Chronic obstructive pulmonary disease (COPD) is a common and worldwide disorder.¹² Its prevalence is increasing in many countries, particularly in Asia, and among women. In the United States, despite the decrease in cigarette smoking in recent decades, both the prevalence of and the mortality associated with COPD have increased and are projected to continue to increase for some years yet. Furthermore, COPD is costly, and acute exacerbations, which occur roughly once a year in patients with COPD of moderate or greater severity, constitute the most expensive component. In 2002, the direct cost of COPD in the United States was $18 billion, whereas the indirect cost amounted to an additional $14 billion.³ These statistics are projected to increase as the population ages.

To address the many issues raised by a disease of such importance, evidence-based guidelines have been developed.⁴⁻⁶ Although they differ somewhat in approach, each provides a basic, graded framework without mandating a specific treatment regimen. This flexibility recognizes the importance of physicians’ judgment in selecting the most appropriate therapy for each individual patient.

Appropriate treatment may vary, depending on the severity of disease, so it is useful to discuss efficacy of the different therapies by stage of disease. The staging system of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) is widely recognized, and it parallels the classification system of the American Thoracic Society and the European Respiratory Society.⁴⁻⁵ Guidelines from the American College of Physicians refer to both these staging systems.⁶ The GOLD guidelines (frequently updated during the past decade by the National Heart, Lung, and Blood Institute and the World Health Organization) were most recently updated in September 2007.⁷ In the current review, we summarize the management recommendations in the latest GOLD guidelines with an emphasis on bronchodilators in light of recent research and publications collected in a PubMed search of articles published from January 1, 2004 to December 31, 2007. The following keywords were searched: chronic obstructive pulmonary disease (major topic) and epidemiology, practice guidelines, clinical trial, and meta-analysis. After identification of studies through the PubMed search, the references of the articles were reviewed for additional relevant data sources.

GOLD defines COPD as “a preventable and treatable disease with some significant extrapulmonary effects…Its pulmonary component is characterized by airflow limitation that is not fully reversible…usually progressive and associated with an abnormal inflammatory response of the lung to noxious particles or gases.”⁷ The current classification identifies 4 stages of severity, from mild to very severe, that are mainly based on spirometry-determined reductions in forced expiratory volume in the first second of...
CHRONIC OBSTRUCTIVE PULMONARY DISEASE

TABLE 1. Classification of Chronic Obstructive Pulmonary Disease Based on Postbronchodilator FEV₁ and FVC

<table>
<thead>
<tr>
<th>Stage</th>
<th>Findings</th>
</tr>
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<tr>
<td>I: mild</td>
<td>FEV₁/FVC &lt; 0.70; FEV₁ &gt; 80% predicted</td>
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<tr>
<td>II: moderate</td>
<td>FEV₁/FVC &lt; 0.70; 50% ≤ FEV₁ &lt; 80% predicted</td>
</tr>
<tr>
<td>III: severe</td>
<td>FEV₁/FVC &lt; 0.70; 30% ≤ FEV₁ &lt; 50% predicted</td>
</tr>
<tr>
<td>IV: very severe</td>
<td>FEV₁/FVC &lt; 0.70; FEV₁ &lt; 30% predicted or FEV₁ &lt; 50% predicted plus chronic respiratory failure</td>
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* FEV₁ = forced expiratory volume in the first second of expiration; FVC = forced vital capacity.

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explanation (FEV₁) and the FEV₁/FVC forced vital capacity ratio (Table 1). Spirometry is considered essential for diagnosing and staging of COPD, which may affect 24 million Americans, half of whom have conditions that remain undiagnosed. By far the most important risk factor for the development of COPD in the United States is, of course, cigarette smoking, although environmental pollution, both indoor and outdoor, has a role. The inclusion of the term preventable in the definition refers to these factors. Genetic factors may also be at work, but the only one that has clearly been identified is α₁-antitrypsin deficiency, which is rare, but laboratory screening makes diagnosis relatively straightforward. GOLD recommends α₁-antitrypsin screening in white patients who develop COPD before the age of 45 years or in those with a strong family history of COPD.

