New Concepts to Improve Health Outcomes for Patients
With Chronic Obstructive Pulmonary Disease

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TARGET AUDIENCE

Clinical pharmacists involved in the care of patients with respiratory disease

LEARNING OBJECTIVES

Upon completion of this program, participants will be better able to

1. identify strategies to address the underdiagnosis of COPD,
2. discuss the common misperception that patients frequently present with both asthma and COPD,
3. describe the differences between COPD and asthma pathophysiology,
4. discuss COPD treatment guidelines, including the benefits of early treatment, and
5. review the role of long-acting bronchodilators in the treatment of COPD, including the importance of adherence to therapy.

Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality in the United States and throughout the world. In 2000, an estimated 10 million U.S. adults reported physician-diagnosed COPD. An additional 14 million adults have evidence of impaired lung function but have not been diagnosed. The prevalence of COPD increases with age. However, contrary to common perceptions, data from the National Health Interview Survey indicate that approximately 70% of COPD patients are younger than 65 years. Furthermore, in a recent study of managed care enrollees, approximately one half of patients with COPD seeking health care services were in the 45- to 64-year-old age group.

According to the Global Burden of Disease Assessment, in 1990, COPD was ranked twelfth in terms of global economic burden of disease, and by 2020, it is expected to be ranked fifth. In the United States, total economic costs associated with COPD exceeded \$18 billion in 2002. The majority of direct costs (i.e., health expenditures) associated with COPD are a consequence of hospitalizations, which are related to acute exacerbations of the disease. COPD also leads to substantial reductions in patients' functional capacity (e.g., walking), ability to perform activities of daily living, and health-related quality of life.

In an effort to help promote national awareness of COPD in the United States, the American College of Chest Physicians (ACCP) recently announced its support for the new Congressional Chronic Pulmonary Disease Caucus. The primary goals of the caucus include issues such as public awareness, patient access to care, early detection and prevention, and research funding. According to Richard Irwin, MD, president of ACCP, "COPD attacks adult patients at the height of their productive years, destroying their ability to earn a living and severely decreasing their quality of life."

Several classes of pharmacologic agents are available for maintenance treatment of COPD. According to the 2003 update to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines, regular treatment with long-acting bronchodilators is more effective and convenient than treatment with short-acting bronchodilators and is recommended as maintenance therapy. Long-acting bronchodilators now include 2 classes of medication: long-acting β -adrenergic agonists and a newly available long-acting anticholinergic tiotropium bromide inhalation powder.

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Analysis of the Current Care Model of the COPD Patient: A Health Outcomes Assessment and Economic Evaluation

NEIL B. MINKOFF, MD

ABSTRACT

OBJECTIVE: Because chronic obstructive pulmonary disease (COPD) is a common but serious illness affecting millions worldwide, we present an overview of the disease and discuss its underdiagnosis and treatment options.

SUMMARY: COPD, a disease encompassing emphysema and chronic bronchitis, is associated with cigarette smoking, chronic exposure to environmental pollutants, and, occasionally, genetic conditions. The disease is severely underdiagnosed and underrecognized. The economic costs of COPD, which accounted for about 14 million office visits and 3.5 million hospital days in 1993, are estimated at more than \$7 billion, and another \$8 billion worth of productivity was lost to morbidity and mortality in the same year.¹ The death rate from COPD is rising, principally among women. Uniform diagnosis and treatment standards are now being realized. The American Thoracic Society and European Respiratory Society recommend treatment, based on worsening symptoms, with bronchodilators and, in more advanced cases, inhaled corticosteroids. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) treatment algorithm also uses a step-care approach. The GOLD guidelines recommend a management program that prevents disease progression, relieves symptoms, improves exercise tolerance and health status, and prevents and treats complications and exacerbations, thereby reducing mortality. The GOLD guidelines recommend avoiding risk factors, using short- or long-acting bronchodilators, and adding rehabilitation and inhaled glucocorticoids. In severe cases, the GOLD guidelines recommend long-term oxygen administration and even surgery. Decisions in managing COPD require a consideration of multiple outcomes measures. Although spirometry remains the foundation for diagnosis and demonstration of efficacy, the patients and their families may be more concerned with symptoms, quality of life, and prevention of exacerbations. In patients with COPD, bronchodilators such as tiotropium produce significant improvements in all of these outcomes measures.

CONCLUSIONS: COPD is a common disease that substantially affects patients, health care systems, and society. With increasing awareness of the disease, improved diagnostic guidelines, and newer cost-effective pharmacologic regimens, this chronic progressive disorder can be effectively recognized and treated, helping to improve patients' overall health and quality of life.

KEYWORDS: Chronic obstructive pulmonary disease (COPD); Treatment, lung diseases, obstructive; Emphysema; Chronic bronchitis

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Chronic Obstructive Pulmonary Disease (COPD)

Definition

COPD is a mixture of separate disease processes that are characterized by chronic inflammation throughout the airways, parenchyma, and pulmonary vasculature.² Most notably, the diseases that fall under the umbrella term of COPD are emphysema and chronic bronchitis. Specifically, emphysema is marked by alveolar wall destruction and irreversible enlargement of the air spaces distal to the terminal bronchioles; chronic bronchitis is defined as a productive cough present for 3 months in each of 2 consecutive years in the absence of other identifiable causes of excessive mucus production. Objectively, COPD is diagnosed through pulmonary function testing (spirometry). In the early stages of the disease, the forced expiratory volume (FEV₁), the amount of air that can be expelled from the lungs in 1 second, is <80% of that expected. In addition, a ratio of FEV₁ over forced vital capacity (FVC), or the volume of air forcibly exhaled after deep inspiration, is <70% of what is considered normal in a person at this stage. Over time, these percentages decrease as the disease progresses to more advanced stages.

Symptoms

The main symptoms of COPD are chronic cough, mucus production, and dyspnea. Even during the early stages of the disease, coughing is usually chronic and productive and tends to persist over several months and even years. Significant production of mucus (sputum) is often associated with the cough. Dyspnea, a hallmark symptom of COPD, is usually noticed first as shortness of breath on exertion. All of these symptoms are progressive.

The underlying causes of these symptoms are multifactorial. One main cause is emphysema: a progressive destruction of alveolar tissue and related vasculature, limiting the surface area for oxygen and carbon dioxide exchange, and the resulting hypoxemia produces pulmonary vasoconstriction. Fibrosis in bronchial walls and smooth muscle contraction around bronchial tubes results in airway narrowing and dyspnea. Bronchospasm, repeated smooth muscle contraction, causes the patient to cough and expel sputum. Progressive blockage of the airways by exudates and mucus also contributes to symptoms of coughing and dyspnea.

Risk Factors

The single most prevalent risk factor for COPD is cigarette smoking,³ to the extent where smoking cessation or even a decrease in smoking can substantially reduce the risk for the development and rate of progression of COPD.⁴ In addition, epidemiologic studies have implicated childhood respiratory infections as an independent

FIGURE 1 Proportion of 1965-1998 Rate Percentage Change in Age-Adjusted Deaths in the United States

Source: Global Initiative for Chronic Pulmonary Disease. GOLD Teaching Slide #10.²⁴
COPD=chronic obstructive pulmonary disease; CVD=cardiovascular disease.

risk factor for the subsequent development of persistent asthma and COPD.⁵ A relatively rare genetic condition, alpha₁ antitrypsin (AAT) deficiency, is also a potential risk for pulmonary disease such as emphysema and COPD.^{6,7} Another main risk factor for developing COPD is chronic exposure to fumes, chemical substances, and dust in the workplace—usually factories. For example, inhalation of grain dust, coal, other mineral dusts, isocyanates, heavy metal adhesives, and welding fumes have been linked to COPD in mining, quarrying, construction, textile, and wood industries.⁸

Impact of COPD

The prevalence of COPD may be much greater than published data indicate because the disease is usually not diagnosed until it is sufficiently advanced to give rise to obvious symptoms.⁹ Although it has been traditionally considered a disease of the elderly, COPD definitely afflicts the working-age population as well.¹⁰ According to the 1995 National Ambulatory Medical Care Survey, approximately 70% of COPD patients were under the age of 65 years, and they accounted for 67% of total COPD office visits and 43% of all hospitalizations.¹⁰ Another common misconception is that COPD is uncommon in the general population.¹¹ It is, in fact, a common chronic disease. In a survey of patients with chronic diseases, the prevalence of COPD was comparable with that of diabetes, asthma, and congestive heart failure in the 45- to 64-year-old age group and increased in prevalence in older patients.¹¹ The disease has been more prevalent in men than in women, but some recent studies suggest that this may be changing. One study showed that, in 2002, more than 33% of COPD patients were female, a figure that is likely to increase.¹² The women's death rate due to COPD is also rising. According to a 2002 mortality and morbidity report,¹³ during the period 1980-2000, the COPD death rate of women rose 2.8 times, from 20.1

to 56.7 per 100,000 women; this is compared with a more modest increase in the death rate for men, from 73.0 to 82.5 per 100,000 men. Meanwhile, in 2000, the number of women dying from COPD surpassed the number of men dying from the disease (59,936 women versus 59,118 men) for the first time.

