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Contemporary Issues in the Care of Patients With Chronic Obstructive Pulmonary Disease

Frank L. Urbano, MD, FACP
Rodolfo M. Pascual, MD, FCCP

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FACULTY

Frank L. Urbano, MD, FACP, is an internist in private practice at Mount Laurel Primary Care Physicians, PC, Mount Laurel, New Jersey. He earned a degree in biology from Rutgers University, PC, New Brunswick, New Jersey and a medical degree from New Jersey Medical School, Newark, New Jersey, and completed his residency in internal medicine at Thomas Jefferson University Hospital, Philadelphia, Pennsylvania, where he served as chief resident. In his practice, Urbano sees patients in the outpatient setting, acute care facilities, and nursing homes, including many patients with chronic obstructive pulmonary disease. He also serves as medical director of PRIME, a health care educational company, and is a consulting medical reviewer for Horizon Blue Cross Blue Shield of New Jersey. Urbano is a fellow of the American College of Physicians and a member of the Case Management Society of America. He has lectured and authored for national health care organizations and served as an expert panelist in the inaugural Physician/Case Management Summit, cosponsored by PRIME and the Case Management Society of America in 2003. Urbano has served on the faculty bureau for Sanofi-Synthelabo, Inc. and Wyeth Pharmaceuticals.

Rodolfo M. Pascual, MD, FCCP, is an assistant professor at Wake Forest University Health Sciences and is an attending physician at Wake Forest University Baptist Medical Center, both in Winston-Salem, North Carolina. He earned a degree in biochemistry from Albright College, Reading, Pennsylvania, and a medical degree from Jefferson Medical College, Philadelphia, Pennsylvania. He completed his residency in internal medicine, serving as chief resident, and his fellowship in pulmonary medicine and critical care at Thomas Jefferson University Hospital, Philadelphia, Pennsylvania. Pascual is board certified in internal medicine, pulmonary diseases, and critical care medicine. His research interests include signal transduction and inflammatory mediator regulation in airway diseases such as asthma and COPD. He is a fellow of the American College of Chest Physicians and a member of the American Thoracic Society and the American Academy of Allergy, Asthma, and Immunology. Pascual has authored several manuscripts related to airway diseases in peer-reviewed journals.

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Target Audience

Managed care pharmacists, clinical pharmacists, pharmacy directors, and medical directors responsible for reviewing treatment strategies for patients with COPD

Learning Objectives

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

1. describe the impact of COPD on health care in the United States,
2. define the pathophysiology and diagnosis of COPD and how to apply guidelines to stage and manage COPD,
3. state how to manage COPD using both medications and nonpharmacological therapies, and
4. assess systems and programs to manage COPD in an evidence-based manner.

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Contemporary Issues in the Care of Patients With Chronic Obstructive Pulmonary Disease

FRANK L. URBANO, MD, FACP, and RODOLFO M. PASCUAL, MD, FCCP

ABSTRACT

OBJECTIVE: Chronic obstructive pulmonary disease (COPD) is the fourth leading cause of death in the United States and is estimated to be responsible for 119,000 deaths in the year 2000 alone. Additionally, COPD places a tremendous burden on the health care system, with estimated annual costs of $24 billion in 2000, and it is generally expected that costs will continue to rise as more individuals are diagnosed. COPD was responsible for approximately 8 million physician outpatient visits, 1.5 million emergency department visits and 726,000 hospitalizations, also in the year 2000. The objective of this article is to review current, pertinent clinical issues in the management of patients with COPD, with estimates of their relative utility and efficacy.

SUMMARY: COPD is a disease characterized by airflow limitation that is not fully reversible. Patients with COPD may frequently experience symptoms of chronic cough with sputum production, dyspnea, and reduced exercise capacity. They may frequently experience exacerbations characterized by increased symptoms that often require medical intervention. The diagnosis of COPD is usually fairly straightforward and made in a cigarette smoker, with the aforementioned symptoms and airflow obstruction measured by spirometry. Spirometry should be performed in all patients in whom COPD is suspected, as it provides useful prognostic information and may be used to stage the disease.

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) has provided evidenced-based management guidelines for COPD. GOLD guidelines advocate staging COPD by spirometry and make specific treatment recommendations based on COPD stage. The most important risk factor for the development of COPD is cigarette smoking, and smoking cessation has been shown to reduce all-cause mortality and to alter the natural history of COPD. Smoking cessation strategies that employ both counseling and medications like buproprion and nicotine replacement are most effective, but relapse rates remain high.

It has not been shown that medications like bronchodilators or inhaled steroids change the natural history of COPD, nor do they reduce mortality, but they can affect other important outcomes. Long-acting bronchodilators, including beta-2-adrenergic agonists such as salmeterol and formoterol, and the anticholinergic agent tiotropium, improve lung function and exercise tolerance, reduce symptoms, and modestly reduce exacerbation rates. Long-acting bronchodilators are indicated for all COPD patients with chronic symptoms. Short-acting bronchodilators are indicated for rescue when acute symptoms occur. Inhaled corticosteroids minimally improve lung function, but, importantly, reduce exacerbation rates and are indicated in severe COPD or when exacerbations are frequent. Continuous oxygen therapy has been shown to reduce mortality when severe hypoxemia is present and can improve quality of life when moderate hypoxia is present. Finally, well-designed, multidisciplinary disease management programs and pulmonary rehabilitation can improve important disease outcomes in a cost-effective manner.

CONCLUSION: COPD is a common, preventable disease that affects a significant number of people. It may be managed by utilizing various readily available medical therapies, as well as other nonpharmacologic interventions, such as pulmonary rehabilitation. Proper coordination of care is important in this disease, and efforts should be focused on improving quality of life and reduction of symptoms.

KEYWORDS: Chronic obstructive pulmonary disease, Pulmonary rehabilitation, Coordination of care, Disease management, Outcomes, GOLD guidelines

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Chronic obstructive pulmonary disease (COPD) is a disease characterized by airflow limitation that is not fully reversible.[1] The major pathologic abnormality in COPD is an abnormal response of the lungs to noxious particles or gases, which results in inflammatory changes that lead to the characteristic signs and symptoms of cough and dyspnea.

Current descriptions of COPD often include the terms chronic bronchitis and emphysema. These 2 conditions are often used synonymously with COPD, although they have very different definitions. Chronic bronchitis is defined by the presence of chronic productive cough for 3 months in each of 2 successive years in the absence of any other etiology for the cough. It is primarily a clinical diagnosis. Emphysema is defined as abnormal permanent enlargement of the airspaces distal to the terminal bronchioles with concomitant destruction of their walls, resulting in trapping of air in the emphysematous portion of the lung.[2]

A more detailed understanding of the pathophysiology of COPD has shown that patients with this disorder may have chronic bronchitis, emphysema, or both conditions simultaneously. The primary physiologic abnormality that is required for the diagnosis of COPD is the aforementioned airflow limitation.[3,4] Patients who have COPD demonstrate an accelerated decline in the forced expiratory volume in 1 second (FEV_1) as compared with the normal decline seen with aging.[5] Many patients with COPD remain relatively asymptomatic until the FEV_1 reaches approximately 50% of the predicted normal value.[6] Once this threshold is reached, patients will often develop the characteristic symptoms of COPD, including cough, dyspnea, wheezing, and expectoration of phlegm. The symptoms of COPD predictably worsen as lung function deteriorates.

