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Chronic obstructive pulmonary disease (COPD) is one of the few diseases whose incidence and prevalence is actually increasing in the United States. The disease makes a considerable impact on primary care physicians' practices due to the associated physical disability it produces, the complexity and often frustrating approaches to treatment, and the propensity for high utilization of resources due to recurrent hospitalization and management of exacerbations. It is currently the fourth-ranked cause of death in the United States, killing more than 100,000 Americans each year. Since 2000, the percentage of females dying annually from the condition exceeds the percentage of males dying from it. This disease is largely preventable if, as a society, we become more effective in accomplishing primary prevention of smoking and utilizing effective means to promote smoking cessation (a topic recently covered in PCR*). This article deals with the epidemiology, pathophysiology, diagnosis, and management of this common disorder.*
—The Editor

Chronic Obstructive Pulmonary Disease (COPD)

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What Is COPD?

The Global Initiative for Obstructive Lung Disease (GOLD) defines chronic obstructive pulmonary disease (COPD) as "a preventable and treatable disease with some significant extrapulmonary effects that may contribute to the severity in individual patients. Its pulmonary component is characterized by airflow limitation that is not fully reversible. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases."[1]

COPD is also known as chronic obstructive airway disease and chronic obstructive lung disease. It refers to a group of diseases that cause airflow obstruction in the respiratory tract, which includes chronic bronchitis and emphysema. Chronic bronchitis

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To reveal any potential bias in this publication, we disclose that Dr. Wise (Editor-in-Chief), Dr. Dhanani (author), Dr. Schwartz (author), and Dr. Bravo (peer reviewer) report no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study.

is defined clinically as a condition characterized by productive cough for three months in a year during two consecutive years. In chronic bronchitis, there is inflammation of the bronchial walls and enlargement of the mucous glands leading to airflow obstruction and excessive mucus production, respectively. Emphysema is an anatomic condition in which there is destruction of the lung parenchyma. This loss of tissue causes poor carbon dioxide-oxygen exchange resulting in shortness of breath. The airflow limitation in COPD is best evaluated by spirometry.

COPD is a leading cause of morbidity and disability that results in a huge economic burden to the society.[1-3] COPD exacerbations also cause a significant economic burden on the health care systems in developed nations.[1] In 2002, COPD costs in the United States amounted to a total of $32.1 billion (direct cost, $18 billion; indirect cost, $14.1 billion).[1]

Epidemiology: Who Gets COPD?

COPD is the fourth most common cause of death in the United States and is the only disease among the leading causes of death that is increasing in frequency.[2] Even though the prevalence of COPD is higher in men than in women,[4] it is rising faster in women, likely due to the increased number of women smokers since the 1940s.[3] Moreover, COPD is under-diagnosed especially in stages I and II of the disease.[3] Studies have shown that COPD prevalence is higher in smokers and former smokers than in nonsmokers, and in those who are over 40 years old than younger individuals.[5,6]

Many risk factors, extrinsic and intrinsic, are involved in COPD. The extrinsic factors include inhalational exposures such as cigarette smoking, occupational dusts and chemicals, indoor and outdoor air pollution, socioeconomic status, recurrent bronchopulmonary infections, perinatal events, and childhood illnesses.[7] The intrinsic factors include genetics, gender, airway hyperreactivity, immunoglobulin (Ig) E, and asthma.

Tobacco use is the most common risk factor for COPD; however, some smokers do not develop clinically significant COPD.[8] Occupation can be an important risk factor for COPD. The fraction of COPD attributable to occupational exposure has been estimated as 19.2% overall and 31.1% in never-smokers.[4] Exposure to passive smoking may also contribute to the development of COPD.[9]

Indoor air pollution may contribute to the development of COPD, especially in developing countries. People using biomass as a source of energy for cooking and heating are most susceptible to the inhalation of this particulate matter, especially the females.[7] High levels of outdoor air pollution cause more severe reactions in people with heart or lung disease;[10] however, effects of long-term exposure to low levels of outdoor air pollution are being investigated[10] and their effects on COPD development remain unclear.[1]

The finding that some smokers do not develop COPD suggests genetic-environmental interactions may have an important role in COPD pathogenesis. In fact, a variety of genes involved in COPD pathogenesis have been implicated, however, a specific functional genetic variant that influences COPD development has not been clearly established.[11]