Mortality, Morbidity, Economic and Human Burdens

COPD often escapes diagnosis and treatment, and primary care physicians and patients underrecognize the large impact of this disease.^{12,13} In 2000, an estimated 10 million U.S. adults reported physician-diagnosed COPD. COPD represents massive and growing economic and social burdens in terms of mortality and morbidity. In 2000, COPD was the second leading cause of disability after heart disease.¹⁴ In that same year, COPD was responsible for 8 million physician office and hospital outpatient visits, 1.5 million emergency department visits, 726,000 hospitalizations, and 119,000 deaths.¹³ In 1997 in the United States alone, obstructive lung disease (i.e., chronic bronchitis, emphysema, asthma) was the fourth most common cause of death, accounting for more than 109,000 deaths.¹³ By 2020, COPD is expected to rise from the fourth to the third leading cause of death. As shown in Figure 1, this is largely because of a continuing reduction in mortality from coronary heart disease and stroke.¹²

The economic burden of COPD is enormous. According to the National Heart, Lung, and Blood Institute, the direct total costs for COPD grew from \$18 billion to \$20.9 billion between 2002 and 2004,^{2,14} a rise attributed to increased hospitalizations. In 2002, COPD was responsible for 1,763 million bed days and 57.5 million lost work days, making it the sixth worst disease for lost work days in the United States.¹⁵ Exacerbations of respiratory symptoms are common and a primary contributor of morbidity, mortality, and costs of the illness.¹⁶ As the disease progresses and exacerbations increase, the patients' health-related quality of life dramatically deteriorates¹⁷ as they experience progressively worsening impairments in their ability to socialize, work, and even walk. Therefore, reducing exacerbations and improving life quality are two of the major outcome measures of treatment.

Treatment of COPD: Differing Approaches

Nonpharmacologic Treatments

There are several nonpharmacologic treatments for COPD, many of which are adjuncts to pharmacologic therapy. *Oxygen therapy*, or the long-term administration of pure oxygen (>15 hours daily) is usually introduced in severe (Stage IV) COPD.² *Ventilatory support* may be administered in severe and end-stage patients.² Several surgical options are also used in more advanced cases of COPD. *Bulectomy* in selected patients can be effective for reducing dyspnea and improving lung function; *lung-volume reduction surgery* is still an unproven palliative procedure; and *lung transplantation*, indicated only for very advanced, end-stage COPD, has been shown to improve quality of life and functional capacity.² *Pulmonary rehabilitation programs* (PRPs) are specifically

designed for patients with chronic lung disease.¹⁸ PRPs focus on improving the quality of life for patients by adhering to a variety of objectives, such as disease education, coping methods, physical exercise strategies, and the importance of self-esteem.¹⁸ While PRPs are recommended as an integral aspect of care for COPD,¹⁹ these programs alone may not improve pulmonary measures. A longitudinal study of one PRP on health outcomes of 36 patients with COPD ($FEV_1 < 60\%$ predicted)²⁰ showed improvement in exercise endurance, reduced dyspnea and hospitalization/length of stay, and improved quality of life. However, in this study, objective measures of lung function (FEV_1 , FVC) or oxygen saturation did not improve during the 12 months following completion of the PRP.

COPD Treatment Algorithms

American Thoracic Society (ATS) European Respiratory Society (ERS) Treatment Algorithm

There has been an increasing focus on treatment standards that incorporate pharmacologic agents with known efficacy. The ATS and ERS published a 2004 update to its treatment algorithm, which recommended step therapy on the basis of worsening symptoms (Figure 2).⁹ According to the ATS/ERS treatment guidelines, patients with intermittent COPD symptoms (coughing, wheezing, exertional dyspnea) should be treated with a short-acting bronchodilator or oral or inhaled anticholinergic agent. Patients with more persistent symptoms (dyspnea, night waking) are recommended for treatment with a long-acting bronchodilator² plus additional reliever medications. If there is only a limited benefit to this approach, alternative classes of drugs or combinations of long-acting bronchodilators and inhaled corticosteroids are recommended. Because of its anticholinergic effects, theophylline is recommended as a third-line agent but is not favored because of the need for drug-level monitoring and certain drug-drug interactions.

Global Initiative for Chronic Obstructive Lung Disease (GOLD) Treatment Algorithm

The other treatment algorithm comes from the GOLD guidelines.¹⁶ The goals outlined in the GOLD guidelines are to (1) prevent disease progression, (2) relieve symptoms, (3) improve exercise tolerance and health status, (4) prevent and treat complications and exacerbations, and (5) reduce mortality.

The GOLD criteria classify COPD into 5 stages:

1. *Stage 0* identifies those patients who are at risk for COPD, such as a patient who has chronic symptoms but normal spirometry measures and is exposed to risk factors, such as cigarette smoking.
2. *Stage I* is mild COPD with an $FEV_1/FVC < 70\%$ and $FEV_1 \geq 80\%$ predicted, with or without symptoms.
3. *Stage II* is moderate, characterized by worsening airflow limitation ($50\% \leq FEV_1 < 80\%$ predicted) and, usually, progression of symptoms, with shortness of breath developing on exertions. Patients often seek medical attention at this stage

FIGURE 2 Algorithm for Pharmacological Treatment of COPD

COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in 1 second; ICS = inhaled corticosteroid; LA-BD = long-acting bronchodilator; SA-BD = short-acting bronchodilator.

Assess effectiveness by treatment response criteria. If FEV_1 is $< 50\%$ predicted and exacerbations of COPD requiring a course of oral corticosteroid or antibiotic occurred at least once within the last year, consider adding regular ICS. If an ICS and a long-acting β -agonist are used, prescribe a combination inhaler. After Celli et al., Figure 1.⁹

because of dyspnea or exacerbation of their disease.

4. *Stage III* is severe COPD characterized by worsening airflow limitation ($30\% \leq FEV_1 < 50\%$ predicted) and repeated exacerbations.
5. By *Stage IV*, there is severe airflow restriction ($FEV_1 < 30\%$ predicted), or the presence of chronic respiratory failure.

As shown in Table 1, the GOLD treatment recommendation uses a step-therapy approach. At Stage 0, the patient should avoid risk factors and obtain an influenza vaccination. As the patient begins to develop mild COPD in Stage I, short-acting bronchodilators should be added. At Stage II (moderate) COPD, regular treatment with at least one long-acting bronchodilator and adjuvant pulmonary rehabilitation is recommended. At Stage III (severe), if the patient continues to have multiple exacerbations, an inhaled corticosteroid is added. By Stage IV (very severe), long-term oxygen therapy is required if there is chronic respiratory failure, and physicians should consider surgical therapy. By Stage IV, patients who need the surgery are often poorer surgical candidates because of significant heart strain and chronic anoxia.

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TABLE 1 Global Initiative for Chronic & Obstructive Lung Disease Schematic: Therapy at Each Stage of Chronic Obstructive Pulmonary Disease

Stage 0. At Risk	Stage I. Mild	Stage II. Moderate	Stage III. Severe	Stage IV. Very Severe
Avoidance of risk factor(s); influenza vaccination				
	Add short-acting bronchodilator when needed			
		Add regular treatment with one or more long-acting bronchodilators Add rehabilitation		
			Add inhaled glucocorticosteroids if repeated exacerbations	
				Add long-term oxygen if chronic respiratory failure Consider surgical treatments

Adapted from Pauwels et al., Table 8.¹⁶

Bronchodilators

Bronchodilators are a central medication class for managing COPD. A patient's symptom relief and adverse-event profile may help direct the type of bronchodilator therapy: anticholinergic, β -agonist, or theophylline. Bronchodilators are prescribed as needed or regularly to prevent or reduce symptoms. The long-acting bronchodilators are more effective and convenient, but acquisition cost is more expensive. Rather than increasing the dose of a specific bronchodilator, it has been theorized that combining short-acting bronchodilators may improve efficacy and decrease the risk of adverse reactions by reducing the dose of one or both agents.¹⁶

COPD is a long-term chronic condition that requires ongoing treatment. Reducing exacerbations can help to lower the costs of treatment. Two separate publications have demonstrated the cost-savings potential of bronchodilators in treating COPD. Friedman et al. evaluated 2 double-blind, randomized, prospective studies with a total of 1,067 patients with COPD that compared inhaled ipratropium/albuterol combination therapy with either drug alone for the treatment of COPD.²¹ Compared with albuterol alone, both the combination therapy and ipratropium alone decreased exacerbations by 33%, translating to a 24% lower cost in each group. The reduced costs resulted from reductions in add-on therapy and hospitalizations. As a result, the total cost of treatment over the duration of the study period was significantly less for ipratropium (\$156 per patient) and ipratropium plus albuterol (\$197 per patient) than for albuterol (\$269 per patient). Increased cost-effectiveness, defined as total estimated treatment cost per mean change in FEV₁, was observed in both treatment arms containing ipratropium. A second study assessed the economic impact of combined inhaled bronchodilator therapy in treating COPD.²² A total of 641 patients were treated with a combination of ipratropium and albuterol in one inhaler while 411 patients received both ipratropium bromide and albuterol in separate

inhalers. Although patients using the combination inhaler did not differ in treatment outcomes from patients in the comparator arms, they realized a significant cost savings due to a difference in medication costs.

