The Role of Long-Acting Bronchodilators in the Management of Stable COPD*

Donald P. Tashkin, MD, FCCP; and Christopher B. Cooper, MD, FCCP

Bronchodilators form the foundation of symptomatic treatment of COPD. Several long-acting bronchodilators are now available for use in COPD, but publications of large-scale studies of their efficacy have, for the most part, postdated the publication of major clinical guidelines. This article provides a critical review of large (≥ 50 patients), double-blind, clinical trials of three long-acting bronchodilators in COPD (the once-daily anticholinergic tiotropium, and the twice-daily β2-agonists formoterol and salmeterol) within the context of the objectives of treatment defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines. Fourteen published studies were identified, of which 12 studies were published since the release of the GOLD guidelines. All three long-acting bronchodilators were found to effectively improve lung function; however, they differed in their effects on outcomes other than bronchodilation, with salmeterol demonstrating inconsistent efficacy compared with placebo in preventing exacerbations and improving health status, and only tiotropium demonstrating consistent superiority to the short-acting bronchodilator ipratropium. Based on this review, a treatment algorithm for the introduction of long-acting bronchodilators to patients with COPD is proposed, which includes the use of long-acting bronchodilators early in the treatment algorithm.

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Key words: bronchodilators; COPD; exacerbations; formoterol; Global Initiative for Chronic Obstructive Lung Disease; health status; lung function; salmeterol; tiotropium

Abbreviations: GOLD = Global Initiative for Chronic Obstructive Lung Disease; ICS = inhaled corticosteroid; SGRQ = St. George Respiratory Questionnaire; TDI = transition dyspnea index

COPD is characterized by reduced airflow on expiration due to airway obstruction that is partially reversible and usually worsens over time. Patients with COPD have reduced lung function and worsening of symptoms (exacerbations). The separate or combined effects of dyspnea, reduced exercise capacity, and repeated exacerbations cause impairment of the health-related quality of life of many patients with COPD,1 as well as causing a greater burden on health-care resources.2

Currently, COPD is the second most common noninfectious disease in the world, causing some 2.75 million deaths annually,3 and global mortality is predicted to more than double by 2030. The increasing burden of COPD has stimulated research into novel treatment approaches (including new pharmacotherapies) and optimized management strategies. An international collaboration has been convened, the Global Initiative for Chronic Obstructive Lung
Disease (GOLD), which seeks, among other objectives, to provide evidence-based recommendations for an integrated COPD management strategy. In 2001, the GOLD committee published guidelines for the diagnosis, management, and prevention of COPD, including recommendations for pharmacologic management.4

The GOLD guidelines provide a staging system for the classification of disease severity based on a combination of spirometric lung function and symptoms. In a departure from earlier guidelines, the GOLD guidelines identify a stage 0, which includes patients who may not have symptoms, and still have normal lung function, but are at risk of acquiring COPD by virtue of tobacco smoking or certain environmental exposures. Beyond stage 0, COPD is identified by the presence of airflow obstruction as primarily defined by a reduction in the forced expiratory ratio (FEV/FVC) below 70%. The severity of COPD is defined in four stages—mild, moderate, severe, and very severe—according to the severity of impairment in the FEV1.

The GOLD guidelines recommend a stepwise approach to disease management, with bronchodilators being the mainstay of treatment. Short-acting bronchodilators are recommended initially, as needed, in mild disease. As the disease progresses, regular maintenance treatment is indicated; for this, the guidelines note that long-acting bronchodilators are more convenient. In more severe disease, polypharmacy becomes common and a trial of inhaled corticosteroids is recommended.

The bronchodilators currently available for use in COPD can be broadly categorized into three classes: anticholinergics, β2-sympathomimetic agonists, and methylxanthines. All three have proven effective in improving lung function in patients with COPD, although the narrow therapeutic range of methylxanthines and their relatively weak bronchodilator effect make them a less attractive initial therapeutic option.

