

# Management of the Symptomatic Patient

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*Chronic obstructive pulmonary disease (COPD) is both preventable and treatable. There has been a significant reduction in premature morbidity and mortality from heart disease and stroke, the number 1 and 3 killers in the United States, respectively, largely because of efforts to increase both clinician and public awareness of these diseases. Early and aggressive management of COPD has not yet reached the same level. Primary care professionals are in the forefront in the early detection, prevention, and treatment of this serious national health problem.*

The majority of patients with or at risk for chronic obstructive pulmonary disease (COPD) do not seek medical care until they either acknowledge that the presence of dyspnea is interfering with their lifestyle or they present to a health care professional at the time of a COPD exacerbation. By the time dyspnea on mild exertion occurs, ~50% of lung capacity is already lost. At this point, other cardinal symptoms of COPD (cough, mucus production, and wheeze) may be retrospectively acknowledged on careful questioning by the health care provider. It is often determined at the time of exacerbation that the symptoms that brought the patient to the office or emergency department have been present for a long time, and this presentation is a worsening of those chronic symptoms.

The National Lung Health Education Program recommends that all patients ≥45 years of age who are current or former smokers or anyone of any age with one of the cardinal symptoms of COPD—chronic cough, mucus production, dyspnea on mild exertion, or wheeze—should have their

## KEY POINT

**Patients do not usually seek treatment until 50% of their lung function is lost.**

**Patients who stop smoking will not regain their lost lung function but will revert to a slower rate of decline similar to that of a nonsmoker, avoiding premature disability and death.**

lung function tested with office spirometry (1). When spirometry confirms that a patient has COPD, a thorough assessment of the patient must be performed to determine if he or she is symptomatic. The recently published Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines for treatment of COPD recommend that patients with symptomatic COPD should be treated early and aggressively with smoking modulation, first-line bronchodilator therapy (inhaled anti-