Measuring Treatment Outcomes

COPD is a progressive disease with frequent exacerbations that deteriorate patients' ability to walk, participate in social activities, and work. Therefore, COPD management assessment must take into consideration improvements in exacerbations and hospitalization as well as other health-related measures such as quality of life and patients' self-assessments.

These measurements are important in assessing successful treatment outcomes and were demonstrated in 2 one-year, head-to-head studies in patients receiving tiotropium 18 μ g once daily (n = 356) or ipratropium 40 μ g 4 times daily (n = 179).²³ Overall, tiotropium led to significant improvements in all of the primary study outcome measures. FEV₁ at one year improved by 0.12 $\pm$ 0.01 L with tiotropium and declined by 0.03 $\pm$ 0.02 L with ipratropium ($P < 0.001$). Significant improvement in PEF, salbutamol use, Transition Dyspnea Index focal score, and the St. George's Respiratory Questionnaire total and impact scores were seen with tiotropium ($P < 0.01$). Also, tiotropium reduced the number of exacerbations by 24%, ($P < 0.01$) and increased time to first exacerbation ($P < 0.01$) and time to first hospitalization for a COPD exacerbation ($P < 0.05$) compared with ipratropium. The number of exacerbations per patient per year was reduced by 24%, and the number of exacerbation days was reduced by 39% for patients receiving tiotropium. The time to first exacerbation was significantly longer in patients receiving tiotropium. Finally, the proportion of patients hospitalized for a COPD exacerbation in the year-long study was significantly reduced in those receiving tiotropium.

While adjunctive therapies, such as pulmonary rehabilitation programs, can be helpful in controlling symptoms and improving quality of life, they do not improve lung function in patients with COPD.¹⁹ To evaluate effective therapy, one must also examine cost-effective therapy to make decisions based on patients' coverage and what would constitute appropriate therapy. Overall, decisions in managing COPD require a consideration of multiple outcome measures, including reductions in exacerbations and hospitalizations. Although spirometry remains the foundation for diagnosis and demonstration of drug efficacy, patients and their families may be more concerned with symptoms, quality of life, and prevention of exacerbations.

Conclusions

COPD is a common disease that substantially affects patients and health care systems and is associated with increasing economic and social burdens. COPD ranks as the fourth leading cause of death in the United States, surpassed only by heart disease, cancer, and cerebrovascular disease. The disease is associated with

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frequent and progressively worsening exacerbations, which are associated with high levels of morbidity and mortality. Despite the substantial burden of illness and the available treatment options, COPD continues to present challenges to patients and physicians. Physicians can help to increase awareness of the disease and increase their patients' understanding of treatment options and guidelines, particularly early in the course of this disease. Placebo-controlled trials and head-to-head comparison trials demonstrate the efficacy of tiotropium as a drug for the maintenance treatment of COPD.

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COPD: Clinical Significance of Early Diagnosis

RICHARD D. LEFF, PharmD, FCCP

ABSTRACT

OBJECTIVE: To explain the differential diagnosis of chronic obstructive pulmonary disease (COPD) and how COPD can be distinguished in patients who present with complaints of dyspnea, (shortness of breath on exertion), with the goal of improving earlier diagnosis.

SUMMARY: It is important to differentiate COPD from other diagnoses when adult patients present with dyspnea. There are several key diagnostic indicators for COPD, including, most notably, a history of smoking and objective lung-function measurements. COPD remains an underdiagnosed disease, chiefly in its milder and more treatable form. The Global Initiative for Chronic Obstructive Lung Disease (GOLD)-defined standards for COPD management consist of 4 components: (1) assess and monitor disease, (2) reduce risk factors, (3) manage stable COPD through education and nonpharmacologic and pharmacologic means, and (4) manage exacerbations.

CONCLUSION: Updated standards for diagnosis and treatment-targeted pharmacologic agents have provided physicians and health care workers with more specific and targeted treatment modalities for early detection and treatment of this progressive disease. Early detection and more accurate diagnosis are key in improving outcomes and altering the progression of the disease.

KEYWORDS: Chronic obstructive pulmonary disease (COPD); Lung diseases, obstructive; Bronchodilators; Tiotropium; Fluticasone; Salmeterol; Corticosteroid

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Chronic obstructive pulmonary disease (COPD), a disease encompassing emphysema and chronic bronchitis, presents with various symptoms. Many of the features of asthma and COPD may be similar in patients, but it is important to differentiate COPD from asthma in adult patients who present with dyspnea (shortness of breath on exertion). The objective of this article is to discuss how COPD is distinguished from asthma. To accomplish this, we will review COPD, its typical presentations, diagnostic tools, and an approach to management.

■ COPD: A Picture of the Disease

An Underdiagnosed Disease

Over the past 30 years, epidemiological data indicate that COPD in the United States is largely underdiagnosed and misdiagnosed.¹ An estimated 10 million adults in this country reported a physician diagnosis of COPD in 2000,¹ and data from the Third National Health and Nutrition Examination Survey (NHANES III) suggest that nearly 24 million U.S. adults have evidence of some type of impaired lung function.¹ During 2000, COPD was responsible for 8 million physician office and hospital outpatient visits, 1.5 million emergency department visits, 726,000 hospitalizations, and 119,000 deaths.¹ Moreover, the Centers for Disease Control and Prevention conclude that “despite its ease of diagnosis, COPD remains an underdiagnosed disease, chiefly in its milder and more treatable form.”¹

Definition and Differentiation of COPD

Global Initiative for Chronic Obstructive Lung Disease (GOLD)

In 2001, the National Heart, Lung, and Blood Institute/World Health Organization (NHLBI/WHO) GOLD workshop set forth standards for diagnosing and managing COPD, which characterize the disease as marked by airflow limitation that is not fully reversible.² This airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases such as cigarette smoke or environmental pollutants. Characteristic symptoms of COPD are cough, with and without sputum production, and dyspnea on exertion and often at rest. The patient may present with a chronic cough and sputum, which often precedes airflow limitation by many years.

Spectrum and Differentiation of COPD

Asthma symptoms overlap with COPD symptoms in some patients, and patients can present with a mixed disease that combines features of both disorders. However, it is important to understand the similarities and differences between their diagnosis and treatment. The NHLBI/WHO GOLD workshop set forth standards for the differential diagnosis of COPD (Table 1).³ Because the symptoms of each disorder are sometimes difficult to distinguish, medical history can be very helpful. For example, asthma often presents in childhood and is characterized by reversible airway reactivity with notable triggers and varying daily

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symptoms. Patients with asthma may have a history of allergies, rhinitis, and eczema. Most cases of asthma respond reasonably well to inhaled corticosteroids. COPD patients often have a history of smoking and/or exposure to pollutants. In comparison with patients with asthma, those with COPD have a largely irreversible airflow limitation and may or may not respond to inhaled or oral corticosteroids; they also present with exertional dyspnea.

Pathophysiology of COPD

Micrographic and Radiologic Evidence

Alveolar destruction with emphysema is one of the signs of COPD. Scanning electron microscopic examination of emphysematous lung sections demonstrate characteristic destruction of tissue, loss and collapse of regularly shaped alveoli, and enlarged alveolar ducts.⁴ The lungs in these patients lose elasticity and undergo airway collapse. As a result, air remains trapped in the lung, which is a characteristic sign of COPD. A typical X-ray of a patient with COPD (Figure 1), shows hyperinflation and air trapping manifested as an enlarged heart diameter, low and flattened diaphragm (left panel), and increased anterior-posterior diameter and retrosternal space (right panel).

