Considerations in the Management of Chronic Obstructive Pulmonary Disease

- Impact of Symptoms on Activities of Daily Living and Quality of Life
- Is It a Systemic Disorder?
- Bronchodilators and Reversibility of Airflow Obstruction
- Treatment Options: Current Recommendations and Recent Findings

MATTHEW L. MINTZ, MD
NICOLA A. HANANIA, MD, MS
DONALD P. TASHKIN, MD
BARBARA P. YAWN, MD, MSc, FAAFP

Funding for this supplement was provided by AstraZeneca LP.
Introduction

Considerations in the Management of Chronic Obstructive Pulmonary Disease
MATTHEW L. MINTZ, MD
George Washington University

Chronic obstructive pulmonary disease (COPD) is a progressive disease with devastating consequences, surpassing stroke as the third leading cause of death in 2008. COPD is estimated to affect 24 million adults in the United States, imparting substantial burden to the patient and to society. Historically, there has been a nihilistic approach to COPD management, but the current Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines define COPD as a “preventable and treatable disease.”

The present understanding of COPD has extended well beyond the perception of COPD patients as “pink puffers” or “blue bloaters.” Although disease pathophysiology still is not understood completely, COPD is characterized by airflow obstruction that is not fully reversible, with disease development and progression associated with chronic inflammation and structural changes in the airways. Progress has been made and research is ongoing to better characterize the disease and improve our current understanding of the factors that contribute to individual differences and variability in COPD. In that regard, research efforts are focused on identifying specific COPD phenotypes that would allow for optimizing treatment and moving beyond a “one drug treats all” approach to COPD management. Despite our current understanding of COPD, misunderstandings persist in certain areas. For example, the concept of bronchodilator reversibility in COPD is poorly understood and often confused with disease reversibility. Contrary to evidence from clinical studies, it is commonly thought that patients with COPD do not exhibit a significant bronchodilator response, which may contribute to confusion in differentiating between asthma and COPD and hinder appropriate disease management.

Despite the lack of major advances recently in novel COPD treatments, many effective pharmacologic and non-pharmacologic treatments are available that can improve COPD symptoms and pulmonary function, reduce exacerbations, and improve quality of life. However, considering the prominent systemic inflammatory component of COPD, novel pharmacologic agents that reduce systemic inflammation are needed. Novel treatments that have the ability to modify disease progression also are needed. Patients with COPD commonly suffer from comorbidities, including arthritis, hypertension, diabetes mellitus, cardiac disorders, lipid disorders, psychiatric conditions, gastrointestinal diseases, cancer, and osteoporosis. Thus, to optimize treatment, COPD management programs should consider the “whole patient” and treat coexisting morbidities that often complicate COPD management.

Primary care physicians are the primary point of contact for many patients with COPD. Therefore, they play a critical role in disease prevention and should encourage smoking cessation in all of their patients who smoke. With the exception of smoking cessation, currently available treatments do not reduce the decline in lung function seen in COPD patients. Thus, timely COPD diagnosis is critical for initiating appropriate treatment as early as possible to minimize the effects of the disease on the patient’s quality of life and daily functioning. In this collection of articles, information surrounding the impact of COPD on the patient is reviewed, in particular with respect to effects on daily activities of living and quality of life. We also discuss the comorbidities commonly experienced by patients with COPD that could contribute to disease severity and complicate disease management, the misconceptions and evidence surrounding bronchodilator reversibility and airflow obstruction in COPD, and current and emerging treatment options in COPD.

REFERENCES:

Dr Mintz is associate professor of medicine, George Washington University School of Medicine, Washington, DC.
**ABSTRACT:** The burden of chronic obstructive pulmonary disease (COPD) to patients and society is substantial. As the disease progresses, activities of daily living—from the most basic of tasks to more involved activities—are limited, and quality of life is diminished. Dyspnea, the most burdensome symptom of COPD, worsens over time, reducing exercise tolerance, which further limits daily activities and reduces health status. Due to the progressive nature of COPD, patients may be unaware of the extent of their disability or unable to recognize worsening of symptoms. Therefore, it is important for primary care physicians to evaluate patients for respiratory symptoms and ability to perform activities of daily living and to educate their patients on the disease and associated risk factors. As the first point of contact for most patients with COPD, primary care physicians play a critical role in diagnosing COPD as early as possible and initiating appropriate therapy, thereby alleviating the detrimental clinical consequences of COPD and its symptoms.

Chronic obstructive pulmonary disease (COPD) has replaced cerebrovascular diseases as the third-leading cause of death in the United States. An estimated 12 million adults have a physician diagnosis of COPD, and 12 million more are estimated to have undiagnosed COPD. The clinical and economic burden of the disease is substantial. In 2006 alone, there were 672,000 hospitalizations due to COPD in the United States. In developed countries, exacerbations of COPD represent the greatest burden on the health care system. The National Heart, Lung, and Blood Institute projected the total cost of COPD to be $49.9 billion in the United States in 2010.

The pathophysiology of COPD is not completely understood, but it is characterized by airflow obstruction that is not fully reversible, chronic inflammation, and structural changes in the airways. In patients who develop COPD, cigarette smoke or other noxious particles cause an exaggerated inflammatory response that is associated with a specific pattern of increase in inflammatory cell types in different parts of the lung. The pathogenesis of COPD is further worsened by an increase in oxidative stress and proteinase activity, which leads to the breakdown of connective tissue such as elastin. In the lungs of patients with COPD, the airways lose their elasticity and many of the walls between the alveoli are destroyed, leading to tissue destruction and gas exchange abnormalities characteristic of emphysema. The airway walls also become thicker and inflamed, and mucus hypersecretion occurs in some patients (Figure 1), clogging the bronchioles and leading to a chronic productive cough characteristic of chronic bronchitis. These pathological changes are coupled with a gradual worsening of COPD symptoms and disease.
severity with increasing impact on patients’ daily lives.3

CHARACTERISTIC FEATURES OF COPD AND DISEASE PROGRESSION

The burden of COPD on an individual is dependent on the degree of airflow limitation and the severity of symptoms, including dyspnea, sputum production, wheezing, and chest tightness.3 Acute exacerbation, which is generally defined as an increase in COPD symptoms (eg, dyspnea, cough, and/or sputum) that is beyond the normal day-to-day variation,2 results in greater disease burden for the patient1 and may contribute to more rapid progression of COPD.6-9

Dyspnea is the most common reason patients with COPD seek medical care.3,10 It occurs as a result of lung hyperinflation, which reduces inspiratory capacity and increases functional residual capacity, making it more difficult for patients to move air in and out of the lungs, particularly during exercise.3,11 Hyperinflation, which occurs as a result of air trapping during expiration, can develop early in COPD.3 Early in the disease, patients generally experience dyspnea only during unusual exertion.3 As COPD and airflow limitation progress, patients experience dyspnea with minimal effort; eventually, it is present during everyday activities or even during rest.3

The gradual progressive and chronic nature of the symptoms of COPD may lead to a diminished ability of patients to recognize the effects of COPD on their daily functioning. In a recent survey (“Confronting COPD in America”) of 573 patients with COPD, many of those with substantial functional impairment, determined by scores from the validated Medical Research Council (MRC) dyspnea scale,12 did not recognize their condition as severe.13 In fact, 36% of patients with the most severe grade of dyspnea (score of 5) described their condition as “mild” or “moderate.”13 Similarly, in a telephone survey of 3265 patients with COPD in North America and Europe, 60% and 36% of patients with the second most severe (score of 4) and the most severe (score of 5) grade of dyspnea, respectively, based on the MRC dyspnea scale reported their condition as “mild” or “moderate.”14 This diminished ability of patients to recognize the severity of their condition may lead to a delay in seeking treatment and a greater impact of the disease.

IMPACT OF COPD SYMPTOMS ON ACTIVITIES OF DAILY LIVING AND QUALITY OF LIFE

The importance of recognizing and treating worsening of COPD symptoms is underscored by the negative impact of these symptoms on patients’ basic activities of daily living.
living and quality of life. Most patients included in the “Confronting COPD in America” survey reported that COPD limits what they can do “some or a lot” in normal physical exertion (70%), lifestyle (58%), household chores (56%), social activities (53%), and sleeping (50%).

Although more than half of the patients surveyed were retired, 51% of patients also reported that COPD limits their ability to work, with 34% reporting that COPD keeps them from working and 17% stating that COPD limits the amount or kind of work they can perform.

In a telephone survey of patients with COPD in North America and Europe, 36% of respondents reported that their COPD kept them from working, limited their ability to work, or caused them working time loss in the past year. In addition, functional limitations in sports and recreation, social activities, household chores, sex life, and family activities due to COPD were reported by significantly fewer middle-aged patients compared with older patients (aged ≥ 65 years). However, limitations in normal physical exertion were reported by significantly fewer middle-aged patients compared with older patients (56% versus 62%, P < .05).

