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Improving Outcomes in Patients With COPD

Brian H. Foresman, DO | Fredric Jaffe, DO

Chronic obstructive pulmonary disease (COPD) is a primary cause of more than 120,000 deaths annually. It is now the fourth leading cause of death in the United States. Clinicians cannot cure this disease but can alleviate the debilitating effects of this disease with early diagnosis and stepwise intervention. A majority of COPD cases can be attributed to firsthand or secondhand tobacco smoke exposure. Remaining cases can be a result of genetic susceptibility followed by recurrent lung damage. This damage can come from infections or toxic exposure to lung-injuring particles. Smoking cessation and avoidance of secondhand smoke can arrest the acceleration of loss of lung function. However, although most COPD interventions can improve patients’ quality of life, such interventions do not reverse the progression of disease.

The present guide provides physicians with a concise review of the latest research on assessing risk factors for COPD, diagnosing the disease, determining the best treatment plan, and recognizing and addressing comorbidities that are not recognized in patients with COPD.

In the first article, “Diagnostic Considerations in Chronic Obstructive Pulmonary Disease,” Rupen P. Amin, MD, analyzes COPD risk factors and symptoms and assesses diagnostic approaches and tools. Dr Amin emphasizes the importance of using simple spirometry in diagnosing COPD. This simple screening tool can help measure the severity of the disease and therefore determine the best course of treatment.

The second article, written by Thomas F. Morley, DO, and Amita P. Vasoya, DO, and titled “Interventions for Chronic Obstructive Pulmonary Disease,” outlines an incremental approach to treating patients with COPD. Paramount to the
management of COPD is smoking cessation in all who continue to smoke. As the
disease becomes more severe, physicians may progress to treating patients with
bronchodilators and inhaled corticosteroids. Long-term oxygen therapy, oral
steroids, and surgical treatments may be indicated for very severe disease. Citing
the recommendations of the Global Initiative for Chronic Obstructive Lung Disease
(known as GOLD), Dr Morley and Dr Vasoya explain how this stepwise approach
improves the efficacy of interventions, minimizes complications, and reduces costs.
The authors provide a review of the various pharmacologic and nonpharmacologic
treatment options for patients with COPD.

Many physicians assume that COPD is a disease of only the lungs, but evidence
suggests that the disease has more far-reaching effects. There are many systemic
manifestations, including an increase in comorbidities such as cardiovascular dis-
ease, osteoporosis, and diabetes mellitus. All these comorbid conditions can affect
quality of life and ultimately morbidity and mortality. In the third article, “Comor-
bidities and Systemic Effects in Chronic Obstructive Pulmonary Disease,”
Kartik Shenoy, MD, and Fredric Jaffe, DO, discuss the interrelationship of comorbid
conditions and COPD and the management of patients with COPD who experience
these diseases.

In the final article, “Osteopathic Manipulative Medicine in Chronic Obstruc-
tive Pulmonary Disease,” Stephen J. Miller, DO, MPH, reports that osteopathic
manipulative treatment (OMT) has yet to be proven to be of much benefit in treating
patients for COPD. Research indicates that OMT may improve patients’ quality
of life and work capacity, but studies show that OMT may paradoxically worsen
COPD patients’ lung function. Dr Miller emphasizes that more research is needed
to fully assess the impact of OMT on patients with COPD. He suggests that research
be conducted to investigate the effects of osteopathic medicine’s whole-patient phi-
losophy on treating patients with COPD.

Chronic obstructive pulmonary disease is a disease that all too often is undiag-
nosed until clinical symptoms become apparent. It is important for every physician
to realize that early detection of the disease, along with systematic intervention as
well as the recognition of comorbidities, can improve the quality of life and ul-
timately the survival rate of your COPD patients. We hope this publication will
help guide your clinical decision-making and raise awareness of the ravages of the
disease. We remain optimistic about the ability to intervene and to help increase
quality of life in our COPD patients.

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Chronic obstructive pulmonary disease (COPD) is the fourth leading cause of death in the United States. Frequently, the diagnosis of COPD is not considered until patients experience symptomatic disease, at which point the disorder is usually more advanced. Furthermore, other disease entities that mimic COPD symptoms are known to occur and have specific treatments that can confound disease progress. In all circumstances, modifying the disease progression associated with COPD remains most effective when the condition is identified early. The present article reviews risk factors for development of COPD and key elements of medical history and physical examination associated with COPD. The article also provides an overview of testing used to obtain a diagnosis of COPD.

Prevalence of “mild” cases of COPD in individuals between the ages of 25 and 75 years is estimated at 6.9%, whereas prevalence of “moderate” cases of COPD (indicating increased severity of airflow obstruction) in this age group is estimated at 6.6%. Unfortunately, the prevalence of COPD is underestimated, because many cases of the disease remain undiagnosed until symptoms become grossly apparent and after irreversible pathophysiologic changes are established. Although COPD remains most prevalent in men worldwide, recent data have revealed alarming increases in COPD incidence, mortality, and morbidity among women. Much of these changes are attributable to the increased rate in smoking among women, though additional, poorly quantified factors appear to be present.

Risk Factors

Smoking

Tobacco exposure, including both first-hand and second-hand exposure, is the single most important risk factor for the development of COPD. Indeed, roughly 73% of mortality from COPD can be attributed to smoking. Despite this high mortality rate, COPD will not develop in all smokers. Observations among individuals in Sweden revealed upwards of 25% of smokers having clinically significant COPD. This finding would argue that while the great majority of COPD cases are attributable to the use of tobacco products, the remaining cases may have other contributing factors. Well-known genetic predispositions result in the development of COPD, as do environmental factors and recurrent pulmonary damage (eg, infection).

The cumulative-dose exposure of smoking has been shown to correlate with the severity of disease. According to data derived in 1984 from a National Health and Nutrition Examination...
Survey in which 14,000 individuals were examined, 8.8% of the individuals were nonsmokers or former light smokers (ie, with a history of <5 packs/year) who had a diagnosis of mild COPD. Among the individuals who had a history of continuous smoking, the severity of COPD escalated in a dose-dependent manner. Studies assessing COPD risk based on different types of tobacco and filtered vs unfiltered cigarettes report only slight variations in COPD risk based on these differences.

There is some controversy regarding the impact of reductions in tar content on lung function as measured by forced expiratory volume in 1 second (FEV1), with some studies showing a beneficial influence and other studies demonstrating no impact. The differences in study findings may be the result of environmental influences, cigarette characteristics, or compensatory mechanisms affecting the degree of smoke inhalation. Although “not inhaling” has been a bit of a political joke, smokers who inhale deeply have substantially higher rates of pulmonary function decline compared to smokers who do not inhale deeply, when controlled for type of cigarette, nicotine and tar content, and filtered vs unfiltered cigarette.

Active cigarette smoking produces adverse affects through the stimulation of lung inflammation and white blood cell activation. This stimulation creates a milieu in which higher concentrations of enzymes are active in the lungs, causing a breakdown of the lungs’ collagen structures. This breakdown accelerates the normal age-related decline in lung function as measured by FEV1. The accelerated decline in FEV1 leads to airflow obstruction, symptomatic dyspnea, and limitations to physical activity—the symptoms that often prompt a diagnosis of COPD.

Smoking cessation, regardless of the severity of COPD, normalizes the rate of lung function decline. To clarify, in individuals who successfully quit smoking, their lung function does not return to normal, but the physiologic age-related decline in lung function (which was accelerated by smoking) returns to a normal rate of decline.

**Childhood Influences**

Reduced lung growth and premature decline of lung function during childhood or adolescence increase the risk for development of COPD in adulthood. Individuals who had recurrent childhood respiratory infections or premature birth often have obstructions in their small airways, with a higher risk for COPD development in adulthood.

**Genetic Makeup**

First-degree relatives of individuals who have been diagnosed as having COPD have a nearly 3-fold increased relative risk for the development of COPD, suggesting a genetic predisposition for the condition. Studies in monozygotic twins have confirmed that a genetic susceptibility exists for the development of airflow obstruction with exposure to tobacco smoke.