Diagnostic Features of COPD

History

A patient's history is important in diagnosing COPD. COPD should be considered in any patient with a smoking history, particularly those with at least ≥ 10 pack-years (number of packs smoked daily multiplied by the number of years smoking) or a history of exposure to other risk factors, such as environmental pollutants.⁵ A diagnosis of COPD should also be considered in an adult patient complaining of dyspnea, a persistent or recurring respiratory infection, or chronic cough with or without sputum. Finally, patients with respiratory symptoms beginning in midlife might be suspected of having COPD.

Spirometry

Lung volume measurements are important diagnostic tools in COPD. Comparison of lung volumes in patients with COPD with normal individuals (Figure 2) reveals large decreases in inspirational capacity (IC), the maximum volume of air that can be inhaled from rest, and large increases in the functional residual capacity (FRC), the volume of air in the lungs at resting end-expiration. There is considerable air trapping in COPD. The tidal volume (VT), the volume of air inhaled and exhaled during each breath, is typically low and does not change dramatically in COPD. As a result, patients cannot expel the large amounts of trapped air in their lungs, and their capacity to bring in fresh air is reduced, resulting in bodily oxygen starvation. Expiratory airflow limitation is the notable physiological change characteristic of COPD.

Evidence indicates that history and physical examination are insufficient for diagnosing mild and moderate obstructive ventilatory impairment.⁶ Spirometry is the preferred assessment of lung

TABLE 1 Differential Diagnosis of COPD

COPD	Asthma
Onset in midlife	Onset in early life (usually childhood)
Symptoms progress slowly; wheezing and chest tightness are nonspecific symptoms that may vary daily and in the course of a single day	Symptoms are often exacerbated by triggers that may vary daily
Long smoking history or history of exposure to environmental pollutants	There may be a family history of allergies or asthma
	Patient may have concomitant allergy, rhinitis, and/or eczema
Airflow limitation largely irreversible.	Airflow limitation largely reversible
Patients may or may not respond to corticosteroids and do not usually benefit from mucolytic agents and antitussives	Patients generally respond to corticosteroids
Dyspnea during exercise	

Adapted from reference 3. COPD=chronic obstructive pulmonary disease.

FIGURE 1 Chest X-ray Picture of Patient With COPD

Left panel shows air trapping and a low, flattened diaphragm. Right panel shows an increased anterior-posterior diameter and retrosternal space.

COPD = chronic obstructive pulmonary disease. Source: Richard D. Leff, PharmD, FCCP.

function impairment for diagnosing COPD because it can produce adequate information in a cost-effective manner. The most important spirometric maneuver is the forced vital capacity (FVC), the air volume exhaled during a maximal forced expiration. Normal lungs generally can empty more than 80% of their residual volume in ≤ 6 seconds. The forced expiratory volume in 1 second (FEV₁) is the volume of air exhaled in the first second of the FVC maneuver. The FEV₁/FVC ratio is expressed as a percentage (e.g., FEV₁ of 0.5 L divided by FVC of 2.0 L gives an FEV₁/FVC ratio of 25%). COPD patients experience a progressive decline of these ratios as their disease progresses.

In the GOLD criteria for staging, Stage 0 includes patients who have normal spirometric measures; Stage I includes an FEV₁/FVC at $< 70\%$ and FEV₁ $\geq 80\%$ predicted; Stage II is characterized by $50\% \leq \text{FEV}_1 < 80\%$ predicted; Stage III is severe COPD characterized by worsening airflow limitation ($30\% \leq \text{FEV}_1 < 50\%$ predicted) and repeated exacerbations; Stage IV includes

FIGURE 2 Comparison of Lung Volume Parameters in Normal Person and Patient With COPD

COPD=chronic obstructive pulmonary disease; ERV=expiratory reserve volume; FRC=functional residual capacity; IC=inspiratory capacity; IRV=inspiratory reserve volume; RV=residual volume; TLC=total lung capacity; V_T =tidal volume.

FIGURE 3 Spirometry Measurement of Forced Expiratory Volume (FEV_1) in a Normal Individual and a COPD Patient Showing a Reduced FEV_1 in 1 Second in COPD

Spirometry measures maximal volume of air forcibly exhaled from the point of maximal inhalation and the volume of air exhaled during the first second.

Adapted from reference 7.

COPD=chronic obstructive pulmonary disease.

patients with severe airflow restriction ($FEV_1 < 30\%$ predicted).² These differences are illustrated in Figure 3, showing the spirometry measurement of a normal individual and a patient with COPD.⁷

COPD is progressive and can be attributed to initial complex biochemical and cellular events in the small airways and surrounding alveoli.⁸ Structural damage leads to a loss of elastic recoil, the lungs begin to increase in size, and FVC increases. This results in early physiologic alterations that can be readily identified by simple spirometry.

An epidemiological study showed that FEV_1 values are associated with a gradual age-related decline over the course of a nonsmoker's life.⁹ In susceptible people, smoking causes irreversible obstructive changes and lost pulmonary function. However, at the time of smoking cessation, further FEV_1 changes will revert to a more normal, age-related decline. Severe or fatal obstructive lung disease could thus be prevented only by smoking cessation.

Clinical and radiographic signs are not observed until COPD is in a moderate-to-advanced stage. Thus, early diagnosis is critical to prevent worsening disease progression.

Patient Presentations

COPD Stereotypes

Two stereotypes of patients with severe COPD have been used to define the extremes of the COPD spectrum. The "pink puffer," which refers to one stricken with emphysema, typically is characterized as an asthenic, barrel-chested patient who exhibits pursed lips breathing with the use of respiratory muscles and has no cyanosis or edema.¹⁰ Usually, such a patient uses extrathoracic muscles to breathe, produces minimal sputum, and experiences little fluctuation in the day-to-day level of dyspnea. The barrel-shaped chest is nonspecific because older persons commonly have increased lung compliance and larger resting lung volumes.¹⁰ Conversely, the "blue bloater," one who presents with chronic bronchitis, is typically overweight, cyanotic, edematous, and exhibits a chronic productive cough. Blue bloaters often have cor pulmonale, which rapidly leads to death if not treated appropriately.¹⁰ Actually, most patients have features of both stereotypes, and today, the refinement in diagnosis has led to a more accurate and complete picture of the disease. Several aspects of COPD are illustrated in the following case presentations.

Three Case Studies

Case 1: Female Aged 47 Years

This patient is a saleswoman who presented with a recent increase in morning cough and mild breathlessness when walking up stairs. Her own assessment was, "I might be allergic to something." When assessing her history, we learn that she has a history of smoking which, along with her exertional dyspnea and morning cough, is strongly suggestive of COPD. Spirometry assessment confirmed that her airflow limitation was not fully reversible: FEV_1 was 80% of normal and FEV_1/FVC was 65% of normal. These tests and her history indicate Stage I (mild) COPD.

Case 2: Male Aged 53 Years

This middle-aged textile mill worker presented with moderate dyspnea and complained that he could not walk from his parked car to his worksite without experiencing shortness of breath. He also complained of a recent increase in morning cough. History revealed he has been a smoker much of his life and works in a textile mill. Chronic symptoms beginning in midlife with this gentleman's history are strongly suggestive of COPD. The patient's postbronchodilator spirometry readings were: $FEV_1 = 60\%$ and $FEV_1/FVC = 59\%$, leading to a diagnosis of Stage II (moderate) COPD.

Case 3: Female Aged 55 Years

This middle-aged professor had a history of smoking one pack a day, but gave up smoking 2 months ago. However, she has continued to cough and produce sputum daily. She complains of being "tired" all the time. She recently caught a cold that rapidly progressed to recurrent bronchitis. The physician noticed wheezing during quiet breathing. A chest X-ray shows hyperinflated but clear lungs, pointing to airflow limitation. Her postbronchodilator spirometry readings were: $FEV_1 = 40\%$ and $FEV_1/FVC = 50\%$. The diagnosis was therefore Stage III (severe) COPD.

These 3 case histories illustrate 3 different stages of COPD with subtly different signs, symptoms, and histories.