Key points in the management of stable COPD, for which evidence is strong, are adapted from GOLD and given in Table 2. In addition, comorbidities (e.g., cardiovascular diseases, depression, lung cancer, and respiratory tract infection) should be identified because they can adversely affect the health status of patients with COPD and complicate the management of COPD.

MILD TO MODERATE COPD: BRONCHODILATORS

For patients with mild disease (stage I), an inhaled short-acting bronchodilator can be prescribed for use on an as-needed basis (Figure 1). This can be a β₂-agonist, such as albuterol, pirbuterol, or terbutaline; the anticholinergic ipratropium; or the fixed combination of albuterol and ipratropium. In general, these agents are given by metered-dose inhalers, but some patients may prefer nebulized medications because of poor manual dexterity due to arthritis, cerebrovascular disease, or poor vision.

Maintenance bronchodilator treatment with an inhaled long-acting agent should be instituted when patients have moderate disease (stage II), their symptoms are poorly controlled, or use of rescue medication exceeds 1 canister per month. The choice among long-term bronchodilators is between the once-daily anticholinergic agent tiotropium and 1 of the long-acting β₂-agonists (LABAs), salmeterol or formoterol, which are given twice daily. In addition to providing once- or twice-daily convenient dosing for patients and providing consistent bronchodilation, the long-acting agents have been shown in some studies to have other patient-centered benefits. These benefits include reducing the number (and possibly severity) of acute exacerbations, improving health status (quality of life), improving exercise tolerance, and improving the efficacy of pulmonary rehabilitation (which GOLD recommends for patients with at least moderate COPD). Adverse effects with each of the long-acting agents are infrequent and relatively minor. The usual precautions should be observed against use of an anticholinergic agent in patients with urinary retention or narrow-angle glaucoma and against use of a β₂-agonist in patients with unstable cardiac disease or tachyarrhythmia. Whichever is chosen, a short-acting β₂-agonist reliever treatment will continue to be needed and should be used for breakthrough wheezing or dyspnea. Ipratropium (either alone or as part of a combination therapy) would be inappropriate reliever therapy if tiotropium is chosen as the long-acting agent.

A methylxanthine (theophylline) could be used in addition to these treatments or as an alternative in patients intolerant of β₂-agonist adverse effects. The doses currently recommended (approximately 300 mg once daily at bedtime) are 1 -antitrypsin deficiency, which is rare, but laboratory screening makes diagnosis relatively straightforward. GOLD recommends α₁-antitrypsin screening in white patients who develop COPD before the age of 45 years or in those with a strong family history of COPD.

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Adapted from GOLD Pocket Guide to COPD Diagnosis, Management, and Prevention (updated 2007), with permission.

TABLE 2. Management of Stable Chronic Obstructive Pulmonary Disease (COPD)

1. Reduction in risk factors is essential. For patients who still smoke, smoking cessation is the most important (and cost-effective) modality, and education plays an important role in bringing this about
2. None of the existing medications for COPD have yet been shown prospectively to modify the long-term decline in lung function. Pharmacotherapy is used to decrease symptoms and reduce complications such as acute exacerbations
3. Bronchodilators, either as needed or on a regular basis, are central to the management of COPD. These include anticholinergics, β₂-agonists, and methylxanthines, used singly or in combination
4. Regular treatment with long-acting bronchodilators is more effective and convenient than treatment with short-acting bronchodilators
5. The addition of maintenance inhaled corticosteroids to bronchodilator(s) is appropriate for symptomatic patients with stage III or IV disease and repeated acute exacerbations. Long-term oral corticosteroids should be avoided if possible
6. Annual influenza vaccination can reduce the frequency and severity of acute exacerbations. Pneumococcal polysaccharide vaccination is also recommended
7. All patients with COPD benefit from exercise training programs (pulmonary rehabilitation)
8. Long-term oxygen administration (>15 h per day) has been shown to improve survival in patients with chronic respiratory failure

Adapted from GOLD Pocket Guide to COPD Diagnosis, Management, and Prevention (updated 2007), with permission.
time or 200 mg every 12 hours) are substantially lower than those typically used at least a decade ago and thus are unlikely to carry a risk of toxicity. Monitoring blood levels at low dosages (plasma concentrations of 5-10 mg/L) is not necessary.\textsuperscript{15}

These treatments can be combined if warranted by persistent symptoms. It is not unusual or inadvisable, for example, for a patient with severe disease to use tiotropium and a LABA on a maintenance basis, a short-acting \( \beta_2 \)-agonist on an as-needed basis, and perhaps a methylxanthine as well. However, it would be inappropriate for a patient to exceed the dosages or frequency of either class of long-acting agents because these agents are not approved for rescue use in the United States.