Evidence suggests that patients particularly are affected by their COPD symptoms during the morning hours. Findings from a quantitative Internet interview of 803 patients with COPD showed that morning was most commonly reported (37%) as the time of day when COPD symptoms were worse than usual. When limiting respondents to those with severe COPD, this percentage was even higher (46%). In particular, patients’ morning activities that were most affected by COPD included walking up and down stairs, putting on shoes and socks, making the bed, showering and bathing, drying the body with a towel, and dressing.

Similar findings were observed in a study of 2441 patients with COPD. Patients reported that all of their COPD symptoms (breathlessness, phlegm, coughing, wheezing, and chest tightness) were most troublesome upon waking up in the morning. The morning activities most affected by COPD symptoms were washing, dressing, drying, and getting out of bed, while the daily activities most affected were going up and down stairs, doing heavy household chores, going shopping, and doing sports or hobbies (Figure 2). In addition, 13% of the patients reported that they needed assistance to perform their daily activities, and a majority of those patients believed that they were a burden to others for this reason.

Dyspnea also showed a strong association with poorer health status in a recent meta-analysis of 66 studies in patients with COPD. In that analysis, other COPD symptoms, including sputum production, chronic cough, wheezing, and fatigue, also were associated with poorer health status. These findings are particularly important, as health status has been recognized as a major factor affecting patients’ quality of life.

Taken together, these data suggest that COPD has a substantial negative impact on patients’ daily functioning, from the most minor of daily tasks to more involved activities, and that it results in substantial decrements to patients’ health status. These effects in turn lead to poorer quality of life in patients with COPD.

### EFFECT OF COPD SYMPTOMS ON EXERCISE TOLERANCE

Exertional dyspnea occurs in patients with COPD as a result of dynamic hyperinflation, which involves an increase in air trapping in the lungs during exercise. This phenomenon contributes substantially to exercise intolerance in patients with COPD. Patients with COPD often experience a downward spiral of reduced ability to exercise and physical
deconditioning and fatigue, leading to further reduction in exercise tolerance and increasing disability.\textsuperscript{18,19}

Findings from a study in elderly patients with COPD (n = 50) and healthy elderly subjects (n = 25) showed that patients with COPD are considerably less active than their healthy counterparts.\textsuperscript{20} They spent a smaller percentage of time during the day walking or standing and a greater percentage of time in the sitting or lying position compared with healthy subjects (Figure 3).\textsuperscript{20} In addition, patients with COPD experienced significantly ($P < .0001$) reduced movement intensity (1.8 m/s$^2$) during walking compared with healthy subjects (2.4 m/s$^2$).\textsuperscript{20} In that study, activity level (walking and standing time) was positively correlated with exercise capacity (based on 6-minute walking distance) in patients with COPD.\textsuperscript{20}

Diminished exercise capacity is a strong indicator of health status impairment\textsuperscript{1,21} and poorer prognosis.\textsuperscript{3} In addition, in a study in 452 patients with COPD, increased disability as measured by the Valued Life Activities scale was associated with onset of depression, assessed using the Geriatric Depression Scale Short Form.\textsuperscript{22} Taken together, these findings highlight the substantial limitations to exercise capacity experienced by patients with COPD and the detrimental clinical consequences of such disability.\textsuperscript{22}

**EFFECT OF COPD SEVERITY ON EXERCISE TOLERANCE AND DAILY ACTIVITIES**

Exercise tolerance and ability to perform daily activities generally worsen as COPD progresses.\textsuperscript{3,12,19,23} As COPD severity increases, patients lose muscle bulk and experience diminished exercise endurance.\textsuperscript{19} This decrement is most noticeable in patients at Global Initiative for Chronic Obstructive Lung Disease (GOLD) stages II (moderate: forced expiratory volume in 1 second [FEV\textsubscript{1}] % predicted 50% to < 80%), III (severe: FEV\textsubscript{1} % predicted 30% to < 50%), and IV (very severe: FEV\textsubscript{1} % predicted < 30% or < 50% plus chronic respiratory failure).\textsuperscript{3} Findings from a study of 100 patients with COPD showed that as patients’ disability (measured using the MRC scale) increases, there is a progressive and significant ($P < .0001$) decline in exercise tolerance (based on shuttle walking distance) and diminished ability to perform daily activities (assessed using the Nottingham Extended Activities of Daily Living scale).\textsuperscript{22}

The effect of COPD disease severity on daily activities and health status was assessed in 2 cross-sectional studies of 1596 patients with moderate COPD and 2012 patients with severe or very severe COPD.\textsuperscript{23} Patients’ ability to perform activities of daily living (assessed using the London Chest Activity of Daily Living), including self-care, household chores, physical activity, and leisure activity, was significantly ($P < .0001$) diminished in patients with severe or very severe COPD compared with patients with moderate COPD.\textsuperscript{23} Approximately two-thirds of patients with severe or very severe COPD versus one-third of patients with moderate COPD reported that their disease affected them “much” in their daily lives.\textsuperscript{23} In addition, patients with severe or very severe COPD had significantly ($P < .0001$) worse health status, based on the EuroQol-5D visual analogue scale, than patients with moderate COPD.\textsuperscript{23} These findings show that the effects of COPD on patients’ ability to perform daily activities and health status worsen with increasing severity of the disease and highlight the need for initiating appropriate COPD therapy as early as possible in the disease process to minimize the negative impact on patients’ daily lives.

**ROLE OF PRIMARY CARE PHYSICIANS**

As the primary point of contact for many patients with COPD,\textsuperscript{24} primary care physicians play an important role in COPD prevention, early diagnosis, and appropriate management. Physicians should encourage smoking cessation in patients with or without a diagnosis of COPD, as smoking is a key factor in the development and progression of COPD.\textsuperscript{3} Educating patients about other inha-
lational exposures that increase the risk of COPD, including dust and chemicals or air pollution, also is important.3

The GOLD guidelines recommend that a diagnosis of COPD, which is confirmed using spirometry (postbronchodilator FEV₁/forced vital capacity [FVC] ratio of < 0.70), should be considered in patients with symptoms of COPD (eg, dyspnea, chronic cough, or sputum production) and/or exposure to risk factors for the disease.3 Recent COPD guidelines issued by the American College of Physicians, American College of Chest Physicians, American Thoracic Society, and European Respiratory Society recommend against using spirometry for COPD screening in patients who do not have respiratory symptoms.25 However, if patients have symptoms of COPD but do not recognize them, they would fail to meet criteria for spirometry screening,25 which may lead to a delay in diagnosis. Given the substantial burden of the disease and the benefits of early intervention, early screening of COPD using alternative or less expensive tools may be beneficial.

The Lung Function Questionnaire (LFQ) recently was developed as a tool to aid in COPD screening.26 The LFQ is a 5-item self-administered questionnaire, where a total score of ≤ 18 suggests an increased risk of airflow obstruction.26 In a study of 1575 patients aged ≥ 30 years who had a smoking history of 10 pack-years and were not taking asthma or COPD medications, an LFQ score of ≤ 18 identified a prevalence of obstructive lung disease of approximately 18% in a primary care setting; these cases were confirmed by an FEV₁/FVC ratio of < 0.70.26 If office spirometry testing is not available, the LFQ is a simple and convenient way for primary care physicians to identify patients who may have COPD and may need a referral for spirometry testing.26

Because patients may fail to recognize the severity of their disease, it is important for primary care physicians to evaluate respiratory symptoms in their patients and explore the impact of dyspnea and other COPD symptoms on their patients’ daily activities and social activities, and work to optimize disease management.3 Patient-physician communication and patient education are critical to this goal because patients’ disease perceptions can affect outcomes,27,28 including quality of life.29 In addition, study findings showed better treatment adherence in patients with compassionate doctors who spend adequate time with them and in patients with greater understanding of their disease and disease management options.30

The Table provides a list of questions that physicians can ask patients to assess their ability to perform activities of daily living and identify disease progression.18 Patients at earlier stages of COPD who experience mild dyspnea on exertion should be able to perform all of the activities listed in the Table, along with additional “productive” activities (employment, gardening, going...
to movies, recreational travel, social activities, sporting or recreational activities, volunteer work). Patients with moderate dyspnea on exertion should be able to perform most of the activities listed as “instrumental” in the Table, while patients with severe COPD may be able to perform only the most basic activities or require assistance completing them. Patient responses to these questions can assist in determining the appropriate treatment.

APPROPRIATE COPD MANAGEMENT

Traditionally, there has been a nihilistic view of COPD management; however, recent guidelines emphasize that this disease is preventable and treatable. Currently available COPD treatment options, including pharmacologic and nonpharmacologic therapies, can control and prevent COPD symptoms, reduce exacerbations, and improve exercise tolerance, quality of life, and functional abilities. Smoking cessation may be the only way to slow the progressive pulmonary function decline in patients with COPD; therefore, primary care physicians should encourage all patients who smoke to quit.

CONCLUSIONS

Symptoms of COPD, including dyspnea, sputum production, wheezing, and chest tightness, negatively affect patients’ ability to perform activities of daily living, which are critical to maintaining quality of life. The chronic and progressive nature of COPD results in gradual decrements to exercise tolerance, health status, and quality of life, which may not always be recognized by the patient. Appropriate COPD management can reduce symptoms and improve patients’ functional abilities, exercise tolerance, and quality of life, underscoring the importance of diagnosing COPD, initiating appropriate treatments, and encouraging smoking cessation as early as possible. As the first point of contact for many patients with COPD, primary care physicians play a critical role in identifying symptoms of COPD in their patients, evaluating patients for disease progression, educating them on their disease and management options, and optimizing treatment.