A well-known genetic risk factor for COPD is the deficiency of alpha-1-antitrypsin (AAT). This protein is a serine protease synthesized mainly by hepatocytes in the liver but also by mononuclear phagocytes and epithelial cells found in the lungs and intestines. and secreted by hepatocytes. AATAlpha-1-antitrypsin serves as an inhibitor of serine proteinases with a preferential target for neutrophil elastase.[12] Neutrophil elastase has been shown to have a which has some destructive effects on lung tissue. This deficiency leads to premature destruction of lung parenchyma tissues causing emphysema. This early-onset emphysema which may manifest in people aged 40 years and younger is often associated with liver disease that may develop into cirrhosis in adulthood.

Socioeconomic background has also been associated with the development of COPD. The cause of this relationship is unclear. Whether this relationship is due to tobacco use, occupational exposure, poor nutrition, air pollution, crowding, or is an indicator of low socioeconomic status is not known.[1]

Childhood respiratory illnesses such as bronchitis, pneumonia, or whooping cough have been shown to reduce adult lung function and retard weight gain in infants.[13] Low birth weight has been associated with impaired lung function in adulthood. Moreover, an association between perinatal events causing low weight gain may affect the growth of the airways.[14,15] A recent study has shown that individuals who had childhood wheezy bronchitis had a more rapid decline in lung function predisposing them to COPD, when compared to the controls.[16]

Malnutrition is a complicating factor in severe COPD.[17] Poor

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Table 1. Differential Diagnosis of COPD

DIAGNOSIS	SIGNIFICANT FEATURES
COPD	Onset in middle age Progressive symptoms Smoking history Mostly irreversible airflow obstruction Dyspnea during exercise
Asthma	Onset at a young age Symptoms vary daily Symptoms present early in the morning or late at night Allergy, rhinitis, and/or eczema may be present Family history of asthma Mostly reversible airflow obstruction
Congestive Heart Failure	Fine basilar crackles on auscultation Chest radiograph hallmark features – cardiomegaly, pulmonary edema, re-distribution of pulmonary blood flow Pulmonary function tests results – lung volume restriction, not airflow obstruction
Bronchiectasis	Large volumes of purulent sputum Commonly associated with bacterial infection Coarse crackles/slubbing Chest radiograph shows bronchial dilation, bronchial wall thickening
Tuberculosis	Onset at any age Chest X-ray shows lung infiltrate or cavity Microbiological confirmation High local prevalence of the disease
Obliterative Bronchiolitis	Onset at a young age No smoking history History of rheumatoid arthritis or fume exposure Chest CT shows hypodense areas
Diffuse Panbronchiolitis	Male preponderance No smoking history High association with chronic sinusitis Chest radiograph and HRCT show hyperinflation and diffuse centrilobular nodular opacities

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nutrition can affect respiratory muscle strength, endurance, and contractility.[17]

Pathophysiology of COPD

The pathological changes in COPD occur in the large (central) airways, the small (peripheral) airways, the lung parenchyma, and the pulmonary vasculature.[7] The airway inflammation in COPD is manifested by the presence of inflammatory mediators. In contrast to asthma in which the presence of CD4+ cells, mast cells, and eosinophils predominate, the cellular composition in the airway inflammation of COPD comprises mostly of CD8+ cells, macrophages, and polymorphonuclear cells (neutrophils).

The macrophages and neutrophils produce elastases that cannot be effectively neutralized by antiproteases. Tobacco smoke induces an inflammatory response in the lungs causing macrophages to produce neutrophil chemotactic factors and elastases, which, in turn, can lead to lung tissue destruction. The imbalance between proteinases and antiproteinases also contribute to COPD. For example, alpha-1-antitrypsin serves as an inhibitor of neutrophil elastase and in its deficiency, neutrophil elastase can lead to destruction of lung parenchyma, a hallmark of emphysema. Oxidative stress also plays a significant role in COPD pathogenesis. Cigarette smoke has noxious substances that increase oxidative stress resulting in tissue destruction.