The GOLD guidelines do not, however, distinguish between anticholinergic and β2-agonist bronchodilators, regarding both as equally effective based on evidence then available. Nor do they provide specific guidance on the choice between inhaled long-acting and short-acting bronchodilators (simply noting that long-acting bronchodilators are more convenient). This position was perhaps inevitable given that, at the time the guidelines were being developed, only two studies5-7 of long-acting bronchodilators in COPD were available, and only one of these5 included an active comparator.

However, since initial publication of the GOLD guidelines in 2001, there have been 17 publications featuring data from large, comparative, double-blind studies of long-acting bronchodilators. These new studies provide a valuable body of evidence on the relative efficacy of short- and long-acting bronchodilators, as well as the relative efficacy of long-acting β2-agonists and anticholinergics. This review seeks to examine these new data within the context provided by the GOLD guidelines.

Rationale for the Use of Bronchodilators in COPD

Impaired lung function in COPD is caused by structural narrowing of the airways, combined with the effects of cholinergic vagal bronchoconstrictive tone and decreased lung elastic recoil.8,9 Bronchodilators improve the airflow limitation observed in patients with COPD by producing airway smooth-muscle relaxation, although β2-agonists and anticholinergics achieve this effect through different mechanisms. Anticholinergic bronchodilators (in particular, tiotropium) produce relaxation of airway smooth muscle through antagonism of acetylcholine at M3-muscarinic receptors on airway smooth muscle,10 whereas β2-agonists induce bronchodilation through stimulation of β2-receptors, leading to an increase in cyclic adenosine monophosphate (as also occurs with phosphodiesterase inhibitors, such as oral methylxanthines).11

The mechanistic differences between these two classes of inhaled bronchodilator are reflected in the relative utility of each for the management of COPD. Short-acting β2-agonists, such as albuterol, have a more rapid onset but shorter duration of action than anticholinergics, and thus are commonly prescribed as a “rescue” medication to help relieve acute bronchospasm. Inhaled anticholinergic medications, such as ipratropium, have a slower onset and slightly longer duration of action. One consequence of the differences in their modes of action is that the effects of combining anticholinergic and β2-agonist bronchodilators are additive, providing greater efficacy than either agent alone.12

The two classes of agent also differ in their nonbronchodilator effects. For example, muscarinic receptors play a role in regulating mucus secretion, although the effect of antimuscarinics on sputum volume is variable.13,14 Viral infections increase cholinergic tone, an effect that may be directly counteracted by anticholinergics.15 Ex vivo, long-acting β2-agonists have shown cellular effects beyond those exerted on bronchial smooth muscle, including effects on mucociliary transport and neutrophils.16-18 These nonbronchodilator effects may provide additional benefits, although the relevance (if any) of these effects to their clinical efficacy in COPD is currently unknown.
LONG-ACTING BRONchodILATORS

Three long-acting, inhaled bronchodilators have been approved in the United States or Europe for use in COPD: tiotropium (the most recently licensed), formoterol, and salmeterol. An overview of published, double-blind studies of long-acting bronchodilators in COPD involving at least 50 patients is given in Table 1.

Tiotropium, which became available in many parts of Europe in 2002, is a once-daily, long-acting, inhaled anticholinergic that, unlike the short-acting anticholinergic ipratropium, acts through prolonged M3-receptor blockade. Salmeterol, the first long-acting β2-agonist to be licensed for COPD, has been available for this indication since 1997 in Europe and since 1998 in the United States. Formoterol, approved for use in COPD in the United States and some European countries in 2001, is a long-acting β2-agonist that is administered, like salmeterol, twice daily.

Only one published trial has directly compared two long-acting bronchodilators; this study comprised two 6-month trials, both placebo controlled, comparing tiotropium with salmeterol. Although no large-scale, direct comparisons of the clinical efficacy of salmeterol and formoterol have been made, smaller studies have found that formoterol has an onset of action that is faster than salmeterol and similar to salbutamol.