ACKNOWLEDGMENTS

The author thanks Anny Wu, PharmD; and Cynthia Gobbel, PhD, from Scientific Connexions (Newtown, PA) who provided medical writing support funded by AstraZeneca LP (Wilmington, DE).

REFERENCES:

ABSTRACT: Chronic obstructive pulmonary disease (COPD) typically is considered a disease of the lungs, but in actuality, it is a complex, multicomponent disease that can affect different systems. An abnormal inflammatory response of the lungs to noxious substances, such as cigarette smoke, is the primary factor contributing to development of airflow limitation characteristic of the disease. However, COPD also is associated with systemic inflammation, which may be linked to the observed significant extrapulmonary effects, including muscle wasting and cachexia, cardiovascular disease, osteoporosis, depression and anxiety, and anemia, which contribute to poor outcomes in some patients. These comorbidities have to be considered and managed in conjunction with COPD treatment for a more holistic approach in order to improve patients’ overall health. Because systemic inflammation may be an important contributor to the comorbidities associated with the disease, future systemic anti-inflammatory therapies may play a role in targeting the extrapulmonary effects of COPD.

Dr Hanania is associate professor of medicine in the section of pulmonary and critical care medicine, Baylor College of Medicine, Houston, TX.

EVIDENCE AND ORIGINS OF SYSTEMIC INFLAMMATION

Airflow limitation that is characteristic of chronic obstructive pulmonary disease (COPD) results from a variety of contributing factors in the lungs, including mucociliary dysfunction, pulmonary structural changes, and airway inflammation. Airway inflammation in patients with COPD most commonly originates from chronic exposure to noxious stimuli, including cigarette smoke, air pollution, and burning of wood or biomass fuels. It involves activated neutrophils, macrophages, and CD8+ T-cell lymphocytes, and increased levels of inflammatory mediators, including leukotriene B4, interleukin (IL)-8, and tumor necrosis factor-α (TNF-α). COPD is also associated with clinically relevant extrapulmonary effects, including poor nutritional status, muscle wasting, and impaired skeletal muscle function, which may further contribute to disease severity in some patients. Several other comorbidities also can contribute to disease severity and/or complicate COPD management. Systemic inflammation has been proposed as a pathogenic link between COPD and some of these comorbidities, such as osteoporosis and cardiovascular disease.4-7

Although it is well known that COPD is associated with chronic airway and lung inflammation, increased levels of oxidative stress, activated inflammatory cells, and proinflammatory cytokines are also seen in the systemic circulation of COPD patients compared with healthy individuals. Serum levels of C-reactive protein (CRP), a marker of inflammation that has been shown to predict cardiovascular events, and of TNF-α, a marker of muscle wasting in patients with cancer, are elevated in COPD patients compared with smokers without COPD, and...
these levels appear to rise with increasing COPD severity. Increased CRP levels have also been shown to be associated with COPD-related hospitalization and death.

Several origins of the systemic inflammation in COPD have been proposed. In the “spillover hypothesis” (Figure), inflammation begins in the lungs following the exposure to tobacco smoke or other oxidants, worsens with increasing airflow obstruction, and spreads to the systemic circulation via inflammatory cells and mediators, potentially causing the extrapulmonary manifestations. Although chronic exposure to cigarette smoke is the most common risk factor for COPD, genetic predisposition and gene-environment interactions also may contribute to COPD susceptibility. According to the “susceptible host hypothesis,” injury from tobacco smoke or other oxidants propagates inflammation in multiple organs including the lung, leading to small airway narrowing and other COPD manifestations in susceptible individuals. Other potential origins for systemic inflammation include lung hyperinflation, tissue hypoxia, and sympathetic and neurohormonal activation.

**SYSTEMIC COMORBIDITIES OF COPD**

Systemic comorbidities are common in patients with COPD and can lead to an increase in the level of disability associated with the disease. Categories of comorbidities include those with common pathways, including other smoking-related diseases such as ischemic heart disease and lung cancer, and those considered to be complications of COPD, including pulmonary hypertension and heart failure. Coexisting coincidental comorbidities, such as bowel or prostate cancer, depression, diabetes, dementia, Parkinson’s disease, and arthritis, are pathogenically unrelated, but they can complicate COPD management. Intercurrent comorbidities, including upper respiratory tract infections, are acute illnesses that may have a more severe impact in COPD patients compared with those without COPD.

In a large study of 2 population-based National Institutes of Health cohorts, patients with severe or very severe COPD were more likely to...
have 1, 2, or 3 comorbid conditions compared with participants with normal lung function.22 In a case-control study, only 6% of 200 patients with COPD did not have another chronic medical condition. Patients with COPD and healthy controls had an average of 3.7 and 1.8 chronic medical conditions, respectively (P < .001).23

Frequent comorbidities of patients with COPD include arthritis, cardiac disorders, hypertension, diabetes mellitus, lipid disorders, psychiatric conditions, gastrointestinal diseases, cancer, and osteoporosis (Table).24-28

Muscle wasting and cachexia. The prevalence of nutritional depletion and associated weight loss has been shown to increase with increasing severity of COPD,29 and low and normal weight is associated with decreased survival compared with overweight and obese patients with COPD.30 Loss of muscle mass is a primary reason for weight loss in patients with COPD.3 A study of muscle biopsies from 15 patients with COPD and 8 healthy participants showed an increased percentage of apoptotic cells in patients with COPD versus healthy controls and in COPD patients with low versus normal body mass index (BMI).31

Skeletal muscle dysfunction has many potential causes, including physical inactivity, nutritional depletion, tissue hypoxia, oxidative stress, and systemic inflammation.3 Increased levels of circulating CRP, IL-6, TNF-α, and other inflammatory mediators have been detected in COPD patients with skeletal muscle wasting versus normal skeletal muscle mass.32 Increased circulation of TNF-α leads to apoptosis and loss of protein in skeletal muscle cells.33,34 Patients with COPD often have an increased basal metabolic rate33,34 and commonly experience cachexia, which is a “wasting syndrome” involving weight loss, skeletal muscle atrophy, and weakness that is associated with systemic inflammation.33 Cachexia is an important predictor of mortality and is associated with functional impairment and reduced quality of life.34 These findings highlight the importance of implementing and maintaining pulmonary rehabilitation programs, including exercise training and nutrition counseling, in appropriate patients early in the disease process.2

Cardiovascular disease. The lung and the heart are physiologically integrated and functionally interdependent.35 The increased work of breathing associated with COPD is particularly problematic in patients with compromised cardiac function because greater cardiac output is required.35 In addition, the presence of COPD can impair cardiac function because pulmonary hypertension leads to increased cardiac strain.35 Evidence suggests a connection between cardiovascular complications and systemic inflammation associated with COPD.36 Circulating levels of TNF-α or CRP as a result of chronic lung inflammation may accelerate development of atherosclerosis.35 High levels of circulating CRP and severity of airflow obstruction have also been correlated with increased risk of cardiac infarction in patients with COPD.2

### Table – Prevalence of common comorbidities in COPD24

<table>
<thead>
<tr>
<th>Source</th>
<th>n</th>
<th>Arthritis</th>
<th>Cardiac</th>
<th>HTN</th>
<th>Diabetes</th>
<th>Lipids</th>
<th>Psych</th>
<th>GI</th>
<th>Cancer</th>
<th>Osteoporosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Van Manen and colleagues24</td>
<td>1145</td>
<td>36</td>
<td>13</td>
<td>23</td>
<td>5</td>
<td>—</td>
<td>9</td>
<td>15</td>
<td>6</td>
<td>—</td>
</tr>
<tr>
<td>Mapel and colleagues22</td>
<td>200</td>
<td>22</td>
<td>65</td>
<td>45</td>
<td>12</td>
<td>—</td>
<td>17</td>
<td>32</td>
<td>18</td>
<td>—</td>
</tr>
<tr>
<td>Soriano and colleagues25</td>
<td>2699</td>
<td>28</td>
<td>22</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>10</td>
<td>26</td>
<td>4</td>
<td>—</td>
</tr>
<tr>
<td>Sidney and colleagues26</td>
<td>45,966</td>
<td>—</td>
<td>18</td>
<td>18</td>
<td>2</td>
<td>9</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Walsh and Thomashow27</td>
<td>3000</td>
<td>70</td>
<td>50</td>
<td>52</td>
<td>16</td>
<td>51</td>
<td>38</td>
<td>62</td>
<td>4</td>
<td>32</td>
</tr>
</tbody>
</table>

—, no available data; COPD, chronic obstructive pulmonary disease; GI, gastrointestinal disturbances; HTN, hypertension.