Epidemiology of COPD

Approximately 10 million to 12 million people in the United States have COPD, according to data reported by the Centers for Disease Control and Prevention (CDC) in 2002.[7] Women have a higher self-reported rate of COPD than men (64% of reported cases), but overall prevalence estimates show that COPD occurs

Authors

FRANK L. URBANO, MD, FACP, is an internist in private practice, Mount Laurel Primary Care Physicians, PC, Mount Laurel, New Jersey; RODOLFO M. PASCUAL, MD, FCCP is an assistant professor, Wake Forest University Health Sciences, Winston-Salem, North Carolina.

Author Correspondence: Frank L. Urbano, MD, FACP, Mount Laurel Primary Care Physicians, PC, 1000 Birchfield Dr., Suite 1004, Mount Laurel, NJ 08054. Tel: (856) 866-1557; Fax: (856) 231-7955; E-mail: Furbano@primeinc.org.

predominantly in men (53% of estimated cases).[7] COPD affects whites more than blacks, and the prevalence increases as patients get older, from 38.5 cases/1,000 persons in the 25-44 years age group to 106 cases/1,000 persons in the >75 years age group.[7]

COPD is the fourth leading cause of death in the United States and the fifth leading cause of death worldwide.[8,9] It is estimated that by the year 2020, COPD will become the third leading cause of death worldwide.[10] The CDC estimates that more than 119,000 people died of COPD in the year 2000. In women, the death rate from COPD has increased 3-fold since 1980, whereas in men, the death rate has remained stable since 1985. This is felt to be due to increased smoking by women since the 1940s, a fact that belies the common advertising theme, "You've come a long way, baby."[11]

COPD places an enormous burden on the health care system, with estimated annual costs that exceed $24 billion, of which $10 billion are indirect costs primarily related to time lost from work.[12,13] In 2000, there were approximately 8 million physician office and hospital outpatient visits, 1.5 million emergency department (ED) visits, and 726,000 hospitalizations for COPD.[7] Of these, only ED visits showed a significant change over the past 10 years, increasing approximately 41%. COPD has also had a significant impact on other areas of health care, including home health care, in which 5.3% of patients in 2000 had COPD as their primary diagnosis, and hospice care, in which 4.3% of patients in 2000 had COPD as their primary diagnosis.[14]

The majority of cases of COPD in developed countries are directly attributable to smoking.[15] Individual susceptibility to the effects of cigarette smoke varies from person to person. Some smokers have a greater decline in lung function than others, and it is this group that is more likely to become disabled as a result of COPD. Smoking cessation is the only measure known to slow the progression of COPD, and while smokers do not regain lost lung function when they stop smoking, the rate of loss approaches that of nonsmokers.[16] In order to promote smoking cessation and other healthy behaviors, the CDC and the National Institutes of Health (NIH) have developed a program titled Healthy People 2010, which contains several goals and objectives to promote respiratory health through better prevention, detection, treatment, and education.[17] The 2 main goals outlined for COPD are (1) to reduce the proportion of adults whose activity is limited due to chronic lung and breathing problems from 2.2% to 1.5% and (2) to reduce deaths from COPD among adults from 119.4 deaths per 100,000 persons (aged 45 years and older) to 60 deaths per 100,000 persons. A significant public health impact would be realized if both of these goals were met.

Diagnosis and Staging of COPD

A diagnosis of COPD should be considered in any patient who has symptoms of chronic cough with sputum production, dyspnea, and exposure to risk factors for the disease.[18] The most important risk factor for COPD is tobacco use, and most patients diagnosed with COPD have been smoking for at least 20 years. Exposure to other toxic substances, however, may also predispose a patient to develop COPD, so such a history should be elicited. The results of physical examinations early in the disease course may be normal or may show a prolonged expiratory phase and wheezing on forced exhalation. As the disease progresses, the anteroposterior diameter of the chest increases and hyperinflation occurs, causing a diminution of both breath sounds and heart sounds. As patients approach end-stage COPD, physical signs become more obvious and include cachexia, use of accessory muscles for breathing, and peripheral edema due to right heart failure. Chest x-ray classically shows hyperinflation, flattening of the diaphragm, and increased retrosternal air space, all of which are characteristic of emphysema.

Measurement of airflow limitation by the use of spirometry is necessary for the proper diagnosis of COPD, largely because of the reproducibility and wide availability of this technique.[19] Spirometry testing is also useful for monitoring the disease course. In patients with COPD, FEV_1 and forced vital capacity, or FVC, should be measured and compared with standardized reference values. Patients with COPD may have a decreased FEV_1, FVC, and a decreased FEV_1/FVC ratio. COPD is therefore a disease state suggested by characteristic symptoms, but confirmed by spirometry.

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria are often used to classify patients by severity (Stage 0 to Stage III) once the diagnosis of COPD has been made.[1] Patients with Stage 0 COPD may be symptomatic with cough and sputum production, but have normal spirometry. Patients with Stage I, or mild, COPD have spirometry characterized by FEV_1/FVC of $< 70\%$ but $FEV_1 > 80\%$, and usually have mild symptoms. Because of the mild nature of the airflow limitation in this group, the patients may not perceive any diminution in lung function in Stage I COPD. Patients with Stage II, or moderate, COPD have worsening airflow limitation, characterized by an FEV_1 of between 30% and 70% of predicted, and often present for the first time to a physician with dyspnea or exacerbations of their condition. Patients with Stage III, or severe, COPD have severe airflow limitation with an FEV_1 of $< 30\%$ or the presence of respiratory failure or signs and symptoms of right heart failure. In this stage, the patient's quality of life is significantly affected and mortality is high.

Treatment of COPD—General Principles

Because the pathophysiologic changes in COPD are irreversible, effective treatment is focused on slowing the decline in lung function, providing symptomatic treatment, and treating acute exacerbations when they occur. The only known therapy that can slow the decline in lung function in patients with COPD is smoking cessation,[20] so this should be addressed at every encounter with the patient. Even with nicotine replacement, behavioral counseling, and frequent office visits, the smoking cessation rate for patients with COPD is alarmingly low. In one study using sustained-release buproprion, the abstinence rate for COPD patients who smoke

was only 28%.[21] In an attempt to improve smoking cessation rates, the U.S. Department of Health and Human Services has released a guideline titled "Treating Tobacco Use and Dependence," which provides an evidence-based systems approach to helping patients stop smoking.[22]

Symptomatic relief is the mainstay of treatment for patients with COPD. Medications used for this purpose include bronchodilators (both short-acting and long-acting), corticosteroids, theophylline, and mucolytic agents. Nonpharmacological therapies for symptom relief of patients with COPD include supplemental oxygen and pulmonary rehabilitation. Lung volume reduction surgery is indicated in some patients. Adjunctive therapies that may improve the overall care of patients with COPD include disease management programs and comprehensive care coordination, including home care, case management services, and self-directed treatment.

