J. Combination inhaled bronchodilator therapy in the management of chronic obstructive pulmonary disease. Pharmacotherapy 2007;27:447–54.

This review evaluates available data for combining inhaled β_2-agonist and anticholinergic bronchodilator therapies for COPD. The combinations reviewed include albuterol plus ipratropium, salmeterol plus ipratropium, formoterol plus tiotropium, and salmeterol plus tiotropium. The FEV_1, as the primary outcome in most studies, showed statistically significant improvement with all combinations. Patient-oriented outcomes such as quality-of-life scores, symptom scores, and exacerbation rates were not evaluated, not reported, or did not reach statistical significance. The studies for combined long-acting inhaled bronchodilators were of relatively short duration.

The documented benefit of combination inhaled bronchodilators is primarily limited to small changes in lung function, which may not result in significant clinical improvement. These data and the greater expense of the long-acting agents explain why current guidelines may recommend long-acting inhaled bronchodilators, but many formularies may not include these agents or may limit their use. Appreciation of these limited data also explains the importance of monitoring therapy in individual patients and stopping therapy if clinical benefit cannot be documented within several weeks or a few months. Unfortunately, the author did not include quantitative results for many of the trials, so the reader was not able to evaluate the clinical significance of the results.

10. van Noord JA, Aumann J-L, Janssens E, Smeets JJ, Verhaert J, Disse B, et al. Comparison of tiotropium once daily, formoterol twice daily and both combined once daily in patients with COPD. Eur Respir J 2005;26:214–22.

This European study compared tiotropium and formoterol monotherapy with the combination of the two agents on FEV_1. This crossover study consisted of three 6-week treatment periods and included patients with a baseline FEV_1 of less than 60% of predicted. The combination of tiotropium plus formoterol performed significantly better during the first 12-hour period after morning inhalation. The improvement in FEV_1 with the combination therapy versus tiotropium ranged from 70 mL to 151 mL and was statistically significant. The improvement in FEV_1 with combination therapy versus formoterol ranged from 110 mL to 164 mL and was also statistically significant.

The results confirm the GOLD guidelines' recommendation of treatment of moderate to severe COPD with two long-acting inhaled bronchodilators of differing mechanisms. Limitations of this trial include its small sample size and its relatively short duration of 6 weeks per treatment arm. Clinical outcomes (symptoms or quality of life) were not evaluated. This study was not included in the recent review article regarding combination bronchodilator therapy discussed in reference 9.

11. Barnett MJ, Milavetz G, Kaboli PJ. β-Blocker therapy in veterans with asthma or chronic obstructive pulmonary disease. Pharmacotherapy 2005;25:1550–9.

This retrospective cohort study evaluated whether subjects with asthma or COPD receiving β-blocker therapy used more health care resources than those receiving other cardiovascular agents. Of the 8000 patients, 37% received β-blocker therapy. Most of these (34%) received a selective β-blocker including atenolol (18%) or metoprolol (16%). Only 3% received a nonselective β-blocker including carvedilol (1%) or propranolol (2%). When adjusted for demographics and comorbid conditions, hospital admissions caused by asthma or COPD were not significantly different. Those not taking β-blocker therapies averaged 2.5 ± 3.1 asthma or COPD clinic visits per year. Those receiving selective β-blocker therapy averaged 2.0 ± 3.1 ($p<0.01$) clinic visits, and those receiving nonselective β-blocker therapy averaged 2.0 ± 2.5 ($p<0.01$) clinic visits compared with those not taking β-blocker therapy. Between the selective β-blocker groups, the atenolol group had fewer hospital admissions compared with metoprolol (hazard ratio = 1.95; 95% CI = 1.55–2.47). The authors concluded that β-blocker therapy did not increase hospital admissions or clinic visits.

Limitations of the study included the inability to control for potential care outside the Veteran's Administration system or for disease severity and the comparatively small number receiving nonselective β-blocker therapy. This study lasted only 1 year, and asthma versus COPD data were not separated. More subtle deteriorations in status not resulting in a clinic visit or hospitalization were not detectable. The recommendation to use atenolol in those with COPD was limited by the lack of outcome data for the significant indications for β-blocker therapy such as after a myocardial infarction. This study can be cited to support β-blocker therapy for patients with COPD with major indications, but individual patients should be monitored for worsening pulmonary symptoms.