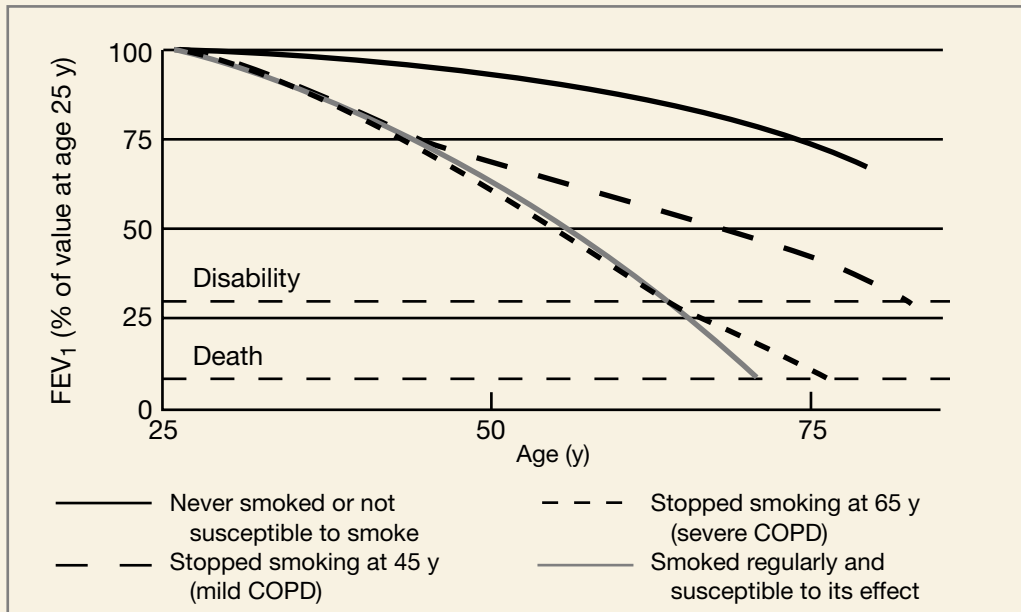
TABLE I.	TREATMENT BASED ON SEVERITY OF COPD AS DEFINED BY THE GOLD CRITERIA	
Stage	Characteristics	Recommended treatment
<b>ALL</b>		<ul style="list-style-type: none"> <li>● Avoidance of risk factors</li> <li>● Influenza vaccination</li> </ul>
0: At risk	<ul style="list-style-type: none"> <li>● Chronic symptoms (cough, sputum)</li> <li>● Exposure to risk factors</li> <li>● Normal spirometry</li> </ul>	
I: Mild COPD	<ul style="list-style-type: none"> <li>● FEV<sub>1</sub>/FVC &lt; 70%</li> <li>● FEV<sub>1</sub> ≥ 80% predicted</li> <li>● With or without symptoms</li> </ul>	<ul style="list-style-type: none"> <li>● Short-acting bronchodilator when needed</li> </ul>
II: Moderate COPD	<p><b>IIA:</b></p> <ul style="list-style-type: none"> <li>● FEV<sub>1</sub>/FVC &lt; 70%</li> <li>● 50% ≤ FEV<sub>1</sub> &lt; 80% predicted</li> <li>● With or without symptoms</li> </ul> <p><b>IIB:</b></p> <ul style="list-style-type: none"> <li>● FEV<sub>1</sub>/FVC &lt; 70%</li> <li>● 30% ≤ FEV<sub>1</sub> &lt; 50% predicted</li> <li>● With or without symptoms</li> </ul>	<ul style="list-style-type: none"> <li>● Regular treatment with one or more bronchodilators</li> <li>● Rehabilitation</li> <li>● Inhaled glucocorticosteroids if significant symptoms and lung function response</li> <li>● Regular treatment with one or more bronchodilators</li> <li>● Rehabilitation</li> <li>● Inhaled glucocorticosteroids if significant symptoms and lung function response or if repeated exacerbations</li> </ul>
III: Severe COPD	<ul style="list-style-type: none"> <li>● FEV<sub>1</sub>/FVC &lt; 70%</li> <li>● FEV<sub>1</sub> &lt; 30% predicted or presence of respiratory failure or right ventricular failure</li> </ul>	<ul style="list-style-type: none"> <li>● Regular treatment with one or more bronchodilators</li> <li>● Inhaled glucocorticosteroids if significant symptoms and lung function response or if repeated exacerbations</li> <li>● Treatment of complications</li> <li>● Rehabilitation</li> <li>● Long-term oxygen therapy if respiratory failure</li> <li>● Consider surgical treatments</li> </ul>

FEV<sub>1</sub> = forced expiratory volume in 1 second; FVC = forced vital capacity; GOLD = Global Initiative for Chronic Obstructive Lung Disease.

cholinergics ± beta-2 agonist), a trial of inhaled corticosteroids (ICS) only after bronchodilation has been maximized, and nonpharmacologic interventions when needed (Table I) (2).

This discussion is limited to the treatment of symptomatic patients identified by spirometry and history to have COPD. Stratification of COPD on the basis of lung function (spirometry) and symp-

toms (activities of daily living or health status) is of paramount importance as the GOLD guidelines base a stepwise approach to therapy on these factors (Table I). Both pharmacologic and nonpharmacologic modalities are available to optimally treat patients with COPD early in the course of the disease. The prerequisite for this statement is that the disease is detected early. Some of the interven-



**Figure.** The age-related decline in forced expiratory volume in 1 second ( $FEV_1$ ) is accelerated in smokers. While the lung function lost at any point in time cannot be regained with smoking cessation, the subsequent loss in lung function is similar to that of healthy nonsmokers. Modified and reprinted with permission from Fletcher C, Peto R. The natural history of chronic airflow obstruction. *BMJ.* 1977;1:1645–1648.

tions outlined below are perceived as being useful only in the later stages of the disease, but many of these interventions are also very useful early on in the time course of COPD.