Patients with COPD are indeed at increased risk for cardiovascular complications and cardiovascular disease.\(^{37,38}\) Compared with healthy controls, patients with COPD have increased arterial stiffness,\(^{38}\) which is an independent predictor of cardiovascular complications.\(^{39}\) In addition, COPD patients have a significantly higher prevalence of and greater risk of hospitalization for arrhythmia, angina, acute myocardial infarction, congestive heart failure, stroke, and pulmonary embolism compared with controls.\(^{35}\) In the Towards a Revolution in COPD Health (TORCH) trial,\(^{40}\) 27% of all deaths were due to cardiovascular disease,\(^{41}\) which is consistent with findings from other studies in patients with COPD (see Chatila and colleagues\(^{24}\) for a summary of studies). Moreover, patients with COPD who have cardiovascular disease are at significantly increased risk for COPD exacerbations and increased costs compared with patients with COPD who do not have cardiovascular disease.\(^{42}\) Together, these findings provide strong support for careful monitoring of cardiovascular health in patients with COPD.

**Osteoporosis.** Results from the Third National Health and Nutrition Examination Survey show that risk of osteoporosis increases with disease severity in both men and women with COPD.\(^{5}\) Reduced physical activity and skeletal muscle mass, changes in body composition, and mediators of chronic systemic inflammation (ie, IL-1 and TNF-\(\alpha\)) may contribute to the pathogenesis of osteoporosis in patients with COPD.\(^{43,44}\) Risk factors for osteoporosis also may include low vitamin D levels, smoking, increased alcohol intake, genetic factors, and treatment with systemic or inhaled corticosteroids (ICS).\(^{44}\)

Corticosteroids are known to reduce calcium absorption, increase calcium excretion, stimulate bone resorption, and reduce bone formation.\(^{44}\) Evidence suggests a strong association between a cumulative prednisone dose of \(\geq 1000\) mg and reduced bone mineral density (BMD).\(^{45}\) However, studies evaluating the effects of ICS treatment on BMD and osteoporosis have shown inconsistent results.\(^{40,46-49}\) Patients with COPD should be screened for osteopenia, which indicates an increased risk for osteoporosis, and regular monitoring of BMD should be conducted in patients who are receiving intermittent courses of oral corticosteroids or long-term ICS therapy.\(^{44}\)

**Depression and anxiety.** Mood disorders, including depression and anxiety, are more prevalent in patients with COPD than in the general population.\(^{20,56,57}\) In a study of 1334 patients with COPD and other chronic breathing disorders, 65% of patients had both depression and anxiety at screening.\(^{50}\) In the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) observational study, depression requiring treatment was more prevalent in women than men with moderate to severe COPD (\(P \leq .004\)).\(^{51}\) Moreover, COPD patients with comorbid major depressive disorder or anxiety have higher rates of COPD-related emergency department visits or hospitalizations and health care costs compared with patients with COPD only.\(^{52}\) Other variables associated with depression and anxiety in patients with COPD include physical disability, fatigue, long-term oxygen therapy, low BMI, severe dyspnea, percentage of predicted forced expiratory volume in 1 second \(< 50\%\), poor quality of life, presence of comorbidity, living alone, current smoking, and low social class status.\(^{53}\)

Depression and anxiety increase the severity of disease symptoms,\(^{54}\) decrease levels of physical activity,\(^{20}\) increase functional impairment,\(^{55}\) and worsen quality of life.\(^{20,56,57}\) In the National Emphysema Treatment Trial (NETT) (\(N = 610\)), approximately 41% of patients were mildly to moderately depressed; these patients had a greater 3-year risk of mortality compared with non-depressed patients.\(^{56}\) Anxiety and depressive disorders are underrecognized (< 40%) and undertreated (approximately 30%) in patients with COPD.\(^{20}\) The adverse clinical consequences of anxiety and depression in patients with COPD highlight the need to implement screening procedures and initiate appropriate treatment, such as antidepressants and/or pulmonary rehabilitation.\(^{37}\)

**Anemia.** Putative mechanisms for anemia in chronic diseases include shortened red blood cell survival time, dysregulation of iron homeostasis, and impaired bone marrow erythropoietic response.\(^{58}\) These changes may occur as a result of systemic inflammation involving increased circulating IL-1, TNF-\(\alpha\), interferon-\(\gamma\), and other cytokines and chemokines, supporting a mechanistic link between COPD and anemia.\(^{59}\)

Anemia occurs in 13% to 17% of patients with COPD\(^{60,61}\) and is associated with worsening of COPD symptoms, decreased exercise capacity, and greater risk of mortality in patients with COPD.\(^{61}\) Although a causal relationship between COPD and anemia has not been established, findings support screening and appropriate treatment in patients with COPD.\(^{62}\) It should be noted that polycythemia can also occur in patients who have arterial hypoxemia and in continuing smokers, and it is identified by a hematocrit of > 55%.\(^{2}\)

**EFFECTS OF COMORBIDITIES ON CLINICAL OUTCOMES**

Comorbidities of COPD are associated with poor clinical outcomes, although their severity and impact

---

**DECEMBER 2011 (SUPPLEMENT)**

**Is It a Systemic Disorder?**
on patient health vary with time and among patients.2 Data from the National Hospital Discharge Survey from 1979 to 2001 indicate that rates of in-hospital mortality due to various cardiovascular, pulmonary, and thoracic conditions are higher in patients with, versus without, COPD.62 COPD currently is the third leading cause of death in adults in the United States64; however, results from several studies suggest that patients with COPD may be more likely to die of comorbid conditions than of COPD,64,65 in particular those related to cardiovascular disease.65,66

THERAPEUTIC IMPLICATIONS

Current Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines recommend that significant comorbidities should be considered during a comprehensive diagnostic assessment of disease severity and determination of appropriate treatment; however, neither the GOLD guidelines nor the American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines give integrated recommendations for management of specific comorbid conditions.2,67 The ATS/ERS guidelines recommend referral to a specialist for patients who have comorbid illness, including osteoporosis, heart failure, bronchiectasis, and lung cancer.67 Considering that 20% of Medicare beneficiaries have ≥ 5 chronic conditions, and half are prescribed ≥ 5 medications for comorbid diseases, it is critical that physicians make efforts to screen for comorbidities and implement disease management programs that consider the “whole patient.”68 The central role of systemic inflammatory process in COPD and its comorbidities supports a need for further research evaluating novel targets for suppression of pulmonary and systemic inflammation, such as phosphodiesterase-4, p38 mitogen-activated protein kinase, and nuclear factor-κB.69

CONCLUSIONS

COPD is associated with chronic airway and systemic inflammation; the latter is a likely mechanism for the many clinically relevant extrapulmonary effects associated with the disease. Systemic comorbidities of COPD may affect multiple physiologic systems and often are associated with poor outcomes in COPD patients. Disease management programs that consider the pulmonary and nonpulmonary effects of COPD and its comorbidities and treat the “whole patient” are critically needed. Research on novel targets for reducing systemic inflammation is also needed in COPD patients with or without existing comorbidities.

Acknowledgments

The authors thanks Kristen Quinn, PhD, and Cynthia Gobbel, PhD, from Scientific Connexions (Newtown, PA) who provided medical writing support funded by AstraZeneca LP (Wilmington, DE).

REFERENCES

 Chronic Obstructive Pulmonary Disease: Is It a Systemic Disorder?


ABSTRACT: A central feature of chronic obstructive pulmonary disease (COPD) is airflow obstruction that is not fully reversible, defined as a postbronchodilator forced expiratory volume in 1 second (FEV₁)/forced vital capacity (FVC) ratio of < 0.70. Although airflow obstruction in COPD is not fully reversible, patients can still exhibit clinically significant bronchodilator reversibility (or responsiveness), based on changes from prebronchodilator values in FEV₁ and/or FVC. The FVC component is particularly important in patients with more severe COPD who have greater hyperinflation, as these patients often show clinically meaningful improvement in FVC without a significant FEV₁ response after bronchodilator treatment. Confusion exists surrounding the concept of bronchodilator reversibility because of the lack of a standardized definition and methodologies for assessing reversibility, inherent day-to-day variability in bronchodilator response, and similarities with asthma in some cases. This article reviews the role of spirometry in COPD diagnosis and ongoing monitoring, definitions of bronchodilator reversibility, and clinical relevance of bronchodilator responsiveness in patients with COPD.

Chronic airflow obstruction is a central feature of chronic obstructive pulmonary disease (COPD). Often, patients with COPD have a significant response to bronchodilator treatment, but the disease is not fully reversible. Airflow limitation that is not fully reversible is defined as a postbronchodilator forced expiratory volume in 1 second/forced vital capacity (FEV₁/FVC) ratio of < 0.70. A common misconception is that patients who exhibit a significant response to bronchodilators but are not fully reversible more likely have asthma than COPD. However, bronchodilator responsiveness is not sensitive or specific enough to differentiate asthma from COPD. According to current COPD management guidelines, measurements of postbronchodilator FEV₁/FVC and FEV₁ are recommended for COPD diagnosis and assessment of disease severity, respectively, but the degree of postbronchodilator response (eg, change in FEV₁) is not recommended for differentiation of COPD from asthma.

