

This supplement to THE JOURNAL OF FAMILY PRACTICE is supported by a grant from Boehringer Ingelheim Pharmaceuticals, Inc. It was submitted by the Primary Care Education Consortium and the Texas Academy of Family Physicians and was edited and peer-reviewed by THE JOURNAL OF FAMILY PRACTICE.

# Chronic Obstructive Pulmonary Disease

## Consensus Recommendations for Early Diagnosis and Treatment

Dennis E. Doherty, MD, FCCP | Mark H. Belfer, DO, FAAFP | Stephen A. Brunton, MD  
Leonard Fromer, MD | Charlene M. Morris, MPAS, PA-C | Thomas C. Snader, PharmD, CGP, FASCP

The mention of a patient with chronic obstructive pulmonary disease (COPD) is likely to conjure up an image of an older man with a cigarette in one hand and an inhaler in the other. Perhaps the person is also receiving oxygen therapy. Yet although this image may describe an older person with symptomatic, severe, or very severe COPD, it does not describe most persons with COPD. First, the COPD population is no longer dominated by men. In fact, in the United States in 2000, more women than men died from COPD.<sup>1</sup> Second, COPD is a silent disease in its early stages. Because humans have extra lung reserve when healthy, considerable lung capacity can be lost due to progression of COPD before symptoms are noticed.<sup>2</sup> In COPD, usually half the lung function (forced expiratory volume in 1 second [FEV<sub>1</sub>] <50% predicted) is lost before symptoms are noticed or acknowledged. It is critical that effective early intervention—prior to the onset of symptoms—be initiated in patients with

### Key points and recommendations

- Current or former smokers 45 years of age or older or anyone who has 1 or more of the cardinal symptoms of COPD (chronic cough, mucus production, shortness of breath on mild exertion, or wheeze) should be assessed using spirometry to detect the presence of airflow obstruction. (SOR: C)
- Differentiating COPD from asthma is critical because the natural history, pathophysiology, and stepwise therapy are different. (SOR: A)
- The ultimate management goal of COPD is prevention, principally by not smoking. (SOR: A)
- Bronchodilators, especially anticholinergics and beta<sub>2</sub>-agonists, are the cornerstone of symptomatic treatment of COPD because of their beneficial effects on expiratory flow, dyspnea, quality of life, and prevention of exacerbations. (SOR: A)
- Patients with stable COPD are best managed with a stepwise increase in therapy based on disease severity as evidenced by FEV<sub>1</sub>. (SOR: A)



#### DISCLOSURES

**Dr Doherty** reports that he is a consultant to Boehringer Ingelheim Pharmaceuticals, Inc., Merck & Co., Inc., and Schering-Plough Corporation and has received grant or research support from ALTANA Pharma, Boehringer Ingelheim Pharmaceuticals, Inc., GlaxoSmithKline, and Novartis Pharmaceuticals Corporation.

**Dr Belfer** reports that he is a consultant to Boehringer Ingelheim Pharmaceuticals, Inc., and Pfizer Inc, and is on the speakers' bureau of AstraZeneca, Boehringer Ingelheim Pharmaceuticals, Inc., and Pfizer Inc.

**Dr Brunton** reports that he is a consultant to Abbott Laboratories, Boehringer Ingelheim Pharmaceuticals, Inc., Ortho-McNeil, Inc., Pfizer Inc, and sanofi-aventis.

**Dr Fromer** reports that he is a consultant to Boehringer Ingelheim Pharmaceuticals, Inc..

**Ms Morris** reports that she is a consultant to Abbott Laboratories and is on the speakers' bureau of Abbott Laboratories, Boehringer Ingelheim Pharmaceuticals, Inc., Pfizer Inc, and Wyeth Pharmaceuticals.

**Dr Snader** reports that he is on the speakers' bureau of Abbott Laboratories, Amgen Inc., Boehringer Ingelheim Pharmaceuticals, Inc., Bristol-Myers Squibb Company, Pfizer Inc, and Ortho Biotech Products, LP.

#### Dennis E. Doherty, MD, FCCP

Professor of Medicine  
Chief, Division of Pulmonary, Critical Care, and  
Sleep Medicine  
University of Kentucky College of Medicine  
Lexington, Kentucky

#### Mark H. Belfer, DO, FAAFP

Professor of Family Medicine  
Northeastern Ohio Universities  
College of Medicine  
Rootstown, Ohio  
Program Director, Family Medicine Residency  
Akron General Medical Center  
Akron, Ohio

#### Stephen A. Brunton, MD

Director of Faculty Development  
Cabarrus Family Medicine Residency  
Concord, North Carolina

#### Leonard Fromer, MD

Assistant Clinical Professor of Family Medicine  
David Geffen School of Medicine  
University of California at Los Angeles  
Los Angeles, California

#### Charlene M. Morris, MPAS, PA-C

Past President, Association of Family Practice Physician  
Assistants  
Staff Physician Assistant  
Halyburton Naval Hospital  
Cherry Point, North Carolina

#### Thomas C. Snader, PharmD, CGP, FASCP

Clinical Associate Professor of Clinical Pharmacy  
University of the Sciences in Philadelphia  
Philadelphia, Pennsylvania  
Consultant Pharmacist and President  
TCS Pharmacy Consultants  
North Wales, Pennsylvania

**TABLE 1**  
Key questions to aid in the diagnosis and staging of COPD

A "yes" to any of the following questions suggests that the patient may have COPD:
• Do you smoke (cigarettes, cigars, a pipe)?
• Do you cough or clear your throat at times?
• Do you bring up colored and/or thick mucus?
• Does your coughing or breathing keep you from doing things that you used to do and enjoy?
• Have you been chronically exposed to environmental or occupational fumes?

**TABLE 2**  
The Medical Research Council dyspnea scale<sup>20</sup>

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

<sup>20</sup>Fletcher CM, et al. *BMJ*. 1959;2:257-266.