### TREATMENT OF SEVERE COPD: ADDITION OF GLUCOCORTICOIDs

A meta-analysis of large, carefully designed multicenter studies showed no significant reduction in the long-term decline in lung function with regular use of an inhaled corticosteroid (ICS).\textsuperscript{16-20} However, in patients with severe or very severe disease (GOLD stage III or IV, respectively), regular ICS use can improve health status.\textsuperscript{21} Patients with stage III or IV COPD may experience 1 or more acute exacerbations of COPD per year. These events are likely to result in a decline in both lung function and quality of life and are also costly. Maintenance use of an ICS can be expected to reduce the rate of these events by approximately 20\% to 25\%.\textsuperscript{9} The addition of a maintenance ICS to the bronchodilator therapies aforementioned is recommended only in stage III and IV disease with frequent exacerbations; the risk-benefit ratio of adding an ICS at an earlier stage of COPD is still unclear. The concern is that early or inappropriate use of an ICS may ultimately lead to corticosteroid-associated adverse events, such as osteoporosis, muscle weakness, or frank myopathy, glaucoma, and cataract. Although these effects have not occurred to a significant extent in trials to date, the trials have been of relatively short duration, and the effects might well take 10 years or more to become manifest. Recently, pneumonia has also been shown to be more common with long-term ICS use.\textsuperscript{22}

If the patient’s condition warrants use of an ICS, he or she should also be receiving a LABA. In this case, it is
appropriate and more convenient for the patient to receive the fixed combination of an ICS and LABA, of which only 1 formulation is currently approved for COPD associated with chronic bronchitis (fluticasone, 250 µg, and salmeterol, 50 µg), although another formulation is under review at the Food and Drug Administration (budesonide, 160 µg, and formoterol, 4.5 µg). Currently, no fixed combinations are available of long-acting anticholinergic and β₂-adrenergic drugs or of long-acting anticholinergic and ICS agents in either metered-dose or nebulized formulation. Some of these gaps in therapy will probably be filled in the next few years. Figure 2 shows 2 possible step-by-step algorithms.

A recent trial of ICS plus LABA therapy, the Towards a Revolution in COPD Health (TORCH) study, examined patients with moderate to severe COPD. The trial demonstrated that 50 µg of salmeterol plus 500 µg of fluticasone twice daily (this dosage is not approved in the United States) reduced exacerbations and improved lung function and health status more than either component or placebo. (TORCH narrowly missed its primary end point, reduction in mortality with the fixed combination regimen compared with placebo.) This trial reinforced evidence that LABA monotherapy is well tolerated and effective in the treatment of COPD and should be preferred to ICS monotherapy. Both the combination and salmeterol alone significantly reduced annual hospital admission rates for severe exacerbation compared with placebo, but fluticasone did not. In addition, patients using an ICS showed an elevated risk of pneumonia compared with those in either the placebo or the salmeterol group. Of interest, a post hoc analysis found a reduction in the rate of lung function decline in all treatment groups compared with placebo.

For patients with GOLD stage IV disease, addition of long-term oxygen therapy is indicated for those with persistent arterial desaturation at rest. In addition, lung volume reduction surgery or lung transplant may be considered in selected patients, the indications for which are outside the scope of this article.