A genetic predisposition to COPD development is further supported by the high incidence of premature emphysema in individuals with a deficiency of α-1-antitrypsin (A1AT), as well as by recent findings regarding the complex interplay of cysteine proteases. Through a different mechanism, patients with cystic fibrosis have a definitive cystic fibrosis transmembrane conductance regulator (CFTR) transporter gene that facilitates the development of early airway obstruction—presumably because of chronic inflammation and alteration of chloride channel physiologic mechanisms. Smoking can accelerate the disease progression in individuals with these genetic conditions. In aggregate, about 50% to 60% of all smokers will eventually have some level of COPD.

**Environmental Exposures**

Environmental risk factors other than tobacco smoke, particularly those related to occupational exposure to inhalants and fumes, may also play a role in COPD onset and progression. However, because of the frequency of concurrent smoking, the risk of COPD from environmental exposure is difficult to clearly define. The clinical presentation of many patients who have COPD from occupational exposure does not differ from that of patients who have had no occupational exposure to inhalants or fumes. Furthermore, quantifying actual environmental exposure in a patient is often difficult because of the variety of environmental and occupational situations that exist.

Despite these clinical difficulties, several environmental substances have been shown to serve as risk factors for the development of COPD, primarily by acting as irritants in the airways, leading to chronic inflammation. These substances are listed in Figure 1.

**Diagnosis**

Spirometry remains the gold standard for diagnosis of COPD. To refer a patient for this test, the physician must have a suspicion of COPD based on the patient’s medical history and physical examination findings. A thorough history should be obtained and a complete physical examination should be performed for patients with suggestive symptoms, family histories of COPD, or risk factors for COPD. Such an approach will aid in obtaining an accurate diagnosis and in developing a treatment plan for patients.
Medical History

The most common symptoms for patients with established COPD include chronic cough, dyspnea at rest or with exertion, and chronic sputum production. Any of these symptoms should prompt the consideration of COPD in the differential diagnosis. In many cases, chronic productive cough (>3 tablespoons/d for >3 months) is 1 of the earliest presenting symptoms of COPD and is typically indicative of chronic bronchitis. However, by the time that patients with COPD present with these symptoms, they already have well-established disease. By contrast, many patients with mild COPD are asymptomatic or simply have a mild but chronic cough.¹⁸

A detailed history of tobacco exposure and environmental and occupational exposures (Figure 1) should be elicited from the patient. Cigarette or cigar smoke exposure should be quantified and defined as to whether it is first-hand or second-hand exposure. For cigarette smoking, the most common method of obtaining the patient’s history is to assess the pack-years of exposure (ie, the number of packs per day multiplied by the number of years). An increasing cumulative dose (ie, exposure) to tobacco smoke increases the likelihood of development of airway obstruction.⁷

Recurrent pulmonary infections can be indicative of a potential cause of COPD, or they may occur as a result of established COPD. Thus, a thorough history of respiratory infections dating to childhood should be elicited from the patient. A pattern of early, severe infections could indicate that the pulmonary damage initially occurred when the patient was a child. Later development of recurrent infections should be correlated with a smoking or environmental exposure history. Other confounding disorders that can be associated with such a history include uncontrolled asthma, cystic fibrosis, or immunodeficiency syndromes (eg, immunoglobulin A deficiency).²

A family history is useful for disclosing early cigarette smoke exposure, potential environmental exposures, and patterns of COPD development that might occur with genetic disorders. Any nonspecific—possibly genetic—associations that exist among first-degree relatives with COPD may increase suspicion of COPD as a clinical diagnosis. Environmental associations, as noted in Figure 1, can be identified by obtaining an occupational history of the patient’s parents.

Age at symptom onset offers clues to the etiologic mechanisms and future progression of COPD. Respiratory manifestations of cystic fibrosis typically present in the first 3 decades of life. Premature emphysema resulting from A1AT deficiency typically manifests in the fourth, fifth, and sixth decades of life. Emphysema and severe COPD are most commonly present in the sixth and seventh decades of life, though they may occur earlier in individuals with heavier smoking burdens.²²

Review of Systems

In asymptomatic patients, an increasingly sedentary lifestyle may point to early stages of COPD, because exercise tolerance decreases with the onset of airway obstruction. At the other extreme, patients presenting with unexplained weight loss or anorexia may have severe COPD, because the high metabolic requirements of advanced COPD may contribute to weight loss. Unexplained disorders of the liver or pancreas may suggest A1AT deficiency.²³

Physical Examination—Early in the disease process, physical examination has relatively little sensitivity from a diagnostic standpoint, except for disorders with multisystem manifestations. As the disease process becomes more advanced, physical examination yields greater diagnostic value. One of the major reasons for a thorough physical examination lies in detecting disorders that mimic or confound COPD.

Yellowing teeth and fingernails are often an indication of substantial cigarette smoke exposure. A cyanotic hue to the lips or fingernails may suggest the presence of severe COPD associated with hypoxia. Clubbing of the fingernails—often as a result of chronic oxygen deficiency—may be present in individuals with advanced COPD, but it may also indicate other disorders. Pursed-lip breathing typically occurs spontaneously in patients with expiratory flow obstruction as a way to ease dyspnea.²⁴,²⁵

Evaluation of the thoracic cavity may reveal an increased anteroposterior diameter, also known as “barrel chest.” This appearance results from air trapping, which in turn results in chronic hyperinflation of the thoracic cavity. Individuals with more severe disease and those in acute respiratory distress may have intercostal or subcostal retractions, leading them to make routine use of accessory respiratory muscles. The use of these muscles is usually a sign of increased work during breathing or respiratory muscle fatigue.
Palpation and percussion have little diagnostic value in detection of COPD in its early stages. However, in the later stages of COPD, an examiner may note the presence of decreased tactile fremitus and hyperresonance to percussion. Both findings are the result of hyperinflation of the lungs caused by airway obstruction.

Auscultation should be performed for all lung fields in a systematic manner. Such a systematic progression allows for the differentiation of focal findings from global findings. In addition, detection of normal breath sounds in abnormal locations should lead to closer inspection and may suggest the need for additional testing. Classic respiratory signs of COPD include a prolonged expiratory phase, wheezing on inspiration, and hyperresonance to percussion. Such a systematic progression allows for the differentiation of focal findings from global findings. In addition, detection of normal breath sounds in abnormal locations should lead to closer inspection and may suggest the need for additional testing.

With the variety of physical manifestations of COPD, many of the aforementioned findings may or may not be present. It should be noted, however, that the presence of diminished breath sounds in combination with a suggestive history is the most consistent physical finding in individuals with moderate COPD.

A somewhat simple test that can be used in the office setting is to time how long the patient can forcibly exhale. Typically, a forced exhale time of greater than 5 seconds may indicate some form of airway obstruction. Similarly, the inability of a patient to blow out a candle at a distance of 12 inches can be a useful indication of severe airway obstruction in some bedside settings.

Cardiac examination may reveal evidence of right ventricular strain or failure, particularly in patients with advanced COPD. Sustained point of maximal impulse, if present, may suggest right ventricular dilatation or hypertrophy. Cardiac auscultation will often reveal distant heart sounds, secondary to lung hyperinflation. A right ventricular gallop, increased intensity of P2 (ie, pulmonic second heart sound), and murmurs of pulmonary or tricuspid insufficiency are suggestive of right heart failure, possibly resulting from severe, chronic COPD. With the onset of right heart failure, increased jugular venous distention and lower-extremity edema may also be observed—findings that are indicative of pulmonary hypertension or cor pulmonale.

Imaging—Like the physical examination, most chest imaging techniques have relatively poor sensitivity for detecting mild to moderate COPD. Plain chest radiographs have a sensitivity of approximately 50% for diagnosing moderate COPD. Radiograph findings may include flattening of the hemidiaphragms, bullae, increased anteroposterior diameter on lateral films, and narrowing of the cardiac silhouette. Localized or regional emphysema can be identified via radiographs in certain cases. A finding of basilar emphysema may suggest A1AT deficiency, especially in younger individuals. Such a finding results from a relative increase in blood flow, contrasting with the usual finding of apical emphysema in smokers.

Computerized tomography (CT) scans are useful in identifying bullous lung disease and regional emphysema. Techniques to assess lung volumes using CT scans are available but are not routinely used.