COPD to obtain significantly improved outcomes.<sup>3,4</sup> The National Lung Health Education Program suggests that anyone 45 years of age or older who is a current or former smoker, or individuals of any age who have 1 or more of the cardinal symptoms of COPD (chronic cough, mucus production, shortness of breath on mild exertion, or wheeze), should be assessed using spirometry to document the presence or absence of airflow obstruction.<sup>5</sup>

Several other organizations have developed guidelines for the diagnosis and management of COPD. These include the Global Initiative for Chronic Obstructive Lung Disease (GOLD),<sup>3</sup> the American Thoracic Society/European Respiratory Society,<sup>4</sup> the United Kingdom National Collaborating Center for Chronic Conditions (NICE),<sup>6</sup> and the Canadian Thoracic Society.<sup>7</sup> The consensus recommendations that follow reflect the similarities and differences among these guidelines, combined with the experience of the panel of authors, and are designed to offer a workable approach to COPD in the primary care setting. These recommendations focus on identifying the patient with early-stage COPD—not severe or very severe COPD—and the pharmacologic steps a primary care clinician can take.

## Epidemiology

COPD is the fourth leading cause of mortality in the United States, accounting for 126,000 deaths in 2003.<sup>8</sup> Prevalence estimates range from a few million to 12 million in the United States alone, with some data suggesting that half of all cases remain undiagnosed.<sup>9,10</sup>

Tobacco smoking is the primary risk factor, estimated to be responsible for 85% to 90% of COPD cases. Cigar and pipe smokers are also at increased risk for COPD, as are passive smokers.<sup>11</sup> Other risk factors include genetics (alpha<sub>1</sub>-antitrypsin deficiency), occupational exposure (dust, vapors, and fumes), environmental pollution, and recurrent bronchopulmonary infections.<sup>3,4,12</sup> Although persons with asthma experience a slightly accelerated loss of lung function compared with individuals without asthma,<sup>13,14</sup> the contribution of airway hyperresponsiveness as a risk factor for COPD is unclear.<sup>3</sup>

## Challenges in diagnosis

COPD should be considered in patients 45 years of age or older who smoke or in any patient who has 1 or more of the cardinal symptoms of COPD (chronic cough, mucus production, shortness of breath on mild exertion, or wheeze).<sup>3,15</sup> The use of office-based spirometry is an effective, simple method to confirm the diagnosis of COPD, because such assessment identifies individuals who have significant airflow obstruction. However, peak flow monitoring is not useful because it is nonspecific and is affected by performance technique.<sup>3</sup>

The greatest diagnostic challenge is not in diagnosing COPD in symptomatic patients—it is in identifying individuals who have early-stage disease with no or minimal symptoms. To assist physicians in the diagnosis and staging of COPD, many screening questions for patients have been suggested.<sup>3,16</sup> Of these, 5 questions appear to be particularly important (TABLE 1). The presence of 1 or more of these signs or symptoms suggests that the patient may have early-stage COPD. For individuals with a smoking history, the number of cigarettes smoked per day and the length of time as a smoker should be determined. A history of passive smoking also should be investigated. Including smoking status (current, former, or never) among the vital signs assessed during patient examinations has been shown to increase the rate of identifying patients who smoke and of physician interventions to assist patients with smoking cessation.<sup>17,18</sup>

Once patients at risk for COPD have been identified, spirometry should be performed for early detection of mild-stage COPD.<sup>3,5</sup> Chest radiography, high-resolution computed tomography scans, and electrocardiograms are not useful as early screening tools.<sup>19</sup> To assess shortness of breath and disability, the Medical Research Council (MRC) dyspnea scale can be used (TABLE 2).<sup>20</sup> A slightly modified form of the MRC dyspnea

scale is one of the variables in the BODE index (TABLE 3).<sup>21</sup> The BODE (body-mass index [B], degree of airflow obstruction [O] and dyspnea [D], and exercise capacity [E], measured by the 6-minute-walk test) index has been validated and shown to be a better predictor of the risk of death from any cause and from respiratory causes than is FEV<sub>1</sub> alone.

### Spirometry

The FEV<sub>1</sub> and its ratio to the forced vital capacity (FVC), or FEV<sub>1</sub>/FVC, are the 2 most important spirometric measurements for initially assessing patients and following the effects of treatment. The hallmark of COPD is an FEV<sub>1</sub> less than 80% predicted, with a relatively normal FVC. The FEV<sub>1</sub>/FVC ratio is the most important measure because a value less than 70% predicted identifies an obstructive impairment. Although symptoms are important, the severity and staging of COPD and the stepwise treatment are based largely on FEV<sub>1</sub> (FIGURE).<sup>3</sup>

### Differential Diagnosis

The signs and symptoms of COPD often overlap other diseases, such as asthma, congestive heart failure, bronchiectasis, tuberculosis, obliterative bronchiolitis, and diffuse panbronchiolitis.<sup>4</sup> Chest radiography is not helpful in the differential diagnosis, because changes in COPD, and more so in asthma, do not usually occur until these diseases are very severe. Chest x-rays can be helpful in evaluating comorbidities of COPD (eg, pneumonia during an acute exacerbation). Distinguishing COPD from asthma is critical because the natural history, pathophysiology, and stepwise therapy are different. Whereas the symptoms of COPD may vary from day to day but are rarely absent, asthma occurs with

**TABLE 3**  
**The BODE Index<sup>21</sup>**

Variable	Points on BODE Index			
	0	1	2	3
FEV <sub>1</sub> (% predicted)*	≥65	50-64	36-49	≤35
Distance walked in 6 min (m)	≥350	250-349	150-249	≤149
MMRC dyspnea scale <sup>†</sup>	0-1	2	3	4
BMI <sup>‡</sup> (kg/m <sup>2</sup> )	>21	≤21	—	—

The cutoff values for the assignment of points are shown for each variable. The total possible values range from 0 to 10, with higher scores indicating a greater risk of death.

\*The FEV<sub>1</sub> categories are based on stages identified by the American Thoracic Society.