DIFFERENTIATING BETWEEN COPD AND ASTHMA

Characteristic COPD symptoms include dyspnea, chronic cough, and sputum production. These symptoms also may be present in patients with asthma, albeit with greater variability. Several clinical features can help distinguish COPD from asthma (Table 1), although these distinguishing features are not absolute. Fixed airflow obstruction is a defining feature of COPD, but airway remodeling occurs often in asthma and may lead to a fixed component of airflow obstruction in some asthma patients. In particular, patients with longstanding asthma may demonstrate irreversible airflow obstruction, and some patients with asthma...
may have a pseudo-emphysematous pattern. While atopy is very common in asthma, some COPD patients also have atopy. Although smoking is the most common cause of COPD, 10% to 15% of patients with COPD have never smoked. While inflammation in asthma is dominated by eosinophils, patients with severe asthma may have predominantly neutrophils in their sputum, a characteristic more typical of COPD. Conversely, up-regulation of sputum eosinophils may occur in patients with COPD during exacerbations. It also is important to recognize that COPD and asthma can coexist in some patients.

Some typical physiologic characteristics of COPD may help in further distinguishing COPD from asthma. The diffusing capacity of the lung for carbon monoxide typically is decreased in patients with the emphysematous phenotype of COPD but is normal or increased in patients with asthma. In addition, patients with COPD tend to have more severe hyperinflation at rest that increases with exertion, while resting hyperinflation usually is present in patients with asthma only during exacerbations. Patients with COPD with an emphysematous component have decreased lung elastic recoil. Lung elastic recoil generally is normal in patients with asthma, although it may be decreased in patients with asthma who have fixed airflow obstruction or transiently decreased during an acute asthma exacerbation. Thus, several clinical and physiologic features may factor into a diagnosis of COPD or asthma.

**SPIROMETRY AND ASSESSING COPD**

Spirometry is essential for confirming a diagnosis of COPD, which should be suspected in current or ex-smokers aged ≥ 40 years with dyspnea, chronic cough, or sputum, particularly those with a smoking history of ≥ 20 pack-years. In addition to a reduced FEV1/FVC ratio, patients with COPD generally have decreases in FEV1 and FVC, with greater declines in both measures as disease severity worsens. Performing conventional spirometry can be expensive and time-consuming, and it requires training and expertise. Handheld spirometers are an inexpensive, convenient, and practical alternative in the primary care setting. They are also accurate, with good correlation in FEV1 measurements between handheld spirometers and full spirometry. If findings from handheld or smaller pocket spirometers are abnormal, patients could be referred to a hospital-based pulmonary function laboratory or a specialist for more rigorous tests with conventional spirometry instruments.

If interpreted correctly, spirometry results can reveal important information about the patient’s disease. An FEV1/FVC ratio of < 0.70 that remains < 0.70 after bronchodilator administration (eg, albuterol 90 µg × 2 to 4 inhalations) confirms airflow obstruction that is not fully reversible, suggesting COPD. In patients who receive a diagnosis of COPD, spirometry findings also are used to assess disease severity and progression of the disease. Patients with FEV1 ≥ 80% predicted, FEV1 to < 80% predicted, 30% to < 50% predicted, or < 30% predicted are classified as having mild (Global Initiative for Chronic Obstructive Lung Disease [GOLD])

### Table 1 – Clinical features distinguishing asthma from COPD

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>COPD</th>
<th>Asthma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoker or ex-smoker</td>
<td>Nearly alla</td>
<td>Possibly</td>
</tr>
<tr>
<td>Symptoms under age 35 years</td>
<td>Rare</td>
<td>Often</td>
</tr>
<tr>
<td>Progression of symptoms</td>
<td>Chronic, slowly progressive</td>
<td>Episodic and highly variable</td>
</tr>
<tr>
<td>Chronic productive cough</td>
<td>Common</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Breathlessness</td>
<td>Persistent and progressive</td>
<td>Variable</td>
</tr>
<tr>
<td>Nighttime awakening with shortness of breath and/or wheezing</td>
<td>Uncommon</td>
<td>Common</td>
</tr>
<tr>
<td>Atopic symptoms and seasonal allergies</td>
<td>Uncommon</td>
<td>Common</td>
</tr>
<tr>
<td>Significant diurnal/day-to-day variability</td>
<td>Uncommon</td>
<td>Common</td>
</tr>
<tr>
<td>Airway inflammation</td>
<td>Neutrophilic</td>
<td>Eosinophilic</td>
</tr>
<tr>
<td>Favorable response to ICS</td>
<td>Inconsistent</td>
<td>Consistent</td>
</tr>
<tr>
<td>Response to bronchodilators</td>
<td>Less</td>
<td>More</td>
</tr>
</tbody>
</table>

aTen percent to 15% of patients with COPD have never smoked. COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroid.
stage I), moderate (GOLD stage II), severe (GOLD stage III), or very severe (GOLD stage IV) COPD, respectively. In addition, spirometry findings are used to assess individual patients’ changes in pulmonary function over time and after bronchodilator administration; several criteria have been established for determining a clinically meaningful bronchodilator response (Table 2).

### ASSESSING BRONCHODILATOR REVERSIBILITY (RESPONSIVENESS)

Confusion exists surrounding the concept of bronchodilator reversibility or responsiveness for several reasons, including the lack of standardized definitions or methodologies for determining bronchodilator reversibility. The American Thoracic Society/European Respiratory Society (ATS/ERS) criteria for bronchodilator reversibility are the most current definition and include an FVC component, defining reversibility using FEV, FVC, or both. The FVC component of the ATS/ERS definition is often overlooked, and although FVC results are more difficult to obtain, volume changes based on FVC may have a better correlation with improvements in exercise tolerance than measures of flow based on FEV, and hence may be more clinically important. Moreover, some patients who do not demonstrate bronchodilator reversibility based on FEV do show a response based on FVC particularly those with more severe COPD and greater hyperinflation.

It should be noted that a patient’s acute response to bronchodilator treatment cannot be used to predict a long-term response to maintenance bronchodilator therapy.

### Table 2 – Definitions used to assess bronchodilator reversibility

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACCP23</td>
<td>Improvement in FEV, of ≥ 15%</td>
</tr>
<tr>
<td>ATS25</td>
<td>Improvement in FEV, or FVC of ≥ 12% and ≥ 200 mL</td>
</tr>
<tr>
<td>ERS24</td>
<td>Improvement in % predicted FEV, of ≥ 10%</td>
</tr>
<tr>
<td>ATS/ERS22</td>
<td>Improvement in FEV, and/or FVC of &gt; 12% and &gt; 200 mL</td>
</tr>
<tr>
<td>GOLD1</td>
<td>Improvement in FEV, of &gt; 12% and &gt; 200 mL</td>
</tr>
</tbody>
</table>

*For all definitions, improvement is referenced to the prebronchodilator value of FEV, or FVC.

ACCP, American College of Chest Physicians; ATS, American Thoracic Society; ERS, European Respiratory Society; FEV, forced expiratory volume in 1 second; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease.

---

**Figure 1** – Mean FEV, before and after treatment with tiotropium on (A) day 1 and (B) day 344.

“Responders” and “poor responders,” respectively, included patients who did or did not meet American Thoracic Society reversibility criteria for FEV, after tiotropium treatment on day 1.

FEV, forced expiratory volume in 1 second.

COPD who exhibited reversibility after maximal bronchodilation (albuterol 400 µg followed 30 minutes later by ipratropium 80 µg) depending on the criterion used, with 42% meeting the ATS criteria for FEV₁ and 23% meeting the ERS criterion for % predicted FEV₁.30 Bronchodilator response also varies based on the bronchodilator used.31 Differences in the percentage of patients exhibiting reversibility have been shown when using ipratropium alone, albuterol alone, or both (Figure 2).31

In addition, there is inherent day-to-day variability in bronchodilator response. In a study of 852 patients with moderate to severe COPD, the percentage of patients exhibiting significant (≥ 15% FEV₁ improvement) reversibility to albuterol, ipratropium, or both varied over 4 separate days, with > 90% of patients demonstrating significant reversibility on at least 1 occasion (Table 3).32 In another study, 52% of patients changed reversibility status to albuterol and ipratropium over the 3 study visits based on the combined ATS criteria.30 However, despite variability in bronchodilator response, many patients with COPD do exhibit significant bronchodilator reversibility.

### STUDIES SUPPORTING BRONCHODILATOR RESPONSIVENESS IN COPD

In a post hoc analysis of 5756 patients in the UPLIFT study, more than half of the patients exhibited bronchodilator responsiveness after maximal or near-maximal bronchodilation.31,32

<table>
<thead>
<tr>
<th>Number of test days with positive response</th>
<th>Albuterol (n = 277)</th>
<th>Ipratropium and albuterol (n = 292)</th>
<th>Ipratropium (n = 283)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 Test days</td>
<td>9</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>≥ 1 Test day</td>
<td>97c</td>
<td>92</td>
<td>91</td>
</tr>
<tr>
<td>≥ 2 Test days</td>
<td>90c</td>
<td>80</td>
<td>79</td>
</tr>
<tr>
<td>≥ 3 Test days</td>
<td>76c</td>
<td>63</td>
<td>66</td>
</tr>
<tr>
<td>All 4 test days</td>
<td>56c</td>
<td>37</td>
<td>46</td>
</tr>
</tbody>
</table>

c: Standard error of the mean < 3% for all data points.

