Use of Bronchodilators in Chronic Obstructive Pulmonary Disease

Gregory H. Howell, MD
Gary A. Salzman, MD, FCCP

Chronic obstructive pulmonary disease (COPD) is a progressive, debilitating disorder of rising prevalence and the leading cause of morbidity and mortality in the United States. In 2000, 10 million adults in the United States reported having physician-diagnosed COPD.[1] Over the past decade, hospitalizations due to COPD have increased, and COPD deaths among women have surpassed those of men.[1] COPD is the fourth leading cause of death in the United States. Given the increasing clinical burden of COPD, it is essential for physicians to be knowledgeable about evidence-based best practices for treating patients with COPD.

Guidelines developed by the American Thoracic Society and European Respiratory Society (ATS/ERS) and by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) give direction for the diagnosis and treatment of COPD and have recently been updated.[2,3] The treatment options available to physicians and patients continue to grow. These include smoking cessation, bronchodilators, glucocorticoids, surgery, pulmonary rehabilitation, vaccination, and supplemental oxygen. Smoking cessation has been demonstrated to improve survival and slow the decline of lung function over time.[4–6] Smoking cessation is of the utmost importance in all patients with COPD who smoke and should be emphasized as the most important step in their treatment. Unfortunately, the only therapeutic agent that has been shown to have a survival benefit in COPD is supplemental oxygen, and this is in only a small subset of patients with very severe disease.[7]

An increasing number of pharmacologic agents are available for the treatment of both stable COPD and COPD exacerbations. Medical therapy is largely aimed at preventing or controlling symptoms and reducing the number and severity of exacerbations, as no medication has been shown to modify the long-term decline of lung function in COPD. Bronchodilator medications are the mainstay of pharmacotherapy at this time. This article reviews the bronchodilators currently available for the treatment of COPD, their role and appropriate use in the management of stable disease and exacerbations, and their side effects. Discussion of all treatment modalities used in COPD is beyond the scope of this article; for information regarding other evidence-based treatments for COPD, the reader is referred to the ATS/ERS and GOLD guidelines.[2,3]

TAKE HOME POINTS

- Chronic obstructive pulmonary disease (COPD) poses an increasing clinical burden in the United States.
- Bronchodilator therapy is the mainstay of pharmacotherapy for COPD and is primarily aimed at symptom control.
- Monitoring response to therapy is important, and adjustments should be made accordingly.
- Bronchodilators do not provide a mortality benefit.
- Bronchodilator therapy may improve quality of life.

DEFINITION AND CLASSIFICATION OF COPD

The ATS/ERS and GOLD guidelines similarly define COPD as a chronic disease characterized by airflow limitation that is not fully reversible, is typically progressive, and is associated with an abnormal inflammatory response of the lungs to noxious gases or particles such as those contained in cigarette smoke.[2,3] The ATS/ERS definition adds that the disease is both preventable and treatable.[2]

Treatment of COPD is driven by the degree of symptoms. Although the GOLD guideline developers

Dr. Howell is a fellow in pulmonary and critical care medicine, and Dr. Salzman is a professor of medicine; both are in the Division of Pulmonary Medicine, Department of Medicine, University of Missouri–Kansas City School of Medicine, Kansas City, MO.

Table 1. Severity Classification of Chronic Obstructive Pulmonary Disease

Stage	Characteristics
0: At risk	Normal spirometry findings Chronic symptoms (cough, sputum production)
1: Mild COPD	$FEV_1/FVC < 70\%$ $FEV_1 \geq 80\%$ predicted With or without chronic symptoms (cough, sputum production)
2: Moderate COPD	$FEV_1/FVC < 70\%$ $FEV_1 \geq 50\%$ to $< 80\%$ predicted With or without chronic symptoms (cough, sputum production)
3: Severe COPD	$FEV_1/FVC < 70\%$ $FEV_1 \geq 30\%$ to $< 50\%$ predicted With or without chronic symptoms (cough, sputum production)
4: Very severe COPD	$FEV_1/FVC < 70\%$ $FEV_1 < 30$ predicted or $FEV_1 < 50\%$ predicted plus chronic respiratory failure

Note: Classification based on postbronchodilator FEV_1.

Adapted from Global Initiative for Chronic Obstructive Lung Disease (GOLD), World Health Organization (WHO), National Heart, Lung and Blood Institute (NHLBI). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Bethesda (MD): 2005. Available at www.goldcopd.com. Accessed 18 Aug 2006.

COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity.

note an "imperfect relationship" between the extent of airflow limitation and presence/extent of symptoms, they recommend a simple scheme for classifying disease severity based on spirometry findings (**Table 1**), acknowledging that the staging tool is meant mainly to be educational.[3] Per the GOLD guidelines, at stage 1 (mild COPD), a person may not be aware of having abnormal lung function.[3] Most affected individuals do not seek medical attention until their disease has progressed to stage 2 (moderate COPD), which is characterized by dyspnea or an exacerbation. In stage 3 (severe COPD), the patient experiences increased shortness of breath and repeated exacerbations, and in stage 4 (very severe COPD), quality of life is significantly decreased and exacerbations may be severe enough to cause death.

BRONCHODILATOR USE IN COPD

Patients with COPD, by definition, have poor reversibility in forced vital capacity and forced expiratory volume in 1 second (FEV_1) on spirometry after administration of a single dose of a bronchodilator. However, this should not discourage the use of these agents in patients with COPD. Other parameters, including residual volume and inspiratory capacity, can improve.[8,9] Additionally, bronchodilators can be effective in improving dyspnea, frequency of exacerbations, and quality of life in patients with COPD. **Table 2** summarizes the outcomes of bronchodilators and other medications commonly used to treat patients with COPD.

Currently, there are 3 main types of bronchodilators used in the management of COPD: inhaled β_2-adrenergic agonists (both short- and long-acting), inhaled anticholinergic agents (both short- and long-acting), and systemic phosphodiesterase inhibitors (methylxanthines). All bronchodilators, in general, have different meaningful clinical effects. For example, a 1999 study attempted to determine which spirometric measures correlate best with exercise tolerance and exertional dyspnea in patients with stable COPD taking acute high-dose ipratropium (a short-acting anticholinergic agent).[10] This study found that resting spirometry improvements had poor correlation with exercise tolerance and dyspnea. A better correlation was seen with inspiratory capacity and vital capacity. The best correlation was found when combining these parameters in patients taking ipratropium in this crossover study.

Decisions regarding which bronchodilator to use should be based on current guidelines, whether or not a specific drug is available to an individual patient, and the individual patient's response to a particular agent. According to the GOLD guidelines, a short-acting bronchodilator should be administered as needed for symptom control in patients with mild COPD.[3] As disease severity increases, so does the intensity of treatment. Short-acting β_2 agonists can be used in conjunction with the other classes of bronchodilators (including long-acting β_2 agonists) as well as with inhaled glucocorticoids.[3] In patients with moderate COPD, a long-acting bronchodilator should be instituted. This can be a long-acting β_2 agonist or a long-acting anticholinergic agent.[3] Short-acting β_2 agonists can still be used in addition to these longer-acting medicines when needed. In summary, short-acting β_2 agonists should be used as needed for mild COPD, and long-acting β_2 agonists or long-acting anticholinergic agents can be used for more persistent symptoms, as are usually seen in more severe stages of COPD.[2] The **Figure** summarizes the ATS/ESR recommended approach to using bronchodilators for the treatment of stable COPD.

It is critical for patients to be instructed in the correct use and administration of prescribed bronchodilator medications initially and at subsequent visits. In

Table 2. Effects of Commonly Used Medications on Important Clinical Outcomes in Chronic Obstructive Pulmonary Disease

	FEV_1	Lung Volume	Dyspnea	HRQoL	AE	Exercise Endurance	Disease Modifier by FEV_1	Mortality	Side Effects
Short-acting β_2 agonists	Yes (A)	Yes (B)	Yes (A)	NA	NA	Yes (B)	NA	NA	Some
Ipratropium bromide	Yes (A)	Yes (B)	Yes (A)	No (B)	Yes (B)	Yes (B)	No	NA	Some
Long-acting β_2 agonists	Yes (A)	Yes (A)	Yes (A)	Yes (A)	Yes (A)	Yes (B)	No	NA	Minimal
Tiotropium	Yes (A)	Yes (A)	Yes (A)	Yes (A)	Yes (A)	Yes (B)	NA	NA	Minimal
Inhaled corticosteroids	Yes (A)	NA	Yes (B)	Yes (A)	Yes (A)	NA	No	NA	Some
Theophylline	Yes (A)	Yes (B)	Yes (A)	Yes (B)	NA	Yes (B)	NA	NA	Important

Note: Letters in parentheses indicate level of evidence grades as per the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guideline. A = randomized trials and abundant evidence; B = randomized clinical trials but limited data; C = nonrandomized trials; and D = panel consensus.

Adapted with permission from Celli BR, MacNee W. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper [published erratum appears in Eur Respir J 2006;27:242]. ATS/ERS Task Force. Eur Respir J 2004;23:937.