### SMOKING MODULATION

By far, the most important and efficacious intervention at any stage of COPD is to reduce risk factors. In the United States, this translates into the modulation and eventual cessation of smoking tobacco, including efforts to reduce inhalation of second-hand tobacco smoke. However, ~10% to 15% of COPD in the United States and a greater percentage worldwide occurs in people who never smoked. Therefore, avoiding other environmental and occupational exposures (eg, biomass fuels) leading to COPD must also be emphasized. By the age of 20 years most normal individuals have fully developed lungs and maximal lung function. In nonsmokers the normal aging past this point leads to a decrease in forced expiratory volume in 1 second ( $FEV_1$ ) of

#### KEY POINT

**Bronchodilators (anticholinergics, beta-2 agonists) are the first-line therapy for symptomatic COPD and should be maximized before moving to other medications.**

25 to 30 mL per year, compared with an average decline of 45 to 60 mL per year in smokers (**Figure**) (3–5). Approximately 20% of smokers are very sensitive to cigarette smoke and have an accelerated decline in  $FEV_1$  of up to 150 to 200 mL per year. Currently, there are no markers to identify these latter individuals other than serial spirometry. The more cigarettes smoked, the steeper the decline in lung function (4–6). Those who stop smoking at any age will not regain lung function

TABLE II.

## STRATEGIES TO HELP THE PATIENT WILLING TO QUIT SMOKING (8)

1. **ASK:** Systematically identify all tobacco users at every visit. Implement an office-wide system that ensures that for every patient at every clinic visit, tobacco-use status is queried and documented.
2. **ADVISE:** Strongly urge all tobacco users to quit. In a clear, strong, and personalized manner, urge every tobacco user to quit.
3. **ASSESS:** Determine willingness to make a quit attempt. Ask every tobacco user if he or she is willing to make a quit attempt at the present time (eg, within the next 30 days).
4. **ASSIST:** Aid the patient in quitting. Help the patient with a quit plan; provide practical counseling; provide intra-treatment social support; help the patient obtain extratreatment social support; recommend use of approved pharmacotherapy except in special circumstances; provide supplementary materials.
5. **ARRANGE:** Schedule follow-up contact either in person or via telephone.

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already lost, but over time they will have better pulmonary function, slower rates of decline in lung function, and an increased survival based on lung function compared with those individuals who continue to smoke (6,7).

The fight against tobacco should utilize several approaches at different levels: (a) persuade individuals not to start smoking, (b) provide education and treatments that modulate tobacco smoking, and (c) provide support and therapies for sustained smoking cessation. The specifics of smoking cessation can be reviewed in the guidelines published by the US Agency for Health Care Policy and Research (8), which advocate a 5-step program for intervention: Ask, Advise, Assess, Assist, Arrange (Table II). Advice from the primary care provider is an important motivator for a patient to consider smoking cessation. A smoker must have a true desire to stop smoking before any program can be successful. Some smokers can quit cold turkey, but most must seek help via programs that guide them in behavioral modification and provide self-help materials, nicotine replacement, and other methods to begin and sustain smoking cessation. Smokers must set a quit date, modify their social environment to make it less conducive to smoking, utilize nicotine replacement, in some cases in conjunction with bupropion (9), and gather peer support. Patients should not be discouraged if they relapse but be encouraged to try again as the average smoker makes 3 to 4 attempts to quit before long-

term success is achieved. Smokers should be encouraged to make more than one attempt to quit because those making several attempts at smoking cessation experience less loss of lung function than those who smoke continuously. Often, the practitioner is not satisfied with anything less than total cessation; however, the practitioner should realize that even a reduction in daily cigarette use is beneficial, with an eventual goal of total abstinence—thus the term “smoking modulation.”

### PHARMACOLOGIC MODALITIES

Any therapeutic regimen utilized in the management of a disease, including COPD, should be chosen with certain objectives in mind, some of which are outlined in Table III.

It is incorrect to assume that COPD is totally irreversible; in fact, it is partially reversible. A portion of the obstruction present in COPD can often be reversed with the use of bronchodilator medications, especially during the early stages of the disease. The recent GOLD guidelines state that “bronchodilator medications are central to the symptomatic management of COPD.” This is in line with their definition of COPD as “... a disease state characterized by airflow limitation that is not fully reversible...” A hallmark of asthma, which is often used to differentiate it from COPD, is that the entire obstructive defect is reversed with bronchodilators. The GOLD guidelines stratify the use of medications in COPD based on lung function

TABLE III.