A pulmonary function test performed on days 1, 29, 57, and 86.

Reprinted with permission from: Donohue JF. Therapeutic responses in asthma and COPD. Chest. 2004;126:125S-137S.
lation with ipratropium followed by albuterol treatment based on the combined ATS criteria for FEV₁ improvement of ≥12% and ≥200 mL. Similarly, in 2 studies of 1109 patients with moderate to very severe COPD, a large percentage of patients demonstrated meaningful improvements in FEV₁ based on the combined ATS criteria after administration of formoterol-containing treatment on the day of randomization (51% to 54%) and at the end of treatment (57% to 76%). Notably, at the screening visit, only 34% to 39% of patients exhibited reversibility to albuterol based on the combined ATS criteria for FEV₁. These findings suggest that patients’ bronchodilator responsiveness may be underestimated if based on albuterol reversibility testing alone.

A patient’s response to a bronchodilator can be influenced by disease severity, depending on the criterion used. Studies have shown that bronchodilator response based on FEV₁ may vary by disease severity, but response based on FVC remains more consistent across severity groups (Figure 3). In both the UPLIFT study analysis and the study conducted by Celli and colleagues, the percentage of patients demonstrating a bronchodilator response (FEV₁ improvement ≥12% and ≥200 mL) progressively decreased with increasing COPD severity. These findings suggest that patients’ bronchodilator responsiveness may be underestimated if based on albuterol reversibility testing alone.

A patient’s response to a bronchodilator can be influenced by disease severity, depending on the criterion used. Studies have shown that bronchodilator response based on FEV₁ may vary by disease severity, but response based on FVC remains more consistent across severity groups (Figure 3). In both the UPLIFT study analysis and the study conducted by Celli and colleagues, the percentage of patients demonstrating a bronchodilator response (FEV₁ improvement ≥12% and ≥200 mL) progressively decreased with increasing COPD severity. These findings suggest that patients’ bronchodilator responsiveness may be underestimated if based on albuterol reversibility testing alone.

A patient’s response to a bronchodilator can be influenced by disease severity, depending on the criterion used. Studies have shown that bronchodilator response based on FEV₁ may vary by disease severity, but response based on FVC remains more consistent across severity groups (Figure 3). In both the UPLIFT study analysis and the study conducted by Celli and colleagues, the percentage of patients demonstrating a bronchodilator response (FEV₁ improvement ≥12% and ≥200 mL) progressively decreased with increasing COPD severity. These findings suggest that patients’ bronchodilator responsiveness may be underestimated if based on albuterol reversibility testing alone.

A patient’s response to a bronchodilator can be influenced by disease severity, depending on the criterion used. Studies have shown that bronchodilator response based on FEV₁ may vary by disease severity, but response based on FVC remains more consistent across severity groups (Figure 3). In both the UPLIFT study analysis and the study conducted by Celli and colleagues, the percentage of patients demonstrating a bronchodilator response (FEV₁ improvement ≥12% and ≥200 mL) progressively decreased with increasing COPD severity. These findings suggest that patients’ bronchodilator responsiveness may be underestimated if based on albuterol reversibility testing alone.

A patient’s response to a bronchodilator can be influenced by disease severity, depending on the criterion used. Studies have shown that bronchodilator response based on FEV₁ may vary by disease severity, but response based on FVC remains more consistent across severity groups (Figure 3). In both the UPLIFT study analysis and the study conducted by Celli and colleagues, the percentage of patients demonstrating a bronchodilator response (FEV₁ improvement ≥12% and ≥200 mL) progressively decreased with increasing COPD severity. These findings suggest that patients’ bronchodilator responsiveness may be underestimated if based on albuterol reversibility testing alone.

A patient’s response to a bronchodilator can be influenced by disease severity, depending on the criterion used. Studies have shown that bronchodilator response based on FEV₁ may vary by disease severity, but response based on FVC remains more consistent across severity groups (Figure 3). In both the UPLIFT study analysis and the study conducted by Celli and colleagues, the percentage of patients demonstrating a bronchodilator response (FEV₁ improvement ≥12% and ≥200 mL) progressively decreased with increasing COPD severity. These findings suggest that patients’ bronchodilator responsiveness may be underestimated if based on albuterol reversibility testing alone.
based on a FVC improvement of \( \geq 12\% \) and \( \geq 200 \) mL generally was consistent across disease severities.\(^4\,^5\)

**BRONCHODILATORS FOR TREATING COPD**

Bronchodilators are the mainstay of treatment for COPD.\(^1\) Combining different classes of bronchodilators may result in greater efficacy and a decreased risk of side effects compared with increasing the dose of a single bronchodilator.\(^1\) There also may be clinical benefits of adding an inhaled corticosteroid to long-acting bronchodilator therapy, in addition to reducing exacerbations.\(^2\) Data from the 2 studies of 1109 patients with moderate to severe COPD showed that patients receiving budesonide/formoterol pressurized metered-dose inhaler (pMDI) generally had numerically greater mean improvements in 1-hour postdose FEV\(_1\) and FVC versus formoterol alone on the day of randomization.\(^3\) For the whole population (including all patients with moderate to very severe COPD), mean improvements in 1-hour postdose FEV\(_1\) and FVC on the day of randomization were 220 to 230 mL and 400 to 410 mL, respectively, in the budesonide/formoterol pMDI groups compared with 160 mL and 350 mL, respectively, in the formoterol group.\(^1\)

**CONCLUSIONS**

COPD is characterized by airflow obstruction that is not fully reversible; however, confusion exists surrounding the concept of reversibility. Although the disease is not fully reversible, patients with COPD often exhibit a clinically significant bronchodilator response, as defined by several different published criteria for FEV\(_1\) and/or FVC improvement (eg, American College of Chest Physicians, ATS/ERS, ATS). In particular, patients with more severe COPD show benefits of reduced air trapping and hyperinflation after bronchodila- tor treatment, as measured by FVC. Bronchodilators are central to COPD management, and although variability exists in bronchodilator response between and within patients, patients with COPD do show a clinically meaningful response to bronchodilator therapy, administered alone or in combination.

**Acknowledgments**

The author thanks Anny Wu, PharmD, and Cynthia Gobbel, PhD, from Scientific Connexions (Newtown, PA) who provided medical writing support funded by AstraZeneca LP (Wilmington, DE).

**REFERENCES:**


15. **Scibura FC. Physiologic similarities and differ- ences between COPD and asthma.** *Chest.* 2004;125:1175-1184.


ABSTRACT: Pharmacologic treatments and pulmonary rehabilitation improve symptoms, health status, and exercise tolerance in patients with chronic obstructive pulmonary disease (COPD). Short-acting and long-acting bronchodilators are the mainstays of therapy for as-needed symptom relief and long-term maintenance, respectively. Disease severity, device characteristics, medication costs, and patient preferences are factors to consider when making pharmacologic treatment decisions. Changes in symptoms, adherence to treatment, and existence of comorbidities should be assessed when evaluating the effectiveness of pharmacologic therapy. Pulmonary rehabilitation, including exercise training, nutritional counseling, psychosocial support, and patient education, has shown clinical benefits at all COPD severity stages. Oxygen therapy and surgical options may be considered in carefully selected patients. Research is ongoing to develop novel therapies that can modify disease progression and to identify COPD phenotypes for greater individualization of therapy. This article reviews current COPD treatment recommendations and potential novel COPD treatment options for the future.

Patients with chronic obstructive pulmonary disease (COPD) can exhibit a significant response to bronchodilator therapy, as such, short-acting and long-acting bronchodilator therapies are the mainstays of COPD treatment. Goals of pharmacotherapy and other elements of COPD management (eg, pulmonary rehabilitation, smoking cessation) are to relieve symptoms; prevent disease progression; improve exercise tolerance, health status, and quality of life; prevent and treat complications and exacerbations; and reduce mortality. Identification of comorbidities, which can complicate treatment and result in poor outcomes, also is necessary. COPD treatment is selected based on severity and exacerbation frequency, clinical presentation, speed of lung function decline, extrapulmonary effects, comorbidities, and patient factors.

PHARMACOLOGIC TREATMENT OPTIONS

Table 1 summarizes available COPD medications. Regardless of other therapies, all COPD patients should have short-acting β₂-adrenergic agonists (SABAs) and short-acting anticholinergics available for rapid symptom relief. SABAs relax airway smooth muscles, while short-acting anticholinergics block the bronchoconstrictive effects of acetycholine on airway smooth muscle cells.

Long-acting bronchodilators, including long-acting muscarinic antagonists (LAMAs) and long-acting β₂-adrenergic agonists (LABAs), are the mainstays of therapy for long-term COPD symptom management. Despite concerns stemming from asthma studies, the safety of LAMAs and LABAs has been shown in patients with COPD.