Table 1—Overview of Published Double-Blind Studies of Long-Acting Bronchodilators in COPD Conducted in > 50 Patients

<table>
<thead>
<tr>
<th>Source</th>
<th>Long-Acting Bronchodilator</th>
<th>Control</th>
<th>Trial Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Casaburi et al (2002)</td>
<td>Tiotropium 18 μg/d</td>
<td>Placebo</td>
<td>1 yr</td>
</tr>
<tr>
<td>Vanclen et al (2002)</td>
<td>Tiotropium 18 μg/d</td>
<td>Ipratropium 40 μg qid</td>
<td>1 yr</td>
</tr>
<tr>
<td>Donohue et al (2002)</td>
<td>Tiotropium 18 μg/d</td>
<td>Placebo</td>
<td>6 mo</td>
</tr>
<tr>
<td>Brusasco et al (2003)</td>
<td>Tiotropium 18 μg/d</td>
<td>Placebo</td>
<td>6 mo</td>
</tr>
<tr>
<td>Aalbers et al (2002)</td>
<td>Formoterol 6 μg bid</td>
<td>Placebo</td>
<td>12 wk</td>
</tr>
<tr>
<td>Szafranski et al (2003)</td>
<td>Formoterol 4.5 μg bid</td>
<td>Placebo</td>
<td>12 mo</td>
</tr>
<tr>
<td>Jones and Bosh (1997)</td>
<td>Salmeterol 50 μg bid</td>
<td>Placebo</td>
<td>16 wk</td>
</tr>
<tr>
<td>Mahler et al (1999)</td>
<td>Salmeterol 50 μg bid</td>
<td>Placebo</td>
<td>12 wk</td>
</tr>
<tr>
<td>Rennard et al (2001)</td>
<td>Salmeterol 50 μg bid</td>
<td>Ipratropium 40 μg qid</td>
<td>12 wk</td>
</tr>
<tr>
<td>van Noord et al (2000)</td>
<td>Salmeterol 50 μg bid</td>
<td>Placebo</td>
<td>12 wk</td>
</tr>
<tr>
<td>Cazzola et al (2000)</td>
<td>Salmeterol 50 μg bid</td>
<td>Placebo</td>
<td>3 mo</td>
</tr>
<tr>
<td>Calverley et al (2003)</td>
<td>Salmeterol 50 μg bid</td>
<td>Placebo</td>
<td>52 wk</td>
</tr>
</tbody>
</table>
LONG-ACTING BRONchodilators and GOLD Treatment Goals

The GOLD guidelines⁴ specify the following practical objectives that define effective disease management: to relieve symptoms, improve exercise tolerance, prevent and treat exacerbations, prevent and treat complications, improve health status, reduce mortality, and prevent disease progression. The GOLD guidelines also note that these objectives should be achieved with a minimum of side effects.

In the following sections of this article we will compare published clinical trial data for each long-acting bronchodilator in the context of the objectives recommended by the GOLD committee. While preventing disease progression, preventing and treating complications, and reducing mortality are important goals of treatment, there have as yet been no published studies that have investigated the efficacy of long-acting bronchodilators with respect to these outcomes. We have, therefore, confined our review to the effects of these treatments on relieving symptoms, increasing exercise tolerance, preventing exacerbations, and improving health status. We have also reviewed the effects on lung function data since, although improved lung function is not explicitly stated by the GOLD as an objective of treatment, it is a fundamental measure of bronchodilator efficacy. A summary of the findings is shown in Table 2.

LUNG FUNCTION

All the long-acting bronchodilators have shown substantial improvements in lung function compared with placebo, although comparisons are made difficult by the multitude of end points employed. All three long-acting bronchodilators produce acute improvements in lung function that are similar to those observed with ipratropium. These are sustained for 24 h in the case of tiotropium, and 12 h in the cases of salmeterol and formoterol,⁵,¹⁹,²⁰,²⁴,²⁵,²⁸,³² although the improvement in FEV₁ area under the curve from 0 to 12 h with salmeterol compared with ipratropium was seen at only half the time points in one of two studies.⁵,²⁸ With long-term administration, both tiotropium and salmeterol significantly improved morning trough (predose) FEV₁ when compared with both placebo and ipratropium at all time points over 1 year.⁵,¹⁹,²⁰