Spirometry—As previously noted, spirometry is essential in making a diagnosis of COPD and in grading the severity of the disease. Standard flow-volume loop assessments can often be performed in the office with good reliability. The objective of these assessments is to determine a gross estimation of effective lung volume (ie, forced vital capacity [FVC]), the effect on airflow (ie, the ratio of FEV1/FVC), and whether there is any reversibility. Reversibility is defined as a significant improvement in the FVC, FEV1, or FEV1/FVC after the administration of a bronchodilator (ie, >200 mL improvement in FVC or FEV1 or 12% increase from prebronchodilator measurements).

Physiologic severity of COPD may be graded by using the spirometric indices shown in Figure 2. Symptomatic grading is often more useful from a clinical standpoint.

A diagnosis of airflow obstruction is typically based on a reduction in the FEV1/FVC ratio. For practical purposes, a ratio value less than 0.7 confirms the presence of airflow obstruction. A lack of reversibility or an incomplete reversibility of the obstruction after bronchodilator use secures the diagnosis of COPD. Furthermore, the degree to which FEV1 is decreased correlates with the severity of COPD (Figure 2).

It should be noted that spirometric severity of disease does not necessarily correlate with functional debilitation. To assess functional limitations, exercise testing is typically necessary.

Office-based spirometry has been validated for use in the diagnosis of COPD. However, despite recommendations in national COPD guidelines, recent data suggest that spirometry in the office remains underutilized. Equipment maintenance and quality control requirements, practitioner attitudes, and inability to interpret results are the major speculative reasons for its underutilization. Further information
on the use of office-based spirometry is available through the National Lung Health Education Program (noted in the recommended reading in Figure 3).

**Differential Diagnoses**

Many other conditions can have similar clinical presentations as COPD. These conditions may at times be difficult to differentiate from COPD.

Of special note, asthma and COPD can be difficult to differentiate. Both diseases have a primary presentation of airway obstruction and are associated with environmental exposures. However, the single most definitive means of differentiation between these 2 entities concerns the identification of reversibility of airway obstruction. Chronic obstructive pulmonary disease has classically been defined as airway obstruction that is not reversible or that is only partially reversible with use of bronchodilators. Asthma, by contrast, is a disease in which nearly complete airway reversibility can be achieved. As such, airway obstruction that is fully reversible with administration of bronchodilators is considered to be asthma—not COPD. Patients with airway obstruction that is not fully reversible with administration of bronchodilators are considered to have COPD.34

These 2 conditions may coexist in the sense that an individual with asthma as a child may have COPD as an adult. Unfortunately, the overlap of asthma and COPD, which occurs occasionally, creates some difficulty for practitioners in regard to diagnosis and treatment.35 For practical purposes, however, irreversibility in airway obstruction should lead to a diagnosis of COPD. Differential diagnosis criteria for COPD, based on the American Thoracic Society Task Force report,36 are shown in Figure 4.

**Conclusion**

Without question, every healthcare practitioner will encounter patients with COPD, either as a primary condition or as a confounding illness contributing to another medical condition. Earlier diagnosis of COPD can be achieved by keeping the disorder in mind when patients present with known risk factors, dyspnea, chronic cough, and/or chronic sputum production. Furthermore, additional cues derived from the patient’s family history, tobacco history, age at onset of symptoms, and environmental exposures provide insights that may lead the practitioner to suspect COPD as the culprit.

Spirometry is considered the diagnostic tool of choice for determining the presence or absence of obstructive airway disease, as well as for grading the severity of any obstruction. Furthermore, office-based spirometry used by properly trained technicians and practitioners appropriately trained in its interpretation is a recognized and effective means of evaluating and tracking patients with COPD.

**Take-Home Points**

- COPD should be considered in any patient presenting with chronic cough, dyspnea, or chronic sputum production.
- Information on family history, tobacco use, and potential occupational exposures should be elicited to discern a patient’s risk for having COPD.
- Spirometry remains the gold standard for COPD diagnosis, whether performed in a full pulmonary-function laboratory or in an appropriately staffed office-based practice.
- Consider α-1-antitrypsin deficiency and cystic fibrosis in patients younger than 40 years who present with a diagnosis of COPD.

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**Figure 4.** Differential diagnosis criteria for chronic obstructive pulmonary disease (COPD), based on a report by the American Thoracic Society Task Force.36 continued...
References


Chronic obstructive pulmonary disease (COPD) is a preventable and treatable disease with substantial extrapulmonary effects that may contribute to disease severity in some patients. The current emphasis from researchers and physicians on prevention and management of COPD, even with established disease, represents an extension of our prior understanding of this condition. Various interventions can modify the course of COPD and survival, as found in a 2008 review by Celli. These interventions include smoking cessation, long-term oxygen therapy in hypoxemic patients, noninvasive ventilation in selected patients, and lung volume reduction surgery (LVRS) in patients with upper lobe predominant emphysema and poor exercise capacity.

The cornerstone of interventions at all stages of COPD remains focused on prevention and smoking cessation. The Lung Health Study clearly demonstrated that smoking cessation decreased the rate of decline in lung function and reduced the rate of death for all-cause mortality. Similarly, the use of vaccines has proven effective for avoiding and reducing the severity of several infectious diseases. Vaccination is especially valuable in patients with more severe stages of COPD in which acute illnesses can lead to muscle loss and permanent declines in lung performance.

In 1998, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) was formed by experts from the World Health Organization and the US National Heart, Lung, and Blood Institute. The major goals of the group were to promote greater awareness of COPD, publish evidence-based recommendations regarding the prevention and management of COPD, and promote clinical research. The evidence-based guidelines from these initiatives were made available on the Internet and have been recently updated in the report The Global Initiative for Chronic Obstructive Pulmonary Disease. Similar recommendations for patients with COPD have also been published by the American Thoracic Society and European Thoracic Society and the American College of Physicians.

Overall, the current approach to COPD interventions is based on the severity of disease as determined by spirometry readings and clinical symptoms defined by GOLD (Figure 1). Based on a patient’s disease severity, the physician adds interventions in an incremental or step-wise manner, starting with smoking avoidance and cessation. This approach improves the overall efficacy of interventions, reduces cost by avoiding unnecessary interventions, and minimizes complications. While relatively simple, the GOLD panel treatment recommendations are applicable to patients with stable COPD and those with acute exacerbations. The recommendations also provide a good foundation for physicians who treat patients with COPD.

Medical interventions for patients with COPD can be divided into 2 interventions: (1) those that are directed at symptomatic relief but typically have little or no survival benefit and (2) those that have limited short-term symptomatic benefit but may impart survival benefit or disease avoidance.
With 1 possible exception, neither inhaled corticosteroids nor long-acting β₂-adrenergic agonists have been shown to reduce the rate of decline in lung function in COPD patients. In the TORCH study, an inhaled steroid alone or in combination with a long-acting β₂-adrenergic agonist decreased the rate of lung function decline, but this finding did not translate into significant survival benefit. Ultimately, the goal of medical therapy for COPD is to reduce symptoms, avoid adverse effects and complications, and reduce exacerbations. In the present article, we review the currently used treatment options (Figure 2) for patients with COPD.

Pharmacologic Options

Delivery Mechanisms

Commonly used formulations of medications for patients with COPD are presented in the Table. When medications are administered by inhalation, careful attention must be given to the choice of agent. For most patients, metered dose inhalers are as effective as other inhaled preparations and are substantially less costly. For metered dose inhalers, patients must be instructed on the proper technique for inhalation. Proper use remains a challenge for many patients attempting to coordinate the inhaler with the actuator. Under most circumstances, the use of a chamber or spacer for the delivery of inhaled medications will improve delivery and efficacy. Powder formulations of medications are typically designed to avoid the need for a chamber and may be technically easier for some patients. Patients with severe COPD (ie, forced expiratory volume in 1 second [FEV₁], <500 cc) may require an aerosol device for optimal delivery. The choice of inhalation device will depend on the medication, cost, and availability, as well as the technical skills of the individual patient.

Bronchodilator Therapy

The cornerstone of pharmacologic treatment for COPD patients is bronchodilator therapy. Medications with bronchodilator effects include β₂-adrenergic agonists, anticholinergic medications, and methylxanthine agents. The β₂-adrenergic agonists and anticholinergic medications are most commonly given by inhalation to reduce systemic adverse effects. Short- and longer-acting preparations are available for each of these medications. Long-acting β₂-adrenergic agonists and long-acting anticholinergic agents can be used as monotherapy in more stable patients and are associated with improved performance status, better lung function, and reduced exacerbations. Although all of these bronchodilators have been shown to improve exercise capacity, this benefit does not always correlate with improvements in FEV₁.