Management of COPD

According to GOLD guidelines, there are four components in the effective management of COPD. They include: assessment and monitoring of disease; reduction of risk factors; management of stable COPD; and management of exacerbations. An effective management plan should focus on achieving the following goals with minimal side effects: relief of symptoms, prevention of disease progression, improvement of health status and exercise tolerance, prevention and treatment of exacerbations and complications, and reduction of mortality.[1]

Assessment and Monitoring of Disease

Medical History. A comprehensive medical history is an important part of the assessment. The hallmark symptoms of COPD (dyspnea, chronic cough, and chronic sputum production) should be assessed. Important aspects of the history should include: past history of respiratory diseases such as asthma, childhood illnesses that predispose to poor lung function and allergies; family history of COPD and other chronic respiratory diseases; history of inhalational exposure (smoking, environmental, and occupational); co-morbidities; medications; personal and social history including the impact of disease on patient's life, family and social support available to the patient and possible interventions such as smoking cessation, and review of systems including identification of any unexplained weight loss as hypoxia can cause nutrient debt in the peripheral tissues.[1,7]

Physical Examination. Vital signs should be obtained and a complete physical examination should be performed. A normal physical examination is not uncommon in early COPD.[3] In the early stages, only prolonged expiration or wheezing on forceful

expiration may be noted. As the disease progresses, reduced air movement, distant heart sounds, bibasilar coarse crackles, and wheezing may be apparent. In the advanced stage of the disease, tachypnea, pursed-lip breathing, use of accessory respiratory muscles, retraction of the lower intercostal muscles during inspiration, neck vein distension during expiration, downward displacement of the liver, and cyanosis are observed. This disease affects multiple organ systems, including extrapulmonary effects, famously manifested in the old classification of "pink puffers" and "blue bloaters."[18] "Pink puffers" are characterized by cachexia, preserved blood gases, and dyspnea at rest.[18] "Blue bloaters" are characterized by hypoxemia, possible CO2 retention, and complications associated with pulmonary hypertension and right-sided heart failure.[18]

Pulmonary Function Tests. Spirometry measures the airflow limitation and is used to diagnose COPD in patients with respiratory symptoms and associated risk factors. It measures forced vital capacity (FVC) and forced expiratory volume in one second (FEV1) from a simple respiratory maneuver. Patients with COPD have decreased FEV1 and FVC measurements but the FEV1 is disproportionately reduced, and a postbronchodilator FEV1/FVC ratio of < 0.70 is used to diagnose COPD. Appropriate reference values based on age, sex, race, and height should be used when interpreting spirometry findings for each patient.[19] Acceptable spirometry should be done at least two to three times, and the two highest FEV1 values should be + 0.15 L from each other.[19] There is some evidence that using 0.7 as a lower limit of the FEV1/FVC ratio may lead to an overdiagnosis of COPD in elderly never-smokers.[20]

Lung volume measurements by body plethysmography, although not required, can reveal hyperinflation and air trapping. This is manifested by an increase in total lung capacity, functional residual capacity, and residual volume. Plethysmography can also reveal an increase in functional residual capacity, and a decrease in the vital capacity. The single breath carbon monoxide diffusing capacity is decreased in proportion to the degree of emphysema.

Chest Radiography. Plain chest radiographs are not sensitive in diagnosing COPD, however, an abnormal film can help exclude other diseases being considered in the differential diagnosis of COPD. The most common radiographic abnormalities in chronic bronchitis are increased bronchovascular markings and thickened bronchial walls, often manifested as parallel line shadows or "tramlines."[21] The hallmark radiographic signs of emphysema include lung hyperinflation associated with flattening of the diaphragm, a long narrow heart shadow, an increased retrosternal space on a lateral chest radiograph, bullous formation, and reduced pulmonary vasculature.[21] Bullae manifest as air-containing spaces ranging from one to 2 cm in diameter up to encompassing the entire hemithorax.[21]

Computed Tomography. Computed tomography (CT) of the chest is not used in the routine care of COPD patients. CT can show specific anatomical characteristics of emphysema but this information does not change the management of the condition. However, CT is used in assessing emphysematous patients who are being considered for lung volume reduction surgery.[22] High resolution CT of the chest can be useful if there is uncertainty in the diagnosis of COPD.[1]

Arterial Blood Gas Assessment. Measurement of arterial blood gases (ABG) is important in assessing patients with severe COPD. Analysis of ABG on room air should be performed in patients with FEV1 less than 50% and in patients with clinical symptoms and signs of right heart failure or respiratory failure. ABG on room air is an important test to determine whether a patient needs home oxygen therapy. In addition, ABG analysis is useful in the evaluation and management of patients with COPD exacerbations.