Disclosures
Barbara P. Yawn, MD, MSc, FAAFP
Recipient of research support:
Boehringer Ingelheim, Novartis
### Table 1 – Formulations and typical doses of COPD medications

<table>
<thead>
<tr>
<th>Drug</th>
<th>Inhaler (µg)</th>
<th>Solution for nebulizer (mg/mL)</th>
<th>Oral</th>
<th>Vials for injection (mg)</th>
<th>Duration of action (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ß&lt;sub&gt;2&lt;/sub&gt;-agonists</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Short-acting</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fenoterol</td>
<td>100-200 (MDI)</td>
<td>1</td>
<td>0.05% (syrup)</td>
<td>4-6</td>
<td></td>
</tr>
<tr>
<td>Levalbuterol</td>
<td>45-90 (MDI)</td>
<td>0.21, 0.42</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salbutamol (albuterol)</td>
<td>100, 200 (MDI &amp; DPI)</td>
<td>5</td>
<td>5 mg (pill), 0.024% (syrup)</td>
<td>0.1, 0.5</td>
<td>4-6</td>
</tr>
<tr>
<td>Terbutaline</td>
<td>400, 500 (DPI)</td>
<td>2.5, 5 (pill)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Long-acting</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Formoterol</td>
<td>4.5-12 (MDI &amp; DPI)</td>
<td>0.01&lt;sup&gt;b&lt;/sup&gt;</td>
<td>12+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arformoterol</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indacaterol</td>
<td>150-300 (DPI)</td>
<td>24</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salmeterol</td>
<td>25-50 (MDI &amp; DPI)</td>
<td>12+</td>
<td>12+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anticholinergics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Short-acting</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ipratropium bromide</td>
<td>20, 40 (MDI)</td>
<td>0.25-0.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxitropium bromide</td>
<td>100 (MDI)</td>
<td>1.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Long-acting</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tiotropium</td>
<td>18 (DPI), 5 (SMI)</td>
<td>24+</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combination short-acting ß&lt;sub&gt;2&lt;/sub&gt;-agonists plus anticholinergic in 1 inhaler</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fenoterol/ipratropium</td>
<td>200/80 (MDI)</td>
<td>1.25/0.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salbutamol/ipratropium</td>
<td>75/15 (MDI)</td>
<td>0.75/0.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methylxanthines</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aminophylline</td>
<td></td>
<td>200-600 mg (pill)</td>
<td>240 mg</td>
<td>Variable, up to 24</td>
<td></td>
</tr>
<tr>
<td>Theophylline (SR)</td>
<td></td>
<td>100-600 mg (pill)</td>
<td></td>
<td></td>
<td>Variable, up to 24</td>
</tr>
<tr>
<td>Inhaled glucocorticosteroids</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beclomethasone</td>
<td>50-400 (MDI &amp; DPI)</td>
<td>0.2-0.4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Budesonide</td>
<td>100, 200, 400 (DPI)</td>
<td>0.20, 0.25, 0.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluticasone propionate</td>
<td>50-500 (MDI &amp; DPI)</td>
<td>25-500 (MDI)</td>
<td>25/50, 125, 250 (MDI)</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>Combination long-acting ß&lt;sub&gt;2&lt;/sub&gt;-agonists plus glucocorticosteroids in 1 inhaler</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Formoterol/budesonide</td>
<td>4.5/160, 9/320 (DPI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salmeterol/fluticasone propionate</td>
<td>50/100, 250, 500 (DPI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systemic glucocorticosteroids</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prednisone</td>
<td></td>
<td>5-60 mg (pill)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td></td>
<td>4, 8, 16 mg (pill)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phosphodiesterase-4 inhibitors</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Roflumilast</td>
<td></td>
<td>500 µg (pill)</td>
<td></td>
<td></td>
<td>24</td>
</tr>
</tbody>
</table>

<sup>a</sup>Not all formulations are available in all countries; in some countries, other formulations may be available.

<sup>b</sup>Formoterol nebulized solution is based on the united dose vial containing 20 µg in a volume of 2.0 mL.

COPD, chronic obstructive pulmonary disease; DPI, dry powder inhaler; MDI, metered-dose inhaler; SMI, soft-mist inhaler; SR, sustained release.

Treatment Options in Chronic Obstructive Pulmonary Disease: Current Recommendations and Recent Findings

Understanding Potential Long-term Impacts on Function With Tiotropium (UPLIFT) study and a subsequent meta-analysis of 19 studies with tiotropium, including UPLIFT, showed no evidence of an increased risk of cardiovascular events.12,13 The safety of LABA monotherapy in COPD is well documented6,14; LAMAs and LABAs can be administered alone or as combination therapy for bronchodilation and reduction of symptoms and exacerbations.6,14

Regular inhaled corticosteroid (ICS) therapy may further reduce exacerbation frequency for patients with severe or very severe COPD and a history of frequent exacerbations.6,14 ICS treatment has not been proven to slow lung function decline in patients with COPD.6,15-18 but Towards a Revolution in COPD Health (TORCH) post hoc data suggest a slowing of lung function decline that should be further evaluated.19 ICS use in persons with COPD has been shown to increase the risk of pneumonia, which may vary by ICS type,6,20-23 and high-dose ICS therapy increases fracture risk.20 No increased risk of pneumonia was seen with inhaled budesonide (up to 640 µg/d) compared with placebo or formoterol alone over 12 months.24 Oral corticosteroids are not recommended for long-term therapy in patients with COPD.6 However, a 7- to 10-day burst of oral prednisone is a mainstay of COPD exacerbation therapy.6

HOW TO SELECT PHARMACOLOGIC THERAPY

Treatments should be selected based on the patient’s disease severity and COPD exacerbation frequency (Figure 1).6 The type of delivery device25 (eg, pressurized metered-dose inhaler, dry powder inhaler, or nebulizer), the skills and ability of the individual patient,6 the cost of each treatment (commonly US$36 to $210 per month26), and the patient’s financial status also should be considered. Patients with COPD routinely take 4 to 10 medications daily for various indications.27,28 Use of multiple types of inhaler devices can lead to confusion and errors in medication use29,30; therefore, it may be advantageous for physicians to keep the device consistent if possible.30 When used correctly, the device does not affect treatment efficacy11; however, it is important to ensure proper inhaler technique. At each clinic visit, a clinical team member should recheck the patient’s inhaler technique to ensure correct inhaler use.6 Information about inhaler devices, inhalation technique, and recommendations for training can be

Figure 1 – Therapy at each stage of COPD.6

FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity.

found here: http://advanceweb.com/web/AstraZeneca/focus_on_copd_issue3_DevicesForAerosol/focus_on_copd_issue3.html.

CHANGING PHARMACOLOGIC THERAPY

Patients with COPD should be monitored carefully for treatment response and side effects, and therapy should be individualized. Over time, all patients will require additional treatments or an increase in dose as disease severity worsens. However, COPD progression may not be recognized by patients over time. It is important for physicians to evaluate patients for signs and symptoms of disease worsening, including decreased exercise tolerance (what can the patient not do now that he/she could do last year?), impaired quality of life (what does the patient want to be able to do?), increased breathlessness at rest or during exercise (how many stairs can the patient go up before having to stop?), increased sputum (tablespoon versus a shot glass versus a cup full in a day), low or reduced oxygen saturation (pulse oximetry testing), change in ability to perform activities of daily living independently, and increased wheeze.

Assessment tools may help disease evaluations by providing physicians with clear and validated questions to ask patients. The Modified Medical Research Council (MMRC) dyspnea scale (http://copd.about.com/od/copdbasics/a/MMRC-dyspneascale.htm) and the modified...
Borg scale\(^\text{36,27}\) (http://www.yourlunghealth.org/testing/6min_walk/index.cfm) can be used to follow disease progression if used repeatedly over time. The 8-item COPD Assessment Test (CAT) can be used to measure overall COPD-related health status (Figure 2),\(^\text{28}\) and the 14-item Exacerbations of Chronic Pulmonary Disease Tool-Patient-Reported Outcome (EXACT-PRO)\(^\text{39,40}\) (http://www.exactproinitiative.com/default.php) can be used to quantify the severity of a COPD exacerbation.\(^\text{39}\)

**IMPORTANCE OF PATIENT ADHERENCE TO COPD MANAGEMENT**

COPD requires life-long medication therapy, and adherence to therapy is critical to achieving treatment goals. Poor adherence is common in patients with COPD, and adherence tends to decline over time.\(^\text{41,42}\) Thus, efforts to improve treatment adherence are worthwhile. Data from the TORCH study showed that good adherence (> 80% of doses) to inhaled COPD medication is associated with a significantly decreased risk of mortality and hospital admission for severe exacerbations over 3 years.\(^\text{43}\)

Factors related to the patient (eg, health beliefs, self-efficacy, comorbidities, psychologic profile), the treatment (eg, dosing regimen, polypharmacy, side effects, method of administration), society (eg, social support, patient-prescriber relationship, access to medication, inhaler technique training), and health professionals (eg, education, goal setting, regular follow-up visits) can affect adherence.\(^\text{41}\) In particular, depression is a major contributor to poor adherence in patients with COPD, and its treatment substantially improves quality of life.\(^\text{44}\) Questionnaires including the Hospital Anxiety and Depression Questionnaire\(^\text{44}\) and the Patient Health Questionnaire-9\(^\text{45}\) (http://www.phqscreeners.com/pdfs/02_PHQ-9/English.pdf) can help to identify patients who have significant anxiety and depression.