β₂-Adrenergic Agonists

β₂-Adrenergic agonists work directly on the β₂-receptor to cause bronchodilation. Short-acting β₂-adrenergic agents (eg, albuterol) are used for patients with infrequent symptoms or as a rescue medication in a more intensive regimen. Long-acting β₂-adrenergic agonists (eg, formoterol, salmeterol) provide bronchodilation for at least 12 hours and are used to control more frequent or persistent symptoms. Patients on long-acting β₂-adrenergic agonists must be instructed to use the medications as directed and not to use them for acute symptoms (ie, rescue medication). Most of these patients will need to be given a second, short-acting agent for acute symptoms. In general, the use of long-acting β₂-adrenergic agonists is associated with decreased exacerbations, whereas chronic use of short-acting β₂-adrenergic agonists is not. If acute symptoms do not abate after rescue medications are taken, if medications are needed more than every 4 hours, or if symptoms are worsening despite the therapy, then immediate evaluation with a physician is needed. Adverse effects associated with β₂-adrenergic agonists are generally mild and include headache, tremors, throat irritation, dizziness, and hypersensitivity reactions.

Anticholinergics—Anticholinergic medications, available only via in-
Osteopathic Physicians’ Guide: COPD

**Figure 2.** Treatment options for patients with chronic obstructive pulmonary disease.

halation, became more widely available in the early 1990s. Working through a cholinergic blockade mechanism, these agents provided a bronchodilator effect through a different pathway than β₂-adrenergic agonists. In COPD, as compared to asthma, the relative bronchodilatory effect of anticholinergics was often greater than that of the β₂-adrenergic agonists. Adverse effects were common until the first of the new generation agents, ipratropium bromide, was released. The duration of action was about 6 hours. Newer and longer-acting agents are now available and have improved the management of COPD symptoms. For example, the long-acting anticholinergic agent, tiotropium, is efficacious for at least 24 hours. Adverse effects associated with the newer anticholinergic medications are usually mild but may include dry mouth, urinary retention, narrow angle glaucoma, and hypersensitivity reactions.

The combination of short-acting anticholinergic and short-acting β₂-adrenergic agonists has been examined in patients with moderately severe, stable COPD. A 12-week prospective, double-blind trial compared the combination of albuterol and ipratropium with each agent alone to determine the degree of spirometric improvement during the first 4 hours after administration. The agents were administered by metered-dose inhaler. Results from the study indicated that combination therapy was more effective than either agent alone in terms of spirometric improvement. Symptom scores did not change over time and did not differ among treatment groups. Similar findings have been noted when a nebulized combination product containing both albuterol and ipratropium was compared to single agent therapy.

**Methylxanthine Agents**—Methylxanthine agents are older and less used today because of their greater adverse effects, lesser efficacy, and need for serum monitoring. However, these medications offer some selected patients benefit through improved diaphragmatic function and effects on mucociliary function. Theophylline, the primary agent in this class, is a less potent bronchodilator than β₂-adrenergic or anticholinergic agents. Theophylline is given either intravenously or orally. Serum levels should be monitored and plasma levels should generally not exceed 12 μg/mL because higher levels are associated with greater toxicity in older patients. Dosing may also be affected by food, drug interactions, and slowed metabolism in some patient populations (eg, elderly patients, cirrhotic patients). Theophylline is most beneficial for patients with severe COPD in whom other therapies failed and particularly patients with carbon dioxide retention.

**Corticosteroids**

Corticosteroids, which are not approved for use as monotherapy, are available in inhalation, oral, and intravenous forms. Regular treatment with inhaled corticosteroids has been shown to reduce the frequency of acute exacerbations, improve health status, improve lung function, and reduce use of rescue medication. Most studies of inhaled corticosteroids have not demonstrated any improvement in the rate of decline in lung function. However, the TORCH study group was able to demonstrate a slower rate of decline in lung function in patients treated with either fluticasone propionate alone or the combination of fluticasone propionate and salmeterol. This trial was a large, randomized, double-blind, placebo-controlled study that followed patients with moderate to severe COPD for 3 years. When compared to placebo, the differences in the primary end point of all-cause mortality was not statistically significant for any treatment group.

The adverse effects of inhaled corticosteroids are usually minor, including upper airway thrush and dysphonia. However, an increased potential for pneumonia has been reported with the use of inhaled corticosteroids and withdrawal of inhaled corticosteroids may also be associated with acute exacerbations in certain patients.

The use of oral maintenance corticosteroids is not recommended for patients with stable COPD because the systemic adverse effects of corticosteroids outweigh their potential benefits. However, oral corticosteroids are indicated as outpatient therapy for patients with acute COPD exacerbations. Intravenous corticosteroids may be used for inpatient acute exacerbations, although oral steroids are probably equally efficacious.

**Combined Bronchodilators and Corticosteroids**

Multiple studies have demonstrated that an inhaled corticosteroid combined with a long-acting β₂-adrenergic agonist is more effective than either component alone in improving lung function and health status and reducing exacerbations. However, such combined therapy may increase the risk of pneumonia. Survival benefit of these combined agents remains uncertain. As noted previously, a large prospective trial was unable to demonstrate a survival benefit from combined therapy. To our knowledge, only 1
study\textsuperscript{13} to date has shown that inhaled salmeterol, fluticasone, or both salmeterol and fluticasone reduced the rate of FEV\textsubscript{1} decline in COPD patients with moderate or severe disease. A 6-week, multicenter, randomized, double-blind trial of patients with moderate COPD demonstrated superiority in lung function of the combination of inhaled tiotropium plus formoterol compared with the combination of salmeterol and fluticasone.\textsuperscript{45} These data suggest that some disease modification might occur with combination bronchodilators and corticosteroids; however, confirmation of this effect awaits the completion of long-term studies.

**Nonpharmacologic Therapy**

**Oxygen**

Oxygen therapy has a positive impact on hemodynamics, hematologic features, exercise capacity, lung mechanics, and mental state.\textsuperscript{46} Long-term oxygen given for longer than 12 hours per day by nasal cannula has been shown to improve survival in chronically hypoxic COPD patients.\textsuperscript{4,5} Further benefit is derived when used 24 hours per day. Patients should be evaluated for the need of oxygen therapy using arterial blood gas or an assessment of oxygen saturation when they are clinically stable breathing room air. In most instances, an exercise evaluation may also be helpful. If the arterial oxygen saturation is less than or equal to 88%, or the arterial oxygen tension is less than or equal to 55 mm Hg, then the patient qualifies for supplemental oxygen. In circumstances where the arterial oxygen tension is 56 to 59 mm Hg or the saturation is 89%, the patient qualifies for supplemental oxygen if they have dependent edema suggesting congestive heart failure, pulmonary hypertension, cor pulmonale, or a hematocrit greater than 56%.

**Lung Volume Reduction Surgery**

During LVRS, severely emphysematous tissue is removed from both upper lung lobes. This operation allows the remaining lung to expand and the

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### Osteopathic Physicians’ Guide: COPD