Bronchodilators

Bronchodilators are indicated for symptom relief in all patients with COPD. They have several beneficial effects, including alleviation of dyspnea, reduction in exacerbations of COPD, improvement in exercise tolerance, and improvement in quality of life.[23,24] Short-acting bronchodilators include beta-agonists such as albuterol and the anticholinergic agent ipratropium bromide. These drugs are usually used to treat acute dyspnea, as they provide bronchodilation for approximately 4 to 6 hours. Combination products including both of these drugs are often used in patients with COPD. The different mechanisms of bronchodilation are thought to offer a better overall response than each agent alone. One study of 652 patients with COPD showed that treatment with a combination of nebulized ipratropium and albuterol achieved better bronchodilation than either agent alone without any increase in side effects.[25] Another study of 534 patients with COPD showed that the same treatment regimen administered via metered-dose inhaler achieved better bronchodilation than either agent alone.[26]

While short-acting bronchodilators may be quite effective in treating intermittent dyspnea in patients with COPD, regularly scheduled treatment with a long-acting bronchodilator is usually required due to the chronic nature of the airflow limitation. Currently, 2 long-acting beta-agonists, salmeterol and formoterol, and 1 long-acting anticholinergic, tiotropium, are available, all of which have been extensively studied in the treatment of patients with COPD.

Salmeterol

Salmeterol xinafoate (Serevent) is a beta-2-adrenergic agonist that is indicated for the maintenance treatment of asthma and COPD as well as for the prevention of exercise-induced asthma. It is available as a powder for oral inhalation and in a combination inhalation product with fluticasone (Advair). It is not indicated for use in acute exacerbations of COPD, as its onset of action is approximately 10 minutes and its peak effect does not occur until 2 to 4 hours. Salmeterol has a duration of action of about 12 hours and is indicated for twice-daily use. Side effects are uncommon, but include headache, tachycardia, insomnia, and nausea.[27]

In one study of COPD patients, use of salmeterol resulted in lower daytime and nighttime symptom scores and less use of rescue inhalers both during day and night as compared with placebo. Morning peak expiratory flow (PEF) rates were also increased.[28] Another study examined the effect of salmeterol on health-related quality of life (HRQOL) using the St. George's Respiratory Questionnaire (SGRQ). In this study, patients with COPD who received salmeterol twice a day exhibited modest improvement in lung function and a clinically significant gain in health and well-being.[29] Yet another study compared the efficacy and safety of salmeterol with both ipratropium and placebo. A total of 411 patients were enrolled and randomized to salmeterol, twice daily; ipratropium bromide, 4 times daily; or placebo, 2 puffs 4 times daily. In comparison with patients who were taking ipratroprium or placebo, patients who received salmeterol showed a significantly greater increase in lung function over the 12 weeks of the study, with decreased utilization of supplemental albuterol, longer time to first COPD exacerbation, and no significant difference in side effects.[30]

Formoterol

Formoterol fumarate (Foradil) is a beta-2-adrenergic agonist that is indicated for the maintenance treatment of asthma and COPD, as well as for the treatment of exercise-induced bronchospasm. It is available as a powder for oral inhalation, to be given twice daily, and is expected to be approved in the United States as a combination product with budesonide (Symbicort). Formoterol acts quickly after administration, with an onset of action of approximately 3 minutes, a time to peak effect of 15 minutes, and a duration of action of about 12 hours. Because of its quick onset, formoterol has an indication for acute relief of bronchoconstriction in some countries, but not in the United States. It is very well tolerated, with the most common side effects being viral infections and bronchitis.[31]

One study of 692 patients with COPD compared formoterol twice daily with placebo. Patients who were treated with formoterol demonstrated reduced mean total symptom score (including reduced symptom scores for breathlessness), increased percentage of nights without awakenings due to dyspnea, reduced need for rescue medication, and increased symptom-free days.[32] Another study compared formoterol with ipratropium bromide or placebo in 780 patients with COPD. Patients who received formoterol had significantly improved symptoms and quality of life when compared with placebo in this study, while ipratropium produced no such effects, leading the authors to conclude that formoterol is more effective than ipratropium in the treatment of COPD.[33]

Salmeterol and formoterol have been studied in several head-

to-head clinical trials. One Canadian study compared formoterol with salmeterol in 47 patients with stable, moderate-to-severe COPD. The results of this small study showed that patients who were treated with formoterol experienced a faster onset of bronchodilation and a larger improvement in FEV_1 at all time points up to 60 minutes than patients who were treated with salmeterol.[34] Another study, conducted in Europe, confirmed these findings. Patients who received formoterol in this study exhibited an increased inspiratory capacity and faster onset of action than those who received salmeterol.[35] Neither study directly compared the agents for their effects on symptom reduction or improvements in quality of life.

Tiotropium

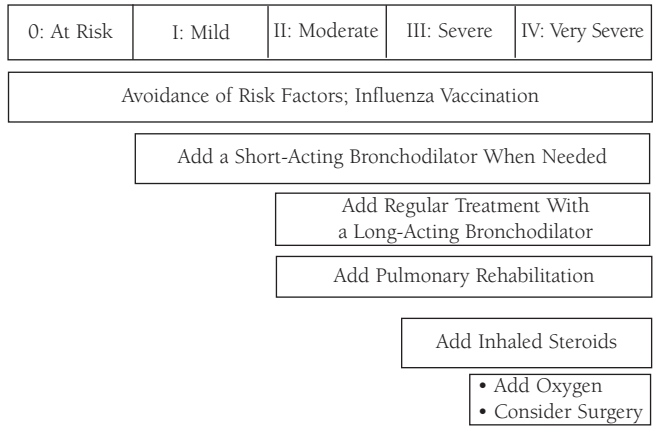
Tiotropium (Spiriva) is an anticholinergic agent that is indicated for the maintenance treatment of patients with COPD. It is available as a powder for oral inhalation, to be given once daily. Peak clinical effects occur within 3 hours of the administration of the dose. Tiotropium is not indicated as a rescue agent. The drug is well tolerated, with the most common side effects being xerostomia, pharyngitis, and edema.[36,37]

Tiotropium has been studied extensively alone and in combination with other drugs used to treat COPD. In one placebo-controlled study of 921 patients with stable COPD, treatment with tiotropium resulted in superior bronchodilation when compared with placebo, as demonstrated by an improvement in FEV_1. Patients treated with tiotropium reported less dyspnea, improved health status scores (obtained through the SGRQ and Health Status Index [SF-36]), decreased COPD exacerbations, and fewer hospitalizations. The only significant adverse event that was statistically different from placebo was dry mouth.[38]