**PULMONARY REHABILITATION**

Pulmonary rehabilitation improves exercise capacity and health-related quality of life and reduces hospitalizations, perceived dyspnea intensity, anxiety, and depression in patients across all COPD severity levels.\(^\text{4}\) Components include exercise training, nutrition counseling, psychosocial support, and education.\(^\text{46}\) Exercise training programs generally range from 4 to 10 weeks, with greater benefits observed with longer programs.\(^\text{4,44}\) Strength training is especially important for patients with substantial muscle atrophy,\(^\text{46}\) while inspiratory muscle training may improve inspiratory muscle strength and decrease dyspnea.\(^\text{47}\) As part of nutrition counseling, physicians should ensure that patients with COPD who are underweight have adequate caloric intake and overweight patients have a diet that encourages fat loss.\(^\text{46}\) Maintenance of pulmonary rehabilitation is important, as benefits wane without continued exercise.\(^\text{6}\)

**LONG-TERM OXYGEN THERAPY**

Patients with very severe COPD may require oxygen therapy to ensure that vital organs receive adequate oxygen.\(^\text{6}\) Supplemental oxygen therapy improves exercise capacity, ventilation, and neuropsychological performance (ie, memory and learning).\(^\text{48}\) The need for long-term oxygen therapy (> 15 hours per day), which increases survival in patients with chronic respiratory failure,\(^\text{6}\) is determined by the patient’s arterial blood gas values. Treatment goals include increased baseline partial pressure of arterial oxygen to \(\geq 60\) mm Hg and/or production of \(\geq 90\%\) oxygen saturation.\(^\text{9}\)

**SURGICAL TREATMENTS AND NEW AND EMERGING PHARMACOLOGIC TREATMENTS**

Certain surgical treatments may be considered in carefully selected patients. Bullectomy, which involves removal of a large bulla in select patients with bullous emphysema, decompresses pulmonary parenchyma and improves pulmonary function and dyspnea.\(^\text{6}\) Lung volume reduction surgery improves expiratory flow rate by reducing hyperinflation and increasing lung elastic recoil.\(^\text{6}\) Compared with optimal medical therapy for severe COPD, lung volume reduction surgery has been shown to reduce the frequency of COPD exacerbations and increase the time to first exacerbation;\(^\text{49}\) it also has been shown to decrease mortality in patients with upper-lobe predominant COPD and low exercise capacity.\(^\text{50}\) However, this costly procedure is recommended only in carefully selected patients.\(^\text{6}\) Lung transplantation is a rare therapy for COPD.\(^\text{8}\)

Combinations of existing therapies and new pharmacological approaches are available or are currently in development. Data from a randomized, double-blind study of patients with COPD suggest that LABA/LAMA combination treatment may provide improved bronchodilator efficacy versus LABA/ICS combination treatments.\(^\text{31}\) “Triple therapy” with a LAMA, LABA, and ICS can improve pulmonary function and COPD symptoms and reduce the rates of exacerbations versus an anticholinergic alone.\(^\text{6,32-34}\) The phosphodiesterase-4 inhibitor roflumilast was US FDA-approved in 2011 as an oral medication.\(^\text{55}\) Patients with severe or very severe COPD and a history of exacerbations have fewer moderate or severe exacerbations.
### Table 2 – Characteristics of and treatment recommendations for specific phenotypes of COPD

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Characteristics</th>
<th>Recommendations for treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchitic</td>
<td>Mucus hypersecretion resulting in chronic productive cough</td>
<td>GOLD guidelines by disease severity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Treatment with mucolytic agents</td>
</tr>
<tr>
<td>Emphysematous</td>
<td>Gas exchange abnormalities</td>
<td>GOLD guidelines by disease severity</td>
</tr>
<tr>
<td></td>
<td>Limitations in functional capacity</td>
<td></td>
</tr>
<tr>
<td>Rapid, recurrent exacerbations</td>
<td>Presence of chronic cough and sputum production</td>
<td>ICS and long-acting bronchodilator therapy, according to GOLD 2010 guidelines</td>
</tr>
<tr>
<td></td>
<td>Faster rates of lung function decline</td>
<td>Addition of an ICS/LABA combination to LAMA improves lung function and decreases symptoms and rates of exacerbations compared with an anticholinergic alone.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PDE-4 inhibitor (e.g., roflumilast) reduces exacerbations in patients with severe COPD and history of exacerbations.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Antibiotics only for treating infectious exacerbations of COPD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Acute treatment with oral corticosteroids during exacerbations; chronic treatment should be avoided</td>
</tr>
<tr>
<td>Rapid decline in lung function</td>
<td>May be associated with chronic mucus hypersecretion</td>
<td>GOLD guidelines by disease severity</td>
</tr>
<tr>
<td></td>
<td>May occur in patients with rapid, recurrent exacerbations</td>
<td></td>
</tr>
<tr>
<td>Disease characteristics similar to asthma</td>
<td>Patients with asthma who are exposed to noxious agents (e.g., cigarette smoke)</td>
<td>GOLD guidelines by disease severity</td>
</tr>
<tr>
<td></td>
<td>Patients with long-standing asthma who develop fixed airflow limitation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Patients with COPD who may have features of asthma, such as a mixed inflammatory pattern with increased eosinophils</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Patients with late-onset tobacco-related COPD with an airway-dominant phenotype and relatively little emphysema</td>
<td></td>
</tr>
<tr>
<td>Systemic inflammation</td>
<td>Presence of elevated biomarkers (e.g., C-reactive protein, serum amyloid A, interleukin-6, interleukin-8, tumor necrosis factor α, leukocytes)</td>
<td>GOLD guidelines by disease severity</td>
</tr>
<tr>
<td>Systemic involvement and multiple morbidities</td>
<td>Extra-pulmonary manifestations, which may be poorly related to the degree of airflow limitation</td>
<td>GOLD guidelines by disease severity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Treatment specific to comorbidity</td>
</tr>
</tbody>
</table>

COPD, chronic obstructive pulmonary disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ICS, inhaled corticosteroid; LABA, long-acting β2-adrenergic agonist; LAMA, long-acting muscarinic antagonist; PDE-4, phosphodiesterase-4.
with roflumilast versus placebo, regardless of concomitant use of LABAs. Once-daily LABAs, termed “ultra-LABAs,” such as indacaterol (US FDA-approved in 2011), may help improve adherence, although this has not been shown in clinical trials. Ultra-LABA/LAMA combinations (eg, indacaterol/glycopyrronium) are currently in development.

Existing pharmacologic therapies for COPD do not reduce long-term declines in lung function; there are no novel therapies that modify disease progression. Potential approaches for future COPD treatments may include agents that activate histone deacetylase-2 or inhibit phosphoinositide 3-kinase to improve sensitivity to ICS and inhibitors of p38 kinase and cathepsin C to decrease inflammation.

COPD PHENOTYPING

Early studies suggest that COPD clinical subpopulations, such as “frequent exacerbators,” may require more aggressive COPD management earlier in the disease. Data from the COPDGene study showed an association between chronic bronchitis and younger age, smoking, worse respiratory symptoms, and a greater history of severe exacerbations. These findings suggest that for patients with COPD with chronic bronchitis, reducing mucus production and smoking cessation may be extremely important.

Other research is ongoing in the Subpopulations and Intermediate Outcomes Measures in COPD Study (Spiromics; http://www.cscce.unc.edu/spir/), the COPDGene Study (http://www.copdgene.org/), and the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) study (http://www.eclipse-copd.com/) assessing mechanisms and identifying potential measures of disease progression.

Historical phenotypes (chronic bronchitis and emphysema) and those that have been proposed based on clinical manifestations are described in Table 2.

CONCLUSIONS

Several pharmacological therapies are available for the treatment of COPD. Current Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines recommend treatment selection according to the patient’s disease severity. Within a severity category, patient phenotypes and other disease characteristics, device selection, and costs may influence the choice of therapy. Initiation and maintenance of pulmonary rehabilitation programs are important for optimal COPD management in all patients with COPD. Careful monitoring of patients during therapy is necessary to recognize disease worsening and the need for changes in treatment. Improving patient adherence and screening for comorbidities such as depression also contribute to better disease management. In the future, novel therapies may improve bronchodilator efficacy and reduce side effects compared with current treatments and modify disease progression.

Acknowledgments

The author thanks Kristen Quinn, PhD, Amny Wu, PharmD, and Cynthia Gobbel, PhD, from Scientific Connexions (Newtown, PA) who provided medical writing support funded by AstraZeneca LP (Wilmington, DE).

REFERENCES


Sciurba FC. Physiologic similarities and differences between COPD and asthma. Chest. 2004;126:1179-124S.