#### Table. Commonly Used Formulations of Drugs Used in Chronic Obstructive Pulmonary Disease

<table>
<thead>
<tr>
<th>DRUG</th>
<th>INHALER, pg</th>
<th>SOLUTION for NEBULIZER, mg/mL</th>
<th>ORAL</th>
<th>VIALS for INJECTION, mg</th>
<th>DURATION of ACTION, hr</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>β\textsubscript{2}-agonists</strong></td>
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<tr>
<td>Short-acting</td>
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<tr>
<td>Fenoterol</td>
<td>100-200 (MDI)</td>
<td>1</td>
<td>0.05% (syrup)</td>
<td>4-6</td>
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</tr>
<tr>
<td>Levobuterol</td>
<td>45-90 (MDI)</td>
<td>0.21, 0.42</td>
<td></td>
<td>6-8</td>
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<tr>
<td>Salbutamol (albuterol)</td>
<td>100, 200 (MDI, DPI)</td>
<td>5</td>
<td>5 mg (pill), 0.024% (syrup)</td>
<td>0.1, 0.5</td>
<td>4-6</td>
</tr>
<tr>
<td>Terbutaline</td>
<td>400, 500 (DPI)</td>
<td>2.5, 5 (pill)</td>
<td>0.2, 0.25</td>
<td>4-6</td>
<td></td>
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<tr>
<td>Long-acting</td>
<td></td>
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<tr>
<td>Formoterol</td>
<td>4.5-12 (MDI, DPI)</td>
<td>0.01*</td>
<td></td>
<td>12+</td>
<td></td>
</tr>
<tr>
<td>Arformoterol</td>
<td></td>
<td>0.0075</td>
<td></td>
<td>12+</td>
<td></td>
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<tr>
<td>Salmeterol</td>
<td>25-50 (MDI, DPI)</td>
<td></td>
<td></td>
<td>12+</td>
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<tr>
<td><strong>Anticholinergics</strong></td>
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<tr>
<td>Short-acting</td>
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<tr>
<td>Ipratropium bromide</td>
<td>20, 40 (MDI)</td>
<td>0.25-0.5</td>
<td></td>
<td>6-8</td>
<td></td>
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<tr>
<td>Oxitropium bromide</td>
<td>100 (MDI)</td>
<td>1.5</td>
<td></td>
<td>7-9</td>
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<tr>
<td>Long-acting</td>
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<tr>
<td>Tiotropium</td>
<td>18(DPI), 5 (SMI)</td>
<td></td>
<td></td>
<td>24+</td>
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<tr>
<td><strong>Combination short-acting β\textsubscript{2}-agonists plus anticholinergic in 1 inhaler</strong></td>
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<tr>
<td>Fenoterol/ Ipratropium</td>
<td>200/80 (MDI)</td>
<td>1.25/0.5</td>
<td></td>
<td>6-8</td>
<td></td>
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<tr>
<td>Salbutamol/ Ipratropium</td>
<td>75-15 (MDI)</td>
<td>0.75/4.5</td>
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<td>6-8</td>
<td></td>
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<tr>
<td><strong>Methylxanthines</strong></td>
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<tr>
<td>Aminophylline</td>
<td></td>
<td></td>
<td>200-600 mg (pill)</td>
<td>240</td>
<td>Variable, up to 24</td>
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<tr>
<td>Theophylline (SR)</td>
<td></td>
<td></td>
<td>100-800 mg (pill)</td>
<td></td>
<td>Variable, up to 24</td>
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<tr>
<td><strong>Inhaled glucocorticosteroids</strong></td>
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<tr>
<td>Beclomethasone</td>
<td>50-400 (MDI, DPI)</td>
<td>0.2-0.4</td>
<td></td>
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<tr>
<td>Budesonide</td>
<td>100, 200, 400 (DPI)</td>
<td>0.20, 0.25, 0.5</td>
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<tr>
<td>Fluticasone</td>
<td>50-500 (MDI, DPI)</td>
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<tr>
<td>Triamcinolone</td>
<td>100 (MDI)</td>
<td>40</td>
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<tr>
<td><strong>Combination long-acting β\textsubscript{2}-agonists plus glucocorticosteroids in 1 inhaler</strong></td>
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<tr>
<td>Formoterol/ budesonide</td>
<td>4.5/60, 9/320 (DPI)</td>
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<tr>
<td>Salmeterol/ fluticasone</td>
<td>50/100, 250, 500 (DPI)</td>
<td>25/50, 125, 250 (MDI)</td>
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<tr>
<td><strong>Systemic glucocorticosteroids</strong></td>
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<tr>
<td>Prednisone</td>
<td></td>
<td></td>
<td>5-60 mg (pill)</td>
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<tr>
<td>Methylprednisolone</td>
<td></td>
<td></td>
<td>4, 8, 16 mg (pill)</td>
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</tbody>
</table>

* Formoterol nebulized solution is based on the unit dose vial containing 20 μg in a volume of 2.0 mL.

Abbreviations: DPI, dry powder inhaler; MDI, metered dose inhaler; SMI, soft mist inhaler.

Source: Reprinted with permission from U.S. Health Network.
than for other solid organs. About 5 years and is significantly lower survival for lung transplantation is.

Of note, the benefits of transplantation may not be appropriate candidates for lung transplantation candidates include a FEV1 of less than 30% predicted, PaO2 less than 55 to 60 mm Hg, PaCO2 greater than 50 mm Hg, and secondary pulmonary hypertension.53,54

Pulmonary Rehabilitation
Pulmonary rehabilitation is a multidisciplinary program designed to maximize lung function, improve gas exchange, optimize conditioning, and address nutritional issues. Typically, pulmonary rehabilitation programs are outpatient based. Patients in pulmonary rehabilitation are usually GOLD stage 2 or 3 (Figure 1) in terms of disease severity, but patients with more or less severe disease may also benefit. Patients who cannot ambulate, have unstable cardiac disease, or have neurologic problems or cognitive dysfunction may not be appropriate candidates for rehabilitation.

Pulmonary rehabilitation does not directly improve lung mechanics or gas exchange.55 Rather, it optimizes the function of other body systems to reduce the impact of lung dysfunction.56 These effects are derived from improved muscle function, reduction in dynamic hyperinflation, and desensitization to dyspnea.57 Improvements in depression and social interactions may also contribute to the benefits of pulmonary rehabilitation.57

The major element of a pulmonary rehabilitation program is exercise. Generally, exercise of the legs is emphasized with walking (eg, on a treadmill) or cycling. High-intensity (target, 60% of maximal endurance) or lower-intensity regimens are determined based on patient tolerance. Upper extremity training can improve patients’ ability to perform their activities of daily living. Respiratory muscle training is no longer commonly used because it does not lead to increased functional capacity.58 Ancillary treatments, including optimal bronchodilation during rehabilitation session and use of supplemental oxygen, are also helpful.57

Cachexia in patients with COPD causes a depletion of lean body mass and is associated with a poor prognosis. Nutritional evaluation identified the patients with cachexia so that nutritional support can be provided; therefore, nutritional evaluations are a routine part of pulmonary rehabilitation. Unfortunately, nutritional interventions have not been uniformly effective in clinical trials for a variety of reasons.59 Patients with COPD who are overweight have a greater degree of exercise limitation because of the effects of obesity on lung function. Weight loss is uniformly prescribed for these patients, but data on efficacy are lacking.

Studies60-62 have shown a positive effect for pulmonary rehabilitation regarding reductions in hospitalizations and other measures of healthcare utilization, as well as improvements in cost-effectiveness. Although pulmonary rehabilitation has not been shown to improve survival in COPD patients, the randomized trials that have investigated survival were inadequately powered to detect this effect.58

Conclusion
Treatment of patients with COPD warrants an aggressive approach beginning with smoking cessation at the earliest...
COPD is a chronic lung disease characterized by chronic airflow obstruction, which results in repeated exacerbations and progressive disability. The main components of COPD are chronic bronchitis and emphysema. 

**References**


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Chronic obstructive pulmonary disease (COPD) has been viewed as a disease that is confined to the lungs. However, recent evidence suggests that COPD is a systemic disease with associated comorbidities that can affect quality of life, morbidity, and mortality. Conditions such as cardiovascular disease, musculoskeletal dysfunction, osteoporosis, and diabetes mellitus are all part of the systemic manifestations of COPD. The present article reviews the causal link between COPD and these comorbid conditions and touches on management of these diseases in patients with COPD.

Mortality and Cardiovascular Disease

Currently, COPD is the fourth leading cause of death in the United States, and compared with other diseases, such as heart disease or stroke, death rates are on the rise. In patients with COPD, it is unclear whether patients are more likely to die from other comorbidities or whether COPD is the main cause of death. Cardiovascular disease, one of the leading causes of death in the United States, is the most common comorbidity in patients with COPD. In a cohort of nearly 400,000 patients from Veterans Administration (VA) clinics, researchers found that the prevalence of coronary artery disease was significantly higher in those with COPD than those without COPD (33.6% compared with 27.1%). In another study of 45,000 patients, Sidney et al found that those patients with COPD had a higher risk of hospitalization and mortality from cardiovascular disease. Similarly, Holguin et al studied comorbidity and mortality in COPD-related hospitalizations. They found that there was an increased prevalence and higher in-hospital mortality in patients with COPD who had ischemic heart disease and congestive heart failure than in those without COPD.

