ABSTRACT

There are now 2 recent guidelines to help US practitioners determine the best treatment practices for chronic obstructive pulmonary disease (COPD): from the American Thoracic Society in conjunction with the European Respiratory Society, and from the Global Initiative for Chronic Obstructive Lung Disease. Based on the symptoms and stages of severity, the guidelines employ a stepwise approach to treatment. COPD is clearly best managed by a comprehensive strategy, first and foremost including smoking cessation and patient education. Bronchodilators (anticholinergics and beta agonists) are the mainstay of COPD pharmacotherapy, and long-acting versions are preferred for long-term maintenance treatment. The effects of bronchodilators are enhanced when different classes of drugs are combined and by the addition of inhaled corticosteroids. These drugs provide benefit to COPD patients not only in terms of lung function and dyspnea, but also exacerbation rates and quality of life. Pulmonary rehabilitation can be added to medications to achieve additional benefits. Most exacerbations can be managed as an outpatient by the patient (with appropriate education) in conjunction with the primary care team. Primary care practitioners play a leading role in the management of COPD at all stages of the disease. Even when patients require referral for more specialized therapies, primary care physicians may remain the “team captain.” A collaborative provider-patient relationship is important to achieve optimal health outcomes in this chronic disorder. (Adv Stud Med. 2004;4(10A):S756-S766)

Healthcare practitioners have a new guideline from the American Thoracic Society (ATS), in conjunction with the European Respiratory Society, to help determine the best treatment practices for patients with chronic obstructive pulmonary disease (COPD); the guideline is summarized in Figure 1. The updated guideline is based on and in accordance with the guidelines from the Global Initiative for Chronic Obstructive Lung Disease (GOLD), discussed elsewhere in this issue and summarized in Figure 2. This article focuses on the ATS guidelines because they are tailored to COPD treatment in the US healthcare setting (ie, approved drugs and healthcare delivery systems unique to this country). Both sets of guidelines suggest that the stages of severity may be a useful guide to determine points of initiation for each type of therapy. As with guidelines for any chronic disease, the cut points for disease staging are not precise and are influenced by the myriad other factors that determine COPD severity.

At-risk Patients

Patients considered to be “at risk” for COPD include those with a history of exposure to risk factors for COPD (namely active smoking or passive tobacco smoke, indoor or outdoor pollution, or patient occupation), and those who present with symptoms of cough, sputum production, or dyspnea. Both the
GOLD and ATS guidelines promote prevention of COPD in at-risk patients, through smoking cessation efforts and avoiding risk factors. Pollution is a more prominent risk factor in the GOLD guidelines because it considers the global population, with varying levels of risk factors depending on cultural variation. For example, wood-burning fires used for heat and cooking is a well-established risk factor for COPD worldwide, but it is rarely a problem in the United States. Nonetheless, in cities with high outdoor pollution levels, COPD patients should be encouraged not to exercise outdoors when pollution is high, and treatment regimens (dose or frequency) may need to be adjusted for pollution levels associated with an increase in symptoms. Also, those who cook or heat their homes with solid “biomass” fuels (eg, coal furnaces) should assure that adequate ventilation is provided.1

The influenza vaccine can reduce serious illness and death from influenza in COPD by about 50%.3 Thus, the ATS guidelines recommend the most recent influenza vaccination for elderly persons in accordance with national recommendations.1,4 Vaccination against pneumococcal disease is also important because it reduces bacteremia in patients with pneumonia.2,5 We recommend pneumococcal vaccine for all patients with COPD.