Several studies have compared tiotropium with its shorter-acting counterpart, ipratropium bromide. One study of 288 patients compared the effects of tiotropium inhaled once daily with ipratropium inhaled 4 times daily on lung function, measured by standard spirometry. Patients in the tiotropium group achieved a significantly greater improvement than the ipratropium group in both FEV_1 and FVC levels. There were also improvements in morning and evening PEF measurements and a decreased use of rescue inhaler in the tiotropium group. Side effects were comparable, with approximately 15% of patients in the tiotropium group and 10% of patients in the ipratropium group experiencing dry mouth.[39] A second study compared tiotropium with ipratropium in 356 patients with COPD. In this study, patients in the tiotropium group experienced significant improvements in PEF, decreased rescue inhaler use, and improved health status scores as compared with the ipratropium group. The tiotropium group also exhibited fewer exacerbations and hospitalizations, as well as a longer time to the first exacerbation. This led the authors to conclude that tiotropium is an effective first-line maintenance drug for the treatment of patients with COPD.[40]

Other studies have compared tiotropium with salmeterol. In one study, tiotropium, once daily, was compared with salmeterol, twice daily, for effects on lung function and health status. Patients treated with tiotropium experienced greater morning FEV_1 and average FEV_1 throughout the study as well as significant improvements in the SGRQ and the Transitional Dyspnea Index (TDI). Both tiotropium and salmeterol reduced the need for rescue inhalers in this study.[41] Another study examined the effects of tiotropium versus salmeterol on health resource utilization. Patients treated with tiotropium exhibited fewer exacerbations and an increased period of time to the first exacerbation. Hospital utilization was decreased in the tiotropium group, and patients in this group also had significantly fewer days when they were unable to perform their usual activities of daily living. Both SGRQ and TDI scores were improved in both groups, as were standard spirometric parameters.[42]

FIGURE 1 Therapy at Each Stage of COPD[43]



Adapted from Global Initiative For Chronic Obstructive Lung Disease (GOLD) Executive Summary; 2004 update.
COPD = chronic obstructive pulmonary disease.

In light of these data, the GOLD guidelines recommend bronchodilators as a first-line drug in the management of symptomatic COPD[43] (Figure 1). The choice of bronchodilator depends on individual response in terms of symptom relief and side effects. Although long-acting bronchodilators are both more effective and more convenient, they are also more expensive, and this must be taken into account when considering an individual treatment plan. The GOLD guidelines also note that combination therapy with more than 1 bronchodilator may be desirable, since it provides symptom relief by 2 mechanisms and may limit dosages of each individual medication. This committee has made no recommendations regarding specific drugs.

Corticosteroids

The use of corticosteroids in COPD patients is controversial because there has not been clear and convincing evidence of their benefit in the majority of patients. The etiology of COPD is

thought to involve inflammation, although the inflammation seen in COPD is different from that seen in asthma. The airways in patients with asthma show a predominant eosinophilic infiltration, and this type of inflammation responds quite readily to the administration of corticosteroids. In COPD, the cellular infiltration consists of neutrophils, macrophages, and CD8+ T cells, and steroid responsiveness is not as consistent.[44] Recent research has shown that there may also be an eosinophilic component to the inflammation seen in the airways of patients with COPD, which may explain why some patients with COPD respond to corticosteroids.[45] Additionally, corticosteroids have been shown to decrease levels of expired nitric oxide in patients with COPD, which correlates to an anti-inflammatory effect, but the clinical significance of this is uncertain.[46]

The role of inhaled corticosteroids has been studied in the treatment of patients with COPD, although with some conflicting results. Some studies have shown no clinical benefit, whereas others have shown symptomatic improvement only (without tangible spirometric benefits), and still others have shown small but significant spirometric benefits. In one study, patients with advanced COPD were randomly assigned to inhaled budesonide, 1,600 mcg per day, or placebo, and effects on spirometry, exercise capacity, dyspnea on exertion, quality of life, PEF, and other respiratory symptoms were observed. The researchers found no differences between the groups in change in FEV_1 or in any other end point.[47] In another study, patients with COPD who continued to smoke were randomly assigned to either budesonide, 400 mcg twice daily, or to placebo, and the effects on FEV_1 were assessed. In the first 6 months of the study, patients treated with inhaled budesonide showed an improvement in FEV_1, but from 9 months to the end of the study, the rate of decline was the same in both treatment groups. There was more skin bruising in the corticosteroid group as compared with the placebo group (10% versus 4%).[48]

In a large study of 1,116 patients with COPD, inhaled triamcinolone acetonide, 600 mcg twice daily, was compared with placebo, and the effects on FEV_1, respiratory symptoms, use of health care services, airway reactivity, and bone density were evaluated. Patients in the treatment group showed no difference in the rate of decline in FEV_1 over 40 months of follow-up, but this group had fewer respiratory symptoms and fewer physician visits. Patients who received triamcinolone exhibited lower airway reactivity in response to a methacholine challenge, but there was a significant decline in bone density at the lumbar spine and the femur in this group.[49] The authors concluded that the benefits seen in the patient group that received triamcinolone should be balanced with the decrease in long-term bone density observed.

In the Inhaled Steroids in Obstructive Lung Disease in Europe (ISOLDE) study, 751 patients with moderate-to-severe COPD were randomized to receive fluticasone proprionate, 500 mcg twice daily, or matching placebo. Effects of active treatment on rate of decline in FEV_1, health status, frequency of exacerbations, and adverse effects were evaluated. There was no significant difference between the groups in the decline of FEV_1, although the mean FEV_1 after bronchodilator administration remained significantly higher in the fluticasone group throughout the duration of the study. Patients in the active treatment group experienced fewer exacerbations and a slower decline in health status according to SGRQ. Adverse effects were similar between groups, with the exception of those events directly attributable to the inhalation of the corticosteroid (i.e., dysphonia, sore throat), which were higher in the fluticasone group.[50]

The International COPD Study Group was a study of 281 patients with COPD who were randomized to inhaled fluticasone propionate, 500 mcg twice daily, or to placebo. Outcomes were measured by the number and severity of exacerbations, overall lung function, symptoms, PEF, and a 6-minute walking distance. Patients who received fluticasone had similar numbers of exacerbations as the placebo group, but the severity of those exacerbations was diminished. There was a significant improvement in PEF, FEV_1, and FVC in the active treatment group, and symptom scores for cough and sputum volume were significantly lower in this group as well. Patients who received fluticasone were able to increase their 6-minute walking distance significantly over patients who received placebo, and adverse effects were similar between groups.[51]

In light of these data, the GOLD guidelines recommend regular use of inhaled corticosteroids in symptomatic patients with an $FEV_1 < 50\%$ predicted and in those who have experienced repeated exacerbations (at least 3 in 1 year). This recommendation is based on data showing that inhaled corticosteroids reduce the frequency of exacerbations and improve health status in patients with advanced COPD. However, it is acknowledged that inhaled corticosteroids do not modify the decline in FEV_1 seen in patients with COPD.