Alpha-1 Antitrypsin Deficiency Screening. Patients who develop COPD at a young age (younger than 45 years), who have associated liver disease, and who have a strong family history should be screened for alpha-1 antitrypsin deficiency.[1] About 75% of patients with this deficiency often develop emphysema before 40 years of age.[23] This screening can lead to genetic counseling and may benefit family members of the affected patients.

Sputum Analysis. Sputum analysis can sometimes be useful in COPD exacerbations requiring hospitalization. Microscopic examination of sputum, although controversial, may help differentiate colonization from infection as well as influence the choice of antimicrobial therapy.[24,25]

COPD patients have been known to harbor *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Streptococcus pneumoniae* in the normal flora of their respiratory airways. These three organisms account for about 90% of acute exacerbations of COPD due to bacterial infection.[26] Acute COPD exacerbations have been associated with the development of new bacterial strain of *Haemophilus influenzae*,[27,28] and it has been suggested that this new strain accounts for approximately 50% of acute exacerbations of COPD due to bacterial infection.[29]

Hemogram. Some COPD patients may develop erythrocytosis, especially those with hypoxemia. An increase in white blood cell count may indicate infection.

Differential Diagnosis of COPD. Table 1 lists the common conditions that are easily differentiated from COPD.[1] In some patients, it may be difficult to distinguish COPD from chronic asthma, and the management of those patients is similar to that of asthma.

Reduction of Risk Factors

Smoking Cessation. Smoking cessation is the most important intervention in slowing disease progression and reducing mortality in COPD. A significant part of a clinician's management strategy for COPD is to encourage patients to stop smoking. It has been shown that even a brief counseling by physicians results in a 5-10% cessation rate.[30,31] This intervention should be done during every clinical visit.[30,31] In addition to counseling, several effective pharmacotherapies for smoking cessation include nicotine replacement therapy in various forms (gum, inhaler, nasal spray, transdermal patch, sublingual tablet, or lozenge), antidepressants such as bupropion and nortriptyline, and a nicotinic acetylcholine receptor partial agonist called varenicline.[32,33]

Environmental Exposures. Reduction of exposure in the workplace involves cooperation between employers and patients. Primary prevention in the workplace is necessary for decreasing

Table 2. COPD Stages Based on Severity as Measured by Spirometry

Stage I: Mild	FEV1/FVC < 0.70 FEV1 ≥ 80% predicted
Stage II: Moderate	FEV1/FVC < 0.70 50% ≤ FEV1 < 80% predicted
Stage III: Severe	FEV1/FVC < 0.70 30% ≤ FEV1 < 50% predicted
Stage IV: Very Severe	FEV1/FVC < 0.70 FEV1 < 30% predicted or FEV1 < 50% predicted plus respiratory failure

Definitions: FEV1 = forced expiratory volume in one second; FVC = forced vital capacity; respiratory failure = arterial partial pressure of oxygen (PaO2) less than 8.0 Kpa (60 mmHg) with or without arterial partial pressure of CO2 (PaCO2) greater than 6.7 kPa (50 mmHg) while breathing air at sea level

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Table 3. Therapy at Each Stage of COPD

STAGE	THERAPY
All stages	• Avoidance of risk factor(s) • Influenza vaccination
I: Mild	• *Add* short-acting bronchodilator as needed
II: Moderate	• *Add* regular treatment with one or more long-acting bronchodilators • Pulmonary rehabilitation
III: Severe	• *Add* inhaled steroids if repeated exacerbations
IV: Very severe	• *Add* long-term oxygen if chronic respiratory failure • Consider surgical options

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exposure to substances that are known risk factors for COPD. Air pollution, both indoor and outdoor, would require adjustments in the way COPD patients live. For example, patients should monitor the air quality in their locales and stay indoors when there is poor air quality in their areas. Adequate ventilation should be used in homes or facilities that use solid fuels for heating and cooking.