12. Fiore MC, Bailey WD, Cohen SJ, Dorfman SF, Goldstein MG, Gritz ER, et al. Treating Tobacco Use and Dependence. Clinical Practice Guideline. Rockville, MD: U.S. Department of Health and Human Services, Public Health Service, June 2000.

This Public Health Service–sponsored guideline provides evidence-based suggestions for helping patients quit using tobacco. Because most patients with COPD will have a smoking history, and smoking cessation can decrease disease progression, knowledge of these guidelines is important. These guidelines were meant to be easily implemented in various clinical settings and diverse patient populations. All recommendations are labeled based on the strength of evidence, with A being the strongest. The smoking cessation guidelines have not been updated since 2000, so the nicotine lozenge and varenicline are not included. The intended audience is any health care provider who works with patients who use tobacco. It is recommended that any patient willing to make a quit attempt be offered pharmacotherapy. Not only are first- and second-line pharmacotherapy options discussed, but techniques are also offered on motivating patients to quit and helping them overcome barriers to quitting. Relapse prevention is covered in depth.

13. Jorenby DE, Hays JT, Rigotti NA, Azoulay S, Watsky EJ, Williams KE, et al. Efficacy of varenicline, an $\alpha_4\beta_2$ nicotinic acetylcholine receptor partial agonist versus placebo or sustained release bupropion for smoking cessation. JAMA 2006;296:56–63.

This is one of the first large trials evaluating varenicline for smoking cessation. Cessation rates of varenicline were compared with placebo and sustained-release bupropion after 1 year. All subjects received smoking cessation counseling weekly. The primary end point was continuous abstinence for weeks 9–12. At the end of 12 weeks, 49% in the varenicline

group were continuously abstinent versus 17.6% in the placebo group (p<0.001) and 29.8% in the bupropion group (p<0.001). During weeks 9–24 and weeks 9–52, varenicline group abstinence rates were statistically superior to placebo and bupropion. A high drop-out rate of 35% was reported, but this is comparable with similar smoking cessation trials.

A strength of this trial was that smoking status was objectively assessed. Subjects were relatively young and healthy; patients with cardiovascular disease and COPD were excluded. Motivation was possibly increased by the use of objective measurements of smoking status and intensive counseling and behavioral modification, which are not normally provided in the typical practice. The 1-year quit rate in this study with varenicline was significantly higher than for other currently available agents but was still only 23%. Once in general use, it will become important to evaluate the actual effectiveness of this agent. At this time, there are no data comparing varenicline with nicotine replacement. The combination of varenicline and nicotine replacement therapy is not warranted based on the mechanism of action of varenicline. However, studying the effect of long-term abstinence rates using a combination of varenicline with bupropion might be appropriate.

14. Tonstad S, Tonnesen P, Hajek P, Williams KE, Billings CB, Reeves KR, et al. Effect of maintenance therapy with varenicline on smoking cessation. A randomized controlled trial. JAMA 2006;296:64–71.

Tobacco relapses 6 months and 1 year after initially successful quit attempts are very common. These investigators hypothesized that using varenicline for an extra 3 months for a total of 24 weeks would improve long-term cessation rates. Subjects who successfully quit for 7 days after completing an open-label 12-week treatment period with varenicline were randomly assigned to receive either an additional 12 weeks of varenicline or placebo. At each follow-up visit, the results from carbon monoxide testing were compared with self-reported cigarette use to evaluate abstinence. Subjects received brief counseling sessions with behavioral modification techniques. The primary objective was abstinence from smoking during weeks 13–24 and weeks 13–52. At 52 weeks, the continued abstinence rates were 43.6% in the varenicline group compared with 36.9% in the placebo group (odds ratio [OR] = 1.34; 95% CI = 1.06–1.69). The number needed to treat in order for one person to maintain abstinence through week 52 was 14. The authors concluded that the continuation of varenicline use to 6 months helps maintain abstinence and prevent tobacco relapse.