Risk Factors for Developing COPD

The risk factors must be clearly identified while taking a patient's history.³ Cigarette smoking is the most common preventable risk. Approximately 80% to 90% of patients with COPD have a smoking history of at least 10 to 20 pack-years.³ Occupational and environmental pollutant exposure, in which there is chronic exposure to fumes, chemical substances, and dust in the workplace, are important risk factors. Frequent bacterial or viral infections are also risk factors for COPD.⁵ A relatively rare genetic condition, α_1 antitrypsin (AAT) deficiency, is a potential risk factor for pulmonary diseases such as emphysema and COPD in children.^{11,12} Finally, protease enzyme production that may occur in some inflammatory reactions may enhance pulmonary tissue damage and predispose an individual to COPD.¹³

■ GOLD Management Guidelines

The GOLD-defined standards for COPD management consist of 4 components: (1) assess and monitor disease, (2) reduce risk factors, (3) manage stable COPD, and (4) manage exacerbations.³ This management plan has several goals to achieve effective outcomes: prevent the progression of the disease, improve exercise tolerance and overall health, prevent and treat complications and exacerbations and relieve symptoms as they occur, and reduce the mortality and morbidity associated with the disease.

■ Conclusion

COPD is a disorder commonly diagnosed by clinicians. Yet, COPD remains underdiagnosed, largely in its milder and more treatable

form.¹ Increasing knowledge of this disease, key diagnostic features, and more familiarity with published standards for its diagnosis and medical management will help to improve its early detection and treatment. COPD should be considered in any patient who has (1) a smoking history of at least 10 to 20 pack-years and/or exposure to other risk factors, (2) chronic cough with or without sputum production, (3) dyspnea, (4) onset of respiratory symptoms after the age of 40, and (5) respiratory infection that persists or recurs. The hallmark diagnostic marker of COPD is expiratory airflow limitation. Patients with COPD experience decreases of FEV_1 , FVC, and FEV_1/FVC . Spirometry is the "gold standard" for diagnosis, being reproducible, objective, and standardized.

DISCLOSURES

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New Treatment Options in COPD

DANIEL E. HILLEMANN, PharmD

ABSTRACT

OBJECTIVE: To review the role of long-acting bronchodilators in the treatment of chronic obstructive pulmonary disease (COPD), including the importance of treatment adherence.

SUMMARY: Overall, clinical trials show that compared with placebo and ipratropium, tiotropium significantly improves spirometric measures, increases quality-of-life scores, and is associated with fewer exacerbations. In addition, compared with salmeterol, tiotropium is associated with greater improvements in spirometric measures and clinically meaningful increases in quality-of-life measures. In comparison with either fluticasone or salmeterol alone, the fluticasone/salmeterol combination is associated with statistically greater improvement in spirometric and dyspnea measures; however, the combination is not associated with fewer exacerbations than either fluticasone or salmeterol used by itself.

CONCLUSIONS: The 2003 update to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines recommends regular treatment with long-acting bronchodilators for maintenance COPD therapy because of superior effectiveness and convenience compared with short-acting bronchodilators. The results from trials presented in this article demonstrate that inhaled tiotropium is effective in treating COPD and might be considered as a first-line agent for maintenance therapy in view of its outcomes data. The convenience of once-daily administration would probably contribute to patient adherence and thus to the overall efficacy of this agent.

KEYWORDS: Chronic obstructive pulmonary disease (COPD); Lung diseases, obstructive; Bronchodilators; Tiotropium; Fluticasone; Salmeterol; Corticosteroid

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Chronic obstructive pulmonary disease (COPD) is characterized by a great reduction in expiratory airflow, chronic cough, and dyspnea.¹ Improved airflow and reduced breathlessness are important treatment outcomes in COPD. Maintenance treatment with bronchodilators, including β -agonists, anticholinergic agents, and theophylline, has been the standard of care for COPD, since these agents treat the bronchoconstriction associated with COPD.² Specifically, ipratropium bromide, an inhaled anticholinergic agent, emerged in the 1970s as a safe and effective treatment for COPD, but its effectiveness may be limited by a frequent (up to 4 times daily) dosing schedule.^{1,3,4} Several other agents with a once- or twice-daily dosing schedule have now been approved for COPD. Recently, 2 inhaled, long-acting bronchodilators from different pharmacologic classes, the once-daily anticholinergic tiotropium (Spiriva, Boehringer Ingelheim/Pfizer) and the twice-daily steroid/bronchodilator fluticasone/salmeterol (Advair, GlaxoSmithKline) have demonstrated efficacy and safety in treating COPD.^{2,3} These agents differ, however, in outcomes measures such as quality of life, dyspnea, spirometric measures, and COPD exacerbations. This article will discuss the outcomes of several pivotal clinical trials that illustrate how these agents differ in the management of COPD.

Long-term Tiotropium Versus Placebo

Trial Introduction and Method

Casaburi and colleagues evaluated the effects of tiotropium in 2 identical randomized, double-blind, placebo-controlled 1-year studies involving 921 patients from 50 clinical centers in the United States.³ Patients inhaled tiotropium 18 μ g (N = 550) or placebo (N = 371) once daily as a dry powder. Medication use and adverse events were recorded. Previous treatment with short-acting β -agonists, theophylline, or steroids was accepted as long as the therapy was relatively stable. Primary outcomes were based on spirometry, quality of life, and exacerbations: the primary spirometric outcome was trough forced expiratory volume in 1 second (FEV₁; i.e., FEV₁ prior to dosing), changes in dyspnea were measured using the Transition Dyspnea Index (TDI), and health status was measured by the disease-specific St. George's Respiratory Questionnaire (SGRQ) and the generic Short Form 36 (SF36).

Results

Overall, patients taking tiotropium showed statistically significant improvements in FEV₁/forced vital capacity (FVC), peak expiratory flow rate (PEFR), TDI, and SGRQ/SF36 scores compared with patients who were receiving placebo. Specifically, during the 1-year study, tiotropium provided significantly superior bronchodilation for trough FEV₁ response (~12% over baseline, $P < 0.01$) and mean response during the 3 hours after dosing (~22% over baseline, $P < 0.001$). Compared with patients receiving placebo, patients taking tiotropium had less dyspnea ($P < 0.001$), superior

health status scores, fewer COPD exacerbations (36% vs. 42%, $P < 0.05$), fewer hospitalizations (5.5% vs. 9.4%, $P < 0.05$), and fewer hospital days (0.6 days/year vs. 1.2 days/year, $P = 0.023$). A similar percentage of patients in the tiotropium and placebo groups experienced adverse events during the 1-year study, with 9.6% patients receiving tiotropium and 13.7% receiving placebo who dropped out of the study as a result. Dry mouth was the only adverse reaction that was significantly more frequent in patients receiving tiotropium (16%) than in those receiving placebo (2.7%). In most cases, the dry mouth was reported to be mild and $<1\%$ of the patients withdrew because of it. There were no significant differences between the groups in the percentage of patients with serious adverse events, in those withdrawing due to adverse events, or in deaths during the study.³

Tiotropium Versus Ipratropium

Trial Introduction and Method

In 2000, van Noord et al. published a study of 288 patients with COPD, documenting significant improvements in spirometric values over 3 months in patients receiving tiotropium 18 μg once daily compared with ipratropium 40 μg 4 times daily.⁵ These patients continued on to a 1-year randomized, double-blind trial, and the results were combined with those of a second large multicenter 1-year trial.⁶ Both studies incorporated a randomized double-blind, parallel-group design. From 29 clinical centers in the Netherlands and Belgium, 356 patients with COPD were randomized to tiotropium 18 μg once daily in the morning (from a metered dose inhaler [MDI]) while 179 patients were randomized to ipratropium 40 μg 4 times daily. Patients in both studies were permitted albuterol MDIs as needed for acute symptom relief, but bronchodilators other than study drugs were not permitted. Outcome criteria included lung function by spirometry, dyspnea frequency, exacerbation rate, and health-related quality-of-life (HRQOL) scores.