AE = exacerbation of COPD; FEV_1 = forced expiratory volume in 1 second; HRQoL = health-related quality of life; NA = evidence not available.

addition, education about COPD in general as well as the goals of therapy, adverse effects of prescribed medications, and the importance of smoking cessation should be provided.

β_2 Agonists

The β_2-adrenergic receptor, when stimulated in the airways, causes smooth muscle relaxation and improved lung emptying. β_2 Agonists have also been found to decrease central respiratory drive and to improve the sensation of breathlessness.[11] Although β_2 agonists have been shown to increase diaphragmatic contractility in rats,[12] a study evaluating the effect of β_2 agonists on diaphragmatic contractility in patients with COPD found no effect.[13] Albuterol has been shown to improve mucociliary clearance,[14] which may be of particular importance in a disease with impaired mucociliary clearance such as COPD.[15]

Short-acting β_2 agonists. Short-acting β_2 agonists are primarily indicated for acute symptom control and treatment of exacerbations. The rapid onset of action of these agents makes them desirable for this use. Short-acting β_2 agonists are not recommended for maintenance therapy. A randomized controlled crossover study evaluating the use of a short-acting β_2 agonists on a scheduled versus an as-needed basis in stable COPD found no benefit to the scheduled regimen in this patient population.[16] Another study showed that the effect of a scheduled short-acting β_2 agonist (albuterol) is additive to the effect of a short-acting anticholinergic agent (ipratropium) in stable COPD; however, while this study showed that pulmonary function improved, symptom scores were unchanged.[17]

Short-acting β_2 agonists that are currently available in the United States include albuterol, levalbuterol, metaproterenol, pirbuterol, and terbutaline. Albuterol, metaproterenol, and terbutaline are available in systemic preparations, but inhaled formulations are preferred due to the increased risk of toxicity of systemic agents. The main toxicities listed in the package inserts for these agents all relate to the stimulation of the β_2 receptor and include nervousness, tachycardia, palpitations, tremor, headache, gastrointestinal symptoms, and dizziness. Levalbuterol, the R-isomer of racemic albuterol, produces bronchodilation without the tachycardia seen with racemic albuterol. A recent study in patients with COPD found no advantage of levalbuterol over albuterol in COPD patients with regard to duration of bronchodilation or degree of tachycardia.[18] Due to the added expense of levalbuterol, there appears to be little role for this medication in the management of most patients with COPD, but its use could be considered in patients with life-threatening arrhythmias or other coexisting serious cardiac conditions.

Inhaled short-acting β_2 agonists can be administered by metered dose inhaler (MDI) with a spacer device or via a nebulizer. MDIs have the benefit of being economical and convenient, but improper technique can blunt their effectiveness. Dry powder inhalers and pressurized MDIs are replacing chlorofluorocarbon-containing inhalers due to new environmental laws. Nebulizers require less patient education and coordination but are more expensive and demand the teaching time of a respiratory therapist. The decision of which mechanism to use should be based on the severity of symptoms and the patient's ability to administer the drug. The use of intermittent positive pressure breathing (IPPB) to

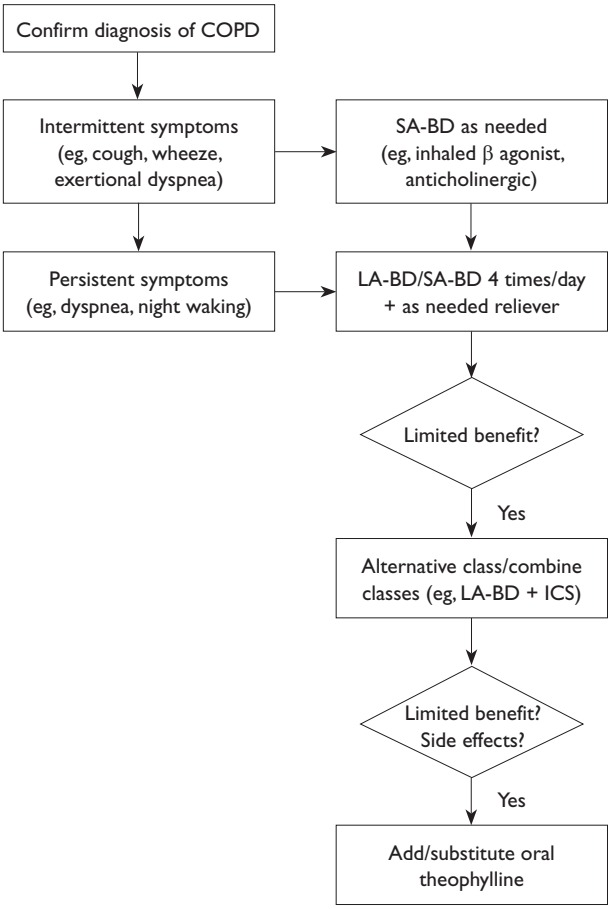

Figure. American Thoracic Society/European Respiratory Society (ATS/ERS) recommended approach to pharmacologic treatment of stable chronic obstructive pulmonary disease (COPD). ICS = inhaled corticosteroid; LA-BD = long-acting bronchodilator; SA-BD = short-acting bronchodilator. (Adapted with permission from Celli BR, MacNee W, Agusti A, et al. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper Eur Respir J 2004;23:9326.)

deliver bronchodilators is not recommended; IPPB is more expensive and offers no benefits over compressed air nebulization.