It can be argued that the common risk factor of smoking has increased the incidence of cardiovascular disease in patients with COPD. However, there is evidence that patients with COPD have a risk that is above and beyond that related to smoking alone. In one study, patients with symptoms of chronic bronchitis had a 50% increase in cardiovascular mortality when controlled for age, sex, and amount of smoking.

There is also a link between lower forced expiratory volume in 1 second (FEV1), a surrogate measure of smoking, and cardiovascular disease. Hole et al found that subjects with lower FEV1 (<73% of predicted) had an increased risk of ischemic heart disease (hazard ratio: 1.56 in men, 1.88 in women). Interestingly, there was also an increased risk of heart disease among those with FEV1 between 73% and 83% than in those with FEV1 measurements that were higher. Although specific questions about cumulative cigarette consumption (eg, pack-years) were not
asked, risk of cardiovascular mortality was present whether the patients were current smokers, previous smokers, or never smokers.

Still, questions remain as to why there is an elevated risk of cardiovascular disease in patients with COPD; this has not been fully elucidated. One reason may be related to systemic inflammation, as there have been strong links between systemic inflammation and cardiovascular disease. Serum markers of inflammation such as C-reactive protein (CRP) have been linked to increased risk of cardiac disease and have also been shown to be increased in patients with stable COPD as well as in those with exacerbations. An inflammatory link between cardiovascular disease and COPD can thus be speculated. Once again, smoking tobacco may play a role in that smoking can increase inflammatory markers. Some have postulated that in addition to smoking cessation, the use of statin medications may be of benefit in those with COPD by exerting an anti-inflammatory effect. Although there have been no prospective studies, some retrospective studies have shown the use of statins along with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers may reduce cardiovascular mortality in patients with COPD.

β-Blockers are a cornerstone drug in the medical management of coronary artery disease. Some clinicians fear precipitating bronchospasm in those with COPD with β-blockers. Data suggest that cardioselective β-blockers can be used safely in COPD patients for the management of known coronary disease. Nonetheless, caution should be exercised when treating patients with reversible airflow obstruction such as asthma. The large amount of data that support the use of these medications in patients with heart disease suggests that every effort should be taken to administer these medications. Coexistent cardiovascular disease should be carefully considered in a patient with COPD. Efforts to diagnose and treat cardiovascular disease likely will improve patient outcomes.

Skeletal Muscle Dysfunction and Nutritional Status

Musculoskeletal dysfunction can cause significant morbidity in patients with COPD and affects survival in these patients. Patients with a low body mass index (BMI) and decreased fat-free mass have been linked to increased mortality compared to patients with a normal BMI. The cause of musculoskeletal dysfunction in COPD is multifactorial. A combination of malnutrition, decreased activity, and use of glucocorticoids all play a role in musculoskeletal dysfunction. Recent data point to oxidative stress and systemic inflammation contributing to muscle dysfunction. Clinicians may assume that musculoskeletal dysfunction only occurs in those with more severe disease; however, new evidence suggests otherwise. For instance, Coronell et al assessed quadriceps endurance in patients with mild to moderate COPD. Even during normal physical activity, these patients had decreased strength and endurance. Therapies that exist to ameliorate muscle dysfunction in patients with COPD consist of pulmonary rehabilitation, modified nutritional supplementation, and use of pharmacologic agents to increase fat-free mass.

The GOLD II guidelines recommend pulmonary rehabilitation in all patients with moderate COPD, but it is likely that even those with mild disease can derive benefit. Upper and lower extremity strength training with light aerobic exercise increases endurance, improves symptoms of dyspnea, and enhances quality of life. Cote et al found, in patients with severe COPD (mean FEV1, 32%), that rehabilitation provided a survival advantage and decreased hospital utilization. Unfortunately, improvements conferred by pulmonary rehabilitation diminish if exercise is discontinued, and patients should be urged to continue exercises at home. Fewer data are available on the optimal time to begin rehabilitation and whether repeating rehabilitation program has benefit. Overall, patients who start to develop even subtle functional limitations should be referred to a rehabilitation program.

Having a low BMI is a risk factor for all-cause mortality, but the optimal timing of referral to nutritional support has not been established in patients with COPD. Most studies of nutritional support involve patients whose COPD is well controlled without multiple exacerbations. More evidence suggests that weight loss follows a stepwise progression and worsening nutritional status may be related to acute exacerbations of COPD.

Schols and Wouters proposed a simple screening process that involves measurement of BMI and weight course (Figure 1). First, patients are characterized as underweight (BMI <21), normal weight (BMI ≥21–<25), and overweight (BMI ≥25–<30). Second, weight loss is determined, defined by greater
than 10% loss in the past 6 months or greater than 5% in 1 month. Nutritional supplementation would then be indicated in specific subgroups. Nutritional interventions may only involve diet modification; however, some patients require energy-dense supplements. These products should be spaced out throughout the day to avoid appetite loss and adverse ventilatory effects due to higher caloric encumbrance.

Other options to help combat musculoskeletal dysfunction involve the use of anabolic steroids and growth hormone replacement therapy. Unfortunately, most studies with these agents have yielded less than ideal results with respect to increases in weight, muscle mass, and exercise tolerance, but others have shown modest yet consistent increases in muscle function. In one study, addition of growth hormone in patients with COPD increased muscle mass but did not increase exercise tolerance. The use of testosterone in healthy subjects increases muscle mass and power, which are compounded by strength training; however, as with growth hormone, use of testosterone in patients with COPD has yielded mixed results.

There are many factors related to COPD that may cause musculoskeletal dysfunction, including inactivity, steroid use, malnutrition, and oxidative stress. Goals of increased physical activity, improved nutritional intake, limitation of systemic steroids, and possible pharmacologic interventions may improve quality of life and possibly mortality in patients with COPD by improving skeletal muscle function.

**Osteoporosis**

Patients with COPD are at risk for osteoporosis for several reasons, such as smoking tobacco, inactivity, malnutrition, and a low BMI. These risk factors, combined with increased age and corticosteroid use, all play a role in putting these patients at high risk for the development of osteoporosis. For patients with COPD, the approach to minimize osteoporosis risk should involve screening, risk reduction, and treatment.

Traditionally, screening was offered to postmenopausal women or patients with COPD taking oral glucocorticoids. However, screening a larger cohort of patients with COPD may be prudent. Evidence from Praet et al., who studied bone mineral density (BMD) in men with chronic bronchitis, suggests more patients may be at risk. They found that patients who were on bronchodilators alone had substantially worse BMD than an age-matched control population. Pino-Montes et al. also studied COPD patients who had no prior use of glucocorticoids and found that they had lower BMD compared to age-matched controls.

The risk of osteoporosis in patients on inhaled corticosteroids is debatable. Studies specifically looking at patients with COPD who use inhaled corticosteroids lack conclusive evidence. Some have found worsening BMD, while others have found no significant difference compared with placebo arms. Overall it seems short-term use of ICS at low doses does not pose a statistically significant risk. However, those who are on inhaled corticosteroids at higher doses may be at a risk above and beyond the already increased risk of being a patient with COPD.

Osteoporosis or osteopenia is often asymptomatic and may cause little morbidity. However, the fractures related to them can be detrimental, especially in patients who are respiratory limited. Thoracic and vertebral fractures can substantially alter lung function. Hip fractures can cause pain and immobility. Worsening lung function coupled with immobility worsens the quality of life for patients with COPD. Further studies are needed to specifically address morbidity and mortality effects of fractures in COPD.

With the high potential for morbidity and mortality in patients with osteoporosis and COPD, physicians should screen and treat these patients aggressively. Establishing which patients should be screened can be difficult. It can be argued that screening every COPD patient for osteoporosis is important because of the fact that
patients with COPD have worsened BMD compared to age-matched populations, as previously discussed. However, Biskobing suggested a more narrow population of screening postmenopausal women, premenopausal women, men with hypogonadism, and men and women with low BMI or history of fracture related to osteoporosis (Figure 2). Screening is also recommended for patients who are about to start long-term, high-dose inhaled corticosteroids or an oral corticosteroid program (>7.5 mg/d). These patients should be followed with repeat BMD testing every 2 years. Those taking long-term oral glucocorticoids should be evaluated more frequently, generally every 6 to 12 months.