Combination therapies appear to improve the bronchodilator effects of long-acting β₂-agonists. The simultaneous administration of salmeterol and ipratropium produced an additive effect on postdose FEV₁,²⁹ and a combination with either theophylline or fluticasone increased the effect of salmeterol on trough FEV₁.³¹ The combination of formoterol twice daily and ipratropium four times daily also improved morning trough FEV₁ compared with a combination of salbutamol and ipratropium.²⁶

All the long-acting bronchodilators, therefore, have shown efficacy over periods of either 12 h (salmeterol, formoterol) or 24 h (tiotropium). The only direct comparison of different classes of long-acting bronchodilators found that salmeterol and tiotropium had similar effects on day 1, but peak and average FEV₁ were significantly higher with tiotropium from day 15 onwards, and trough FEV₁ was significantly higher at 24 weeks.²¹,²² It appears that the difference at the end of the study (24 weeks) may be due, in part, to the fact that the response to tiotropium was maintained, whereas the response to salmeterol decreased over the time course of the study,²¹ suggesting the development of tachyphylaxis.

Other studies have not demonstrated tachyphylaxis to the bronchodilator effect of salmeterol. The latter observation may reflect the relatively shorter (12 to 16 weeks) duration of most trials, since another 24-week trial showed that the bronchodilator efficacy of salmeterol relative to placebo diminished over time, suggesting tachyphylaxis.³¹ Such tachyphylaxis would be consistent with the reduction in bronchodilator efficacy seen in long-term (90-day) studies of albuterol (since both albuterol and salmeterol are partial β-agonists).³⁸ In contrast, a 12-month study of formoterol (a full β-agonist) did not

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Improve Lung Function</th>
<th>Relieve Symptoms</th>
<th>Improve Exercise Tolerance</th>
<th>Reduce Exacerbation Frequency</th>
<th>Improve Health Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salmeterol</td>
<td>++</td>
<td>+</td>
<td>-</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>Formoterol</td>
<td>++</td>
<td>+</td>
<td>-†</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Tiotropium</td>
<td>+ ++</td>
<td>++</td>
<td>†</td>
<td>+</td>
<td>+ +</td>
</tr>
</tbody>
</table>

* = no demonstrated efficacy; +/- = equivocal efficacy; + = superior to placebo; ++ = superior to placebo and ipratropium; +++ = superior to placebo, ipratropium, and salmeterol.
† One study with < 50 patients found an improvement in exercise tolerance with formoterol.
‡ No published data.
reveal evidence of tachyphylaxis, although the earliest time point assessed in this study was 3 months after initiation of study drug, so that the possibility of early onset tachyphylaxis cannot be excluded.25

SYMPTOMS

One of the most important symptoms in COPD is dyspnea, or the perception of breathlessness.39 Most of the studies examined here used the transition dyspnea index (TDI), a validated instrument for the measurement of dyspnea that is incurred by activities of daily living in COPD.40 The TDI focal score is a total of three component scales, and a 1-U change is considered to be clinically meaningful.41

Tiotropium has been shown to improve TDI focal scores compared with both placebo and ipratropium at all time points over a 12-month period.19,20 Salmeterol did not improve TDI focal scores compared with theophylline,32 and it does not provide consistent benefit compared with placebo.5,22,28,34 Formoterol, 24 μg bid, but not 12 μg bid, improved TDI focal scores compared with placebo over 3 months,23 but formoterol has not yet been compared on this measure with other active treatments.

A second measure of COPD symptoms is patient use of “reliever” short-acting β₂-agonists, since a treatment that effectively reduces symptoms should also reduce the need for rescue medication. Tiotropium reduced the use of rescue medication compared with both placebo and ipratropium,19,20 whereas salmeterol at 50 μg and 100 μg reduced rescue medication use compared with placebo but not compared with ipratropium or theophylline.5,6,29,32,34 The effect of formoterol on the use of rescue medication has not been reported.

In many of these studies,5,6,19,27,28,32 COPD symptoms were also assessed by means of a patient diary record. The details of this assessment varied from study to study, but always involved assigning a score either to overall symptoms or to a series of symptoms commonly associated with COPD, such as cough, breathlessness, and chest tightness; however, there was no consistent effect of any long-acting bronchodilator on these outcomes, which may suggest that this instrument is not a sensitive outcome measure in COPD.