During COPD exacerbations, short-acting β_2 agonists should be administered in the standard dose every 2 to 4 hours.[2,3] A recent outcomes study evaluated albuterol 2.5 mg versus 5 mg and found no significant difference between the 2 doses.[19] Short-acting β_2 agonists are sometimes given in conjunction with short-acting anticholinergic agents, depending on the severity of the exacerbation.[2,3] This drug combination can be administered to patients who require endotracheal intubation and mechanical ventilation, with delivery through either an MDI with an adapter or a nebulizer.

Adverse effects associated with short-acting β_2 agonists include tachycardia, arrhythmias, hypokalemia, tremor, throat irritation, bad taste, paradoxical bronchospasm, and cough. Interestingly, these agents can cause a transient decrease in arterial oxygen content, which is thought to be due to activation of the β_2 receptors on the pulmonary arteries causing perfusion of poorly ventilated areas with resultant worsening of the ventilation/perfusion mismatch. This is thought to be clinically insignificant.[20]

Long-acting β_2 agonists. Unlike short-acting β_2 agonists, long-acting β_2 agonists should not be used to control symptoms or to treat exacerbations (ie, as rescue medications) but are intended for maintenance therapy. According to the GOLD guidelines, patients with more symptomatic disease (moderate COPD and beyond by the severity classification in Table 1) should be treated with a long-acting β_2 agonist (or with a long-acting anticholinergic agent).[3] Patients who are having symptoms can take short-acting β_2 agonists in addition to their maintenance long-acting β_2 agonists with some benefit.[21] These agents do not appear to increase tolerance to short-acting β_2 agonists.[22] Long-acting β_2 agonists have been shown to improve spirometric values,[8,23–25] symptoms,[8,25,26] and health-related quality of life.[24–26] They also may delay exacerbations.[26]

The long-acting β_2 agonists currently available in the United States are salmeterol (given in 50 μg doses) or formoterol (given in 12 μg doses). These medications are administered every 12 hours. Both agents are inhaled as dry powder without propellant, instead of via conventional MDI devices. Salmeterol is also available in combination with fluticasone, an inhaled glucocorticoid, at varied doses.

The safety of long-acting β_2 agonists is still debated. Because these drugs can cause tachycardia and hypokalemia, cardiovascular side effects are the most feared. Patients taking these medications typically have a high disease burden and several cardiovascular risk factors (eg, smoking), making it difficult to interpret safety data. The Salmeterol Multicenter Asthma Research Trial (SMART) showed that salmeterol monotherapy in asthma patients was associated with a small but statistically significant increase in asthma- and respiratory-related deaths.[27] Pooled data from 7 separate studies evaluating the cardiovascular safety of salmeterol in COPD patients showed no significant increase in cardiovascular events in patients treated with salmeterol compared with those taking placebo.[28] However, a smaller study performed in higher-risk patients with preexisting mild-to-moderate arrhythmias and hypoxemia showed that salmeterol and formoterol may have

an adverse effect on the myocardium.[29] Other adverse effects associated with long-acting β_2 agonists include paradoxical bronchospasm, pharyngitis, tremor, and urticaria. Like the short-acting β_2 agonists, these drugs can also cause transient but clinically insignificant decreases in arterial blood oxygen content. Both salmeterol and formoterol are contraindicated in life-threatening or acutely worsening asthma.

Anticholinergic Agents

The only anticholinergic medications currently available for COPD treatment are inhaled agents: ipratropium (short-acting) and tiotropium (long-acting). Because the airways are under both sympathetic and parasympathetic control, it is intuitive that bronchodilation can be achieved not only by stimulating the β_2-adrenergic receptor but also by inhibiting the muscarinic receptor. Inhaled anticholinergic agents—competitive inhibitors of acetylcholine at the airway muscarinic receptors—are effective in relieving cholinergic-mediated bronchoconstriction and have an important role in the management of COPD. However, these agents lack the effect on mucociliary clearance that β_2 agonists have.[14,30] Ipratropium and tiotropium have a positively charged quaternary amine structure and only limited systemic absorption.