Combination Therapy With Bronchodilators and Corticosteroids

Despite strong evidence of the effectiveness of inhaled bronchodilators in COPD, some patients still fail to respond adequately and may require additional medications to control symptoms. Studies have addressed the potential benefits of inhaled long-acting bronchodilator and corticosteroid combination therapy. The appropriate niche for such combination therapies may be for patients in whom optimal bronchodilation fails to result in complete symptomatic relief, thus requiring the use of additional medications to control symptoms.[23]

One study compared the efficacy and safety of budesonide/formoterol in a single inhaler (Symbicort) with placebo, budesonide alone, and formoterol alone for 12 months in 812 adults with moderate-to-severe COPD. Patients who were treated with budesonide/formoterol experienced 24% fewer COPD exacerbations than placebo, 23% fewer COPD exacerbations than formoterol alone, and 11% fewer COPD exacerbations than budesonide alone (P=NS). FEV_1 increased by 15% versus placebo,

9% versus budesonide alone, and 1% versus formoterol alone (P = NS). There were improvements in PEF throughout the study in the combination group, and there were significant reductions in both symptoms and the use of rescue inhalers. Lastly, HRQOL was improved with the use of the combination inhaler as compared with the placebo group, and side effects were minimal.[52]

A similar study compared the benefits of combination therapy with fluticasone proprionate and salmeterol (Advair diskus) with those of placebo, fluticasone alone, and salmeterol alone for 24 weeks in 691 patients with COPD. Patients were randomized to 1 of the 4 treatment groups, and relevant outcomes were measured. Those treated with fluticasone/salmeterol experienced greater increases in FEV_1 than the other treatment groups. Those treated with fluticasone/salmeterol had highly significant improvements in the TDI as compared with all other groups, and adverse effects were similar among treatment groups, with the exception of an increased rate of oral candidiasis, which occurred in both the combination treatment group and the fluticasone group.[53]

A 12-month study of 1,465 patients compared the benefits of fluticasone/salmeterol 500/50 combination therapy with each individual component alone and with placebo. Each treatment was administered twice daily. The results showed that FEV_1 improved in all the active treatment groups, but there was a greater increase in the combination group. Exacerbations were significantly decreased in the combination group compared with placebo, but not when compared with either agent alone. SGRQ scores were significantly improved in the combination group compared with all other groups, as was the use of rescue medications. Side effects were comparable among all active treatment groups, with the exception of an increased rate of oral candidiasis in the combination and fluticasone alone groups.[54] In light of this and other evidence, the GOLD guidelines recommend that the combination of an inhaled long-acting bronchodilator and an inhaled corticosteroid is more effective than the individual components and gives this treatment a level A recommendation, the highest level of evidence supporting its use.

Theophylline

The use of theophylline in the treatment of patients with COPD is controversial. Theophylline is a nonselective phosphodiesterase inhibitor that causes bronchodilation in patients with COPD. Other proposed actions of theophylline include anti-inflammatory and immunomodulatory effects, improvement in mucociliary clearance, and possible direct stimulatory effects on the respiratory musculature.[55] Many of the actions of theophylline have not been consistently demonstrated, and because of this, in addition to its narrow therapeutic range, it has been recommended as a third-line therapy in patients with COPD by the GOLD guidelines.

A recent review by the Cochrane Collaboration addressed the effectiveness of theophylline when compared with placebo in patients with COPD. This review included 20 randomized controlled clinical trials. Overall, results from the majority of the trials reviewed demonstrated a significant increase in FEV_1 and FVC with theophylline as well as an improvement in arterial oxygen tension. No improvement was observed in walking distance, or breathlessness scores, and side effects were greater with theophylline than placebo.[56] The authors noted that the trials included patients on a number of different therapies in addition to theophylline, thereby limiting the generalizability of the studies.

Theophylline has been extensively studied in patients with COPD, and its effects have been inconsistent. Some studies have shown improvements in dyspnea, whereas others have shown no difference. Some studies have shown an improvement in exercise tolerance, whereas others have not. Many studies have shown an improvement in respiratory mechanics, including FEV_1 and PEF, with theophylline either alone or in combination with other agents. Most studies have shown that theophylline is not effective during acute exacerbations of COPD.[57-59]

Lung Volume Reduction Surgery

Symptoms of COPD are, in part, related to the degree of obstruction, to static and dynamic hyperinflation, and to the load that those changes place on the respiratory pump. Lung volume reduction surgery (LVRS) in selected patients may result in improved airflow, increased exercise tolerance, and decreased perception of dyspnea. LVRS involves removing a percentage of the damaged lungs so that the remaining tissue and surrounding muscles can work with greater efficiency, making breathing easier for the patient. The mechanism by which LVRS causes such improvements includes increased lung elastic recoil and airway conductance, improved respiratory muscle function, and decreased dynamic hyperinflation.

In 1997, 17 centers participated in the National Emphysema Treatment Trial through the National Institutes of Health in an effort to determine the best treatment for people with severe emphysema. The study found that patients with upper-lobe emphysema seemed to function better after LVRS than did those with medical treatment alone, even if they had low exercise capacity. However, the results were not as favorable for non-upper-lobe emphysema patients.[60] Further discussion about LVRS is beyond the scope of this article.

Pulmonary Rehabilitation

Pulmonary rehabilitation is defined as a multidisciplinary program of care for patients with chronic respiratory impairment that is individually tailored and designed to optimize physical and social performance and autonomy.[61] Components of a typical pulmonary rehabilitation program are listed in Table 1. Expected benefits of pulmonary rehabilitation are listed in Table 2. Ideally, a pulmonary rehabilitation program should include the participation of several different types of health professionals, including physicians, physical therapists, dieticians, and pharmacists, and all of these people can help to develop a multidisciplinary plan of care that will benefit patients to the greatest extent.