The evidence suggests, therefore, that tiotropium is superior to ipratropium in relieving dyspnea, and it also appears to have a more consistent effect compared with placebo than does salmeterol. There are fewer data for formoterol, but the data that do exist suggest that formoterol is superior to placebo.23–25

EXERCISE TOLERANCE

There have been few publications describing large-scale studies of the effects of long-acting bronchodilators on exercise tolerance in COPD, and those that have been published have yielded largely negative results. Formoterol did not improve shuttle walking test distances compared with placebo,21 and salmeterol did not improve the distance walked in the 6-min walking test.5,6,28 A more elaborate test of exercise performance is cycle ergometry, and a small study42 has found a significant effect of formoterol on time to exhaustion during an incremental work rate protocol. Recent presentations at national meetings indicate that larger studies (with > 50 patients) using cycle ergometry have been performed comparing the effects of tiotropium and placebo on exercise dyspnea (Borg scale) and endurance time. While results of these studies in abstract form43,44 suggest that tiotropium improves exercise tolerance, definitive peer-reviewed publications have not yet appeared.
based (worsening in two or more symptoms on any 1 day, coupled with a > 20% reduction in peak expiratory flow rate), and so is likely to have detected events that would not conventionally be thought of as exacerbations. The health-care–based definition was similar to that used in the salmeterol studies.

In addition to employing varying definitions of exacerbations, the studies reviewed here are of different lengths. The differences in study duration are important because exacerbations, in general, occur with an average annual frequency of one to two times and at most only a few times per year in any individual patient, so that longer studies are more likely to reveal significant effects.45

The 1-year studies19,20,22 of tiotropium found that it reduced the incidence of symptom-based exacerbations, the time to first exacerbation, and the time to first hospitalization compared with either placebo or ipratropium. However, although tiotropium also reduced the incidence of hospitalizations for COPD compared with placebo, it did not significantly reduce the incidence of hospitalizations compared with ipratropium.

Formoterol has been shown to reduce the number of bad days compared with placebo and theophylline, but not with ipratropium.21–25 Formoterol at 24 μg, but not lower doses, also reduced the number of exacerbations that were serious enough to require additional therapy compared with placebo.26,27

Salmeterol alone did not reduce the exacerbation rate compared with placebo in six of seven studies,5,6,22,25,29,31,34 although the combination of salmeterol plus ipratropium did29; in one study salmeterol did reduce the exacerbation rate in patients with a history of exacerbations. Salmeterol also does not seem to have a consistent effect on exacerbations compared with ipratropium,5,28 and did not reduce the incidence of exacerbations compared with theophylline.32

In summary, tiotropium has been shown to reduce the incidence of exacerbations over 12 months compared with both placebo and ipratropium. Salmeterol did not significantly reduce the incidence of exacerbations compared with placebo in five of six 12- to 16-week studies, although a combination of salmeterol and ipratropium may provide a protective effect against exacerbations. Formoterol at 24 μg, but not 12 μg, appears to offer a protective effect against moderate-to-severe exacerbations over 12 months, while lower doses reduce the incidence of mild exacerbations.

**HEALTH STATUS**

Health status is a broad term that encompasses the patient’s overall health, with particular emphasis on the impact of impaired health on his or her quality of life. Measures of health status can be either generic (ie, applicable across a range of diseases) or disease specific. In COPD, the most commonly used measure of health status is the disease-specific St. George Respiratory Questionnaire (SGRQ), which consists of three components (symptoms, activity, and impacts).49 The Chronic Respiratory Disease Questionnaire is also commonly used.50 For both scales, thresholds of change have been defined that are regarded as clinically meaningful.51

Tiotropium improved health status as measured by SGRQ compared with both placebo and ipratropium.19,20 Tiotropium, but not salmeterol, improved SGRQ scores compared with placebo, and more patients achieved a clinically meaningful improvement in SGRQ scores with tiotropium vs placebo as compared with salmeterol vs placebo.22 Formoterol was superior on the SGRQ total score to placebo and ipratropium over 12 weeks, but not to placebo over 1 year or theophylline over 12 months.24,25,27