<sup>†</sup>Scores on the MMRC dyspnea scale can range from 0 (the patient is not troubled with breathlessness except with strenuous exercise) to 4 (the patient is too breathless to leave the house or becomes breathless when dressing or undressing).

<sup>‡</sup>BMI values were 0 or 1 because of the inflection point in the inverse relation between survival and BMI at a value of 21.

BMI, body-mass index; BODE, BMI (B), degree of airflow obstruction (O) and dyspnea (D), and exercise capacity (E), measured by the 6-minute-walk test; FEV<sub>1</sub>, forced expiratory volume in 1 second; MMRC, modified Medical Research Council.

Reprinted with permission. Celli BR, et al. *N Engl J Med*. 2004;350:1005-1012. Copyright © 2004 Massachusetts Medical Society. All rights reserved.

clear-cut exacerbations separated by symptom-free intervals (TABLE 4).<sup>12,19</sup> In addition, airflow limitation is usually totally reversible with a bronchodilator in asthma, whereas it is only partially reversible in COPD.

### Pathophysiology

Chronic inflammation throughout the central and peripheral airways, parenchyma, and pulmonary vasculature is a hallmark of COPD. Other processes thought to be involved in COPD are an imbalance between proteinases and antiproteinases in the lungs, and oxidative stress. The major inflammatory cells present in COPD are neutrophils, macrophages, and CD8<sup>+</sup> lymphocytes,

**TABLE 4**  
**Differentiating COPD from asthma<sup>4,12,19</sup>**

Factor	COPD	Asthma
Age of onset	Usually >40 years	Usually <40 years, but any age possible
Smoking history	Often >20 pack-years	Little
History of atopy	Unimportant	Often positive for the patient or family
Pathology Airways Parenchyma Airway hyperresponsiveness	Central (bronchitis), peripheral (emphysema) Destruction May or may not be present	All Minimally involved Present
Mucus secretion	Present, heavy	Present
Response to inhaled bronchodilators	Responsive; pulmonary function tests do not normalize	Quickly responsive; pulmonary function tests often normalize
Response to inhaled corticosteroids	Negative/mildly responsive in mild-to-moderate disease; modestly responsive in some with advanced disease	Responsive; improved pulmonary function tests and other outcomes

<sup>4</sup>Celli BR, et al. *Eur Respir J*. 2004;23:932-946; <sup>12</sup>Doherty DE. *Am J Med*. 2004;117(suppl 12A):11S-23S; <sup>19</sup>Doherty DE. *Federal Forum*. 2002;Nov(suppl):15-21.

whereas in asthma, eosinophils, CD4<sup>+</sup> lymphocytes, and mast cells predominate. Although the inflammatory cells are similar, the magnitude of the response is much greater in smokers who develop COPD compared with smokers who do not. This finding suggests the involvement of other risk factors.<sup>3,12</sup>

Although both COPD and asthma are characterized by an inflammatory response, the cells and their inflammatory mediators in stable COPD (IL-8, LTB<sub>4</sub>, and TNF- $\alpha$ ) are considerably different from those found in asthma (IL-4, IL-5, IL-13).<sup>3</sup> Consequently, stable COPD is poorly responsive to glucocorticosteroids, which are effective agents to control asthma. However, because mast cells, CD4<sup>+</sup> lymphocytes, and, occasionally, activated eosinophils are transiently located in lung tissue during an acute exacerbation of COPD, systemic glucocorticosteroids are often effective during an acute exacerbation.<sup>22-24</sup>

As a consequence of the different pathophysiologic mechanisms involved in COPD, several systemic physiologic abnormalities may be observed. These abnormalities include mucus hypersecretion, airway smooth muscle constriction, airflow limitation and hyperinflation (air trapping), gas exchange abnormalities, pulmonary hypertension, and osteoporosis.<sup>3,4</sup>

## Prevention

Because there is no cure for COPD, the ultimate goal is prevention of the disease—an area in which the primary care clinician plays a critical role. Patients at risk for developing COPD should be identified as early as possible and assessed using spirometry and other tests as appropriate. A management plan that addresses risk factors should be implemented. Given the tremendous importance of smoking as a risk factor for COPD and other diseases, one of the most important actions a primary care clinician can take is to begin patient education at an early age regarding the consequences of smoking, with periodic reinforcement to not start or to attempt to stop smoking.

## Applying COPD treatment guidelines to primary care practice

Once the assessment has been completed and a diagnosis of COPD established, the comprehensive management plan includes 3 components: (1) reduce risk factors, (2) manage stable disease, and (3) manage exacerbations. To be successful, all of these components require that the patient understands the nature of COPD and is motivated and involved in his or her own care. Consequently, patient education is a cornerstone of management and is an ongoing process.

**FIGURE**  
Stepwise therapy for COPD based on disease severity<sup>3</sup>

					<ul style="list-style-type: none"> <li>• Add long-term oxygen if chronic respiratory failure. Consider surgical treatments.</li> </ul>
					<ul style="list-style-type: none"> <li>• Add inhaled glucocorticosteroids if repeated exacerbations despite maximized bronchodilation.</li> </ul>
				<ul style="list-style-type: none"> <li>• Add regular treatment with 1 or more inhaled long-acting bronchodilators, ie, long-acting anticholinergic agent or long-acting beta<sub>2</sub>-agonist.</li> <li>• Alternatively, add oral long-acting methylxanthine.</li> </ul>	
			<ul style="list-style-type: none"> <li>• Add short-acting bronchodilator when needed.</li> </ul>		
	<ul style="list-style-type: none"> <li>• Patient should be advised to do the following:                             <ul style="list-style-type: none"> <li>- Avoid risk factors.</li> <li>- Increase activities and conditioning.</li> </ul> </li> <li>• Physician should:                             <ul style="list-style-type: none"> <li>- Administer influenza vaccine.</li> <li>- Refer patient for formal pulmonary rehabilitation.</li> </ul> </li> </ul>				
Stage of Severity	0: At Risk	I: Mild	II: Moderate	III: Severe	IV: Very Severe
Characteristic	<ul style="list-style-type: none"> <li>• Chronic symptoms</li> <li>• Exposure to risk factors</li> <li>• Normal spirometry</li> </ul>	<ul style="list-style-type: none"> <li>• FEV<sub>1</sub>*/FVC* &lt;70%</li> <li>• FEV<sub>1</sub> ≥80%</li> <li>• With or without symptoms</li> </ul>	<ul style="list-style-type: none"> <li>• FEV<sub>1</sub>/FVC &lt;70%</li> <li>• FEV<sub>1</sub> &lt;80% but ≥50%</li> <li>• With or without symptoms</li> </ul>	<ul style="list-style-type: none"> <li>• FEV<sub>1</sub>/FVC &lt;70%</li> <li>• FEV<sub>1</sub> &lt;50% but ≥30%</li> <li>• With or without symptoms</li> </ul>	<ul style="list-style-type: none"> <li>• FEV<sub>1</sub>/FVC &lt;70%</li> <li>• FEV<sub>1</sub> &lt;30% or FEV<sub>1</sub> &lt;50% predicted plus chronic respiratory failure</li> </ul>