TABLE 1 Components of a Typical Pulmonary Rehabilitation Program[61]

Exercise training
Education
Behavioral modification
Outcomes assessment

TABLE 2 Potential Benefits of a Pulmonary Rehabilitation Program[43]

Improvement of exercise capacity	Reduction in hospitalizations
Reduction of symptoms, including breathlessness	Reduction in anxiety and depression

Exercise Training

Although exercise training is an essential component of any pulmonary rehabilitation program, there have been no studies to demonstrate a beneficial effect of exercise on respiratory muscle impairment. Rather, exercise training in patients with COPD is primarily designed to relieve breathlessness and improve endurance. There have been multiple studies demonstrating that lower extremity exercise improves exercise endurance in patients with COPD.[62] In one study, patients who participated in a comprehensive pulmonary rehabilitation program, including 3 months of daily supervised exercise, exhibited greater improvements than those who received standard care.[63] Specifically, patients in the treatment group experienced less dyspnea and fatigue, achieved improvements in the 6-minute walking distance test, and showed improvements in emotional function as measured by the Chronic Respiratory Questionnaire (CRQ). These benefits were maintained for 2 years. In another meta-analysis of 20 trials of pulmonary rehabilitation, patients who received lower extremity exercise training did significantly better than control groups on measures of walking distance and shortness of breath.[64]

Patient Education

Patient education is a very important part of a comprehensive pulmonary rehabilitation program. Common topics that are addressed in the educational component of such a program are medications and the importance of medication compliance, stress management, avoidance of environmental irritants, self-management skills, and energy conservation and work simplification techniques. Education encourages patients and families to become active participants in their health care, leads to a greater understanding of chronic illness, and helps patients and families, explore ways to cope with the illness and its effects on daily life. Because of the obvious potential for significant positive effects of education, the effectiveness of this practice has been addressed. In one study, 76 patients with COPD were randomized to 1 of 3 treatment groups that included behavior modification, cognitive modification, and behavior-cognitive modification, and these treatment groups were compared with a control group that received no intervention. After 3 months, patients in the active treatment groups exhibited increased exercise endurance and improved quality of life.[65]

Psychosocial Support

A psychosocial component of any pulmonary rehabilitation program is essential, as patients with COPD are at increased risk for developing anxiety and depression.[66] Interventions that may be a part of the psychosocial component include support groups focusing on specific problems, instruction in progressive muscle relaxation and stress management, and control of anxiety and concomitant dyspnea. The effectiveness of these and other psychosocial components of pulmonary rehabilitation has been studied, with conflicting results. One study showed that a 30-day pulmonary rehabilitation program including exercise, education, and psychosocial counseling was effective in reducing symptoms of depression and anxiety as well as having other positive benefits in patients with COPD.[67] Another study showed that an 8-week comprehensive pulmonary rehabilitation program including education, physical and respiratory care instruction, psychosocial support, and supervised exercised training did not reduce measures of depression in patients with COPD.[68] Despite these conflicting results, most available pulmonary rehabilitation programs have a psychosocial component.

Outcomes Assessment

Outcomes assessment has become a critical component of comprehensive pulmonary rehabilitation programs. Many measures may be used to assess the effectiveness of a pulmonary rehabilitation program, including exercise tolerance measurements, severity of exertional and overall dyspnea, HRQOL, and overall functional status. Standardized outcome measures and ongoing evaluation of the program will demonstrate its overall effectiveness. Additionally, monitoring changes in a patient's personal performance may help that patient or their family realize the value of participating in such a program.

Quality of Life

Quality of life is an important outcome measure that has been studied in COPD patients who have undergone pulmonary rehabilitation. In one study, a 3-week pulmonary rehabilitation program incorporating exercise training, education, and psychosocial counseling was assessed to determine quality of life scores in 37 patients with COPD, using the Health Status Index (SF-36). Patients in this study exhibited improvement in 5 of the 9 quality-of-life subscales following participation in pulmonary rehabilitation.[69] Another study showed that a 6-week outpatient-based pulmonary rehabilitation program significantly improved quality of life in patients with COPD, as measured by the SGRQ.[70]

A Cochrane Collaboration review addressed the impact of pulmonary rehabilitation on HRQOL. A meta-analysis of 14 trials included in this review showed that pulmonary rehabilitation improves measures of dyspnea, fatigue, and patients' sense of well-being, and these improvements were described as moderately large and clinically significant.[71]

Because COPD affects both younger and older patients, it is important to address whether or not pulmonary rehabilitation is uniformly effective among different age groups. Since one of the components of a pulmonary rehabilitation program involves exercise training, one might assume that older patients would not be as likely to benefit from such a program because of deconditioning and comorbid conditions. A recent Canadian study attempted to determine whether patients aged 80 years or older gain similar benefits from pulmonary rehabilitation as patients younger than 80 years. In this study, 230 consecutive inpatients with moderate-to-severe lung disease participated in a comprehensive pulmonary rehabilitation program, and outcomes included dyspnea scores, 6-minute walk distance test, and other objective functional scores. The results of this study indicated that such a program was equally likely to have a beneficial effect on both younger and older patients, with older patients demonstrating significant improvements in the 6-minute walk test, dyspnea scores, and global functional scores.[72]

While pulmonary rehabilitation programs are effective for improving clinical parameters, their economic effects are uncertain. A study in Canada investigated the cost-effectiveness of a community-based pulmonary rehabilitation program for COPD patients. Direct costs and disease-specific quality of life (using SGRQ) were compared before and after completion of a 1-year pulmonary rehabilitation program in Edmonton, Canada, in 210 patients with COPD. There was a reduction in overall costs of $344 per person per year after patients completed the program, and there was an associated decrease in health service utilization, including emergency and hospital services.[73]

Oxygen Therapy

Hypoxemia is a secondary development in many patients with severe COPD. In general, supplemental oxygen therapy improves survival in hypoxemic patients, regardless of etiology.[74] In patients with COPD specifically, oxygen use has also been associated with improved survival, but only in patients with partial pressure of oxygen in arterial blood (PaO_2) of ≤ 60 mm Hg. In a landmark study by the British Medical Research Council, 87 hypoxic COPD patients were randomized to treatment with continuous oxygen at 2 liters/minute for at least 15 hours per day or no oxygen therapy. After 5 years of follow-up, 19 of the 42 patients (45%) treated with oxygen died, as compared with 30 of 45 control patients (67%).[75] In the Nocturnal Oxygen Therapy Trial, 203 patients were randomized to either 24-hour continuous oxygen therapy or 12-hour nocturnal oxygen therapy. After 12 months, mortality in the continuous therapy group was approximately 50% less than that in the nocturnal therapy group.[76] A more recent study showed that in hypoxic patients with a higher PaO_2 (i.e., > 60 mm Hg), long-term oxygen therapy may not improve survival.[77]

Supplemental oxygen therapy has also been studied for its effects on quality of life in patients with COPD. A recent study from New Zealand attempted to address the short-term clinical impact of supplemental oxygen therapy in 41 patients with COPD by using the CRQ and the SF-36. These patients experienced dyspnea, but were not necessarily chronically hypoxic, with an average PaO_2 of approximately 70 mm Hg. Patients in the treatment group experienced significant improvements in all aspects of the CRQ and in 4 of the 8 domains of the SF-36. Patients also exhibited less depression and anxiety, as measured by the SF-36.[78]

Because of the expense of long-term oxygen therapy, guidelines have been developed for its appropriate use.[74] In order to qualify for continuous home oxygen therapy, patients must have a resting PaO_2 of ≤ 55 mm Hg (or oxygen saturation of < 88%), or a resting PaO_2 of 56-59 mm Hg (or oxygen saturation of 89%) in the presence of (1) dependent edema, suggesting the presence of right heart dysfunction; (2) pulmonale on the ECG; or (3) erythrocythemia (hematocrit > 56%). Patients with resting PaO_2 of > 59 mm Hg or oxygen saturation > 89% must have extensive documentation proving medical necessity before home oxygen therapy will be covered. Patients may qualify for non-continuous oxygen therapy if they desaturate with exercise or sleep to a PaO_2 of < 55 mm Hg or an oxygen saturation of < 88%.