**SMOKING CESSATION**

Smoking cessation efforts are mandatory at all stages of disease severity, from those at risk to those with severe COPD. As shown by the Lung Health Study, smoking cessation can help to slow lung function decline (Figure 3).6 The ATS guideline states that “all smokers should be offered the best chance to treat [smoking addiction]...smoking cessation activities and support for its implementation should be integrated into the healthcare system.”1

Addressing smoking cessation can have an important impact on the patient. First, by taking an active interest in the patient’s ability and desire to quit smoking, it reinforces the patient’s feeling of trust and concern by the physician, especially as patients may feel that other healthcare providers are abandoning them because of the diagnosis of COPD. The clinician’s message is powerful. As part of the recommended strategy, ATS and GOLD guidelines and the US Public Health Service smoking cessation guidelines suggest that the practitioner (from GOLD) “strongly urge all tobacco users to quit in a clear, strong, per-
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Three types of counseling have been found to be especially effective: practical counseling, social support as part of treatment, and social support arranged outside of treatment. For clinicians with limited time, studies have shown a strong “dose-response” relationship between the intensity of tobacco dependence counseling and its effectiveness. One study showed that even a brief 3-minute period of smoking cessation counseling resulted in smoking cessation rates of 5% to 10%. Thus, as a minimum, the subject of smoking cessation should be addressed with every smoker at every visit, in a message that is personalized to each individual patient. Important elements of successful counseling are encouragement, communication of care and concern, opportunity for the patient to talk about the quitting process (why they want to quit, the challenges they are facing with quitting, level of support from their families). The information about smoking and its risks should be basic and discussed along with the benefits of quitting and well-known quitting techniques that work.

Several types of smoking cessation treatments are currently available: bupropion, nicotine gum, nicotine inhaler, nicotine nasal spray, and nicotine patch. At least 1, and preferably 2, of these treatments should be prescribed in the absence of contraindications in combination with counseling. The different smoking cessation treatments have been compared in several analyses and show success rates ranging from 2% to 16% (Table 1). A multifaceted approach most likely will offer better success rates. In the Lung Health Study, a multicenter controlled clinical trial, a combination of physician advice, group support, skills training, and nicotine replacement therapy achieved a quit rate of 35% at 1 year and a sustained quit rate of 22% at 5 years.

Smoking is an addictive activity and subject to the same power it holds over users of any other addictive substance. Therefore, relapse can easily lead to frustration on the part of the clinician and/or patient. However, relapse is common and does not reflect personal failure. As with other addictive disorders, tobacco dependence is almost always a chronic disorder that warrants long-term clinical intervention.

MANAGING STABLE COPD

PATIENT EDUCATION

Patient education is an inherent part of any treatment plan for COPD and should be practiced in all stages of disease. Treatment for COPD depends not only on disease severity but also on the patient’s adherence with prescribed treatments, which is influenced by knowledge and understanding of the appropriate therapies, willingness to apply the recommended man-

Figure 3. Smoking Cessation Slows Lung Function Decline in Mild COPD: The Lung Health Study at 11 Years

![Graph showing FEV1 (L) over years for sustained quitters, intermittent quitters, and continuous smokers.](Reproduced with permission from Anthonisen et al. Smoking and lung function of Lung Health Study participants after 11 years. Am J Respir Crit Care Med. 2002;166(5):675-679.)

Table 1. Success Rates of Smoking Cessation Interventions

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Studies Evaluated (n)</th>
<th>Absolute Increase in Cessation Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brief physician contact</td>
<td>16 (Cochrane)</td>
<td>2%</td>
</tr>
<tr>
<td>Group counseling</td>
<td>6 (Cochrane)</td>
<td>10%</td>
</tr>
<tr>
<td>Nicotine gum</td>
<td>51 (Cochrane)</td>
<td>8%</td>
</tr>
<tr>
<td>Nicotine nasal spray</td>
<td>4 (Cochrane)</td>
<td>12%</td>
</tr>
<tr>
<td>Bupropion SR (300 mg once daily)</td>
<td>7 (Cochrane)</td>
<td>10%</td>
</tr>
<tr>
<td>US DHHS = United States Department of Health and Human Services; SR = sustained release. Data from Marlow et al.</td>
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</table>
agement, cultural factors, and the availability of and access to medications. Patient education can play a role in improving self-treatment skills (eg, reducing exposure to risk factors, recognizing and managing exacerbations) and the patient’s ability to cope with COPD. However, patient education alone does not improve exercise performance or lung function. Patient education can take place in any setting (eg, office/clinic visit, home visit, pulmonary rehab programs) with the patient, not just the physician’s office. Education should be directed to caregivers as well, to continue encouragement, assist in recognizing exacerbations, and help to ensure appropriate treatment delivery. The information should be simple, practical, and appropriate to the educational and skill level of both the patients and their caregivers.