As indicated in Table 2, the GOLD guidelines support annual influenza vaccination and pulmonary rehabilitation as important components of the overall treatment plan for COPD that should not be neglected in favor of pharmaco-
therapy. Pharmacological treatments that are sometimes used for COPD but for which efficacy evidence is minimal or nonexistent include nonsteroidal anti-inflammatory agents (eg, montelukast and the cromones), antioxidants, mucolytic agents (eg, N-acetylcysteine, which also has antioxidant properties), immunoregulators (eg, anti-tumor necrosis factor α, for which efficacy has not been shown), and long-term antibiotic treatment. α1-Antitrypsin is only indicated for patients with the genetic deficiency and with established emphysema. Observational evidence indicates that statins may substantially decrease the mortality associated with COPD, but this has yet to be established by well-designed, adequately powered, prospective trials.

LONG-ACTING ANTICHOLINERGIC THERAPY: TIOTROPium

Lung Function

Monotherapy. The long-acting anticholinergic tiotropium is the most recent addition to the COPD armamentarium and the only agent of its class that is currently available. We reviewed it at the time of its release in 2004. Since then, tiotropium has been the subject of many important studies, and these will be briefly reviewed because they shed new light on the possible therapeutic benefits of this class of agent, and potentially this particular agent, that may not have been fully appreciated.

Regarding spirometric outcomes, Briggs et al compared the bronchodilator potency of tiotropium with that of salmeterol at the end of 12 weeks of treatment in 653 patients with COPD. At baseline, both groups had the same mean FEV1 (37.7% of predicted). On the last day of the study, the peak postdose FEV1 and mean FEV1 during the 12 hours after dosing were higher with tiotropium than with salmeterol. The differences were not large, in the range of 30 to 46 mL, but were statistically significant. The study by Briggs et al confirms 2 previous 6-month comparisons of the same 2 agents, which showed that tiotropium is a potent long-acting bronchodilator with no evidence of tachyphylaxis.

One of the most interesting recent findings about tiotropium comes from reanalysis of 2 large, 1-year studies that compared tiotropium (n=518) with placebo (n=328). Post hoc analysis showed that trough FEV1, (ie, mean of 23- and 24-hour postdose FEV1) decreased by 58 mL per year in the placebo group (an amount typical in COPD), whereas it decreased by less than 20 mL per year in patients receiving tiotropium. The difference was statistically significant and was greater in ex-smokers, current users of ICSs, and patients whose baseline FEV1 was above 50% of predicted. A similar effect had been suggested previously when tiotropium was compared with ipratropium. Of note, change in trough FEV1 was the primary outcome in these trials, although its rate of decline was calculated post hoc. A smaller, nonsignificant difference in the rate of decrease of peak FEV1 was also noted. Nonetheless, these results suggest that tiotropium may have contributed to the observed difference. To test the hypothesis that tiotropium has an effect in slowing the decrease in FEV1 affecting patients with COPD, an appropriately designed 4-year study—Understanding Potential Long-term Impacts on Function with Tiotropium (UPLIFT)—is under way. Results are expected toward the end of 2008.

Combination Therapy. The addition of a LABA to a maintenance therapeutic regimen with tiotropium is of interest, given that tiotropium is widely used as first-line maintenance treatment of COPD. Therefore, combinations of different classes of agents offer the possibility of increasing bronchodilation and minimizing the potential for adverse effects. In exploring this, 2 single-dose studies by Cazzola et al indicated that the addition of either formoterol (12 µg) or salmeterol (50 µg) to tiotropium (18 µg) increased all postbronchodilator spirometric parameters during the following 24 hours. However, only patients given the formoterol-tiotropium combination had statistically better FEV1 outcomes at 24 hours, largely because of the much more rapid onset of formoterol bronchodilation.

The tiotropium-formoterol combination has been further explored in 4 studies. Cazzola et al conducted a crossover study in which 18 µg of tiotropium was given once daily and 12 µg of formoterol was given twice daily for 5 days. On the sixth day, the 2 drugs were given in sequence but separated by 180 minutes, and pulmonary function was tested before and serially after each treatment. The investigators found that whichever drug was given first, the second drug provided a modest but statistically significant increase in bronchodilation. This finding seems to indicate that, in approved doses, neither tiotropium nor formoterol achieves all the available bronchodilation alone, thereby providing a rationale for the use of combination therapy. In 2 three-way, crossover studies, van Noord et al examined the 24-hour effect of adding formoterol on different schedules to once-daily tiotropium for 2- and 6-week treatment periods. They found that tiotropium once daily resulted in greater average bronchodilation during the 24-hour period than formoterol twice daily. Tiotropium plus formoterol, both given once daily in the morning, improved bronchodilation throughout the 24-hour cycle, but only slightly during the last 12 hours (Figure 3). Moreover, the addition of formoterol twice daily to tiotropium once daily resulted in higher mean FEV1 than the once-daily combination of these agents. A recent randomized, parallel-group trial demonstrated that nebulized formoterol added to
tiotropium significantly improved bronchodilation and dyspnea compared with nebulized placebo plus tiotropium at the end of 6 weeks.\(^3^9\)