Ipratropium. Ipratropium is recommended for maintenance therapy as well as for treatment of COPD exacerbations. The drug is available for use via an MDI or a nebulizer and has been distributed in combination with albuterol. Ipratropium has been shown to improve pulmonary function and breathlessness in COPD patients when stable and during acute exacerbations.[31,32] It has also been shown to improve the perceived quality of sleep, mean nightly arterial oxygen content, and rapid eye movement sleep, particularly in patients with poor sleep quality.[33] There is also evidence that ipratropium taken on a regular basis can improve health-related quality of life.[26]

In most studies, the combination of inhaled ipratropium and albuterol is more effective than either agent alone.[17,34,35] A post hoc cost-effectiveness study of 2 trials comparing the efficacy of ipratropium plus albuterol with that of either agent alone in COPD patients suggests that ipratropium alone and combination ipratropium/albuterol are more cost-effective than albuterol alone.[36] Depending on disease severity, any of these therapeutic choices can be used in the management of COPD.[3]

When used in treating exacerbations of COPD, ipratropium usually is given in combination with albuterol every 2 to 4 hours, if albuterol alone is not effective.[3] As is the case with the short-acting β_2 agonists, the decision whether to administer these drugs with an MDI or a nebulizer should be made on a case-by-case basis, depending on whether or not the patient is mechanically ventilated and the stability, coordination, mental status, and reliability of the patient.

The most common side effect associated with ipratropium is dry mouth. Other reactions include paradoxical bronchospasm, narrow-angle glaucoma, oral irritation, cough, nausea, and rash. When administered via an MDI, ipratropium is contraindicated in patients with hypersensitivity to lecithin, soybeans, or peanuts.

Tiotropium. Tiotropium has recently been introduced as a longer-acting inhaled anticholinergic bronchodilator with the same mechanism of action as ipratroprium. Tiotropium demonstrates prolonged binding to the muscarinic receptors, which is responsible for its longer duration of action.[37,38] Like the long-acting β_2 agonists, tiotropium is typically initiated as maintenance therapy in patients with moderate COPD.[3] It is not indicated for treatment of acute bronchospasm (rescue) or acute exacerbations. Furthermore, there are no data on the concomitant use of short-acting anticholinergics and tiotropium. Therefore, this practice is not advisable. Tiotropium is administered once daily at a dose of 18 μg via dry powder inhalation; there is no propellent used in the delivery device.

Tiotropium has been shown to improve spirometric values,[9,39–42] dyspnea,[42,43] health status,[43] frequency of exacerbations,[44] exercise tolerance,[42,45] and hyperinflation.[9,42] Tiotropium given once daily appears to be superior to ipratropium given 4 times daily for improving pulmonary function tests and decreasing the use of rescue albuterol.[46] In a 6-month study comparing tiotropium to salmeterol, patients in the tiotropium-treated group had a significantly higher FEV_1 than those in the salmeterol group.[41] Both tiotropium and salmeterol improved quality of life and dyspnea to a similar extent.

The most common adverse effect associated with tiotropium is dry mouth. Other anticholinergic side effects seen include glaucoma, constipation, urinary retention, and increased heart rate.

Methylxanthines

This class of bronchodilators includes theophylline (an oral agent) and aminophylline (available for oral or intravenous use). Although methylxanthines have a role in the treatment of COPD, inhaled bronchodilators are preferred due to the lower risk of systemic side effects with inhaled versus systemic agents.[3] The ATS/ERS guidelines suggest using these agents only if patients have limited benefit or side effects from the inhaled agents.[2] Nevertheless, theophylline remains in

common use in certain practice settings, perhaps due to its inexpensive cost and physician familiarity with the drug. The exact mechanism of action of these agents is not fully understood and likely involves several different pathways. One of the mechanisms is phosphodiesterase inhibition, which eventually causes bronchodilation through the increase in cyclic adenosine monophosphate. There also appears to be an anti-inflammatory role for these medications. Theophylline has been shown to reduce neutrophil populations, neutrophil chemotaxis, and neutrophil recruitment in patients with COPD.[47] A novel class of phosphodiesterase-4 inhibitors is currently being studied but is not available. These agents (cilomilast and roflumilast) show promise for decreasing exacerbations of COPD and maintaining pulmonary function.[48,49]

In a study of theophylline for maintenance therapy in patients with COPD, results were mixed. There was a trend toward FEV_1 improvement, but statistical significance was not reached. Older patients had improvement in chest tightness, and younger patients had improved peak flow readings. It should be noted that patients with chronic heart and kidney disease were excluded, and there was no placebo control group in this study.[50] Patients with stable COPD who have been treated with long-acting preparations of theophylline have shown an improvement in FEV_1.[47,51] A trial with patients given salmeterol, theophylline, or a combination of the 2 drugs showed that combination therapy was significantly more effective than either agent alone in improving pulmonary function, dyspnea, albuterol use, and health-related quality of life.[52]