Most studies of salmeterol have not shown any significant effect on health status compared with either placebo,28,30,31,34,35 ipratropium,5,28 or theophylline.52 The combination of salmeterol and ipratropium also did not improve overall health-related quality of life compared with placebo, although the combination did provide clinically and statistically significant improvements in the SGRQ symptom domain.30

Only one study6,7 has found a significant effect of salmeterol on health status compared with placebo, finding a significant benefit of low-dose (50 μg) salmeterol compared with high-dose (100 μg bid) salmeterol. The latter interesting result was hypothesized to be due to greater CNS stimulation as evidenced by the higher incidence of tremor in the high-dose group. These effects may have led to sleep disturbances and worse overall health status, thereby counteracting the improvements that would be expected due to a reduction in respiratory symptoms.

Studies published to date, therefore, show that both tiotropium and formoterol have demonstrated improvements in health status compared with placebo and ipratropium. However, while there may be some benefit on health status with salmeterol compared with placebo, no consistent effect has been demonstrated.

**SAFETY AND TOLERABILITY**

All long-acting bronchodilators appear to have good safety and tolerability profiles. Tiotropium was associated with a higher incidence of dry mouth (a class effect of anticholinergics) in all the studies.
-reviewed, although most cases were mild and there were few resultant withdrawals. Formoterol appeared to be associated with increased tachycardia and tremor in one study. Both tremor and tachycardia are a class effect of β2-agonist use and are unlikely to be problematic at recommended doses unless the patient suffers from preexisting arrhythmia and hypoxemia. Rennard et al. reported that salmeterol was associated with an increased incidence of adverse events related to the ear, nose, and throat, although this was not found in other trials, and salmeterol 100 μg was associated with a higher incidence of tremor.

**DISCUSSION**

This review has sought to examine the evidence for the efficacy of long-acting bronchodilators in COPD from within the framework provided by the GOLD guidelines. To this end, we have examined the mechanistic differences between β2-agonists and anticholinergics, and reviewed the results of important studies of three long-acting bronchodilators: a once-daily M3-antagonist (tiotropium), and two twice-daily β2-agonists (salmeterol and formoterol).

The trials reviewed here used different patient inclusion criteria, employed somewhat different end points, and were of varying duration. These differences in study design and subject characteristics likely influenced the results; therefore, it is difficult to judge the relative efficacy of different pharmacotherapeutic agents based on these trials, underscoring the need for more head-to-head clinical trials.

The studies reviewed have shown that all the available long-acting bronchodilators are effective in improving lung function, but that they vary in their effects on other clinical outcomes. Salmeterol, in particular, has demonstrated inconsistent efficacy in symptom relief, prevention of exacerbations, and improvement of health status. This conclusion is in accord with a formal meta-analysis of the use of salmeterol in COPD. Formoterol, also, has demonstrated inconsistent effects on symptoms compared with placebo, although high-dose formoterol (24 μg) does appear to reduce moderate-to-severe exacerbations. Of the three long-acting bronchodilators, only tiotropium has demonstrated superiority to both placebo and ipratropium on the outcomes reviewed, except for exercise tolerance (for which published data are not yet available). These different effects on outcomes may reflect differences in either the mechanism or the duration of action of these agents, or a combination of both.

As discussed earlier, the GOLD guidelines do not provide much guidance on the role of long-acting bronchodilators in COPD, an inevitable consequence of the paucity of data available when the guidelines were drafted; however, based on the review of data available from clinical trials now published, it is reasonable to propose some specific recommendations with regard to the relative role of tiotropium, formoterol, and salmeterol in the maintenance treatment of COPD. An algorithm for the introduction of the various treatment alternatives, based on the framework of the GOLD guidelines, is suggested in Table 3 and Figure 1. Some of the principles that led to the development of this algorithm will be described briefly below.