Treatment strategies involve calcium and vitamin D supplementation, physical therapy, hormonal replacement, and use of bisphosphonates. Those at risk for osteoporotic fractures should be started on calcium and vitamin D supplementation. Hormone replacement can be offered to those who have hypogonadism unless contraindicated. All patients who are at risk will benefit from physical therapy. Treatment for postmenopausal women has been established by the American College of Physicians. Any postmenopausal woman with a T score on BMD testing of less than -2 or less than -1.5 with risk factors should begin treatment. When it comes to men who are not on oral corticosteroids the data are less clear. Orwoll suggested that men with T scores less than -2.0 may be candidates for treatment.

Every patient on long-term oral corticosteroids should receive calcium and vitamin D supplementation. The use of bisphosphonates in this group should be guided by BMD testing and risk factors. High-risk postmenopausal women with normal BMD can be offered hormone replacement therapy or bisphosphonates if contraindicated. Others should have bisphosphonates added if T score on BMD testing is less than -1. Women on oral corticosteroids with normal T scores and no other risk factors should be followed up every 6 to 12 months to determine if bisphosphonates need to be added. Treatment options for those on inhaled corticosteroids involve the use of calcium and vitamin D and close follow-up with repeat BMD testing thereafter (generally every 12-18 months).

Patients with COPD should be followed closely for bone mineral loss. Those who continue to lose BMD despite calcium and vitamin D therapy should have bisphosphonates or hormone replacement added. Current studies recognize the increased risk for osteoporosis in patients with COPD. Further studies are needed to establish specific recommendations in osteoporosis management in COPD.

Diabetes and Dyslipidemia

Patients with COPD have an increased prevalence of diabetes mellitus. Several risk factors are common between diabetes mellitus and COPD. One major risk factor is smoking. In addition, the use of glucocorticoids may affect blood glucose levels; however, there is likely an independent link between diabetes mellitus and COPD.

Initial evidence of the link between COPD and diabetes mellitus was seen in studies that showed increased risk of development of diabetes mellitus with reduced lung function. One such study, by Walter et al., showed a strong association between diabetes mellitus and reduced lung function. Subjects in the worst quartile of fasting glucose (102-305 mg/dL) had lower FEV₁ compared to predicted FEV₁, whether they were never smokers (-82 mL), current smokers (-104 mL), or former smokers (-98 mL). The reason for this connection may lie in systemic inflammation, which, as previously stated, has been linked to musculoskeletal dysfunction and cardiovascular disease. Studies have shown that there is increased insulin resistance in COPD related to elevations in inflammatory mediators such as IL-6 and tumor necrosis factor α.

Clinically, diabetes mellitus affects COPD morbidity and mortality in patients with COPD. Specifically, in patients hospitalized with acute exacerbations of COPD, those with hyperglycemia have increased mortality. Baker et al. showed that patients admitted for acute exacerbations of COPD with hyperglycemia had an increased relative risk of death or longer hospitalization. This risk increased independent of age, sex, or COPD severity. Diabetes mellitus is also a risk factor for mortality after hospital discharge for AE-COPD. Though long-term mortality increases in COPD patients with comorbidities, more studies are needed to address morbidity and mortality with COPD and diabetes mellitus. More data are also needed to determine optimal glucose control in those admitted.
for acute exacerbations of COPD and in long-term diabetes mellitus management as it relates to COPD.

Dyslipidemia, like diabetes mellitus, has strong links to smoking and cardiovascular disease. Smoking is known to cause an increase in low-density lipoprotein (LDL), triglycerides, and very-low-density lipoproteins. However, studies on lipid profiles and COPD are lacking. It is currently unknown if dyslipidemia is another disease process independent of COPD. A systematic review revealed that there have been small retrospective trials to show the benefit of statin use in COPD. Further data are needed in the optimal treatment of patients with COPD.

Conclusion
Chronic obstructive pulmonary disease has long been thought of as a disease limited to the lungs. However, emerging evidence elucidates the impact of comorbidities in this patient population. Strong links to cardiovascular disease, musculoskeletal dysfunction, and osteoporosis have been made. Weaker links have been made to dyslipidemia and diabetes mellitus. The concept of systemic inflammation is an emerging subject that may link COPD and these comorbidities. For primary care physicians, aggressive management of these comorbidities is paramount to the treatment of patients with COPD. Further data are needed in the optimal management of comorbidities in relation to COPD. Aggressive treatment of these conditions likely will improve quality of life and may alter outcomes in patients with COPD.

References
Chronic obstructive pulmonary disease (COPD) is caused by chronic bronchial and parenchymal inflammation that progressively obstructs expiratory airflow and is not fully reversible. The prevalence of COPD is increasing worldwide. It was the sixth leading cause of death worldwide in 1990, and it is projected to be the third leading cause of death by 2020. Because of the condition’s prevalence, thousands of published studies related to the diagnosis and management of chronic obstructive pulmonary disease exist. However, there are relatively few studies that approach treatment from an osteopathic perspective—specifically, the use of osteopathic principles and practice (OPP), of which osteopathic manipulative treatment (OMT) is a very important and useful modality.

Osteopathic medicine’s philosophy is based on the following 4 principles:
1. The human being is a dynamic unit of function.
2. The body possesses self-regulatory mechanisms that are self-healing in nature.
3. Structure and function are interrelated at all levels.
4. Rational treatment is based on these principles.

The Educational Council on Osteopathic Principles (ECOP) developed a curriculum for osteopathic medical education based on these principles designed to create physicians who are health—rather than disease—oriented by treating each patient as an equal partner (adult-to-adult) in attaining health. The ECOP developed “five basic integrative and coordinated body functions … that were considered in a context of healthful adaptation to life and its circumstances” to nurture such physician growth. These functions are as follows:

1. Posture and motion
2. Gross and cellular respiratory and circulatory factors
3. Metabolic processes of all types
4. Neurologic integration
5. Psychosocial, cultural, behavioral, and spiritual elements.

When practiced together, these functions represent a holistic approach to patient care. Dr. Miller discloses that he sees patients with COPD and uses OMT as part of his treatment plan, for which LMU-DCOM bills and receives payment for in the course of usual healthcare delivery.

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present review to uncover studies that used or supported the use of OPP and OMT with COPD patients.

**Methods**

Between July 2010 and September 2010, I conducted a search on PubMed using the following MeSH terms: pulmonary disease, chronic obstructive; lung diseases, obstructive; primary health care; physicians, family; manipulation, osteopathic; manipulation, orthopedic; smoking cessation; and counseling. I also conducted searches in UpToDate, ClinicalTrials.gov, OSTMED.DR, and http://www.osteopathic-research.com/ using the same terms. During this time, articles were also found by examining the bibliographies of helpful articles. Review articles, trials with results, and other articles were chosen based on their containing relevant content. Articles with similar content, such as management techniques for smoking cessation, were sometimes excluded when another article provided more relevant, more extensive, or newer coverage of the topic. Findings were grouped to better understand the role of OPP in COPD management.

**Results**

Two articles were found through the PubMed search on the use of OPP and OMT in patients with COPD. The bibliographies of the articles were used to find additional articles. The PubMed search was expanded to include MeSH terms for lung diseases, primary care, family physicians, and orthopedic manipulation as well as appropriate keywords. Of the more than 300 articles found, recent articles were chosen based on relevance and other criteria. A PubMed MeSH search that incorporated terms for smoking cessation, primary healthcare, family physicians, and COPD yielded 34 articles, which are referenced in the remainder of the present article.

**Recognizing the Presence of Disease**

Despite its common occurrence, COPD remains difficult to diagnose in its prodromal and early stages. Clinical signs may be vague,1-3 5-7 and spirometry remains underutilized as a simple, office-based diagnostic tool because of reimbursement issues and other factors.8,9 Clinical guidelines such as the Global Initiative for Chronic Obstructive Lung Disease (GOLD) have set objective standards for diagnosis and staging of COPD by pulmonary function.1 In addition, several researchers, such as Stallberg et al,10 have developed clinical questionnaires in an effort to improve disease recognition and to encourage treatment.