Methylxanthines are available in several different preparations, but most studies have been done with long-acting formulations. Dosing can be quite problematic because of the narrow therapeutic window of theophylline. Conventionally, theophylline levels between 10 and 20 μg/mL have been considered therapeutic and levels greater than 20 μg/mL considered toxic. Theophylline was shown to have an effect on inflammatory parameters at lower concentrations of 8 to 15 μg/mL, and this may translate to clinical benefit.[48]

During exacerbations of COPD, addition of an oral or intravenous methylxanthine can be considered but requires careful monitoring of serum concentrations.[3] Theophylline is used in selected cases for acute exacerbations but is controversial. A meta-analysis of randomized trials shows that the side effects of these agents may outweigh the benefits in the setting of an exacerbation.[53]

Prior to the administration of a methylxanthine, a thorough review of the patient's current medications and medical history should be undertaken to avoid drug interactions or adverse reactions. Metabolism is primarily by the cytochrome P-450 system, but 10% of drug excretion is through the urine, so extra caution is needed in patients with kidney or liver insufficiency. As these drugs are similar to the dietary xanthenes caffeine and theobromine, adverse reactions are similar and include nausea, vomiting, headache, and insomnia when levels are in the therapeutic range. At toxic levels, however, one can experience cardiac arrhythmias and seizures, which can be lethal.[54] These cautions may change with the new phosphodiesterase-4 inhibitors (ie, roflumilast and cilomilast).

CONCLUSION

COPD is a serious, life-limiting illness that is of increasing clinical significance due to its rising numbers. Bronchodilators will produce modest improvements in the symptoms of COPD, but most patients will continue to have dyspnea despite maximal therapy. Patients need to understand that bronchodilator therapy will rarely completely eliminate symptoms. The individual patient response to bronchodilator therapy will be variable, so it is important to monitor symptoms, lung function, and adverse events to determine optimal therapy. Smoking cessation is the only therapy in COPD that modifies the long-term decline in lung function and should take priority over bronchodilator therapy. Patients with COPD who continue to smoke will continue to have an accelerated decline in lung function despite bronchodilator therapy. COPD not only takes years away from life but also takes life away from years. Although it cannot prolong life, bronchodilator therapy may improve the quality of life for patients with COPD. **HP**

REFERENCES

1. Mannino DM, Homa DM, Akinbami LJ, et al. Chronic obstructive pulmonary disease surveillance—United States, 1971–2000. MMWR Surveill Summ 2002;51:1–16.
2. Celli BR, MacNee W. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper [published erratum appears in Eur Respir J 2006;27:242]. ATS/ERS Task Force. Eur Respir J 2004;23:932–46.
3. Global Initiative for Chronic Obstructive Lung Disease (GOLD), World Health Organization (WHO), National Heart, Lung and Blood Institute (NHLBI). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Bethesda (MD): 2005. Available at www.goldcopd.com. Accessed 18 Aug 2006.
4. Anthonisen NR, Connett JE, Murray RP. Smoking and