\*FEV<sub>1</sub> and FVC values are a percentage of predicted values and are postbronchodilator measurements.

Reprinted with permission. Global Initiative for Chronic Obstructive Lung Disease (GOLD) website. Available at: <http://www.goldcopd.org/Guidelineitem.asp?I1=2&I2=1&contId=989>. Accessed July 28, 2006.

### Reducing Risk Factors

The identification, reduction, and control of risk factors are important steps toward the prevention and treatment of COPD. Although potentially difficult, preventing exposure to risk factors for COPD can dramatically reduce symptoms, analogous to avoiding triggers for asthma or migraine. It is not trivial for patients who smoke to stop this lifelong, chronic, relapsing addiction. Avoidance of environmental and occupational risk factors outside the home can be especially difficult because the patient usually has little control over them. Within the home, avoiding smoke from the burning of biomass fuels or cooking oil vapors and fumes from cleaning solutions can also be helpful.

One risk factor over which the patient has control is tobacco smoking. For smokers, the most intensive smoking intervention possible should be offered. Tobacco dependence is similar to dependence on opioids, amphetamines, and cocaine, and can be characterized by periods of relapse. As is the case with abuse of other substances, or chronic diseases such as diabetes and hypertension, smoking is a chronic condition that may require long-term treatment consisting of continuous counseling, support, or appropriate pharmacotherapy. A variety of resources are available from the US Surgeon General (<http://www.surgeongeneral.gov/tobacco>).

Influenza vaccines containing killed or live, inactivated viruses can reduce by half the incidence of serious illness and death among patients with COPD.<sup>25,26</sup> The vaccine should be administered yearly. The benefits of a pneumococcal vaccine containing 23 virulent subtypes are controversial and have not been clearly demonstrated.<sup>27</sup>

Early referral for pulmonary rehabilitation also is advised so that the patient will be in a better position to understand COPD and its comorbidities, reduce symptoms, improve quality of life, and maintain physical and emotional participation in everyday activities.<sup>3</sup> Specific benefits of pulmonary rehabilitation have been demonstrated in several large clinical trials, with some trials demonstrating a reduction in healthcare costs.<sup>28-30</sup> A comprehensive pulmonary rehabilitation program includes exercise training (during and after the 6- to 8-week formal program), nutrition counseling, and education. Patients also should be provided with tips to conserve their energy, such as doing chores early in the morning, especially during hot weather, or doing chores in short intervals rather than continuously over a period of hours. Patients also should be provided explanations of how to use their maintenance and rescue medications.

### Managing Stable Disease

Managing stable COPD involves a stepwise approach in treatment that is based on severity of disease. Unlike

asthma in which a step-up/step-down approach is useful, step-down therapy rarely plays a role in COPD because COPD is generally a stable, but progressive disease.

### Pharmacologic treatment

Besides smoking cessation and long-term oxygen therapy in patients with more severe disease, no existing medications or nonpharmacologic therapies for COPD have been shown to modify the disease. However, long-term clinical studies that may shed light on these benefits are in progress or are soon to be published. Nonetheless, pharmacologic agents are used for maintenance therapy of COPD in a stepwise fashion based on disease severity to prevent and control symptoms, improve health status, and improve exercise tolerance (**FIGURE**).<sup>3</sup>

**Bronchodilators.** The cornerstone of symptomatic treatment of COPD are bronchodilators because of their beneficial effects on expiratory flow, dyspnea, quality of life, and prevention of exacerbations (**TABLE 5**). The improvement in FEV<sub>1</sub> is generally modest, but is often accompanied by relatively larger changes in lung volume, a reduction in air trapping (if present), and a subsequent increase in inspiratory capacity.<sup>31</sup> The net result is a reduction in perceived breathlessness and an increase in exercise capacity.<sup>32-40</sup> This optimistic approach is based on COPD often being a partially reversible disease, not an irreversible process. Although bronchodilators may not always improve FEV<sub>1</sub>, they should be continued as the primary maintenance therapy, as they may diminish air trapping and reduce dyspnea.

The bronchodilator group includes anticholinergics, beta<sub>2</sub>-agonists, and methylxanthines, all of which are available in short-acting and long-acting preparations. In general, for anticholinergics and beta<sub>2</sub>-agonists, the inhalation route is preferred for maintenance therapy, whereas additional oral or intravenous medications (eg, corticosteroids, methylxanthines) may be needed during certain cases of acute exacerbations. It is critical to periodically ensure that the patient's inhaler technique is correct so that drug particles are deposited in the lungs as efficiently as possible. A variety of inhaler types are now available, including breath-activated and metered-dose inhalers (MDIs). Dry-powder inhalers (DPIs) may provide improved lung deposition, although this has not been established in patients with COPD. Nebulizers are not recommended for regular treatment because they are inefficient in delivery of medication into the lungs, relatively expensive, and require appropriate maintenance.<sup>3</sup> However, their use may be necessitated by certain medical conditions, for example, stroke, dementia, inability to use an MDI or DPI, etc.