Management of Stable COPD

The management of the disease depends on the stage of COPD, which is classified according to the postbronchodilator FEVI. (*See Table 2.*) The management is summarized in Table 3.

Patients with stage I or mild COPD should be treated with short-acting bronchodilator inhalers, as needed. They can be beta-2-agonists or anticholinergics. Short-acting beta-2-agonists include albuterol, salbutamol, fenoterol, and terbutaline. Short-acting anticholinergics include ipratropium bromide and oxitropium bromide. Their onset of action is in about 10-20 minutes and the effect lasts for 4-6 hours. They are well tolerated, but in high doses beta-2-agonists can cause tachycardia and tremor. Albuterol is the most commonly used inhaled bronchodilator and is administered as 2 puffs every 4-6 hours.

Active reduction of risk factors in these patients should also be pursued such as annual influenza vaccine which has been shown to reduce serious illness in COPD patients.[34] Smoking cessation should always be encouraged.

Patients with stage II or moderate COPD should be treated similar to stage I with the addition of one or more inhaled long-acting bronchodilators. Several types of long-acting bronchodilators are available. Long-acting beta-2-agonists include salmeterol and formoterol. Of note, the onset of action for formoterol is 5 minutes, which is faster than the onset of action for salmeterol, which is 20 minutes.[35] Because of their long duration of action, they are administered twice per day. Tiotropium is an example of an inhaled long-acting anticholinergic agent. Because of receptor selectivity, it has a long duration of action and can be administered once a day, therefore greatly improving compliance. It is more likely to cause to cause dry mouth than ipratropium.

In patients who are symptomatic on long-acting inhalers, theophylline can be considered as an add-on therapy. Because of frequent adverse events and drug interactions, its use has diminished in recent years. Serum theophylline level should be monitored closely, and a level of 8 to 12 mcg/mL may provide benefits with less toxicity.

Patients with stage II or higher disease should also be referred for pulmonary rehabilitation. Pulmonary rehabilitation is a multidisciplinary program that has been shown to improve symptoms, exercise capacity, and health-related quality of life. It can also reduce hospitalization, anxiety, and depression associated with COPD. Pulmonary rehabilitation can be administered in inpatient, outpatient, and home settings.[36-38] The program lasts for four to 10 weeks, but the benefits extend well beyond the immediate period of rehabilitation. Baseline and outcome assessments of COPD patients participating in pulmonary rehabilitation are essential to determine individual gains and to evaluate areas that need more improvement.

Patients with stage III or severe COPD should be treated similar to stage II with the addition of inhaled glucocorticosteroids if patients have repeated acute exacerbations of COPD. Examples

of inhaled glucocorticosteroids include beclomethasone, budesonide, fluticasone, and triamcinolone. A recent randomized, double-blind trial[39,40] comparing long-acting beta-agonists and inhaled corticosteroids, alone or in combination showed reduction in the frequency of COPD exacerbations in the combination group. It also showed improvement in health status and spirometric values, but no difference in mortality. The adverse effects of inhaled corticosteroids include dysphonia, oral candidiasis, skin bruising, and accelerated bone loss.

Patients with stage IV or very severe COPD should be treated similar to stage III with the addition of long-term oxygen in patients with chronic respiratory failure. In addition, surgical interventions may be considered for these patients.

Administration of long-term oxygen has been shown to increase survival and has a beneficial effect on hemodynamics, hematologic characteristics, exercise capacity, lung mechanics, and mental state.[41-43] Long-term oxygen therapy has been shown to improve mortality in COPD patients.[35]

Long-term oxygen therapy is indicated in patients with:

• PaO2 at or below 55 mm Hg or SaO2 at or below 88%;

• PaO2 at or below 59 mm Hg or SaO2 at or below 89%, if patient has evidence for pulmonary hypertension, cor pulmonale, peripheral edema suggestive of congestive heart failure, or polycythemia (hematocrit > 55%);

• PaO2 at or above 60 mm Hg or SaO2 at or above 90%, if patient has lung disease and sleep apnea with nocturnal desaturation.

If oxygen is prescribed during an exacerbation, the need for continued oxygen therapy should be reassessed 30 to 90 days later.