## GOALS OF THERAPY IN THE TREATMENT OF COPD

- Improve lung function
- Relieve symptoms
- Prevent and treat complications (decrease exacerbations and hospitalizations)
- Improve health status (quality of life)
- Prevent disease progression (decrease accelerated decline in lung function)
- Increase life expectancy
- Accomplish above in a cost-effective manner

(FEV<sub>1</sub> and FEV<sub>1</sub>/FVC [forced vital capacity]) and stress to first maximally attempt to reverse bronchoconstriction as assessed by spirometry (**Table I**).

In all stages of COPD one should avoid risk factors and receive the influenza vaccine yearly. In stage 0 (at risk for COPD), no additional specific therapy is currently recommended. In stage I (mild COPD), a short-acting bronchodilator should be used. In stage IIA (moderate COPD), regular treatment with 1 or more bronchodilators is recommended with referral to a pulmonary rehabilitation program as needed. In stage IIB (moderate COPD with an FEV<sub>1</sub> between 30% and 50% of predicted), pulmonary rehabilitation should definitely be utilized, and if bronchodilation is maximized with use of multiple bronchodilators and the patient is having frequent exacerbations (ie, 3 to 4 per year), a 6-week to 3-month trial of ICS can be evaluated as outlined below. In stage III other therapies can be considered as outlined in **Table I**.

Accordingly, bronchodilators are the foundation of symptomatic treatment of the reversible component of airway obstruction in COPD and are recommended by several published guidelines, including the recent GOLD guidelines (3,5,10–12). It is important to point out that this does not mean that 1 specific medication is first-line therapy but rather that bronchodilators (all classes—anticholinergics, beta-2 agonists, and methylxanthines) should be maximized prior to the initiation of additional medications (ie, currently available anti-inflammatory agents) that could potentially modulate other mechanisms involved in COPD. Bronchodilators improve lung

function, relieve symptoms, decrease exacerbations, and decrease hospitalizations (13–16). Another statement in the GOLD guidelines is that metered-dose or dry-powder inhalers are preferred over wet nebulizers to deliver bronchodilators to the lung, based on better delivery to the lung, as well as cost and maintenance factors (2). This statement is largely dependent on careful patient education with respect to inhaler technique, which is ideally reviewed at each visit.

Anticholinergic agents such as ipratropium are a first-line maintenance therapy for COPD (2,5,10). Bronchodilation with ipratropium has been shown to decrease the rate of exacerbations, leading to lower treatment costs (13,14). Bronchodilation leads to a reduced work of breathing and in most patients less of a sense of dyspnea. Extended therapy with ipra-

## KEY POINT

**The inflammation of COPD is different and much less responsive to steroids from the inflammation of asthma.**

tropium has been shown to improve baseline lung function (17). Ipratropium is negatively charged, minimally absorbed systemically, and therefore does not have side effects previously observed with nebulized atropine. The most important effect of this anticholinergic agent is its blockage of acetylcholine binding to the M3 receptors of lung smooth muscle cell and mucus-secreting glands. This blockage

leads to bronchodilation and decreased sputum volume without thickening secretions. The bronchodilating effect of ipratropium lasts 6 to 8 hours versus the 3- to 4-hour effect of short-acting beta-2 agonists (reviewed in GOLD guidelines).

Both short- and long-acting beta-2 agonists (LABAs), such as albuterol, salmeterol, and formoterol, are also useful in dilating the airways of patients with COPD. These medications are considered first- or second-line bronchodilator therapy in COPD, depending on the study read (2,10). The end result of bronchodilation is often a reduced work of breathing, and in many cases less of a sense of dyspnea. Depending on cost and patient compliance versus a short-acting beta-2 agonist (albuterol), LABAs (salmeterol, formoterol) are utilized for maintenance therapy, often in addition to an anticholinergic. However, if a LABA is used, a short-acting beta-2 agonist (albuterol) must also be prescribed for rescue during worsening of symptoms.