Coordination of Care in Patients With COPD

COPD is a complex medical condition, and most patients with COPD have multiple comorbidities. The financial and public health impact of COPD on society is very large, and systems to manage the burden of this disease seem warranted. Therefore, the concept of care coordination has evolved to manage patients with costly chronic conditions, including COPD. Broadly defined, care coordination is "optimal management of people with multiple chronic medical diseases to improve outcomes and cut costs."[79] It may involve many types of practices, including case management and disease management, and it involves different types of health care professionals working together. Care coordination also involves the active participation of the patient. There have been numerous studies of different types of COPD care coordination, and, based upon the results of some of these studies, the outlook for improvements in care of these patients is promising.

Case Management Services

Case management is defined as "…a collaborative process which assesses, plans, implements, coordinates, monitors, and evaluates options and services to meet an individual's health needs through communication and available resources to promote quality, cost-effective outcomes."[80]

A 2001 study examined the provision of case management services through the participation of a COPD clinical nurse

specialist who followed patients longitudinally in both the community and the hospital. The nurse provided education on the disease process and medications and made sure that patients received all appropriate care, including vaccinations. The nurse also assisted in discharge planning when the patient was admitted to the hospital. A total of 16 patients with at least 4 hospital admissions for COPD in the preceding 2 years were enrolled in the program, and various parameters were measured before and after their inclusion into the program. Patients with COPD in this study who received case management had a nonsignificant decrease in the rate of hospital admission for COPD exacerbation, but a highly significant decrease in the median length of stay once hospitalized, from 5.6 days to 3.5 days. There was also a significant improvement in the CRQ score for the case-managed patients. In order for the program to be cost-effective, it was determined that a decrease of 3.5 bed days per patient per year was needed to cover the cost of the program. Calculations showed that there was an actual decrease of 13.5 bed days per patient per year in the case management group, thus proving the program's cost-effectiveness.[81] Other studies have confirmed these findings.[82,83]

The provision of home-based care has been studied to determine its ability to improve the care of patients with COPD. In one study, 122 patients with severe COPD on chronic supplemental oxygen therapy were randomized to either conventional care without any home-based component versus a home-care management program that included monthly telephone calls, home visits by a respiratory nurse every 3 months, and home or hospital visits by the nurse on an "on-demand" basis. The results of the study demonstrated a decrease in ED visits, hospital admissions, and length of stay. While there was no difference in quality of life, survival, or other clinical indicators, the program was found to be cost-effective, with a savings of nearly $47,000 during the study period.[84] In another study, 177 hospitalized patients with COPD were randomized to a postdischarge community-based intervention program consisting of 2 visits by a nurse who provided appropriate education versus no intervention. The results of the study demonstrated an improvement in activity scores and increased satisfaction in the intervention group, and a worsening of symptom scores in the control group. Two concerning findings of this study were (1) there were no differences in hospital readmissions compared with placebo and (2) the patients' primary care providers were not effectively engaged in the care process. The authors suggested that further study was needed to determine which aspects should be included in such a home-based management program.[85]

Patient Self Management

Active participation by the patient is essential to effective care of the chronically ill patient, and this notion certainly holds true for patients with COPD. It has been hypothesized that self-management plans may help improve care in patients with COPD, but results have been generally unimpressive. An example of such a plan is the "COPD Action Plan," which was examined in a 1997 study in New Zealand. In this study, patients received education about a self-management plan designed to assist them in managing their conditions and prevent exacerbations. The plan consisted of a printed booklet with an action plan regarding what specific action should be taken based upon the patient's symptoms, as well as a list of medications that could be self-initiated, such as prednisone, antibiotics, and rescue inhalers, with the appearance of certain symptoms. Close communication with the primary care physician was emphasized. In this study, 56 patients were randomized to either education about using the action plan or conventional therapy. In the intervention group, patient responses on quality-of-life scales were measured before and after institution of the action plan. While there was no difference in quality-of-life scores between the intervention and control groups, the study showed that patients in the intervention group exhibited a significant improvement in their SGRQ score after adoption of the action plan. In response to the action plan, more patients in the intervention group self-initiated prednisone and antibiotics in response to deteriorating symptoms than in the control group. Overall lung function was unchanged.[86]

A 2003 systematic review of 12 trials found that self-management programs had no effect on hospital admissions, emergency room visits, or lost days from work and lung function, and there were inconclusive results obtained on quality of life, symptoms, and health care utilization. Patients who were in self-management programs showed a decreased need for rescue medication and an increased use of oral corticosteroids and antibiotics for worsening respiratory symptoms. Because no significant clinical benefits were identified in this review, it is not clear if the self-initiation of medications in COPD patients should be routinely recommended.[87]

Disease Management Programs

Another approach that has been used to manage the care of patients with COPD is disease management, which is defined as "…the use of an explicit systematic population-based approach to identify persons at risk, intervene with specific programs of care, and measure clinical and other outcomes."[88] While there is clearly some overlap between this approach and the others already mentioned, disease management is more systematic and global in its approach to managing patients with chronic illnesses.

Typically, a disease management program for COPD contains components that identify eligible patients and ascertains a current level of disease severity. Specific interventions can be targeted to patients according to their disease severity. These interventions may include one-on-one telephonic disease management, education of patients on topics specific to their disease severity, and availability of an "on-call" line to establish communication when urgent concerns or questions arise.

Studies have been performed to determine if disease management programs are beneficial in COPD patients. The COPD Disease Specific Care Management Program at National Jewish

Medical and Research Center, Denver, Colorado, has demonstrated impressive anecdotal results with their program, including a 6% reduction in daytime symptoms and a 39% reduction in nighttime symptoms; an 11.7% absolute increase in the utilization of bronchodilators; and statistically significant decreases in missed work days, ED visits, hospitalizations, intensive care unit admissions, unscheduled physician visits, and oral antibiotic usage.[89] A 2004 systematic review, however, did not yield such impressive results. Of 22 disease management programs identified for this review, only 9% (2 of 22) demonstrated statistically significant improvements in patient care. This was in comparison with disease management programs for depression and diabetes mellitus in which 48% and 36% of programs identified showed significant benefits.[90] In light of this, it is clear that further study needs to be done to determine the effectiveness of such programs.