lung function of Lung Health Study participants after 11 years. Am J Respir Crit Care Med 2002;166:675–9.
5. Wise RA, Kanner RE, Lindgren P, et al. The effect of smoking intervention and an inhaled bronchodilator on airways reactivity in COPD: the Lung Health Study. Lung Health Study Research Group. Chest 2003;124:449–58.
6. Anthonisen NR, Skeans MA, Wise RA, et al. The effects of a smoking cessation intervention on 14.5-year mortality: a randomized clinical trial. Lung Health Study Research Group. Ann Intern Med 2005;142:233–9.
7. Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive lung disease: a clinical trial. Nocturnal Oxygen Therapy Trial Group. Ann Intern Med 1980;93:391–8.
8. Ramirez-Venegas A, Ward J, Lentine T, Mahler DA. Salmeterol reduces dyspnea and improves lung function in patients with COPD. Chest 1997;112:336–40.
9. Celli B, ZuWallack R, Wang S, Kesten S. Improvement in resting inspiratory capacity and hyperinflation with tiotropium in COPD patients with increased static lung volumes. Chest 2003;124:1743–8.
10. O'Donnell DE, Lam M, Webb KA. Spirometric correlates of improvement in exercise performance after anticholinergic therapy in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1999;160:542–9.
11. Pino-Garcia JM, Garcia-Rio F, Gomez L, et al. Short-term effects of inhaled beta-adrenergic agonist on breathlessness and central inspiratory drive in patients with nonreversible COPD Chest 1996;110:637–41.
12. van der Heijden HF, Dekhuijzen PN, Folgering H, van Herwaarden CL. Inotropic effects of salbutamol on rat diaphragm contractility are potentiated by foreshortening. Am J Respir Crit Care Med 1997;155:1072–9.
13. Hatipoglu U, Laghi F, Tobin MJ. Does inhaled albuterol improve diaphragmatic contractility in patients with chronic obstructive pulmonary disease? Am J Respir Crit Care Med 1999;160:1916–21.
14. Kobayashi K, Wanner A. Mucociliary clearance and ciliary activity. In: Chung, editor. Pharmacology of the respiratory tract. New York: Dekker; 1993:621–54.
15. Wanner A. Clinical aspects of mucociliary transport. Am Rev Respir Dis 1977;116:73–125.
16. Cook D, Guyatt G, Wong E, et al. Regular versus as-needed short-acting inhaled beta-agonist therapy for chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2001;163:85–90.
17. In chronic obstructive pulmonary disease, a combination of ipratropium and albuterol is more effective than either agent alone. An 85-day multicenter trial. COMBIVENT Inhalation Aerosol Study Group. Chest 1994;105:1411–9.
18. Datta D, Vitale A, Lahiri B, ZuWallack R. An evaluation of nebulized levalbuterol in stable COPD. Chest 2003; 124:844–9.
19. Nair S, Thomas E, Pearson SB, Henry MT. A randomized controlled trial to assess the optimal dose and effect of nebulized albuterol in acute exacerbations of COPD. Chest 2005;128:48–54.
20. Khoukaz G, Gross NJ. Effects of salmeterol on arterial blood gases in patients with stable chronic obstructive pulmonary disease. Comparison with albuterol and ipratropium. Am J Respir Crit Care Med 1999;160:1028–30.
21. Cazzola M, Di Lorenzo G, Di Perna F, et al. Additive effects of salmeterol and fluticasone or theophylline in COPD. Chest 2000;118:1576–81.
22. Nelson HS, Berkowitz RB, Tinkelman DA, et al. Lack of subsensitivity to albuterol after treatment with salmeterol in patients with asthma. Am J Respir Crit Care Med 1999;159(5 Pt 1):1556–61.
23. Weiner P, Magadle R, Berar-Yanay N, et al. The cumulative effect of long-acting bronchodilators, exercise, and inspiratory muscle training on the perception of dyspnea in patients with advanced COPD. Chest 2000; 118:672–8.
24. Jones PW, Bosh TK. Quality of life changes in COPD patients treated with salmeterol. Am J Respir Crit Care Med 1997;155:1283–9.
25. Boyd G, Morice AH, Pounsford JC, et al. An evaluation of salmeterol in the treatment of chronic obstructive pulmonary disease (COPD) [published erratum appears in Eur Respir J 1997;10:1696]. Eur Respir J 1997;10:815–21.
26. Mahler DA, Donohue JF, Barbee RA, et al. Efficacy of salmeterol xinafoate in the treatment of COPD. Chest 1999;115:957–65.
27. Nelson HS, Weiss ST, Bleecker ER, et al. The Salmeterol Multicenter Asthma Research Trial: a comparison of usual pharmacotherapy for asthma or usual pharmacotherapy plus salmeterol [published erratum appears in Chest 2006;129:1393]. SMART Study Group. Chest 2006; 129:15–26.
28. Ferguson GT, Funck-Brentano C, Fischer T, et al. Cardiovascular safety of salmeterol in COPD. Chest 2003; 123:1817–24.
29. Cazzola M, Imperatore F, Salzillo A, et al. Cardiac effects of formoterol and salmeterol in patients suffering from COPD with preexisting cardiac arrhythmias and hypoxemia. Chest 1998;114:411–5.
30. Hasani A, Toms N, Agnew JE, et al. The effect of inhaled tiotropium bromide on lung mucociliary clearance in patients with COPD. Chest 2004;125:1726–34.
31. Karpel JP. Bronchodilator responses to anticholinergic and beta-adrenergic agents in acute and stable COPD. Chest 1991;99:871–6.
32. Karpel JP, Pesin J, Greenberg D, Gentry E. A comparison of the effects of ipratropium bromide and metaproterenol sulfate in acute exacerbations of COPD. Chest 1990;98:835–9.
33. Martin RJ, Bartelson BL, Smith P, et al. Effect of ipratropium bromide treatment on oxygen saturation and sleep quality in COPD. Chest 1999;115:1338–45.
34. Levin DC, Little KS, Laughlin KR, et al. Addition of anticholinergic solution prolongs bronchodilator effect of beta 2 agonists in patients with chronic obstructive