**Anticholinergics.** The short-acting anticholinergic agent ipratropium has a duration of action (4-6 hours) that is longer than the short-acting beta<sub>2</sub>-agonists (3-4

**TABLE 5**  
**Selected characteristics of treatments used in COPD<sup>3</sup>**

	Short-Acting Beta <sub>2</sub> -Agonists	Ipratropium Bromide	Long-Acting Beta <sub>2</sub> -Agonists	Tiotropium	Inhaled Glucocorticosteroids	Theophylline
FEV <sub>1</sub>	Yes (A)	Yes (A)	Yes (A)	Yes (A)	No	Yes (A)
Lung volume	Yes (B)	Yes (B)	Yes (A)	Yes (A)	NA	Yes (B)
Dyspnea	Yes (A)	Yes (A)	Yes (A)	Yes (A)	Yes (B)	Yes (A)
HRQOL	NA	No (B)	Yes (A)	Yes (A)	Yes (A)	Yes (B)
Exercise capacity	Yes (A)	Yes (A)	Yes (A)	Yes (A)	NA	Yes (A)
Side effects	Some	Some	Minimal	Minimal	Some	Significant
Duration of action (h)	4-6 (A)	6-8 (A)	>12 (A)	>24 (A)	—	≤24*

Letters in parentheses represent the level of evidence as defined by GOLD 2005.<sup>3</sup> A, randomized controlled trials, rich body of data; B, randomized controlled trials, limited body of data.

\*No level of evidence cited.

FEV<sub>1</sub>, forced expiratory volume in 1 second; HRQOL, health-related quality of life; NA, not applicable.

<sup>3</sup>Global Initiative for Chronic Obstructive Lung Disease (GOLD) website. Available at: <http://www.goldcopd.org/Guidelineitem.asp?l1=2&l2=1&intId=989>. Accessed July 28, 2006.

hours),<sup>41</sup> but improves health status less than long-acting beta<sub>2</sub>-agonists<sup>42</sup> and the long-acting anticholinergic tiotropium.<sup>32,36,40,43</sup> Tiotropium improves dyspnea, increases inspiratory capacity (by reducing air trapping), improves exercise capacity, and reduces exacerbations and hospitalizations compared with placebo.<sup>32,36,37,44</sup> In a study comparing salmeterol (50 mcg twice daily) with tiotropium (18 mcg once daily), tiotropium was shown to cause significantly greater increases in FEV<sub>1</sub> and FVC 12 hours postdose after 12 weeks of treatment.<sup>45</sup> Another study found that after 6 weeks of treatment, tiotropium (18 mcg once daily) caused a significantly greater increase in average daytime FEV<sub>1</sub> compared with formoterol (12 mcg twice daily); no difference was found in average nighttime FEV<sub>1</sub>.<sup>46</sup>

**Beta<sub>2</sub>-agonists.** Short-acting beta<sub>2</sub>-agonists (eg, albuterol, terbutaline) are used primarily for rescue or the acute management of breathlessness since they have a relatively rapid onset but a short duration of action that requires frequent daily dosing. Some studies have shown that long-acting inhaled beta<sub>2</sub>-agonists (eg, formoterol, salmeterol) reduce symptoms and use of rescue medication and increase the time between exacerbations compared with placebo.<sup>34,42,47-49</sup>

The methylxanthine theophylline is effective in COPD, but is used less often than inhaled bronchodilators because of the potential for toxicity, given its narrow therapeutic index.<sup>3</sup> The selection of one bronchodilator over another generally rests with the prescribing clinician based on an assessment of individual response, cost, and medication adherence. It is recommended that an inhaled short-acting beta<sub>2</sub>-agonist or a combination inhaler containing both a short-acting beta<sub>2</sub>-agonist and a short-acting anticholinergic be prescribed for all COPD patients for rescue or the acute management of breathlessness.

Bronchodilators are generally well tolerated, with adverse effects only occasionally causing discontinuation. The adverse effects of the beta<sub>2</sub>-agonists are primarily related to stimulation of the beta<sub>2</sub> receptor, with tremor and sinus tachycardia the most troublesome, especially among older patients treated with higher doses.<sup>3</sup> Unlike short-acting beta<sub>2</sub>-agonists, long-acting beta<sub>2</sub>-agonists have not been associated with an accelerated loss of lung function (desensitization). Whereas black box warnings in the prescribing information for long-acting beta<sub>2</sub>-agonists have been issued by the US Food and Drug Administration (FDA) regarding their use as monotherapy in asthma,<sup>50</sup> no studies have definitively shown that long-acting beta<sub>2</sub>-agonists lead to an increased mortality in COPD.<sup>3</sup> The inhaled anticholinergic agents ipratropium and tiotropium are safe, primarily due to a potent local effect in the lung and poor systemic absorption. The primary adverse effect is dry mouth. Theophylline causes a variety of adverse effects due to its nonspecific inhibition of phosphodiesterase. Arrhythmias and grand mal seizures are among the most serious, but occur infrequently. More common adverse effects include headache, insomnia, nausea, and heartburn, which may occur within the therapeutic range of serum theophylline.

Combining 2 bronchodilators with different mechanisms of action generally provides for improved symptom control with reduced side effects.<sup>41,49,51-53</sup> For this reason, patients achieving some but inadequate benefit or dose-limiting adverse effects with 1 bronchodilator should be treated with 2 bronchodilators with different mechanisms of action,<sup>3,4</sup> preferably a beta<sub>2</sub>-agonist and an anticholinergic. Although the cost of medication is higher than for short-acting bronchodilators, long-acting bronchodilators may be preferable because of their need for less frequent dosing and a decreased need for rescue therapy, which should improve medication adherence.

One study showed that the benefits of tiotropium and pulmonary rehabilitation were additive when used in combination, and these positive effects were sustained for 3 months after completion of pulmonary rehabilitation.<sup>54</sup> Compared with pulmonary rehabilitation alone, combined treatment improved dyspnea, endurance of a constant work treadmill task, and health status.