**Pharmacologic Treatment**

Managing COPD with drug treatments may require a stepwise increase in the number of recommended medications in patients with more severe disease. Because COPD is progressive, the incremental increases in treatment continue through the lifespan and are determined by the severity of the symptoms (mainly shortness of breath) and to a lesser extent to the severity of the disease. COPD treatment is unlike asthma management, which allows for “step-up” as well as “step-down” therapy. Sidebar 1 lists the currently available treatments for COPD, both pharmacologic and nonpharmacologic. Of note, none of the drugs used to manage COPD modify long-term decline in lung function; they are used to improve dyspnea and reduce frequency and severity of exacerbations. Also, not all of the drugs are US Food and Drug Administration (FDA)-approved for use in COPD. The treatments need to be maintained for long periods of time, often lifelong, unless there are significant side effects that preclude their use. Response to these treatments varies from patient to patient, so each patient requires close monitoring and evaluation of the effectiveness of therapy. The guidelines use stages to suggest treatment strategies; however the actual choice of therapy in an individual is determined by each patient’s symptoms, response to treatment, and preference.

**Bronchodilators.** Bronchodilators are considered the mainstay of COPD treatment. They are initiated as intermittent therapy (short acting, lasting from 4-6...
hours), as needed, in patients with intermittent dyspnea and mild COPD. As symptoms worsen and the disease progresses, long-acting bronchodilators, lasting 12 hours or more, are preferred. In COPD, bronchodilators are used to widen the airways, improve lung emptying, reduce lung hyperinflation, reduce dyspnea, and improve quality of life and exercise performance. The side effects with bronchodilators are well known and dose dependent. The biggest challenge with bronchodilator use is the correct use of the delivery device. Most are delivered via a metered-dose inhaler (MDI), but there will be greater use of dry powder inhalers as the chlorofluorocarbons in MDIs are phased out due to environmental concerns. If the patient is unable to use the MDI correctly, a spacer device or dry powder inhaler (DPI) should be tried. In any case, patient inhalation technique needs to be checked frequently. Because COPD patients are older, the problems with inhaler use are common and require diligent monitoring and attention. A large number of delivery devices are currently available and more are under development; images of each type and directions on their use can be found online (www.goldcopd.com/inhalers; www.ginasthma.com/inhalers/list.html). Every type of device requires patient education and monitoring, and the GOLD guidelines even recommend consideration of delivery device as part of the selection process for drug treatment.1

Table 2 lists the commonly used formulations of bronchodilators and other drugs used in the management of COPD. There are 2 classes of inhaled bronchodilators: beta agonists and anticholinergics. The most recent addition to the long-acting bronchodilators is tiotropium, a long-acting anticholinergic agent that lasts 24 hours, allowing for once-daily administration. Tiotropium has shown in several recent studies with COPD patients to result in significant improvement in lung function and reductions in exacerbations and hospitalizations compared with ipratropium (a short-acting anticholinergic) [Table 3] or salmeterol (a long-acting beta agonist [LABA]) [Figure 4].20-24

Treatment strategies for COPD are now adopting the philosophy of using several components of COPD therapy simultaneously.
Combination bronchodilators (both with short-acting and long-acting beta agonist added to short-acting anticholinergics) have shown significant benefits. For example, the combination of ipratropium and albuterol results in greater improvements in forced expiratory volume in 1 second (FEV₁) than either drug alone and 32% fewer exacerbations versus beta agonist alone (relative risk [RR] 0.68, 0.51-0.91) but not versus anticholinergic alone (RR 1.04, 0.65-1.68). Another study showed a 43% reduction in exacerbation rate with combination bronchodilator therapy versus beta agonist alone and a 64% reduction versus placebo. Therefore, even with established therapies, continual patient education has an important effect.