The introduction of bronchodilator and other treatments is stratified according to the classification and staging of COPD proposed in the GOLD guidelines. Table 3 illustrates this classification and staging along with the defining pulmonary function impairments at each level, and what are regarded as typical symptoms for each stage. The fact that individual patients might not exactly fit all categories shown in Table 3 is noted. Instead, the stratification chosen is meant as a general guide to disease severity. A typical age of presentation is assigned to each level of disease severity, and again this is meant only as a general expectation recognizing that individual patients may differ in age of presentation due to varying disease susceptibility and rates of disease progression. Also, patients often consciously or unconsciously avoid symptoms by adjusting their lifestyle, thus choosing to limit their range and magnitude of physical activities to prevent experiencing dyspnea. In these patients, maintenance bronchodilator therapy might permit an increase in physical activity while not necessarily reducing breathlessness. The list of investigations in Table 3 is also meant as a guide to what might be deemed an appropriate degree of investigation for each stage. While Table 3 separates bronchodilator therapy from other treatments, Figure 1 focuses on inhaled therapies, including corticosteroids, in order to illustrate a proposed three-step approach.

Figure 1 illustrates two alternative pathways for the staged introduction of long-acting bronchodilator therapy with increasing COPD severity. Both pathways lead from as-needed, short-acting bronchodilators alone in mild disease (stage I) to a single long-acting bronchodilator plus an as-needed, short-acting agent in moderate disease (stage II), to the combination of long-acting anticholinergic and long-acting β2-adrenergic therapy with progression of disease severity with or without the addition of inhaled corticosteroids for patients with frequent exacerbations or inadequate symptom control despite optimal treatment with bronchodilators alone (stage III/IV). However, available evidence, already
Table 3—COPD Staging by Symptoms, Pulmonary Function, and Management Algorithms*

<table>
<thead>
<tr>
<th>Classifications</th>
<th>GOLD Stage</th>
<th>Typical Age, yr</th>
<th>Typical Symptoms</th>
<th>Appropriate Investigations</th>
<th>FEV&lt;sub&gt;i&lt;/sub&gt;/FVC, %</th>
<th>FEV&lt;sub&gt;i&lt;/sub&gt;, % Predicted</th>
<th>Bronchodilator Therapy</th>
<th>Other Treatments</th>
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<tr>
<td>At risk</td>
<td>O</td>
<td>&gt; 20</td>
<td>None</td>
<td>None</td>
<td>Normal</td>
<td>Normal</td>
<td>None</td>
<td>Smoking cessation</td>
</tr>
<tr>
<td>Mild I</td>
<td>&gt; 35</td>
<td>None</td>
<td>Productive cough</td>
<td>Screening spirometry</td>
<td>&lt; 70</td>
<td>≥ 80</td>
<td>As needed, short-acting bronchodilator (eg, ipratropium, albuterol or combination therapy)</td>
<td>Smoking cessation</td>
</tr>
<tr>
<td>Moderate II</td>
<td>&gt; 50</td>
<td>Productive cough; reduced physical activity with or without exertional dyspnea, episodes of acute bronchitis</td>
<td>Spirometry before and after bronchodilator</td>
<td>&lt; 70</td>
<td>&lt; 80 and ≥ 50</td>
<td>Tiotropium (algorithm step 1); with or without short-acting bronchodilator (eg, albuterol)</td>
<td>Smoking cessation; rehabilitative exercise</td>
<td></td>
</tr>
<tr>
<td>Moderately severe III</td>
<td>&gt; 60</td>
<td>Productive cough; dyspnea with moderate exertion; occasional exacerbations</td>
<td>Annual pulmonary function testing; annual arterial blood gas analysis; chest radiograph</td>
<td>&lt; 70</td>
<td>&lt; 50 and ≥ 30</td>
<td>Tiotropium; long-acting β-agonist bronchodilator (algorithm step 2) [eg, salmeterol or formoterol]</td>
<td>Smoking cessation; rehabilitative exercise; supplemental oxygen if indicated; with or without trial of ICS</td>
<td></td>
</tr>
<tr>
<td>Severe IV</td>
<td>&gt; 70</td>
<td>Productive cough; dyspnea with mild exertion or at rest; frequent exacerbations; with or without ankle swelling</td>
<td>Six-monthly pulmonary function testing; annual arterial blood gas analysis; chest radiograph</td>
<td>&lt; 70</td>
<td>&lt; 30</td>
<td>Tiotropium; long-acting β-agonist bronchodilator (eg, salmeterol or formoterol); with or without methylxanthine</td>
<td>Smoking cessation; rehabilitative exercise; with or without supplemental oxygen; ICS (algorithm step 3)</td>
<td></td>
</tr>
</tbody>
</table>