Disease management programs that utilize the services of a specific type of health care practitioner have also been evaluated. A 2002 study investigated the effectiveness of care for patients with asthma and COPD by community drugstore pharmacists.[91] In this study, patients were randomized to a pharmaceutical care program versus usual care. In the pharmaceutical care program, the pharmacist monitored patient symptoms, provided medication counseling, helped to resolve drug-related problems, and facilitated communication with prescribing physicians. After 12 months, patients in the intervention group had significantly higher peak flow rates and higher patient satisfaction but showed no improvement in medication compliance or quality-of-life scores. The authors speculated that the pharmaceutical care program failed to prove a benefit because it was labor-intensive and some components of the program were underused.[91]

Another study examined the effect of the use of a respiratory health worker in reducing respiratory impairment and disability experienced by patients with COPD who attended an outpatient respiratory department. In this study, 152 patients were randomized to usual care or care by the respiratory health worker, who provided health education and symptom and treatment monitoring in conjunction with the primary care provider. Those patients who received the assistance of the respiratory care worker were less likely to die and more likely to adhere to outpatient follow-up and be prescribed appropriate medications. There was no effect on spirometric values or disability.[92]

Conclusion

COPD is a serious health problem with a significant burden of disease. Smoking is the most common risk factor for development of COPD, and smoking cessation is the only measure that has been shown to reduce the progression of the lung function decline. Yet smoking cessation programs show dismal success rates; therefore, efforts may be better directed toward smoking prevention. Once COPD has become clinically apparent, intensive, guideline-based care is essential. Utilization of bronchodilators is the mainstay of treatment in COPD, but inhaled corticosteroids and theophylline may also be useful in selected patients. Coordinated care is important in COPD patients and should be administered by different but complementary health care professionals, including physicians, nurses, pharmacists, and case managers, and in different care settings, including the home, physician's office, outpatient pulmonary rehabilitation center, and, if needed, in the inpatient setting.

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Contemporary Issues in the Care of Patients With Chronic Obstructive Pulmonary Disease

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Posttest Worksheet: Contemporary Issues in the Care of Patients With Chronic Obstructive Pulmonary Disease

1. Chronic obstructive pulmonary disease (COPD) is a disease state characterized by airflow limitation that is not fully reversible.
   a. True
   b. False

2. It is reported that men have a higher self-reported rate of COPD than women.
   a. True
   b. False

3. The main tool to properly diagnosis COPD and to measure airflow limitation is
   a. chest x-ray.
   b. CAT scan.
   c. spirometry.
   d. lung biopsy.

4. Measures of effective treatment in the management of patients with COPD includes
   a. slowing the decline in lung function.
   b. providing symptomatic treatment.
   c. treating acute exacerbations.
   d. All of the above

5. Treatments for COPD include all of the following EXCEPT
   a. morphine.
   b. bronchodilators (both short-acting and long-acting).
   c. corticosteroids, theophylline, and mucolytic agents.
   d. supplemental oxygen and pulmonary rehabilitation.

6. Common topics addressed as part of patient education include
   a. effective medication compliance.
   b. stress management, self-management skill, energy conservation, and work-simplification techniques.
   c. avoidance of environmental irritants.
   d. All of the above

7. Outcomes associated with rehabilitation programs include all but
   a. increasing exercise capacity.
   b. curing the disease.
   c. decreasing symptoms/exacerbations.
   d. improving quality of life.

8. The main components of a disease management program for COPD include
   a. a mechanism to identify eligible patients.
   b. ascertaining current level of disease severity.
   c. designing specific interventions targeted to patients according to their disease severity.
   d. All of the above

9. A COPD Action Plan can be used in all of the following ways EXCEPT to
   a. assist patients in becoming active participants in their plan of care.
   b. replace physicians visits.
   c. educate patients how to better manage their disease.
   d. decrease anxiety for family members through knowledge of medication management.

10. Which of the following is true regarding the epidemiology of COPD?
    a. COPD is the fourth leading cause of death in the United States.
    b. The death rate from COPD has remained relatively stable since the 1940s.
    c. COPD affects people of all races equally.
    d. Most of the cost of COPD is due to indirect costs, such as time lost from work.

11. All of the following statements accurately describe the Healthy People 2010 program EXCEPT:
    a. One of the goals of the program is to reduce the proportion of adults whose activity is limited due to chronic lung and breathing problems from 2.2% to 1.5%.
    b. One of the goals of the program is to reduce deaths from COPD.
    c. The program could have a significant public health impact if its goals were met.
    d. The federal government will be using this program in its pay-for-performance programs.

12. At what stage of the GOLD criteria do patients with COPD usually first present to a physician?
    a. Stage 0
    b. Stage I
    c. Stage II
    d. Stage III

13. Which is true regarding the long-acting beta-adrenergic agonists?
    a. Formoterol has a faster onset of action than salmeterol.
    b. Salmeterol is indicated only for the maintenance treatment of COPD.
    c. Salmeterol produces a larger increase in the FEV_1 than formoterol when the drugs are compared head to head.
    d. No study has demonstrated that these drugs improve quality of life.

14. Tiotropium
    a. is indicated for the maintenance treatment of patients with asthma and COPD.
    b. is superior to ipratropium when compared head to head in measures of improvement of FEV_1 and PEF.
    c. is indicated for use as a rescue agent.
    d. is ineffective in decreasing the numbers of exacerbations of COPD and consequent hospital utilization.

15. Which of the following is true of corticosteroids in COPD?
    a. They are routinely recommended in all patients with COPD.
    b. The overwhelming majority of studies have shown clinical, spirometric, and quality-of-life benefits.
    c. In some, but not all, studies, they have been shown to have a beneficial effect upon objective measures of lung function.
    d. They have virtually no side effects.

16. Combination therapy with beta-agonists and inhaled steroids is recommended highly by the GOLD Science Committee in the treatment of COPD.
    a. True
    b. False

17. Theophylline
    a. is a selective phosphodiesterase inhibitor that causes bronchodilation in patients with COPD.
    b. may have immunomodulatory effects as well as anti-inflammatory effects.
    c. significantly improves walking distance in COPD patients when compared with placebo.
    d. is well tolerated without significant side effects.

18. Pulmonary rehabilitation improves measures of dyspnea, fatigue, and patients' sense of well-being.
    a. True
    b. False

19. Which of the following is not a criterion for the coverage of home oxygen in a COPD patient?
    a. Resting PaO2 of less than 55 mmHg
    b. PaO2 of 56-59 in the presence of dependent edema.
    c. Anemia (hematocrit < 30%)
    d. Desaturation with exercise or sleep to PaO2 of less than 55 mmHg.

20. Which best describes the impact of disease management on COPD?
    a. Multiple studies have uniformly shown a benefit.
    b. Studies have shown reductions in both daytime and nighttime symptoms.
    c. Pharmacist care has little, if any, effect on patients with COPD.
    d. Respiratory health workers have little impact on patients with COPD.

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NOTES

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