Theophylline is used as a second-line agent. Although it is effective in the management of COPD, it has a narrow/toxic/therapeutic ratio and more monitoring is required than with use of inhaled bronchodilators.

Inhaled corticosteroids (ICS) are not recommended for chronic use in COPD management. ICS are more frequently used as combination therapy with bronchodilators in COPD, and the only FDA-approved combination of ICS and LABA is fluticasone 250 µg plus salmeterol 50 µg administered together in a DPI. A recent meta-analysis indicates that ICS offer 24% to 30% reduction in COPD exacerbations (Figure 6). Two additional recent meta-analyses have addressed the impact of ICS on lung function deterioration. One study concluded that “ICS probably do not modify long-term decline in lung function in patients with COPD” (Figure 7). However, results from the other meta-analysis and an additional review of the literature suggest some slowing of the rate of lung function decline in COPD with ICS, particularly with high-dose regimens.

The ATS guideline acknowledges the additional benefit with combination therapies compared with
their components, especially in those with an FEV₁ of less than 50% predicted. Studies of long-term combination therapy (ICS + LABA: salmeterol + fluticasone or formoterol + budesonide) show important benefits compared with single components in frequency of exacerbations, lung function, dyspnea, use of rescue medications, and health-related quality of life; the effect on symptoms scores in these comparisons remains to be evaluated for the combination of salmeterol and fluticasone. The guidelines recommend adding an ICS to existing bronchodilator therapy, but there are now formulations of both drugs in one inhaler, which is more convenient. A study comparing salmeterol and fluticasone in a single inhaler versus either drug alone showed improved pre- and postdose lung function compared with either agent alone or placebo (Figures 8A and 8B) up to 24 weeks. Similar results were found in 12-month studies of budesonide and formoterol in a single inhaler. A recent meta-analysis of 3 clinical trials indicates significantly improved exacerbation rates with combination therapy compared with LABA alone and a trend compared with ICS alone. The authors suggest that the benefit of combination therapy (LABA + ICS) therefore appears to be additive, not synergistic. A recent, short-term study (8 weeks) comparing fluticasone and salmeterol (LABA + ICS) with ipratropium and albuterol (short-acting beta agonist + anti-cholinergic) showed that both treatments improved lung function, symptoms, and supplemental albuterol use compared with baseline. However, comparisons between the 2 treatment groups show a significantly stronger effect with fluticasone and salmeterol in numerous measures, including morning predose FEV₁, morning peak expiratory flow, 6-hour FEV₁ area under the curve, measures of dyspnea, daytime symptom scores, night-time awakenings, sleep symptoms, and albuterol-free nights. The incidence and severity of adverse events were comparable, with the exception of 9 cases (5%) of candidiasis with the fluticasone/salmeterol combination versus none with the ipratropium/ albuterol combination. Thus, although not formally recommended in all current guidelines, ICS have 2 roles in maintenance treatment of COPD—improvement of airflow (associated with improved symptoms and quality of life) and reduction in exacerbations.

One of the most common concerns with long-term ICS use is the effect on bone mineral density. Two recent population, case-control studies showed no overall increase in fracture risk with long-term ICS use, except at high doses. However, a comprehensive meta-analysis of pertinent controlled trials (peer-reviewed by a World Health Organization expert group) showed a significant effect size on bone mineral density, fracture risk, and bone markers, which varied by ICS; the ICS inducing the least deleterious effects on bone was budesonide, followed by beclomethasone and triamcinolone. We recommend assessing baseline bone mineral density (BMD) before using ICS and monitoring BMD during therapy, particularly in those taking higher doses, with severe COPD, and in older patients. There is also some evidence of a relationship between ICS use and cataracts, but the relationship is not clear; nonetheless, regular monitoring for cataracts is prudent.