pulmonary disease. Am J Med 1996;100:40S–48S.
35. Campbell S. For COPD a combination of ipratropium bromide and albuterol sulfate is more effective than albuterol alone. Arch Intern Med 1999;159:156–60.
36. Friedman M, Serby CW, Menjoge SS, et al. Pharmacoeconomic evaluation of a combination of ipratropium plus albuterol compared with ipratropium alone and albuterol alone in COPD. Chest 1999;115:635–41.
37. Disse B, Reichl R, Speck G, et al. Ba 679 BR, a novel long-acting anticholinergic bronchodilator. Life Sci 1993;52: 537–44.
38. Takahashi T, Belvisi MG, Patel H, et al. Effect of Ba 679 BR, a novel long-acting anticholinergic agent, on cholinergic neurotransmission in guinea pig and human airways. Am J Respir Crit Care Med 1994;150(6 Pt 1):1640–5.
39. Littner MR, Ilowite JS, Tashkin DP, et al. Long-acting bronchodilation with once-daily dosing of tiotropium (Spiriva) in stable chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2000;161(4 Pt 1):1136–42.
40. Casaburi R, Briggs DD Jr, Donohue JF, et al. The spirometric efficacy of once-daily dosing with tiotropium in stable COPD: a 13-week multicenter trial. The US Tiotropium Study Group. Chest 2000;118:1294–302.
41. Donohue JF, van Noord JA, Bateman ED, et al. A 6-month, placebo-controlled study comparing lung function and health status changes in COPD patients treated with tiotropium or salmeterol. Chest 2002;122:47–55.
42. O'Donnell DE, Fluge T, Gerken F, et al. Effects of tiotropium on lung hyperinflation, dyspnoea and exercise tolerance in COPD. Eur Respir J 2004;23:832–40.
43. Vincken W, van Noord JA, Greefhorst AP, et al. Improved health outcomes in patients with COPD during 1 yr's treatment with tiotropium. Dutch/Belgian Tiotropium Study Group. Eur Respir J 2002;19:209–16.
44. Niewoehner DE, Rice K, Cote C, et al. Prevention of exacerbations of chronic obstructive pulmonary disease with tiotropium, a once-daily inhaled anticholinergic bronchodilator: a randomized trial. Ann Intern Med 2005; 143:317–26.
45. Maltais F, Hamilton A, Marciniuk D, et al. Improvements in symptom-limited exercise performance over 8 h with once-daily tiotropium in patients with COPD. Chest 2005;128:1168–78.
46. van Noord JA, Bantje TA, Eland ME, et al. A randomised controlled comparison of tiotropium and ipratropium in the treatment of chronic obstructive pulmonary disease. The Dutch Tiotropium Study Group. Thorax 2000;55:289–94.
47. Culpitt SV, de Matos C, Russell RE, et al. Effect of theophylline on induced sputum inflammatory indices and neutrophil chemotaxis in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2002;165:1371–6.
48. Rabe KF, Bateman ED, O'Donnell D, et al. Roflumilast —an oral anti-inflammatory treatment for chronic obstructive pulmonary disease: a randomised controlled trial. Lancet 2005;366:563–71.
49. Rennard SI, Schachter N, Strek M, et al. Cilomilast for COPD: results of a 6-month, placebo-controlled study of a potent, selective inhibitor of phosphodiesterase 4. Chest 2006;129:56–66.
50. Chen CY, Yang KY, Lee YC, Perng PP. Effect of oral aminophylline on pulmonary function improvement and tolerability in different age groups of COPD patients. Chest 2005;128:2088–92.
51. Rossi A, Kristufek P, Levine BE, et al. Comparison of the efficacy, tolerability, and safety of formoterol dry powder and oral, slow-release theophylline in the treatment of COPD. Formoterol in Chronic Obstructive Pulmonary Disease (FICOPD) II Study Group. Chest 2002;121:1058–69.
52. ZuWallack RL, Mahler DA, Reilly D, et al. Salmeterol plus theophylline combination therapy in the treatment of COPD. Chest 2001;119:1661–70.
53. Barr RG, Rowe BH, Camargo CA Jr. Methylxanthines for exacerbations of chronic obstructive pulmonary disease: meta-analysis of randomised trials [published erratum appears in BMJ 2003;327:919]. BMJ 2003;327:643.
54. Shannon M. Predictors of major toxicity after theophylline overdose. Ann Intern Med 1993;119:1161–7.

Copyright 2006 by Turner White Communications Inc., Wayne, PA. All rights reserved.