**Glucocorticosteroids.** The benefits of glucocorticosteroids in COPD are much less significant than in asthma. Oral glucocorticosteroids play a minimal role in the maintenance management of stable COPD. Evolving evidence refutes an earlier report suggesting that short-term use of an oral glucocorticosteroid identifies patients who might benefit from long-term treatment with an oral or inhaled glucocorticosteroid. Long-term use of an oral glucocorticosteroid is not recommended in stable COPD because of a lack of evidence of benefit and its well-known adverse effects.<sup>3,4,7</sup>

Regular treatment with an inhaled glucocorticosteroid alone has not been conclusively shown to improve outcomes in mild-to-moderate COPD.<sup>3,4,6,7</sup> No inhaled glucocorticosteroid as a single agent has been approved for use in COPD by the FDA. However, in patients with severe or very severe disease who remain symptomatic and have repeated exacerbations despite maximal bronchodilation (using inhaled anticholinergics or beta<sub>2</sub>-agonists), the addition of an inhaled glucocorticosteroid to maximal bronchodilator therapy is appropriate. The combined use of an inhaled glucocorticosteroid and a long-acting beta<sub>2</sub>-agonist is more effective than individual agents in reducing the frequency of exacerbations and improving health status.<sup>55-58</sup> When the benefits of an inhaled glucocorticosteroid are uncertain, a trial of withdrawing treatment is reasonable. In those patients who subsequently experience an exacerbation, reinstatement of treatment with the inhaled glucocorticosteroid is appropriate.<sup>3,4</sup> Only 1 formulation containing an inhaled corticosteroid has been approved for use in COPD by the FDA (250 mcg fluticasone/50 mcg salmeterol; Advair™ Diskus®), although other formulations are often used off-label. The long-term safety of inhaled glucocorticosteroids in COPD has not been established.

**Other therapies.** The role of prophylactic, continuous antibiotic therapy has been investigated extensively and shown to have no effect on the frequency of exacerbations in COPD.<sup>20,59,60</sup> Antibiotics are, therefore, not recommended except for treating exacerbations of COPD and other bacterial infections.<sup>3</sup>

The evidence regarding the benefits of mucolytics in COPD is inconsistent,<sup>61,62</sup> although a meta-analysis indicates that a mucolytic significantly reduced the number of episodes of chronic bronchitis compared with placebo.<sup>63</sup> Nonetheless, mucolytics should probably be considered only in patients with viscous sputum.<sup>3</sup>

Because progression of COPD often leads to psychological complications, for example, anxiety and depression and feelings of isolation, pulmonary rehabilitation is often helpful in relieving these symptoms by increasing exercise capacity.

Oral and parenteral opioids appear to provide some relief from dyspnea in COPD, although adverse effects may be troublesome. Nedocromil, leukotriene modifiers, and complementary and alternative medicine therapies have not been adequately investigated, but existing studies do not show any efficacy for these medications in the management of COPD. Antitussive agents and the vasodilator nitric oxide are contraindicated in COPD.<sup>3</sup>

## Summary

COPD is a slowly progressive disease that is commonly caused by tobacco smoking. However, the disease is partially reversible, especially if diagnosed early. In its early stage, the signs and symptoms of COPD are easily overlooked, in part because the patient often makes small adjustments in physical functioning to perform activities that do not lead to dyspnea, which is the symptom that most often brings the COPD patient to seek medical care. Because lung damage will progress without intervention, it is essential that patients with early-stage COPD be identified using spirometry so that effective treatment can be initiated.

Patients with stable COPD are best managed with a stepwise increase in therapy based on disease severity as evidenced by FEV<sub>1</sub>. Smoking cessation is the single most important treatment objective. Pharmacologic management of acute dyspnea in mild COPD includes a short-acting bronchodilator alone. For moderate-to-severe COPD, a short-acting bronchodilator is coupled with 1 or more regularly scheduled long-acting bronchodilators (beta<sub>2</sub>-agonist or anticholinergic). A long-acting bronchodilator—for example, formoterol, salmeterol, or tiotropium—may be preferred to a short-acting beta<sub>2</sub>-agonist or ipratropium for maintenance therapy because of increased efficacy and safety, as well as patient convenience and adherence with the long-acting bronchodilators. Theophylline is an option, but it is less desirable because of its narrow therapeutic range. Glucocorticosteroids play a minimal role in stable mild and moderate COPD, although they may be helpful in severe or very severe disease when the patient remains symptomatic and continues to have exacerbations despite maximized bronchodilator therapy.

## REFERENCES

- Centers for Disease Control and Prevention website. Chronic obstructive pulmonary disease. Available at: <http://www.cdc.gov/nceh/airpollution/copd/copdfaq.htm>. Accessed August 1, 2006.
- National Lung Health Education Program website. Frequently asked questions. Available at: <http://www.nlhep.org/faqs.html>. Accessed August 1, 2006.
- Global Initiative for Chronic Obstructive Lung Disease (GOLD) website. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Available at: <http://www.goldcopd.org/Guidelineitem.asp?1=2&l2=1&clntld=989>. Accessed July 28, 2006.