One possible conclusion from these studies is that combinations of agents with different pharmacological actions, when given at approved dosages, predictably produce greater bronchodilation than do single agents. Whether this is because of activation of more bronchodilatory pathways or simply because more bronchodilator is being given is unclear; however, the former conclusion is supported by dose-response studies of formoterol that showed no additional bronchodilation with a 24-\(\mu\)g dose compared with a 12-\(\mu\)g dose, and a dose-response study of tiotropium showed a maximal spirometric effect at an 18-\(\mu\)g dose.\(^4^0,4^1\) Whichever is the case, the practical implication is that, as with combinations of short-acting bronchodilators, fixed combinations of long-acting bronchodilators would likely be a therapeutic advantage in improving lung function and relieving COPD symptoms. Unfortunately, none of the currently available LABAs are suitable for once-daily administration. The possibility of a fixed combination may become a reality if and when once-daily \(\beta_2\)-agonists become available.

**Triple-Combination Therapy.** Investigators in 2 trials examined the effect of triple therapy by combining tiotropium with a fixed LABA-ICS combination. In the smaller and shorter study, the addition of tiotropium to the LABA-ICS combination resulted in modest improvements in lung function and health status based on St. George’s Respiratory Questionnaire, but when tiotropium was subsequently withdrawn, these measures deteriorated.\(^4^2\) In a larger 1-year study, patients were randomized to 1 of 3 arms: once-daily tiotropium plus placebo, tiotropium plus twice-daily salmeterol, and tiotropium plus twice-daily salmeterol plus fluticasone, 500 \(\mu\)g.\(^4^3\) The incidence of acute exacerbations of COPD, the primary outcome, did not differ significantly among the 3 groups. In the triple-combination group, however, a significant reduction in the number of hospitalizations and an improvement in health status were seen. However, predose \(FEV_1\) (a secondary outcome) was significantly increased with triple-combination therapy compared with tiotropium alone, whereas no difference was found between the tiotropium and tiotropium plus salmeterol groups.

**Exercise Performance and Hyperinflation**

Dyspnea and effort intolerance are the primary symptoms of most patients with COPD.\(^1^4\) The physiologic factors that are associated with these symptoms and that are believed to cause them have been examined in detail in the past few years. Hyperinflation, the increase in lung volumes (principally functional residual capacity in advanced disease), has long been recognized as a feature of COPD. In static hyperinflation, the work of breathing is increased, even at rest, because changes in lung elasticity require the patient to breathe at volumes that place the chest wall and respiratory...
muscles at a mechanical disadvantage. Dynamic hyperinflation, which may be present in mild disease or superimposed on static hyperinflation, can rapidly increase during effort as the respiratory rate increases. Under these conditions, airway resistance can compound expiratory limitations because of the reduced time available for lung emptying. Although all bronchodilators tend to diminish hyperinflation temporarily, it has not been possible to demonstrate consistent improvements in dyspnea or effort tolerance with short-acting bronchodilators.14 In contrast, long-acting agents appear to have clinically meaningful effects by reducing both static and dynamic lung volumes, improving dyspnea measurements, and increasing effort tolerance. Tiotropium appears to be an effective agent in these respects.13

O’Donnell et al13 showed that lung volumes were reduced and inspiratory capacity was increased both at rest and during exertion with regular use of tiotropium. Maltais et al15 performed a similar placebo-controlled study and showed that lung hyperinflation was reduced during exercise and at rest and that endurance time increased by a mean of 40%. Furthermore, these benefits correlated with a reduction in exertional dyspnea and were sustained at least 8 hours postdosing after 6 weeks of treatment with tiotropium.