An inhaler that simultaneously delivers both the anticholinergic ipratropium and the short-acting beta-2 agonist albuterol (Combivent<sup>®</sup>) is available for combination bronchodilator therapy in COPD. Combivent<sup>®</sup> has been shown to dilate the airways more than ipratropium or albuterol alone, to decrease exacerbations and hospitalizations, and to improve quality of life (13). This is because 2 medications working by 2 distinct mechanisms to dilate are being delivered to the affected airways. A short-acting beta-2 agonist (albuterol) or the combination inhaler itself, if cost-effective, should be used as rescue therapy during worsening of COPD symptoms. The combination of a LABA (salmeterol or formoterol) and an anticholinergic (ipratropium) can often lead to additional bronchodilation above that of either agent alone and also lead to a reduction of exacerbations (18,19).

If the outcome of using an anticholinergic plus or minus a short-acting beta-2 agonist or LABA therapy is not optimal, addition of a long-acting theophylline can be considered. Theophylline has only mild bronchodilatory effects, but it has been shown to reduce nocturnal declines in FEV<sub>1</sub> (20). The dosage should be titrated to yield serum concentrations in the range of 10 to 12 µg/mL. Careful observation of drug levels and

side effects is needed because of theophylline's narrow therapeutic margin and the fact that many situations alter the metabolism of this drug, particularly in the presence of other diseases or interacting drugs.

An important point made by the GOLD guidelines is that "... all categories of bronchodilators have been shown to increase exercise capacity in COPD, without necessarily producing significant changes in FEV<sub>1</sub>,"(21,22) which reinforces that an historical review of activities of daily living and exertional activities is important, *in addition* to spirometry, when evaluating the efficacy of maintenance bronchodilator therapy.

In contrast to asthma, the inflammatory reaction in COPD under stable conditions is not extremely responsive to corticosteroid treatment. The cells and mediators that are dominant in asthma (ie, eosinophils, mast cells, CD4-T<sub>H</sub>2 lymphocytes) are not predominant in stable COPD. COPD is predominantly a neutrophilic and macrophage disease process, with some contribution from lymphocytes of the CD8 phenotype. It has now been clearly demonstrated by 4 multicenter international studies that maintenance ICS do not slow the accelerated decline of FEV<sub>1</sub> or significantly improve outcomes in patients with mild or moderate COPD (23–25) and only decrease exacerbations in end-stage COPD patients who have frequent exacerbations (26), which account for ~10% to 20% of patients diagnosed with COPD. This percentage will probably decline as more patients with mild

### KEY POINT

**Vaccination and early pulmonary rehabilitation are imperative in patients with COPD.**

COPD are identified earlier by spirometry. The GOLD guidelines recommend that if in the judgment of the clinician first-line bronchodilation therapy with both an inhaled anticholinergic and beta-agonist is maximal, a trial of inhaled corticosteroids can be instituted. Further, if there are no

changes in lung function (spirometry) and the clinical condition after a 6-week to 3-month trial of ICS, the inhaled steroids should be discontinued. If patients are responsive to ICS, based on the above criteria, care should be taken in tapering the dose from 500 µg BID of fluticasone or its equivalent (26) because exacerbations may recur sooner (27). However, a short course of systemic glucocorticosteroids can be useful during acute exacerbations, perhaps when more steroid-sensitive cells, ie, eosinophils are present.

The effects of all of these agents on lung function should be monitored by spirometry. Other measurements of quality of life, measures of exercise capacity, and activities of daily living should also be monitored as the spirometry of some patients does not improve with the use of bronchodilators but their overall health status does improve (21,22).

### OTHER TREATMENTS FOR COPD

Vaccination against influenza and pneumococcal pneumonia is useful in all patients with COPD. All patients with COPD should receive the influenza vaccine annually unless they have a history of anaphylaxis to egg protein. Studies have shown that the influenza vaccine is 30% to 80% effective in preventing illness, complications, and death in high-risk populations. It is recommended that the pneumococcal vaccine be given to all COPD patients; those patients  $\geq 65$  years should be revaccinated if they received the vaccine  $>5$  years earlier or if their vaccination status is uncertain. The pneumococcal vaccine can be given at the same time as the influenza vaccine, as long as the vaccines are administered at different sites of the body.