*This is a general schema. Individual patients may not exactly fit the classifications of COPD shown.
†Alternatively, the right-hand pathway shown in Figure 1 could be selected at this step.
‡A short-acting bronchodilator can be used for rescue medication.
§Low-dose methylxanthines can be prescribed if the response to inhaled bronchodilator therapy is insufficient.
‖ICS indicated if repeated exacerbations requiring treatment with antibiotics and/or oral glucocorticoids.
reviewed, suggests certain advantages in choosing the left-hand pathway (in bold in figure) in less severe disease (stage II). The rationale for preferring the three-step algorithm (presented in the left of Fig 1) over alternatives is presented below.

All the long-acting bronchodilators have demonstrated superior efficacy on at least some outcomes compared with short-acting bronchodilators. Therefore, the use of short-acting bronchodilators should be restricted to symptomatic relief for patients with infrequent, intermittent symptoms, and long-acting bronchodilators should be used for maintenance treatment.

Patients whose symptoms are not adequately controlled with short-acting bronchodilators, or whose use of relief medication becomes more frequent or regular rather than intermittent, should be given a long-acting bronchodilator. The proposed algorithm provides a three-step schedule for introducing these to the patient, depending on the level of disease severity.

The evidence reviewed above suggests that, of the long-acting bronchodilators, tiotropium provides the most consistent improvements on the widest range of outcomes. Therefore, the recommended step 1 is the introduction of tiotropium. As with other long-acting bronchodilators, tiotropium should be given in combination with a reliever medication (short-acting rescue β₂-agonist medication was available to all patients in the studies reviewed).

Studies of the combination of long-acting anticholinergics and long-acting β₂-agonists have not been published. However, both salmeterol and formoterol in combination with ipratropium have additive ef-

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**Figure 1.** The proposed three-step algorithm (1, 2, and 3; bold arrows) for mild, moderate, and severe COPD. #Alternatively, the right-hand pathway (arrows) could be selected at this stage. §A short-acting bronchodilator can be used for rescue medication. ‡ICS indicated if repeated exacerbations requiring treatment with antibiotics or oral glucocorticoids; or if favorable response (decreased symptoms, increased lung function, and/or decreased health care utilization). †Low-dose methylxanthines can be prescribed if the response to inhaled bronchodilator therapy is insufficient.
fects on lung function and other outcomes, so that it seems reasonable to expect that the combination of long-acting anticholinergics and long-acting β2-agonists will provide additive benefits similar to those observed with a combination of short-acting bronchodilators. In patients with more severe symptoms, it is reasonable, therefore, to add salmeterol or formoterol to tiotropium.

As suggested in the GOLD guidelines, other pharmacotherapeutic agents, such as an inhaled corticosteroid (ICS) and theophylline, should be reserved for patients whose symptoms are not adequately controlled and/or have frequent exacerbations despite treatment with inhaled bronchodilators, although these recommendations may change as clinical trials of combinations of ICS and long-acting bronchodilators are published.27,34,35 The placement of these in Table 3 and Figure 1 follows the GOLD precedent.

The treatment algorithm shown represents the first attempt to provide an evidence-based rationale for the appropriate use of long-acting bronchodilators in COPD. In future, new studies comparing combinations of long-acting bronchodilators with one another and with ICS will help to define further the role of combination therapy in COPD. Moreover, since some of the treatment goals listed by GOLD have not been adequately studied, it is important for future studies to address the potential effects of long-acting bronchodilators on long-term outcomes, such as disease progression and mortality. However, a substantial body of data on these long-acting bronchodilators has already been published and, as reviewed here, the evidence for the utility of long-acting bronchodilators, alone and in different combinations (with or without ICS), in COPD is well established.

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