One-year abstinence rates in this study were more than 40%. A possible reason that abstinence rates were higher than in other published trials is that only those individuals completing the initial 12 weeks of varenicline were enrolled. Behavioral modification was also continued. Continuous abstinence at week 52 was similar to placebo. However, continuing varenicline for up to 6 months may help patients remain abstinent; such therapy might be recommended to those at high risk of relapse.

15. Wu P, Wilson K, Dimoulas P, Mills EJ. Effectiveness of smoking cessation therapies: a systematic review and meta-analysis. BMC Public Health 2006;6:300–16.

This meta-analysis included randomized controlled trials with nicotine replacement therapy, bupropion, and varenicline for smoking cessation. The primary end point was cessation rates at 1 year. The results from more than 70 nicotine replacement trials combined for this meta-analysis showed a pooled OR favoring nicotine replacement with patch or gum over placebo at 1 year (OR = 1.71; 95% CI = 1.55–1.88). The results of 12 trials assessing bupropion versus placebo at 1 year showed an OR of 2.13 (95% CI = 1.71–2.64) favoring bupropion. Using indirect comparisons, varenicline was superior to nicotine replacement therapies at 3 months (OR = 1.66; 95% CI = 1.17–2.36) and at 1 year (OR = 1.73; 95% CI = 1.22–2.45). In direct comparison, varenicline was more effective than bupropion at 1 year (OR = 1.58; 95% CI = 1.22–2.05). The authors concluded that varenicline is the most effective therapy available at this time.

Although there are no studies directly comparing the three approaches, these data are important because they point to a possible hierarchy between the three agents. Further prospective and comparative studies are needed to strengthen this finding regarding the superiority of varenicline. Future therapies for smoking cessation should stratify drug use according to patient-specific factors such as Fagerstrom questionnaire results or pharmacogenomics.

16. Mancini GBJ, Etminan M, Zhang B, Levesque LE, FitzGerald JM, Brophy JM. Reduction of morbidity and mortality by statins, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers in patients with chronic obstructive pulmonary disease. JACC 2006;47:2554–60.

Patients with COPD often have concomitant cardiovascular disease, possibly caused by long-term smoking and other risk factors. This observational study evaluated whether common cardiovascular drugs prevented cardiovascular morbidity in patients with COPD. Results showed fewer hospitalizations for COPD in those using statins (relative risk = 0.72; 95% CI = 0.56–0.92) and in those using statins and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (relative risk = 0.66; 95% CI = 0.51–0.85). In those with COPD considered at high risk of myocardial infarctions, risk ratios were reduced by all three drugs (risk ratio = 0.39; 95% CI = 0.31–0.49).

Long-term prospective trials are needed to confirm these findings. The results of this trial should remind providers that those with COPD are also at high risk of cardiovascular morbidity and mortality and encourage the use of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and statins. These prescribing habits could lead to cardiovascular risk reduction in patients with COPD. The recommended audience is any pharmacist who currently cares for patients with COPD.

17. Nici L, Donner C, Wouter E, Zuwallack R, Ambrosino N, Bourbeau J, et al. American Thoracic Society/European respiratory society statement on pulmonary rehabilitation. Am J Respir Crit Care Med 2006;173:1390–413.

Pulmonary rehabilitation is a comprehensive, multidisciplinary approach to improving patients' symptoms such as dyspnea, exercise capacity, and health-related quality of life. The statement discusses differences between exercise training and the more comprehensive pulmonary rehabilitation, which typically includes psychosocial support, self-management skills, and device technique and training. Other topics include breathing techniques (e.g., pursed-lip breathing) and energy conservation, proper nutrition and caloric intake to avoid or correct muscle wasting, ensuring adequate support systems at home, end-of-life decision-making, anxiety and depression screening, and smoking cessation assistance. This comprehensive statement recommends sessions of at least 20 minutes three times per week. Both upper and lower extremity training is encouraged. The authors also suggest outcomes for programmatic

assessment such as performance, symptoms, quality of life, and staffing requirements.

This article is recommended reading for pharmacists who wish to clarify the role and benefits of pulmonary rehabilitation and determine which subset of patients to be referred. Although not listed as required health care professional participants, pharmacists should be encouraged to become involved in their institution's pulmonary rehabilitation program.