Surgical treatments for COPD include bullectomy, lung volume reduction surgery (LVRS), and lung transplantation. Bullectomy has been shown to improve lung function and dyspnea in carefully selected patients. LVRS, albeit an expensive surgical palliative modality, has been shown to provide benefits in a select group of patients. A large multicenter study showed that COPD patients with upper lobe emphysema and low exercise capacity who underwent LVRS had improved survival, exercise capacity, and health-related quality of life.[44] Lung transplant surgery may be considered in select patients with very advanced COPD. The criteria for lung transplantation include FEV1 less than 35% predicted, PaO2 less than 55-60 mmHg, PaCO2 greater than 50 mmHg, and secondary pulmonary hypertension.[1]

Management of COPD Exacerbations

These patients require frequent administration of short acting inhaled bronchodilators. Albuterol 2 puffs every one to two hours can be administered as metered dose inhaler (MDI) with a spacer. Alternatively, it can be administered in the dose of 500 mcg as a nebulizer every one to two hours. Ipratropium can be added if patients fail to respond quickly. It can be administered as 2 puffs of MDI or as a 500 mcg nebulizer every two to four hours. Many clinicians frequently combine the two drugs for added benefit. MDI with spacers, when used appropriately, provide similar results as nebulizers.

Systemic steroids are added in the inpatient management of acute exacerbations. The exact dose is unknown, but GOLD guidelines recommend 30-40 mg of oral prednisone daily for 7-10 days. A short course of antibiotic should be given if there is clinical evidence of infection or for severe exacerbations that require mechanical ventilation. The choice of antibiotics depends on the pathogens and local resistance patterns. The most common bacterial pathogens in COPD exacerbations are *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Moraxella catarrhalis*. Antibiotics such as amoxicillin, tetracycline, doxycycline, and trimethoprim plus sulfamethoxazole achieve a cure rate of 80-90% in mild to moderate cases. However, in severe cases, and particularly with comorbid conditions, beta-lactam antibiotics with a beta-lactamase inhibitor, fluoroquinolones or macrolides may be used.

Supplemental oxygen may be needed to assure adequate oxygenation. Nasal cannulae, simple face masks, or venturi masks can be used to administer oxygen. However, venturi masks are preferred to permit more precise oxygen delivery. In some patients, mechanical ventilation in the form of noninvasive positive pressure ventilation or intubation and assisted mechanical ventilation may be required.

Some patients with COPD exacerbation can be managed as an outpatient but many require hospitalization and close monitoring.

Risks of Surgery in COPD. COPD patients have a 2.7 to 4.7 fold increased risk of postoperative pulmonary complications.[45-47] In general, the closer the incision site is to the diaphragm, the higher the risk of postoperative pulmonary complications. Prior to any elective surgery, COPD should be optimally treated and patients should be strongly advised to quit smoking at least 4-8 weeks before the surgery. In addition, early mobilization, deep breathing, intermittent positive-pressure breathing, incentive spirometry, and adequate analgesia may reduce post-operative complications.

Prognostic Factors in COPD. The FEV1 is the most commonly used parameter to predict clinical outcome in patients with COPD.[48] However, recently a multidimensional grading system (BODE Index) was developed to assess the risk of death from any cause, including respiratory etiology, among patients with COPD.[49] The "BODE Index" is the acronym for B – body mass index, O – degree of airflow obstruction, D - dyspnea, and E – exercise capacity measured by the six-minute walk test. Each variable is scored as 0 to 3 except the body mass index which is scored as 0 or 1. The higher BODE scores are associated with higher death risk. BODE index is a better predictor of mortality than FEV1.

Changes in the Inhaler Propellants. The Food and Drug Administration (FDA) would prohibit the sale of albuterol MDIs containing chlorofluorocarbon (CFC) propellants in the United States in 2008.[50] This rule was in response to the public's concern about the negative effects of CFC on the ozone levels in the stratosphere. CFC will be replaced by Hydrofluoroalkane (HFA) propellant, which is used in albuterol metered-dose-inhalers in Europe. There are differences between CFC and HFA propelled MDIs such as the taste and feel of the propellants. In addition, HFA formulation is associated with tachycardia and hypokalemia with higher doses of albuterol due to systemic beta-2-agonist effects.[51,52] A cost increase for these new products will also be

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Physician CME Questions

11. In a patient with clinical signs and symptoms of COPD, the diagnosis can be confirmed by:
    A. sputum analysis.
    B. high resolution computer tomography of the chest.
    C. spirometry.
    D. skin allergy testing.