PULMONARY REHABILITATION

Pulmonary rehabilitation refers to comprehensive programs designed to reduce symptoms and improve quality of life for patients with COPD, including increased participation in everyday activities. Exercise

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**Figure 7. Long-term ICS Do Not Influence FEV₁ Deterioration in COPD: A Meta-Analysis**

<table>
<thead>
<tr>
<th>Study (Reference)</th>
<th>Patients, n</th>
<th>3.1 ± 11.4 (-12.8 to 19.0)</th>
<th>-36.3 ± 22.6 (-80.6 to 8.0)</th>
<th>-12.0 ± 14.0 (-39.4 to 15.4)</th>
<th>-2.8 ± 4.03 (-11.0 to 5.4)</th>
<th>-30.0 ± 93.8 (-213.8 to 153.8)</th>
<th>-9.0 ± 6.38 (-21.5 to 3.5)</th>
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<tbody>
<tr>
<td>Vestbo et al</td>
<td>290</td>
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<td>Weir et al</td>
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<td>Lung Health Study Research Group</td>
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<td>Burge et al</td>
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ICS = inhaled corticosteroids; FEV₁ = forced expiratory volume in 1 second; COPD = chronic obstructive pulmonary disease.

training, psychosocial counseling, nutrition counseling, and patient and family education comprise the main components of pulmonary rehabilitation. A more detailed description is shown in Sidebar 2 (page S764). This type of program ideally involves several types of healthcare providers, with the primary care or pulmonary physician acting as team captain.

Well-documented benefits of pulmonary rehabilitation include improved exercise capacity, reduced dyspnea, and improved health-related quality of life. Pulmonary rehabilitation also appears to reduce the number of hospitalizations and days in hospital, as well as anxiety and depression associated with COPD. A study of long-term pulmonary rehabilitation in 200 patients (83% of whom had COPD) showed that 6 weeks of rehabilitation followed by voluntary weekly meetings resulted in improved exercise capacity and quality of life. As seen in Figure 9, the benefits extend beyond the period of training and are maintained over a period of 1 year compared with control subjects. All stages of COPD appear to benefit from this treatment.

**MANAGING EXACERBATIONS**

Acute increases in symptoms are a common part of the COPD process and include increased breathlessness, often accompanied by increased cough and sputum production and purulence. Some studies indicate that only about half of episodes of symptom changes are ever reported to the physician. Through education from their physician, patients need to understand, however, that reporting these changes is important to prevent possible hospitalization or prolonged worsening of lung function (possibly partially irreversible), which ultimately impairs quality of life. Most exacerbations can be managed as outpatients. Common causes of exacerbations include tracheobronchial infection (viral and bacterial) and worsening airflow limitation possibly related to air pollution. Healthcare providers should also recognize that increases in symptoms may be caused by pneumonia, pulmonary embolism, pneumothorax, rib fractures/chest trauma, or cardiac disease (myocardial infarction, right and/or left heart failure, or arrhythmias). Antibiotics are usually prescribed when there is sputum purulence; the most common bacteria are *Haemophilus*, *Streptococcus*, and *Moraxella*. Thus, in patients with more advanced disease (FEV₁ <50% predicted), an antibiotic that covers these organisms should be chosen. For outpatients, oral steroids should be considered for severe symptoms, particularly if

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**Figure 8A. ICS + LABA: Improved Predose Lung Function versus ICS or LABA Monotherapy**

<table>
<thead>
<tr>
<th></th>
<th>PLA</th>
<th>Salmeterol</th>
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<tr>
<td>Mean Predose FEV₁ (mL)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Time (weeks)</td>
<td>-50</td>
<td>0</td>
<td>50</td>
<td>100</td>
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<td>Endpoint</td>
<td>9%</td>
<td>17%*</td>
<td>1%</td>
<td>11%</td>
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</table>