Results

Patients receiving tiotropium showed significant improvement in spirometry measures, with a mean FEV₁ of 1.25 ± 0.43 L (41.9 $\pm$ 12.7% of the predicted value) compared with 1.18 ± 0.37 L (39.4 $\pm$ 10.7% of the predicted value) in patients receiving ipratropium. Trough FEV₁ measurements at 1 year improved by 0.12 ± 0.01 L with tiotropium, but declined by 0.03 ± 0.02 L with ipratropium ($P < 0.001$).⁶

Exacerbations and hospitalizations were less frequent in the tiotropium group. The percentage of patients experiencing one or more exacerbations during the 1-year treatment period was significantly lower in the tiotropium group than in the ipratropium group (35% vs. 46%, respectively, $P = 0.014$). The frequency of exacerbations/patient/year was 24% lower for patients taking tiotropium ($P = 0.006$). In addition, the number of exacerbation days/patient/year was 39% lower in the tiotropium group (10.8 vs. 17.7, $P = 0.002$). The first exacerbations occurred significantly later

FIGURE 1 Mean FEV₁ Before and After Administration of Tiotropium, Salmeterol, and Placebo on Days 1, 15, and 169 of Treatment

$P < 0.001$ for tiotropium versus placebo on all test days posttreatment; $P < 0.05$ for tiotropium versus salmeterol on all test days except day 1 and -1 hour on day 15.⁷ FEV₁=forced expiratory volume in 1 second.

in patients receiving tiotropium ($P = 0.008$). Hospitalizations due to COPD exacerbations during the 1-year treatment period showed a similar pattern, with a total of 7.3% of patients hospitalized in the tiotropium group and 11.7% in the ipratropium group ($P = 0.11$). The number of hospitalizations/patient/year for a COPD exacerbation was 38% lower in the tiotropium group (0.10 vs. 0.16, $P = 0.08$), while the number of hospitalization days/patient/year was 33% lower in patients receiving tiotropium (1.42 vs. 2.13, $P = 0.09$). Furthermore, the time to first hospitalization due to a COPD exacerbation was significantly longer in the tiotropium group than in the ipratropium group ($P = 0.048$). On average, patients in the tiotropium group had approximately 4 fewer albuterol inhalations per week than patients who were receiving ipratropium ($P < 0.05$ for 40 of the 52 weeks).⁶

There was no statistically significant difference in the number of patients in each treatment group who withdrew from the study because of adverse side effects. Dry mouth was the only adverse effect classified as drug-related; it was reported by 14.7% of patients in the tiotropium group and 10.3% of patients in the ipratropium group. None of the patients in the study withdrew because of dry mouth.⁶

FIGURE 2 SGRQ Total Score at Baseline and at Days 57, 113, and 169 for the Tiotropium, Salmeterol, and Placebo Groups

* $P < 0.05$ for tiotropium versus placebo at day 57 and day 169. Salmeterol and tiotropium versus placebo are not statistically significant.⁷
SGRQ=St. George's Respiratory Questionnaire.

FIGURE 3 Change in SGRQ Total and Impacts Scores From Baseline to Day 169 for the Tiotropium, Salmeterol, and Placebo Groups

* $P < 0.05$ for tiotropium versus placebo. Salmeterol versus placebo and tiotropium versus salmeterol are not statistically significant.⁷
SGRQ=St. George's Respiratory Questionnaire.

Tiotropium Versus Salmeterol

The comparative efficacy of tiotropium and salmeterol in the treatment of COPD was compared in 2 recent 6-month, randomized clinical trials.^{7,8}

Tiotropium Versus Salmeterol Trial 17

Trial Introduction and Method

This was a 6-month, randomized, placebo-controlled, double-blind, double-dummy, parallel-group comparison of tiotropium, 18 µg once daily via dry-powder inhaler, and salmeterol, 50 µg twice daily via MDI. Efficacy was assessed by 12-hour monitoring of spirometry, TDI, and the SGRQ HRQOL measure. A total of 623 patients were included: 209 receiving tiotropium, 213 receiving salmeterol, and 201 receiving placebo.

Results

As shown in Figure 1, tiotropium was associated with significantly greater improvement of FEV₁ than salmeterol on day 15 and at the end of treatment (day 169) ($P < 0.05$). Both active compounds had a significantly greater effect than placebo on FVC values, but tiotropium was superior to salmeterol for trough FVC and peak FVC measurements. At the end of the study, mean trough FVC in the patients receiving tiotropium was 112 mL ($P < 0.01$) higher than in the patients receiving salmeterol. As with FEV₁, the differences in TDI focal scores between tiotropium and salmeterol appeared to increase over time.

Despite the similarity of objective measurements, the patients receiving tiotropium were significantly more likely than those receiving salmeterol to consider that the treatment had improved their clinical condition (Figure 2). In the SGRQ test, a decrease of 4 units or more is associated with clinical improvement. The difference is demonstrated dramatically by the comparison of SGRQ total and impacts scores in Figure 3.

Patients used a mean 2.65 puffs/day of albuterol during the baseline run-in period. Their mean weekly requirement for albuterol, in comparison with the placebo group, underwent an equal decrease with tiotropium (-1.45 puffs per day) and salmeterol (-1.44 puffs per day). This represented a statistically significant ($P < 0.0001$) decrease in albuterol use for both tiotropium and salmeterol groups.

A larger percentage of patients left the trial in the salmeterol (13.6%) and placebo groups (19.4%) due to adverse events compared with 5.7% in the tiotropium group ($P < 0.001$). Somewhat fewer patients left the study because of exacerbations of COPD (36.8% vs. 38.5%), but the difference was not statistically significant. The most common adverse event related to tiotropium treatment was dry mouth (10%), which did not cause any of the participants to leave the study. Other than dry mouth, there were no significant differences in the incidence of adverse events among the treatment groups.

Tiotropium Versus Salmeterol Trial 28

Trial Introduction and Method

A second 6-month trial that employed a similar design to the Donohue study compared treatment outcomes in 402 patients receiving tiotropium, 405 patients receiving salmeterol, and 400 patients receiving a matching placebo.⁸ The study results were combined for comparison of exacerbations, health resource use, dyspnea (assessed by the transitional dyspnea index, TDI), HRQOL (assessed by SGRQ), and spirometry.

Results

As shown in Figure 4, both tiotropium and salmeterol showed equal efficacy after the first doses in improving trough, peak, and mean FEV₁, but by day 15, tiotropium showed a statistically greater effect than salmeterol on these measures. Compared with placebo, the mean improvement in trough FEV₁ for tiotropium and salmeterol was 0.12 L and 0.09 L, respectively ($P < 0.01$ for either active treatment compared with placebo; $P < 0.05$ tiotropium versus salmeterol), on the last day of the study. Tiotropium was statistically superior to salmeterol in modifying peak FEV₁ and the area under the curve from 0 to 3 hours in combined and individual studies. Similarly, trough FEV₁ values were improved to a statistically significant degree in patients who received tiotropium in one of the individual studies, and this finding was carried over when the study results were combined. At the conclusion of the study (day 169), patients receiving tiotropium showed significant improvement in lung function compared with patients receiving salmeterol or placebo. These results were nearly identical to those seen by Donohue et al.⁷

Figure 5 shows that compared with placebo, tiotropium significantly delayed the time to the first COPD exacerbation ($P < 0.01$), which is significant considering the short trial period. The percentage of patients with at least one exacerbation was 32%, 35%, and 39% in the tiotropium, salmeterol, and placebo groups, respectively ($P > 0.05$). Patients who received tiotropium had significantly fewer COPD exacerbations per patient year (1.07; $P > 0.05$) than those who received salmeterol (1.23) or placebo (1.49). The difference between salmeterol and placebo was not significant.

Three studies have examined the fixed-dose combination of fluticasone and salmeterol versus each individual component and placebo. These studies are described below.

Fluticasone/Salmeterol Versus Placebo

Trial Introduction and Method

Mahler et al. conducted a randomized, double-blind, placebo-controlled trial comparing the effects of combination therapy with fluticasone/salmeterol and each of these agents alone in patients with COPD.² The 4 treatment groups consisted of patients receiving placebo (N = 181), salmeterol 50 µg (N = 160), fluticasone 500 µg (N = 168), or fluticasone/salmeterol 500 µg/50 µg (N = 165), each administered twice daily for a total of 24 weeks. Treatment

FIGURE 4 Mean FEV₁ Before and After Treatment on Days 1, 15, and 169 of Study

$P < 0.001$ for tiotropium versus placebo on all test days after treatment; $P < 0.05$ for tiotropium versus salmeterol on all test days except day 1 and -1 hour on day 15.8. FEV₁ = forced expiratory volume in 1 second.

FIGURE 5 Kaplan-Meier Estimates of the Probability of No COPD Exacerbations Over 6 Months of Treatment

* $P = 0.005$ for tiotropium versus placebo (log rank test).⁸

COPD = chronic obstructive pulmonary disease.

TABLE 1 Estimated Treatment Differences in Efficacy Parameters at End Point²

Evaluation	Treatment Group Comparison				
	FSC vs. P	FSC vs. F	FSC vs. S	F vs. P	S vs. P
Predose FEV ₁	159*	54*	67*	105*	92*
2-hour postdose FEV ₁	231*	129*	40	101*	191*
TDI	1.7*	0.7*	1.2*	1.0*	0.5
CRDQ	5.3*	4.8*	1.6	0.5	3.8
CBSQ	0.6*	0.4	0.2	0.2	0.3

* $P < 0.05$.