12. A patient was found to have FEV1/FVC < 0.70 and FEV1 >80% predicted. According to the spirometric classification of COPD, this patient has:
    A. Stage I: Mild COPD.
    B. Stage II: Moderate COPD.
    C. Stage III: Severe COPD.
    D. Stage IV: Very Severe COPD.

13. A 40-year-old nonsmoker male patient was diagnosed with COPD. His liver function test showed abnormal AST and ALT on routine examination. He has lived in Los Angeles all his life. What test should be ordered?
    A. Thyroid function test
    B. Hemoglobin A1C
    C. Arterial blood gas measurement
    D. Serum alpha-1 antitrypsin level

14. Stage I, mild COPD can be treated with:
    A. short-acting beta-2-agonist or ipratropium inhaler as needed.
    B. long-acting beta-2-agonist inhaler as needed.
    C. steroid inhaler as needed.
    D. tiotropium inhaler once daily.

15. Glucocorticosteroid inhalers are indicated in:
    A. stage I: mild COPD.
    B. stage II: moderate COPD.
    C. stage III: severe COPD with frequent exacerbations.
    D. all of the above.

16. Long-term oxygen therapy is indicated in patients with the following:
    A. PaO2 at or below 55 mmHg.
    B. O2 saturation at or below 88%.
    C. PaO2 at or below 59 mmHg in a patient with Cor Pulmonale.
    D. All of the above.

CME Answer Key

11. C; 12. A; 13. D; 14. A; 15. C; 16. D

PHARMACOLOGY WATCH

Supplement to Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Infectious Disease Alert, Internal Medicine Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports, Travel Medicine Advisor.

SSRIs Associated With Low Rate of Birth Defects, Studies Show

In this issue: *SSRIs are safer in pregnancy than previously thought; Estrogen therapy in younger women may be of benefit in preventing cardiovascular disease; Warfarin is substantially better than antiplatelet therapy in preventing stroke in patients with atrial fibrillation; The FDA tightens regulations regarding dietary supplements, Lyrica is approved for treatment of fibromyalgia.*

SSRIs are associated with a low rate of birth defects according to 2 new studies in the *New England Journal of Medicine*. SSRIs are often taken by women in their childbearing years, but the risk of birth defects has been unclear. Paroxetine (Paxil) specifically has been associated with omphalocele and heart defects, but there is little data on the risk of other SSRIs. In the first study from Boston University and Harvard, researchers assessed the association between first-trimester maternal use of SSRI and birth defects among nearly 10,000 infants with and over 5,800 infants without birth defects who participated in the Sloan Epidemiology Center Birth Defects Study. Use of SSRIs was not associated with significantly increased risk of craniosynostosis (odds ratio 0.8), omphalocele (odds ratio 1.4), or heart defects overall (odds ratio 1.2). Analysis of specific SSRIs and specific deficits showed significant associations between use of sertraline (Zoloft) and omphalocele (odds ratio 5.7) and septal defects (odds ratio 2.0) and between use of paroxetine and right ventricular outflow tract obstruction defects (odds ratio 3.3). There were no significant associations with other defects with other SSRIs or non-SSRI antidepressants. In the other study, researchers from the CDC and University of British Columbia looked at data obtained on 9,622 infants with major birth defects and 4,092 control infants born between 1997 and 2002. Records were obtained from birth defects surveillance systems in 8 U.S. states and controls were selected randomly from the same geographic areas. Mothers were interviewed regarding exposure to potential risk factors including medications before and during pregnancy. No significant associations were found between maternal use of SSRIs overall during early pregnancy and congenital heart defects or most other categories or subcategories categories of birth defects. Maternal SSRI use was associated with amencephaly (odds ratio 2.4), craniosynostosis (odds ratio 2.5) and omphalocele (odds ratio 2.8). Their conclusion was that maternal use of SSRIs during early pregnancy was not associated with significantly increased risk of congenital heart defects or most other categories or birth defects. There was an association with SSRI use and 3 types of birth defects, but the absolute risk was small and further studies are warranted (*N Engl J Med* 2007; 356:2675- 2683, 2684-2692). An accompanying editorial points out that 2 previous stud-