4. Celli BR, MacNee W. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. *Eur Respir J*. 2004;23:932-946.
5. Ferguson GT, Enright PL, Buist AS, Higgins MW. Office spirometry for lung health assessment in adults: A consensus statement from the National Lung Health Education Program. *Chest*. 2000;117:1146-1161.
6. The National Institute for Clinical Excellence. British Thoracic Society COPD Consortium. NICE COPD Guidelines 2004. Available at: [http://www.brit-thoracic.org.uk/copd/latest\\_frameset\\_nice.html](http://www.brit-thoracic.org.uk/copd/latest_frameset_nice.html). Accessed May 3, 2006.
7. O'Donnell DE, Aaron S, Bourbeau J, et al. Canadian Thoracic Society recommendations for management of chronic obstructive pulmonary disease--2003. *Can Respir J*. 2003;10(suppl A):11A-65A.
8. National Center for Health Statistics website. National vital statistics reports. Deaths. Final data for 2003. Available at: [http://www.cdc.gov/nchs/data/nvsr/nvsr54/nvsr54\\_13.pdf](http://www.cdc.gov/nchs/data/nvsr/nvsr54/nvsr54_13.pdf). Accessed August 1, 2006.
9. Mannino DM. Chronic obstructive pulmonary disease: definition and epidemiology. *Respir Care*. 2003;48:1185-1191.
10. Anto JM, Vermeire P, Vestbo J, Sunyer J. Epidemiology of chronic obstructive pulmonary disease. *Eur Respir J*. 2001;17:982-994.
11. The National COPD Awareness Panel. Guidelines for early detection and management of COPD. *J Respir Dis*. 2000;21(suppl):S5-S21.
12. Doherty DE. The pathophysiology of airway dysfunction. *Am J Med*. 2004;117(suppl 12A):11S-23S.
13. Lange P, Parner J, Vestbo J, Schnohr P, Jensen G. A 15-year follow-up study of ventilatory function in adults with asthma. *N Engl J Med*. 1998;339:1194-1200.
14. Peat JK, Woolcock AJ, Cullen K. Rate of decline of lung function in subjects with asthma. *Eur J Respir Dis*. 1987;70:171-179.
15. National Collaborating Centre for Chronic Conditions. Chronic obstructive pulmonary disease. National clinical guideline on management of chronic obstructive pulmonary disease in adults in primary and secondary care. *Thorax*. 2004;59(suppl 1):1-232.
16. Doherty DE. Early detection and management of COPD. What you can do to reduce the impact of this disabling disease. *Postgrad Med*. 2002;111:41-50, 53.
17. Ahluwalia JS, Gibson CA, Kenney RE, Wallace DD, Resnicow K. Smoking status as a vital sign. *J Gen Intern Med*. 1999;14:402-408.
18. Fiore MC, Jorenby DE, Schensky AE, Smith SS, Bauer RR, Baker TB. Smoking status as the new vital sign: effect on assessment and intervention in patients who smoke. *Mayo Clin Proc*. 1995;70:209-213.
19. Doherty DE. COPD: an approach for primary care prevention. *Federal Forum*. 2002;Nov(suppl):15-21.
20. Fletcher CM, Elmes PC, Wood CH. The significance of respiratory symptoms and the diagnosis of chronic bronchitis in a working population. *BMJ*. 1959;2:257-266.
21. Celli BR, Cote CG, Marin JM, et al. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. *N Engl J Med*. 2004;350:1005-1012.
22. Aaron SD, Vandemheen KL, Hebert P, et al. Outpatient oral prednisone after emergency treatment of chronic obstructive pulmonary disease. *N Engl J Med*. 2003;348:2618-2625.
23. Sayiner A, Aytumur ZA, Cirit M, Unsal I. Systemic glucocorticoids in severe exacerbations of COPD. *Chest*. 2001;119:726-730.
24. Niewoehner DE, Erbland ML, Deupree RH, et al. Effect of systemic glucocorticoids on exacerbations of chronic obstructive pulmonary disease. Department of Veterans Affairs Cooperative Study Group. *N Engl J Med*. 1999;340:1941-1947.
25. Nichol KL, Margolis KL, Wuorenma J, Von Sternberg T. The efficacy and cost effectiveness of vaccination against influenza among elderly persons living in the community. *N Engl J Med*. 1994;331:778-784.
26. Hak E, van Essen GA, Buskens E, Stalman W, de Melker RA. Is immunising all patients with chronic lung disease in the community against influenza cost effective? Evidence from a general practice based clinical prospective cohort study in Utrecht, The Netherlands. *J Epidemiol Community Health*. 1998;52:120-125.
27. Simberkoff MS, Cross AP, Al Ibrahim M, et al. Efficacy of pneumococcal vaccine in high-risk patients. Results of a Veterans Administration Cooperative Study. *N Engl J Med*. 1986;315:1318-1327.
28. California Pulmonary Rehabilitation Collaborative Group. Effects of pulmonary rehabilitation on dyspnea, quality of life, and healthcare costs in California. *J Cardiopulm Rehabil*. 2004;24:52-62.
29. Goldstein RS, Gort EH, Guyatt GH, Feeny D. Economic analysis of respiratory rehabilitation. *Chest*. 1997;112:370-379.
30. Verrill D, Barton C, Beasley W, Lippard WM. The effects of short-term and long-term pulmonary rehabilitation on functional capacity, perceived dyspnea, and quality of life. *Chest*. 2005;128:673-683.
31. Celli B, ZuWallack R, Wang S, Kesten S. Improvement in resting inspiratory capacity and hyperinflation with tiotropium in COPD patients with increased static lung volumes. *Chest*. 2003;124:1743-1748.
32. Casaburi R, Mahler DA, Jones PW, et al. A long-term evaluation of once-daily inhaled tiotropium in chronic obstructive pulmonary disease. *Eur Respir J*. 2002;19:217-224.
33. Mahler DA. The effect of inhaled beta<sub>2</sub>-agonists on clinical outcomes in chronic obstructive pulmonary disease. *J Allergy Clin Immunol*. 2002;110(suppl):S298-S303.
34. Mahler DA, Donohue JF, Barbee RA, et al. Efficacy of salmeterol xinafoate in the treatment of COPD. *Chest*. 1999;115:957-965.
35. Oostenbrink JB, Rutten-van Molken MP, Al MJ, van Noord JA, Vincken W. One-year cost-effectiveness of tiotropium versus ipratropium to treat chronic obstructive pulmonary disease. *Eur Respir J*. 2004;23:241-249.