CBSQ=Chronic Bronchitis Syndrome Questionnaire; CRDQ=Chronic Respiratory Disease Questionnaire; F=fluticasone propionate; FEV₁=forced expiratory volume in 1 second; FSC=fluticasone propionate and salmeterol combined; P=placebo; S=salmeterol; TDI=Transition Dyspnea Index.

outcomes were assessed by FEV₁, PEF, TDI, QOL (Chronic Respiratory Disease Questionnaire and Chronic Bronchitis Symptoms Questionnaire) measures, and exacerbations.

Results

As shown in Table 1, the patients receiving the combination of fluticasone/salmeterol showed statistically significant improvements in FEV₁, TDI, and both QOL measures in comparison with patients receiving placebo. The combination exhibited clinical superiority over fluticasone, while the results were less clear when it was compared with salmeterol. More specifically, the patients treated with fluticasone/salmeterol showed a significant improvement in TDI, while their QOL scales were not significantly different from those of the salmeterol group. Both active compounds administered alone were more effective than placebo in improving spirometric measurements but not in improving symptoms.

Candidiasis was the only adverse event reported in more patients taking either fluticasone or fluticasone/salmeterol.

No statistically significant differences in time to exacerbation were noted among the treatment groups. However, there was significant reduction in overall albuterol use (i.e., number of inhalations per day and percentage of days without albuterol use) in patients receiving the combination compared with those receiving fluticasone. Significant reductions in albuterol use were also observed in the salmeterol and fluticasone treatment groups. Subjects in all 3 active treatment groups reported significantly more nights with no awakenings during which they used albuterol ($P < 0.001$).

Trial of Inhaled Steroids and Long-Acting β_2 Agonists (TRISTAN)

Trial Introduction and Method

The TRISTAN trial was a randomized, double-blind, placebo-controlled 52-week parallel trial of salmeterol 50 μ g twice daily (N = 372), fluticasone 500 μ g twice daily (N = 374), fluticasone/salmeterol (FSC) 50/500 μ g twice daily (N = 358), and placebo

FIGURE 6 Effect of Treatment on Lung Function Measurements and Health Status

Raw mean changes from baseline are shown: A. Prebronchodilator FEV₁; B. Postbronchodilator FEV₁; C. Daily peak expiratory flow; D. Health status—the fall in St George's score represents an improvement in health status.^{8,9} FEV₁=forced expiratory volume in 1 second; PEF=peak expiratory flow; SGRQ=St. George's Respiratory Questionnaire.

FIGURE 7 Improvement in Predose FEV₁ With Fluticasone/Salmeterol Combination Compared With Individual Active Components and Placebo

* $P < 0.001$, fluticasone/salmeterol combination (FSC) versus placebo; $P = 0.012$, FSC versus salmeterol (SM); $P < 0.001$, fluticasone (FP) versus placebo.¹⁰ FEV₁ = forced expiratory volume in 1 second.

($N = 361$).⁹ Patients admitted to the study had a baseline FEV₁ before bronchodilation that was 25% to 70% of that predicted, an increase of <10% of predicted FEV₁ 30 minutes after inhaling 400 μ g of albuterol, and an FEV₁/FVC ratio of $\leq 70\%$ prior to the use of a bronchodilator. Asthma was ruled out as a potential confounding diagnosis.

Results

As illustrated in Figure 6, by week 2, the 3 active treatments increased pretreatment FEV₁ significantly in comparison with the placebo group (fluticasone/salmeterol $P < 0.001$, salmeterol $P < 0.001$, fluticasone $P = 0.0063$). The increase in FEV₁ associated with combination therapy was significantly greater than that observed with either component alone. By week 52, pretreatment FEV₁ in the combination group had increased by 10% compared with 2% in the other treatment groups, while falling by 3% in patients taking placebo. Combination therapy also led to statistically significant improvement in FEV₁ after the use of a bronchodilator compared with the salmeterol and fluticasone treatments. As shown in Figure 6, the combination had the same effect as the individual components on PEFR in weeks 2 through 52. Finally, combination treatment produced a sustained improvement

in patients' QOL measured by SGRQ.⁹ By week 52, patients taking fluticasone/salmeterol combination had a significantly lower total SGRQ score than patients taking either component alone or placebo.

Compared with placebo, all active treatments significantly reduced the mean number of exacerbations/patient/year as well as the mean number of exacerbations requiring treatment with oral corticosteroids. Compared with placebo, the rate of exacerbations fell by 25% ($P < 0.0001$ in the combination group), and 20% ($P = 0.0027$) and 19% ($P = 0.0033$) in the salmeterol and fluticasone groups, respectively. However, differences were not significantly different among active treatments.

Fluticasone/Salmeterol: In Combination Versus Each Agent Alone

Trial Introduction and Method

A 28-week randomized, double-blind, placebo-controlled, parallel-group trial compared placebo ($N = 185$), fluticasone 250 μ g ($N = 183$), salmeterol 50 μ g ($N = 177$), and fluticasone/salmeterol combination inhaler 50/250 μ g ($N = 178$) in patients with COPD.¹⁰ Outcomes were assessed by predose and postdose FEV₁, peak flow rate, TDI, QOL, and the number of exacerbations.

TABLE 2 Estimated Differences in Efficacy Parameters at End Point¹⁰

Evaluation	Treatment Group Comparison				
	FSC vs. P	FSC vs. F	FSC vs. S	F vs. P	S vs. P
Predose FEV ₁	161*	49	69*	112*	92*
2-hour postdose FEV ₁	214*	124*	74*	89*	140*
TDI	0.8*	0.1	0.1	0.7	0.7*
CRDQ	5.2*	-0.6	3.2	5.8	2.0
CBSQ	0.7*	-0.1	0.3	0.8	0.4

* $P \leq 0.048$.

Estimated differences between treatments may vary from differences between actual means due to model adjustment.

CBSQ = Chronic Bronchitis Syndrome Questionnaire; CRDQ = Chronic Respiratory Disease Questionnaire; F = fluticasone propionate; FEV₁ = forced expiratory volume in 1 second; FSC = fluticasone propionate and salmeterol combined; P = placebo; S = salmeterol; TDI = Transition Dyspnea Index.

Results

Morning predose FEV₁ values over 24 weeks (Figure 7) show that compared with patients receiving placebo (1 mL) or salmeterol (91 mL), patients receiving fluticasone/salmeterol had statistically significant ($P < 0.001$ and 0.012 , respectively) increases in mean FEV₁ values (165 mL) at end point. The end point of patients in the combination therapy group was 16.6% above baseline values. Patients receiving fluticasone had a significantly greater increase in FEV₁ (109 mL, $P < 0.001$) compared with placebo and a statistically similar increase compared with the combination. As shown in Table 2, treatment with the combination also led to significantly better results ($P \leq 0.048$) in 2-hour postdose FEV₁, TDI, and QOL measures compared with placebo. Compared with its individual components, the combination caused statistically significant improvement in the predose FEV₁ and 2-hour postdose FEV₁ but did not show a difference in QOL or dyspnea outcomes. Both fluticasone and salmeterol, separately, performed better than placebo on FEV₁ measures.

A total of 485 patients (67%) experienced at least one adverse event during the study. More patients in the fluticasone and fluticasone/salmeterol groups experienced candidiasis (mouth and throat) than in the placebo and salmeterol groups.

There were no significant differences in the number of exacerbations or the time to first exacerbation among the treatment groups, although exacerbation rates are difficult to interpret in short-term studies.

Discussion and Conclusions

From these trials, several clear conclusions and implications emerge. First, compared with placebo and ipratropium, tiotropium is associated with greater improvement in spirometric measures, better QOL based on the SGRQ, and fewer exacerbations. Second, compared with salmeterol, tiotropium is associated with greater

improvement in spirometric measures and greater improvement in clinically meaningful changes in QOL. Third, the fluticasone/salmeterol combination is associated with greater improvement in spirometric measures and dyspnea than either placebo or its individual components. Last, the fluticasone/salmeterol combination is associated with fewer exacerbations than placebo but not necessarily fewer exacerbations than either salmeterol or fluticasone. It is important to note that these studies had only a 6-month follow-up.

The Global Initiative for Chronic Obstructive Lung Disease, recommends that stage II or moderate disease should be treated with one or more long-acting bronchodilators such as tiotropium and/or salmeterol.¹¹ Available data support the use of tiotropium since it is associated with fewer exacerbations, which are common in moderate-severe disease. Tiotropium and salmeterol should be given to relieve persistent or worsening symptoms, or regularly to prevent or reduce symptoms. Adverse reactions with these agents are pharmacologically predictable and dose-dependent and usually resolve after treatment withdrawal, especially with inhaled agents.