Casaburi et al14 performed a double-blind, placebo-controlled study to determine whether the improvement in lung function and exercise tolerance associated with tiotropium might increase the effectiveness of a pulmonary rehabilitation program. They found that concomitant use of tiotropium improved exercise endurance time by more than 5 minutes, or approximately 35%, compared with pulmonary rehabilitation plus placebo. The benefits were maintained 3 months after the conclusion of the formal rehabilitation program. These benefits need to be confirmed in long-term trials.

PREVENTION OF ACUTE EXACERBATIONS OF COPD
As stated previously, acute exacerbations of COPD are both serious and expensive events. Patients commonly do not recover fully from them, and lung function and quality of life tend to be adversely and permanently affected.45,46 They also account for more than 50% of the total cost of treating COPD in the United States.47 Although data on acute exacerbations have been collected in all long-term studies of tiotropium, the first study to examine this end point as the primary outcome of a trial was performed by Niewoehner et al.8 In this randomized controlled trial conducted within the Veterans Affairs medical system, 1829 patients with severe or very severe COPD received either tiotropium or placebo in addition to their usual COPD treatment. Compared with placebo-treated patients, the proportion of patients given tiotropium experiencing an exacerbation and the proportion with a COPD-related hospitalization decreased by 20% to 25% (P=.04 and P=.06, respectively). In addition, the time to first exacerbation was significantly increased, and the range of secondary health care utilization outcomes was reduced (Table 3). Furthermore, patients receiving concomitant COPD therapies (including ICSs) generally showed a trend toward reduced exacerbations with tiotropium. A similar study performed by Dusser et al48 of 1050 patients with COPD in France showed comparable results. A similar outcome has also been shown for other agents, including LABAs, ICSs, and some short-acting bronchodilators.5,9,49 Turino50 has pointed out that prolonged

| TABLE 3. Comparison of Secondary Outcomes Between Tiotropium and Placebo* b |
|-------------------------------|-------------------|----------------|------------------------|
| Outcome                        | Placebo group (n=915) | Tiotropium group (n=914) | Difference | P value |
| Exacerbations                  | 1.05              | 0.85              | –0.20       | .03     |
| Exacerbation days              | 16.0              | 12.6              | –3.35       | .02     |
| Antibiotic days for COPD        | 9.8               | 8.1               | –1.71       | .02     |
| for COPD exacerbations         |                   |                   |             |         |
| Systemic corticosteroid days   | 7.4               | 6.3               | –1.15       | .25     |
| for COPD exacerbations         |                   |                   |             |         |
| Unscheduled visits for COPD    | 0.49              | 0.39              | –0.11       | .02     |
| exacerbation                   |                   |                   |             |         |
| Hospitalizations for COPD      | 0.25              | 0.18              | –0.08       | .047    |
| exacerbation                   |                   |                   |             |         |
| Hospitalization days for COPD  | 1.7               | 1.4               | –0.27       | .05     |
| exacerbation                   |                   |                   |             |         |
| All-cause hospitalizations     | 0.51              | 0.45              | –0.05       | .68     |
| All-cause hospitalization days | 3.5               | 3.7               | 0.14        | .77     |

* Results are expressed as number of events per patient-year during study. The amounts of missing data were approximately 5% for the tiotropium group and 7% for the placebo group.

COPD = chronic obstructive pulmonary disease.

Adapted from Ann Intern Med,8 with permission from the American College of Physicians.
hyperinflation sets up mechanical forces in the airways and lung parenchyma that, in experimental situations, result in the release of proinflammatory cytokines. These forces may promote airway inflammation and initiate or magnify bronchial smooth muscle reactivity.\textsuperscript{51,52} Thus, the results described herein could be due to a nonspecific class effect of all long-acting agents that reduce lung hyperinflation.