Osteopathic physicians appear to underutilize their palpatory skills to aid in diagnosis or management of COPD. In an Ohio study published in 2003, few osteopathic physician specialists used OMT in patients with COPD.11 This behavior may represent an observed downward trend by residents in osteopathic graduate medical education programs to practice their skills while in training.12 Likewise, a 2003 study by Chamberlain and Yates13 found that most osteopathic medical students believed they would use palpatory diagnosis and osteopathic manipulative treatment (OMT) for fewer than 25% of their patients (and primarily for structural complaints). These studies suggest a downward trend in perceived usefulness of manipulation as a current medical best practice. The value of detecting and treating viscerosomatic reflexes14-17 appears to be on the decline in daily osteopathic medical practice.

**Recognizing and Addressing Risk Factors**

Patients at risk of developing COPD frequently have clinical signs that include chronic cough (with or without sputum production), wheeze, and exertional dyspnea. These signs should alert physicians to the possibility of COPD. The additional presence of smoking tobacco in 80% to 90% of patients with these chronic symptoms should be an obvious signal of increased risk of COPD.5 Nonetheless, physicians routinely fail to recognize and act on these important clues to the absence of health in their patients and prevent progression to COPD.1

In a 2003 review, Mannino found that nearly half of patients with chronic cough suggesting COPD were undiagnosed, despite exhibiting symptoms that might have led their physicians to perform pulmonary function testing.6 van der Molen7 cited a study by van Schayck,18 in which pulmonary function testing found that 1049 of 3016 smokers had COPD undiagnosed by their physicians. Holistic emphasis is an important part of osteopathic medical training. Dating back to Andrew Taylor Still, MD, DO, we understand that practicing healthy behaviors leads to wellness, and we recognize the importance of detecting symptoms that signal incipient disease. We are trained to help the ill patient back to health, rather than just treat disease.19 This training is especially helpful as we craft treatments with our patients.

**Crafting Evidence-Based Treatment Options With Your Patients**

**Smoking Cessation**—Smoking cessation remains the cornerstone for treatment of patients with COPD and are the major interventions known to reduce disease morbidity and mortality.20 However, patients face a difficult task in the decision to quit smoking. They may be emotionally drained, frequently blaming themselves for their
illness, and they may despair that the onset of symptoms heralds an irreversible decline that smoking cessation will not stop.21 They may have a history of several failed attempts to quit that further haunts them. The primary care physician who elicits and addresses these emotional cues in their patients may empower them to successfully quit.

Education for accurate self-assessment of disease risk, co-morbid conditions, and family support are also important factors that the primary care physician must help their patients address as part of their empowerment. Self-help programs and cessation medication can be beneficial as well.22,23 Pulmonary rehabilitation programs are another possible intervention. One such activity led by Bourbeau et al24 in the late 1990s found statistically significant improvements in patients’ health status through in-home weekly visits by health professionals. Another by Norrhall et al25 in 2009 enrolled 84 smokers with COPD in a lifestyle modification course with healthcare professionals. According to the study, 47% of the patients quit smoking tobacco and remained smoke-free up to 1 year after the intervention. A 2008 review of Canadian pulmonary rehabilitation programs using inspiratory muscle training and exercise training showed improved quality of life of the programs’ participants and a nearly 50% reduced risk of hospitalization for acute exacerbations.26

All of these examples highlight the importance of knowing your patients’ needs in order to craft treatment with the most likelihood for success. That success comes most often when physician, patient, family, and available healthcare and community supports work together, yet another example of osteopathic principles in practice.

Pharmacotherapy—The goal of pharmaceuticals in treating patients with COPD is to improve quality of life—no medication has been shown to reduce COPD-related mortality.21 β-Agonists, anticholinergics, combination therapy, and inhaled corticosteroids all are given to reduce patient symptoms, ease exacerbations, enhance possible exercise, and improve ability to perform activities of daily living. Physicians who reduce patients’ symptoms and improve their abilities to perform activities of daily living incur trust. Creating patient trust is an important outcome.21 The physician who practices the holistic approach will emphasize these positive outcomes not as chronic disease treatment, but rather as paths to better health. A patient so motivated and who has well-founded trust in a physician is more likely to consider attempting the most beneficial, but hardest to accomplish, treatment option—smoking cessation.

Osteopathic Manipulative Treatment—Several articles have chronicled the use of OMT in diagnosis and management of chronic COPD. In 1973, Howell et al27 reported results of OMT in a patient with COPD diagnosed by clinical symptoms. The authors progressively applied OMT in the areas of greatest restriction in the thoracic spine and chest cage for 16 months. There was a reported reduction in the patient’s clinical symptoms and improvement in his oxygen saturation, but objective measures did not support the clinical improvement.27 A follow-up study28 of 11 patients followed for 9 months with a similar protocol had similar results.

In a small study of COPD patients, Miller29 found that 92% of patients treated with spinal manipulation and thoracic lymph drainage had improvement in their physical work capacity. Similar to other studies, there was a worsening of patients’ residual volume and total lung capacity.

More recently, in 2006, Noll et al30 conducted a study of 35 patients with COPD based on GOLD criteria. Eighteen patients received a session of OMT and 17 had a sham treatment. Again, the OMT group had a worsening of residual volume and total lung capacity following this single treatment session of 7 protocol techniques, which included thoracic lymphatic pump (TLP) with activation. Patients also had a statistically significant decrease in forced expiratory flow at 25% and 50% of vital capacity and at the mid-expiratory phase. The authors postulated that the worsening residual volume and total lung capacity were due to overmanipulation. In a follow-up study in 2009, Noll et al31 tested this hypothesis in 25 patients with TLP and activation, TLP without activation, rib raising, and myofascial release in sequential sessions of 4-week intervals. Again, all OMT sessions worsened pulmonary function mildly, with the TLP with activation group having the most deleterious effect on residual volume.31 Despite the worsening objective data, all patients reported an easing of symptoms.31 None of these studies identified or determined long-term impact on the subjects.

Monitoring Management Efforts With Evidence-Based Modalities

The most successful monitoring may be diaries that chronic patients’ abilities to perform activities of daily living and exercise and that showcase reduced symptoms alongside smoke-free days.21 Conversely, efforts to link objective data such as peak flow measurements with smoking cessation have had mixed results.32,33 The holistically practicing primary care physicians’ task then is to help patients focus on daily life successes such as symptom improvement, better work capacity, and fewer exacerbations as a result of smoking cessation. Crane34 suggests managing tobacco addiction as a chronic illness requiring expert care, adding counseling to patient-individualized plans and psychosocial support that is overseen by the patient’s primary care physician. Pederson and Blumenthal35 stressed the need for primary care physicians to ask patients about tobacco use—the primary intervention a clinician can do to motivate a patient to quit. Pederson and Blumenthal35 also highlighted the US public health service “five R” clinical guidelines (relevance, risks, rewards, roadblocks, and repetition)36 for those patients who are pre-contemplative or contemplative as a useful method for helping such patients reach the conclusion to plan for and attempt cessation.
A 2005 Cochrane review included an analysis of 58 trials where treatment conditions differed in format (self help, individual counseling with person-to-person contact, proactive telephone counseling, or group counseling) and estimated an odds ratio of 1.7 (95% confidence interval, 1.4-2.0) for successful cessation with individual counseling compared to no intervention. The 2008 update for managing tobacco use and dependence by the US Agency for Healthcare Research and Quality showed that adding tobacco use satisfaction with their primary care physician and their physician's efforts to help them quit smoking. We found no studies that combined such simple sequential intervention with OMT.

Comment

Many studies have demonstrated a beneficial therapeutic effect of OMT in acute pulmonary conditions such as pneumonia. However, in the treatment of patients with chronic COPD, there has been a clear trend that symptomatic improvement occurs with mild worsening of objective pulmonary measurements of lung function. Study design may be a factor—multiple treatment protocols, small patient numbers, and overmanipulation have been postulated as potential explanations for these spirometric findings. Thus, there appears to be a symptomatic benefit from manipulative interventions that may be useful in the clinical setting.

The only treatment modality that has been shown to reduce morbidity and mortality in COPD is smoking cessation. Osteopathic principles and practice strongly support treating the person as a whole, using techniques specific to osteopathic physicians as well as more standard interventions (eg, smoking cessation). Unfortunately, the established benefit of OMT interventions to date is relatively marginal and primarily affects symptomatic improvement.

Conclusion

In the future, osteopathic manipulative medicine protocols might be designed to facilitate smoking cessation as part of a holistic, patient-centered approach to management and support. This may be the best approach and strength of osteopathic manipulative medicine for patients with COPD.

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