Patients suffering from severe disease (stage III-IV) may benefit from inhaled glucocorticoids when there are repeated exacerbations.¹¹ The evidence shows that regular treatment with inhaled glucocorticoids is appropriate for symptomatic COPD patients with FEV₁ < 50% predicted (stage III-IV) and can reduce exacerbation frequency and improve health status.^{11,12} A glucocorticoid in combination with a long-acting β -2 agonist is more effective than either of the individual components administered alone. Finally, while medical treatment of COPD has advanced, failure to adhere to prescribed regimens poses a significant barrier to effective management. In one study of COPD patients using multiple medications, adherence was poor (~50%) and related to dosing intervals.¹³ The use of fewer daily doses is clearly desirable.

DISCLOSURES

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New Concepts to Improve Health Outcomes for Patients With Chronic Obstructive Pulmonary Disease

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The posttest worksheet (below) is provided to assist you in marking your answers prior to entering the online CE center for submission; these pages cannot be submitted for CE credits.

In order to receive CE credit for this program, you must complete the following forms online:

1. Posttest form for this program, "New Concepts to Improve Health Outcomes for Patients With Chronic Obstructive Pulmonary Disease," on the AMCP.org Online Learning Center site—to receive CE credit, you must receive a score of at least 70%. You will have 2 opportunities to pass the posttest.
2. Program Evaluation form

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Note: There will be a \$10 processing fee for nonmembers. (See payment instructions on site.)

Posttest Worksheet: New Concepts to Improve Health Outcomes for Patients With Chronic Obstructive Pulmonary Disease

1. In determining treatment for patients with COPD, the following are important considerations for pharmacologic treatment outcomes:
 - a. Quality of life (QOL)
 - b. Spirometry measures such as FEV₁
 - c. Dyspnea
 - d. COPD exacerbations
 - e. All the above
2. Which of the following best characterizes COPD:
 - a. COPD is chronic lung dysfunction.
 - b. The objective criterion for diagnosis is often the patient's quality of life.
 - c. The symptoms of COPD such as chronic cough and dyspnea get initially worse and then stabilize over time.
 - d. COPD symptoms are caused solely by alveolar destruction.
 - e. One major risk factor for COPD includes genetic predisposition to alpha₁ antitrypsin deficiency.
3. Misconceptions about COPD include:
 - a. It is not a disease of the elderly.
 - b. Women are more likely than men to have COPD.
 - c. Compared with diabetes, asthma, and CHD, COPD is not common.
 - d. All of the above
 - e. None of the above
4. In the period 1965-1998, compared with coronary heart disease and stroke, COPD increased more than 150%.
 - a. True
 - b. False
5. Which of the following statements is false?
 - a. COPD is the fourth leading cause of death in the United States.
 - b. More than one third of the patients with COPD are women.
 - c. Most of the major costs of COPD are a result of lost productivity.
 - d. COPD is responsible for 57 million lost workdays annually.

6. The GOLD management goals for COPD include
 - a. prevent disease progression, relieve symptoms, improve health status, prevent and treat exacerbations, and reduce mortality.
 - b. reduce exercise intolerance, improve quality of life, and reduce cigarette smoking.
 - c. reduce comorbidities, prevent complications, and provide oxygen support.
 - d. improve quality of life, improve FEV₁, and reduce comorbid conditions.
7. Many physicians follow the GOLD guidelines for the use of bronchodilators in stable COPD. The guidelines
 - a. advocate early use of combination therapy.
 - b. stress the importance of injectable therapy.
 - c. state that bronchodilator choice of beta 2-agonists, anticholinergic, theophylline, or combination therapy, depends on individual response and availability.
 - d. State that oral theophylline is the mainstay of treatment.
 - e. None of the above
8. Which of the following is a false statement about COPD:
 - a. The disease is characterized by airflow limitation that is not fully reversible.
 - b. The airflow limitation in COPD is not associated with inflammatory response of the lungs to noxious gases.
 - c. The airflow limitation is progressive.
 - d. In its milder and treatable forms, COPD is under-diagnosed.
9. COPD can be partially differentiated from asthma based on the fact that
 - a. scanning electron microscopy does not reveal characteristic signs of COPD.
 - b. steroids typically provide greater improvement for asthma symptoms than for COPD symptoms.
 - c. COPD has reversible airflow limitations whereas asthma does not.
 - d. symptoms of COPD vary from day to day but are slowly progressive in asthma.
10. Patients with COPD show the following spirometry findings:
 - a. Greatly reduced functional residual capacity
 - b. Increased inspirational capacity
 - c. A large increase in residual volume
 - d. Reduced total lung volume.
 - e. An increase in FEV₁ and FEV₁/FVC due to increased lung volume
 - f. A large increase in tidal volume
11. The diagnosis of COPD should be considered in anyone who
 - a. shows an onset of respiratory symptoms in their 40s.
 - b. has a chronic cough with sputum production.
 - c. has a smoking history of at least 10 pack-years.
 - d. has a history of exposure to environmental pollutants.
 - e. All the above
12. Which of the following statements is true?
 - a. Compared with placebo and ipratropium, tiotropium is associated with better quality of life, improvement in spirometric measures, and fewer exacerbations.
 - b. Compared with placebo, tiotropium showed no significant increases in FEV₁/FVC or PEF.
 - c. Compared with each compound alone, the combination fluticasone/salmeterol is associated with no statistically significant improvements in spirometric measures.
 - d. Patients with Stage IV COPD who receive fluticasone/salmeterol have the same exacerbation rate as those who receive placebo.
13. In trials comparing tiotropium versus ipratropium, the following was found:
 - a. Hospitalizations were significantly higher in the tiotropium group.
 - b. Beta-agonist use was not significantly decreased with either agent.
 - c. Adverse reactions with both drugs was >20%.
 - d. Tiotropium was associated with statistically fewer exacerbations than ipratropium.
14. The following results were reported in a 6-month study of tiotropium versus salmeterol:
 - a. Salmeterol produced superior bronchodilatation.
 - b. Improvements in dyspnea and health-related quality of life were the same on both drugs.
 - c. Compared with placebo treatment, the mean predose morning FEV₁ following 6 months of therapy increased significantly more for the tiotropium group than the salmeterol group.
 - d. Twice-daily dosing compared with once-daily dosing had no effect on patient compliance.
 - e. Compared with placebo, salmeterol had a statistically significantly lower SGRQ score.
 - f. Compared with placebo, salmeterol and tiotropium had similar statistical changes on FEV₁ and TDI focal scores.

15. In a randomized controlled trial that examined the benefits of combining an inhaled corticosteroid (fluticasone) with an inhaled long-acting beta-agonist (salmeterol), the following was found to be true:
 - a. A significantly greater increase in predose FEV₁ was seen with the combination of both drugs compared with salmeterol and placebo.
 - b. The combination of the 2 drugs produced a greater increase in 2-hour postdose FEV₁ at end point compared with placebo and fluticasone.
 - c. Incidence of adverse reactions was similar among treatments.
 - d. All of the above
 - e. None of the above
16. Which of the following statements reflect findings in clinical trials?
 - a. Fluticasone/salmeterol combination shows improvement in spirometric measures and dyspnea to largely the same level as the individual components used alone.
 - b. Compared with placebo, tiotropium is associated with greater improvements in spirometric measures, better QOL, and fewer exacerbations.
 - c. Dry mouth is a common event during use with corticosteroids.
 - d. Fluticasone is associated with lower QOL scores than salmeterol.
 - e. The increases in postbronchodilator FEV₁ occur mostly after the fourth week of treatment.
17. Which of the following statements is not true:
 - a. COPD progresses from biochemical and cellular events through physiological alterations and pathological changes; therefore, early detection is important.
 - b. Patients with COPD may stop smoking or be exposed to noxious agents, but the disease can nonetheless progress.
 - c. Patients present with a normal chest x-ray.
 - d. Patients present with progressive dyspnea with exertion.
18. Which symptoms would be a hallmark of Stage III COPD:
 - a. Spirometry readings of FEV₁ = 60%
 - b. FEV₁/FVC = 65%
 - c. FEV₁ = 40%
 - d. Mild breathlessness in rapid walking
 - e. Smoking history
19. According to the NHLBI, components of COPD management would include
 - a. eliminating exposure to air pollutants.
 - b. reducing risk factors and managing exacerbations.
 - c. managing late-stage COPD with oxygen therapy.
 - d. increasing quality of life for the patient.
 - e. None of the above
20. According to the GOLD criteria for treatment, adding regular treatment with long-acting bronchodilators should begin at
 - a. COPD stage I.
 - b. COPD stage 0.
 - c. COPD stage II.
 - d. COPD stage III.
 - e. COPD stage IV.

To complete this activity, go to www.amcp.org (Learning Center/Online CE), where you will access the posttest and evaluation form.

NOTES

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