Miscellaneous Findings

McNicholas et al\textsuperscript{53} performed a placebo-controlled study of the effect of tiotropium on oxygen saturation during sleep in patients with COPD who had baseline hypoxemia. Although patients were matched at baseline, the authors found that use of tiotropium significantly increased oxygen saturation during sleep by more than 2%. No significant effect of tiotropium on sleep architecture, nocturnal awakenings, or other sleep parameters was observed.

Atropine, a tertiary ammonium compound, is a potent inhibitor of mucus secretion and ciliary activity, both of which are under cholinergic control. The effect of tiotropium, a quaternary congener of atropine, on mucociliary clearance was examined by Hasani et al\textsuperscript{54} using tracheobronchial clearance of inhaled radiolabeled particles. They found no difference between clearance rates before and 21 days after daily tiotropium treatment in 34 patients with COPD. Essentially similar results were found during the development of another quaternary ammonium anticholinergic, ipratropium. Why both agents relax airway smooth muscle without demonstrated evidence of inhibiting mucus secretion is unknown.

Our understanding of the role of anticholinergic bronchodilators has always been that they relax airway smooth muscle and have relatively few other actions. Recent laboratory research suggests, however, that they may have anti-inflammatory effects. Developments in this field deserve continued attention, although the clinical relevance of these findings has yet to be established.\textsuperscript{55-59}

Safety

Adverse event data were collected in all the long-term trials during the development of tiotropium. As expected, dry mouth occurred more frequently in the tiotropium groups than in the control groups, but frequency of serious adverse events was similar for both groups. In 2 recent studies\textsuperscript{60,61} electrocardiologic monitoring detected no evidence of abnormalities in cardiac rhythm, rate, conduction, or QT intervals in patients receiving tiotropium.

The tiotropium safety database includes data on 2159 person-years of exposure to the drug and 1662 person-years of placebo exposure.\textsuperscript{62} In a recent review of this database, dry mouth (relative risk [RR], 3.60; 95% confidence interval, 2.56-5.05) and urinary retention (RR, 10.93; 95% confidence interval, 1.26-94.88) were found to be significantly more common in the active treatment group. Although all-cause and cardiovascular and respiratory mortalities decreased, the decreases were not statistically significant.\textsuperscript{62} In a postmarketing survey of 10,603 Danish patients, 2870 of whom received tiotropium, the RR for all-cause mortality, cardiac mortality, and respiratory mortality were lower with periods of tiotropium use than nonuse, but the reduction was not statistically significant.\textsuperscript{53}

Pharmacoeconomics

Several studies have evaluated the effect of tiotropium use on health care utilization and costs from countries outside the United States, including the Netherlands,\textsuperscript{64} Belgium,\textsuperscript{65} Greece,\textsuperscript{66} Singapore,\textsuperscript{67} and Spain.\textsuperscript{68} Because health care systems differ greatly among countries, studies performed outside the United States have little relevance to the pharmacoeconomics of tiotropium use in this country. Definitive studies from the United States have not been published, although preliminary data are available.

Friedman et al\textsuperscript{69} found that health care utilization costs were reduced with tiotropium use possibly because of a 20% decrease in the frequency of acute exacerbations and a 44% reduction in hospitalization. However, drug acquisition costs were not included in their calculation. In his retrospective analysis of the literature, Oba\textsuperscript{70} calculated that tiotropium resulted in lower costs than salmeterol or ipratropium in head-to-head trials and that this could also result in a gain in quality-adjusted life-years. It seems likely that the reduction in the frequency of acute exacerbations alone, which are responsible for at least half the overall costs associated with COPD, would reduce the costs of treating COPD. In addition to reducing costs, tiotropium use would improve patients’ quality of life and symptoms.

Conclusion

Appropriate treatment of COPD has a demonstrated benefit on outcomes. Appropriate selection of medication can reduce acute exacerbations, which are both clinically significant and expensive and affect other important patient-centered outcomes, such as quality of life, dyspnea, and exercise tolerance. When maintenance therapy is indicated, clinical evidence supports the use of long-acting agents, either an anticholinergic or β\textsubscript{2}-agonist. None of the current therapies have been shown to affect the long-term course of the disease, although the 4-year UPLIFT trial with tiotropium is designed to test this possibility. Results are expected in late 2008.
REFERENCES