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ies had suggested a relationship between paroxetine and cardiac malformations including ventricular septal defects, an association that was not found in these current studies. Although a small rate of congenital heart malformations, including right ventricular outflow tract lesions, were found the rate was still low, less than 1%. The editorialists, Dr. Michael Green from Massachusetts General states, "The 2 reports in this issue of the Journal, together with other available information, do suggest that any increased risks of these malformations in association with the use of SSRIs are likely to be small in terms of absolute risks." (*N Engl J Med* 2007; 356:2732-2733). ■

Estrogen for Younger Postmenopausal Women

Another follow-up study from the Women's Health Initiative suggests that estrogen therapy in younger postmenopausal women may be of benefit in preventing cardiovascular disease. Analysis was done on the "estrogen-only" wing of WHI in women who had undergone hysterectomy prior to enrolling in the study and were not treated with progesterone. Women age 50 to 59 were treated with 0.625 mg per day of conjugated equine estrogens or placebo. CT heart scanning was done at entry to the study and after a mean of 7.4 years of treatment and 1.3 years after the trial was completed. The endpoint of mean coronary-artery calcium scores was lower among women receiving estrogen (83.1) than those receiving placebo (123.1) (P = 0.02 by rank test). After adjusting for coronary risk factors, the odds ratios for coronary-artery calcium scores of more than 0, 10 or more, and 100 or more in the group receiving estrogen as compared to placebo were respectively 0.78, 0.74, and 0.69. The corresponding odds ratios among women with at least 80% adherence to the study estrogen or placebo were 0.64 (P = 0.01), 0.55 (P < 0.001), and 0.46 (P = 0.001). For women who had calcium scores greater than 300 the multivariate odds ratio was 0.58 (P = 0.03) in an intention-to-treat analysis and 0.39 (P = 0.004) among women with at least 80% adherence. The authors conclude that in women age 50 to 59 years old at enrollment, estrogen treatment resulted in a lower calcified plaque burden in the coronary arteries compared to placebo. They also point out that estrogen has complex biological effects and may influence the risk of cardiovascular events and other outcomes through multiple pathways (*N Engl J Med* 2007; 356:2591-2602). An accompanying editorial points out that not only did women in this analysis who were treated with estrogen have lower calcium scores, women in whom hormone replacement therapy was initiated at a younger age also had a 30% reduction in total mortality and did not have significant increases in any adverse outcomes examined. This supports the "timing hypothesis" for hormone replacement therapy that suggests that the cardiovascular benefits of hormone replacement are only evident if treatment is started before atherosclerosis develops. (*N Engl J Med* 2007;356:2639-2641). ■

Warfarin Better for Atrial Fibrillation Patients

Recent meta-analysis has confirmed the value of warfarin in preventing stroke in patients with nonvalvular atrial fibrillation. Twenty-nine trials involving more than 28,000 patients were reviewed. Compared with control, warfarin and antiplatelet agents reduce stroke by 64% (95% CI, 49% to 74%) and 22% (CI, 6% to 35%) respectively. Adjusted-dose warfarin was substantially more efficacious than antiplatelet therapy, and increases in extracranial hemorrhage assisted with warfarin were small. The authors conclude that warfarin is substantially more efficacious at preventing stroke in patients with a fibrillation than is antiplatelet therapy (by approximately 40%). (*Ann Int Med* 2007; 146: 857-867). ■

FDA Actions

The FDA has strengthened its regulations regarding dietary supplements, issuing a "final rule" requiring current good manufacturing practices for dietary supplements. The rule ensures the supplements are produced in a quality manner, do not contain contaminants or impurities, and are accurately labeled. Manufacturers will also be required to report all serious dietary supplement-related adverse events to the FDA by the end of the year.

Pregabalin (Lyrica-Pfizer) has been approved for the treatment of fibromyalgia, the first drug approved for this indication. Fibromyalgia, which is characterized by pain, fatigue, and sleep problems, affects up to 6 million people in United States. Approval was based on 2 double-blind, controlled trials involving 1,800 patients that showed improvement in pain symptoms at doses of 300 mg or 450 mg per day. The drug has already been approved for partial seizures, postherpetic neuralgia, and diabetic neuropathy. ■