Besides sustained smoking cessation, only 1 other therapy has been shown to have a positive impact on prolonging survival in COPD. Studies have established that the use of supplemental oxygen therapy in COPD, for a minimum of 15 to 18 hours each day, prolongs survival in patients with severe COPD (stage III per GOLD criteria) whose  $\text{PaO}_2$  is  $< 55$  mm Hg or whose  $\text{SaO}_2$  is  $< 88\%$  (at rest or with exercise), or when  $\text{PaO}_2$  is 56 to 59 mm Hg in the presence of electrocardiographic evidence of P-pul-

monale, the presence of pedal edema (right ventricular failure), and/or secondary erythrocytosis (28,29).

Pulmonary rehabilitation, which includes smoking cessation, general education on COPD, nutrition programs, individualized exercise programs, and psychosocial programs, has been shown to benefit COPD patients who have moderate pulmonary dysfunction. Pulmonary rehabilitation can improve the health status of patients, improve their exercise endurance and conditioning, and relieve the sense of dyspnea, but it has not been shown to improve survival rates. It is important to refer patients to a pulmonary rehabilitation program early in the course of COPD (stage IIA or IIB) and not wait until the patient is in near disability (stage III) (2). It is also important to encourage patients to continue with the “home exercise program” given to them after discharge from formal rehabilitation sessions to maintain the benefits gained from the rehabilitation visits; if COPD patients do not follow this program, their condition will trend toward that of prerehabilitation status within a few months.

The interventions of nutritional counseling, noninvasive ventilation, and surgical interventions (ie, lung-volume reduction surgery and lung transplant) are beyond the scope of this article but can be reviewed in recent publications (2,10,11).

There are no strong evidence-based studies showing that pharmacologic intervention, with the exception of smoking-cessation medications, is beneficial for “asymptomatic” patients with COPD. However, it is important for the clinician to extensively question all patients to be sure they are not in a state of denial or have modified their lifestyle to mask the symptoms of early COPD. The early stages of COPD can be silent if one solely relies on the history spontaneously offered by the patient. Because the airway obstruction occurs slowly, individuals with early COPD tend to gradually modify their daily lifestyle, decreasing the intensity of their activities to the degree that less lung capacity is needed to routinely function “asymptomatically.” If these behavior modifications unfolded over a number of years, patients might not even realize that they have made any changes. They may attribute the “earlier” symptoms of COPD—cough and mucus production—to the cigarette habit, accepting

that the early morning clearing of their throat is “part of smoking.” The practitioner needs to elicit from these patients their reasons for denial and their modifications of lifestyle and should ask them specific questions relevant to their activities of daily living, perhaps comparing their activities to those of their peers. If patients are indeed symptomatic, they should be managed as suggested by the algorithm proposed in **Table I**.

## SUMMARY

The primary care clinician must play a pivotal role not only in the early identification of individuals with COPD but also in the early treatment of this “killer disease.” Early diagnosis with aggressive intervention is the only way the increasing morbidity and mortality of COPD can be reversed. Regardless of the specific reason for patient presentation, any smoking history indicates the need to evaluate the patient for underlying COPD. At a minimum, the patient should be given in-office spirometry to test pulmonary function. Modulating a COPD patient’s smoking habits and encouraging total cessation of smoking are the most important measures in preventing further deterioration of lung function. Rigorous application of a stepped-care treatment approach, as outlined in the GOLD guidelines algorithm (**Table I**), can improve the overall quality of life in patients who have symptomatic COPD.

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## Dialogue Box

### ADVISORY BOARD

**Is tachyphylaxis associated with the long-term use of inhaled beta-2 agonists in patients with COPD? If the answer is yes, explain the recommendation for chronic daily use in COPD. If no, explain why there is none.**

#### DOHERTY

In multiple studies it has been documented that the increase in bronchodilation, ie, FEV<sub>1</sub>, with the use of inhaled short-acting beta-2 agonists diminishes over time, ie, weeks (tachyphylaxis or tolerance). The initial short-term studies evaluating the bronchodilatory effects of long-acting beta-2 agonists did not show evidence of tachyphylaxis. However, more recent studies, 6 months in duration, have shown that the long-term use of beta-2 agonists can lead to tachyphylaxis. It should be kept in mind that these results represent the average FEV<sub>1</sub> over time of the entire study population and may not occur in all patients. Accordingly, the magnitude, and most importantly, the clinical relevance of this potential loss of effect must be taken into consideration on a patient-to-patient basis. Serial office spirometry and evaluation of each patient's change in activities of daily living can aid in this assessment.