36. Maltais F, Hamilton A, Marciniuk D, et al. Improvements in symptom-limited exercise performance over 8 h with once-daily tiotropium in patients with COPD. *Chest*. 2005;128:1168-1178.
37. O'Donnell DE, Fluge T, Gerken F, et al. Effects of tiotropium on lung hyperinflation, dyspnea and exercise tolerance in COPD. *Eur Respir J*. 2004;23:832-840.
38. O'Donnell DE, Voduc N, Fitzpatrick M, Webb KA. Effect of salmeterol on the ventilatory response to exercise in chronic obstructive pulmonary disease. *Eur Respir J*. 2004;24:86-94.
39. Murciano D, Auclair MH, Pariente R, Aubier M. A randomized, controlled trial of theophylline in patients with severe chronic obstructive pulmonary disease. *N Engl J Med*. 1989;320:1521-1525.
40. van Noord JA, Bantje TA, Eland ME, Korducki L, Cornelissen PJ. A randomised controlled comparison of tiotropium and ipratropium in the treatment of chronic obstructive pulmonary disease. The Dutch Tiotropium Study Group. *Thorax*. 2000;55:289-294.
41. COMBIVENT Inhalation Aerosol Study Group. In chronic obstructive pulmonary disease, a combination of ipratropium and albuterol is more effective than either agent alone. An 85-day multicenter trial. *Chest*. 1994;105:1411-1419.
42. Dahl R, Greefhorst LA, Nowak D, et al. Inhaled formoterol dry powder versus ipratropium bromide in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2001;164:778-784.
43. Vincken W, van Noord JA, Greefhorst AP, et al. Improved health outcomes in patients with COPD during 1 yr's treatment with tiotropium. *Eur Respir J*. 2002;19:209-216.
44. Niewoehner DE, Rice K, Cote C, et al. Prevention of exacerbations of chronic obstructive pulmonary disease with tiotropium, a once-daily inhaled anticholinergic bronchodilator: a randomized trial. *Ann Intern Med*. 2005;143:317-326.
45. Briggs DD Jr, Covelli H, Lapidus R, Bhattacharya S, Kesten S, Cassino C. Improved daytime spirometric efficacy of tiotropium compared with salmeterol in patients with COPD. *Pulm Pharmacol Ther*. 2005;18:397-404.
46. van Noord JA, Aumann JL, Janssens E, et al. Comparison of tiotropium once daily, formoterol twice daily and both combined once daily in patients with COPD. *Eur Respir J*. 2005;26:214-222.
47. Rossi A, Kristufek P, Levine BE, et al. Comparison of the efficacy, tolerability, and safety of formoterol dry powder and oral, slow-release theophylline in the treatment of COPD. *Chest*. 2002;121:1058-1069.
48. Jones PW, Bosh TK. Quality of life changes in COPD patients treated with salmeterol. *Am J Respir Crit Care Med*. 1997;155:1283-1289.
49. van Noord JA, de Munck DR, Bantje TA, Hop WC, Akveld ML, Bommer AM. Long-term treatment of chronic obstructive pulmonary disease with salmeterol and the additive effect of ipratropium. *Eur Respir J*. 2000;15:878-885.
50. US Food and Drug Administration website. FDA Public Health Advisory. Serevent Diskus (salmeterol xinafoate inhalation powder), Advair Diskus (fluticasone propionate & salmeterol xinafoate powder), Foradil Aerolizer (formoterol fumarate inhalation powder). Available at: <http://www.fda.gov/cder/drug/advisory/labam.htm>. Accessed January 20, 2006.
51. COMBIVENT Inhalation Solution Study Group. Routine nebulized ipratropium and albuterol together are better than either alone in COPD. *Chest*. 1997;112:1514-1521.
52. ZuWallack RL, Mahler DA, Reilly D, et al. Salmeterol plus theophylline combination therapy in the treatment of COPD. *Chest*. 2001;119:1661-1670.
53. Gross N, Tashkin D, Miller R, Oren J, Coleman W, Linberg S. Inhalation by nebulization of albuterol-ipratropium combination (Dey combination) is superior to either agent alone in the treatment of chronic obstructive pulmonary disease. Dey Combination Solution Study Group. *Respiration*. 1998;65:354-362.
54. Casaburi R, Kukafka D, Cooper CB, Witek TJ Jr, Kesten S. Improvement in exercise tolerance with the combination of tiotropium and pulmonary rehabilitation in patients with COPD. *Chest*. 2005;127:809-817.
55. Calverley P, Pauwels R, Vestbo J, et al. Combined salmeterol and fluticasone in the treatment of chronic obstructive pulmonary disease: a randomised controlled trial. *Lancet*. 2003;361:449-456.
56. Mahler DA, Wire P, Horstman D, et al. Effectiveness of fluticasone propionate and salmeterol combination delivered via the Diskus device in the treatment of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2002;166:1084-1091.
57. Szafranski W, Cukier A, Ramirez A, et al. Efficacy and safety of budesonide/formoterol in the management of chronic obstructive pulmonary disease. *Eur Respir J*. 2003;21:74-81.
58. Spencer S, Calverley PM, Burge PS, Jones PW. Impact of preventing exacerbations on deterioration of health status in COPD. *Eur Respir J*. 2004;23:698-702.
59. Francis RS, May JR, Spicer CC. Chemotherapy of bronchitis. Influence of penicillin and tetracycline administered daily, or intermittently for exacerbations. A report to the Research Committee of the British Tuberculosis Association by its Bronchitis Subcommittee. *Br Med J*. 1961;2:979-985.
60. Francis RS, Spicer CC. Chemotherapy in chronic bronchitis. Influence of daily penicillin and tetracycline on exacerbations and their cost. *Br Med J*. 1960;1:297-303.
61. Petty TL. The National Mucolytic Study. Results of a randomized, double-blind, placebo-controlled study of iodinated glycerol in chronic obstructive bronchitis. *Chest*. 1990;97:75-83.
62. Guyatt GH, Townsend M, Kazim F, Newhouse MT. A controlled trial of ambroxol in chronic bronchitis. *Chest*. 1987;92:618-620.
63. Poole P, Black P. Mucolytic agents for chronic bronchitis or chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*. 2006;3:CD001287.