*P < 0.001 F+S vs Placebo

**Figure 8B. ICS + LABA: Improved Postdose Lung Function versus ICS Monotherapy**

<table>
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<th>Salmeterol</th>
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<td>Postdose FEV₁ (mL)</td>
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<td>Time (weeks)</td>
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<td>100</td>
</tr>
<tr>
<td>Endpoint</td>
<td>8%</td>
<td>19%*</td>
<td>14%</td>
<td>27%*</td>
</tr>
</tbody>
</table>

ICS = inhaled corticosteroids; LABA = long-acting beta agonist; PLA = placebo; SAL = salmeterol; FP = fluticasone propionate; FEV₁ = forced expiratory volume in 1 second. Because fluticasone and salmeterol exert their benefits by different mechanisms of action, 2 different time points for FEV₁ measurement were used: predose and 2 hours postdose. Fluticasone contributes to decreases in airway obstruction due to reduced inflammation, which were assessed in the predose measurement comparing changes with the combination versus salmeterol alone. Salmeterol contributes to bronchodilation and is thus assessed by comparing 2-hour postdose between the combination and fluticasone alone. Reproduced with permission from Hanania et al. The efficacy and safety of fluticasone propionate (250 microg)/salmeterol (50 microg) combined in the Diskus inhaler for the treatment of COPD. Chest. 2003;124(3):834-843.
there is reduced airflow limitation or worsening of oxygenation.¹

SEVERE COPD

At this point in the disease process, patients should be referred to a pulmonary specialist for consideration of other treatments. However, the long-term care of the patient with severe COPD may remain with the primary care provider in conjunction with the pulmonary specialist.

Long-term oxygen therapy (LTOT) is one of the principal nonpharmacologic treatments for severe COPD; it improves survival, exercise, sleep, and cognitive performance.¹² According to the ATS guideline, there are several criteria for selecting patients eligible for LTOT. These criteria include patients whose disease is stable on a full medical regimen, with PaO₂ below 55 mm Hg (corresponding to an SaCO₂ <88%) as well as patients whose PaO₂ is 55 mm Hg to 59 mm Hg (SaCO₂ 89%), and who exhibit signs of tissue hypoxia, such as pulmonary hypertension, cor pulmonale, erythrocytosis, edema from right heart failure, or impaired mental status. Desaturation only during exercise or sleep warrants consideration of oxygen therapy specifically under those conditions. Of note, these guidelines have been adopted by most healthcare insurers as reimbursement criteria.¹ Two major studies have shown benefits with oxygen therapy, with increased survival and reduced pulmonary vascular resistance.⁴⁷,⁴⁸

Patients with advanced disease may also be evaluated for lung-volume reduction surgery (LVRS) or lung transplantation. LVRS is applied only to patients with emphysema and was created based on the theory that removing 20% to 30% of the damaged lung improves airway mechanics, expiratory flow, and symptoms.⁹ The National Emphysema Treatment Trial (NETT) was a randomized controlled trial in 1218 patients with severe emphysema who received either LVRS or medical therapy. The results showed no overall survival benefit with LVRS compared with medical
therapy, but improved exercise capacity and quality of life. In selected patients, mortality was also reduced. The investigators determined that the patients with the best outcome from LVRS were those with predominantly upper lobe emphysema and low baseline exercise capacity. However, patients with upper lobe disease and high exercise capacity and non-upper lobe emphysema and low exercise capacity also benefit with improved exercise capacity and quality of life, but do not have improved survival.50

CONCLUSION

The ATS and GOLD guidelines provide an important and useful framework for guiding therapy decisions. Based on the severity of the disease and symptoms, the guidelines employ a stepwise approach to treatment. However, while the guidelines use stages to suggest treatment strategies, the actual choice of therapy is determined by each patient's symptoms. COPD is clearly best managed by a comprehensive strategy, first and foremost including smoking cessation, patient education, and eventually pulmonary rehabilitation. Several new pharmacotherapies provide benefit to COPD patients not only in terms of lung function and dyspnea, but also exacerbation rates and quality of life.

REFERENCES

25. COMBIVENT Inhalation Aerosol Study Group. In chronic obstructive pulmonary disease, a combination of ipratropium