### ADVISORY BOARD

**Why is inhaled ipratropium preferred over beta-2 agonist as first-line therapy?**

#### DOHERTY

The answer to this question depends on the severity of COPD in each patient. The GOLD guidelines recommend that first-line therapy in stage I COPD (see **Table I** in my article) is the use of one bronchodilator. One of several classes of bronchodilators can be used as monotherapy—anticholinergics (ie, ipratropium), beta-2 agonists

(short- or long-acting), or a methylxanthine.

GOLD recommends inhaled therapy (anticholinergic or beta-2 agonists) over oral agents (methylxanthines) based on a greater effect in bronchodilation and a lower side-effect profile. The choice of inhaled agent often depends on the patient's compliance with the medication/device and cost as both anticholinergics and beta-2 agonists are excellent bronchodilators. Many prefer ipratropium because of its lower side-effect profile and ability to decrease exacerbations, while others prefer long-acting beta-2 agonists because of their BID dosing and exacerbation control. In patients with stage II or III COPD, multiple bronchodilators are recommended as first-line therapy to maximize bronchodilation. Anticholinergics are definitely in this first-line therapeutic regimen. The decision is whether to use, in addition, a short-versus long-acting beta-2 agonist, and this choice often depends on cost, individualized therapeutic effect, and patient compliance.

### ADVISORY BOARD

**Is there any therapeutic advantage offered by a long-acting beta-2 agonist (ie, salmeterol) over a short-acting beta-2 agonist?**

#### DOHERTY

I think this question is answered above. Short-acting beta-2 agonists bronchodilate to the same degree as long-acting beta-2 agonists; however, due to their shorter half-life there are periods of inferior bronchodilation. This nadir could be minimized depending on the frequency with which patients dose with their short-acting agent. Intuitively it would seem that prolonged bronchodilation would improve efficacy and outcomes, but only a few studies have confirmed this concept. Frequent use of a short-acting beta-2 agonist, if tolerated, can clinically simulate the effects



## Dialogue Box

of a long-acting beta-2 agonist with the caveat of tachyphylaxis. Again, this is highly dependent on patient compliance and side-effect profile with the frequent dosing of short-acting beta-2 agonists. Cost must also be considered.

### ADVISORY BOARD

**Is there any role for leukotriene antagonists in the treatment of COPD?**

#### DOHERTY

There have been no large, randomized, well-controlled studies showing efficacy for the use of leukotriene modifiers in COPD. These anti-inflammatory agents act on cells and the elaboration of mediators that are important in the pathogenesis of asthma. Some practitioners have used these agents in patients with documented COPD who are already on maximized first-line bronchodilator therapy (anticholinergic plus a beta-2 agonist) and have a clear history of asthma that is not optimally controlled. This decision is beyond the scope of my article, that is, whether to add a leukotriene antagonist or an inhaled corticosteroid to the first-line maximal bronchodilatory regimen to control the inflammation of the asthmatic component in this small subset of COPD patients.

### ADVISORY BOARD

**Please comment on the dosage of ICS used in COPD and indicate how their use and dosage compares with the “low-dose, medium-dose, high-dose” categories used in managing patients with asthma.**

#### DOHERTY

Based on several studies, the dose of ICS required to obtain a potential therapeutic effect in severe COPD is high dose only, ie, 500  $\mu$ g BID of fluticasone in the ISOLDE (Inhaled Steroids in Obstructive Lung Disease in Europe) trial. The concept of a gradual increase or step-down approach in the dose of ICS that is useful in the management of asthma should not be extrapolated to COPD. As outlined in my article, a 6-week to 3-month trial of high-dose ICS should be entertained only in those patients with severe COPD who have been maximally bronchodilated with multiple agents, have room for improvement, and have frequent exacerbations (ie, 3 to 4 per year)—those with stage III and maybe IIB. If the FEV<sub>1</sub> does not improve and the exacerbation rate does not decrease within this time frame, the ICS should be discontinued because of lack of efficacy and cost.