

# A Stepwise Approach to Management of Stable COPD With Inhaled Pharmacotherapy: A Review

Ruben D Restrepo MD RRT FAARC

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Although existing evidence confirms that no pharmacologic agent ameliorates the decline in the lung function or changes the prognosis of chronic obstructive pulmonary disease (COPD), inhaled pharmacotherapy is a critical component of the management for patients suffering with COPD. Inhaled agents are directed to provide immediate relief of symptoms and to restore functional capacity in treatment of stable COPD. While COPD may not be cured, knowledge and implementation of currently available guidelines provide the health-care provider alternatives to treat the disease effectively. Respiratory therapists play an important role in the implementation of these guidelines, since they are often responsible for educating patients on the correct use of the inhalers. This paper reviews current evidence regarding the use of inhaled pharmacotherapy in the treatment of COPD and provides a guided approach to the use of different agents in stable COPD. *Key words: anticholinergics,  $\beta$  adrenergics, COPD, chronic obstructive pulmonary disease, Global Initiative for Chronic Obstructive Lung Disease, GOLD, guidelines, inhalation pharmacotherapy.* [Respir Care 2009;54(8):1058–1081. © 2009 Daedalus Enterprises]

## Introduction

Chronic obstructive pulmonary disease (COPD) is a condition estimated to affect approximately 8% of the popu-

lation and approximately 10% of individuals older than 40 years.<sup>1</sup> COPD is expected to become the third leading cause of death by 2020.<sup>2</sup> The Global Initiative for Chronic

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Ruben D Restrepo MD RRT FAARC is affiliated with the Department of Respiratory Care, The University of Texas Health Science Center at San Antonio, San Antonio, Texas.

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Correspondence: Ruben D Restrepo MD RRT FAARC, Department of Respiratory Care, The University of Texas Health Science Center at San Antonio, Texas, MSC 6248, San Antonio TX 78229. E-mail: restrepor@uthscsa.edu.

New	0: At Risk	I: Mild	II: Moderate	III: Severe	IV: Very Severe
Characteristics	<ul style="list-style-type: none"> <li>Chronic symptoms</li> <li>Exposure to risk factors</li> <li>Normal spirometry</li> </ul>	<ul style="list-style-type: none"> <li>FEV<sub>1</sub>/FVC &lt; 70%</li> <li>FEV<sub>1</sub> ≥ 80%</li> <li>With or without symptoms</li> </ul>	<ul style="list-style-type: none"> <li>FEV<sub>1</sub>/FVC &lt; 70%</li> <li>50% ≤ FEV<sub>1</sub> &lt; 80%</li> <li>With or without symptoms</li> </ul>	<ul style="list-style-type: none"> <li>FEV<sub>1</sub>/FVC &lt; 70%</li> <li>30% ≤ FEV<sub>1</sub> &lt; 50%</li> <li>With or without symptoms</li> </ul>	<ul style="list-style-type: none"> <li>FEV<sub>1</sub>/FVC &lt; 70%</li> <li>FEV<sub>1</sub> ≥ 30% or presence of chronic respiratory failure or right heart failure</li> </ul>
Avoidance of risk factor(s); influenza vaccination					
Add short-acting bronchodilator when needed					
Add regular treatment with one or more long-acting bronchodilators Add rehabilitation					
Add inhaled glucocorticosteroids if repeated exacerbations					
Add long-term oxygen if chronic respiratory failure Consider surgical treatments					

Fig. 1. Global Initiative for Chronic Obstructive Lung Disease recommendations for treatment at each stage of chronic obstructive pulmonary disease (COPD). FEV<sub>1</sub> = forced expiratory volume in the first second. FVC = forced vital capacity. (From Reference 3, with permission.)

Obstructive Lung Disease (GOLD) evidence-based guidelines for the treatment and management of COPD are the result of collaborations of worldwide leading experts in COPD and organizations that include the World Health Organization and the National Heart, Lung and Blood Institute. The staging system established by these guidelines defines severity of stable COPD according to airflow limitation, and also guides management (Fig. 1).<sup>3</sup> Additionally, other professional societies have published guidelines for the treatment and management of COPD.<sup>4-6</sup>

Despite the availability of these publications, health-care providers lack awareness and understanding of COPD management.<sup>7,8</sup> Respiratory therapists (RTs) are most often the health-care providers responsible not only for administration of the available pharmacologic agents used in patients who suffer from COPD but also for the instruction on the different delivery devices. It is critical that RTs acquire the necessary knowledge of the guidelines to optimize treatment of their patients with COPD. Awareness and knowledge of a stepwise approach at times allow redirection of therapy, when well communicated to the primary-care physician ultimately responsible for patient management.

While smoking cessation is the most important intervention to manage COPD, pharmacologic agents should be added in a stepwise fashion once the diagnosis of COPD is made. Optimizing bronchodilator therapy is probably the most important pharmacologic approach in stable COPD; however, it is important to realize that to this date, no medication has been shown to conclusively alter the decline in lung function that is the hallmark of COPD or the natural history of COPD.<sup>9</sup> Since treatment does not

alter the natural history of the disease, inhaled pharmacotherapy for COPD is used to prevent and decrease symptoms (especially dyspnea), improve patients' exercise tolerance and health status, ameliorate disease progression, prevent and treat complications and exacerbations, and reduce the risk of death from COPD.<sup>3</sup> The growing interest in newer agents and their combinations, as well as controversial findings coming from recent meta-analysis, have emerged as the reasons why the last word on optimal pharmacotherapy for patients with COPD is far from being written. This paper is an attempt to review the existing evidence to support the current stepwise approach to inhaled pharmacotherapy in the management of patients with stable COPD.

### Available Agents

Two different categories of inhaled agents are available for the management of stable COPD: bronchodilators and corticosteroids.

### Bronchodilators

Aerosolized bronchodilators are the cornerstone of the inhaled pharmacotherapy for patients with COPD. They include β<sub>2</sub> adrenergic agents and anticholinergics in their short-acting and long-acting formulations. Although several studies have failed to demonstrate improvement in lung function following a single dose, it is unquestionable that bronchodilators have been shown to induce significant long-term improvements in symptoms, exercise capacity, and airflow limitation.<sup>10-13</sup> Despite the staging of COPD,

all symptomatic patients should be prescribed a short-acting bronchodilator to be used on an as-needed basis.<sup>3</sup> If symptoms are inadequately controlled with short-acting bronchodilator therapy, a long-acting bronchodilator should be added to the regularly scheduled therapy. Although most bronchodilators can be administered orally, subcutaneously, or intravenously, inhalation is the recommended route of delivery. A nebulizer, metered-dose inhaler (MDI), or dry-powder inhaler (DPI) maximize the bronchodilator's direct effect on the airways, while minimizing systemic effects. Any of these devices, when used properly, achieve an equivalent bronchodilator response.<sup>14</sup>

Since all of the short-acting bronchodilators improve symptoms and lung function, the question that the RT has to answer when managing a patient with mild symptoms is which short-acting bronchodilator is the best. Short-acting  $\beta_2$  adrenergic agents (SABAs) and short-acting anticholinergics (SAACs) can be used alone or in combination. While SABAs have a rapid onset of action, combination therapy (SABA/SAAC) may be more effective in achieving a bronchodilator response than either agent alone.<sup>15</sup>

### Anticholinergics

Inhaled anticholinergic medications decrease bronchoconstriction by reducing smooth muscle tone and glandular mucus.<sup>16,17</sup> Available anticholinergics, such as ipratropium and tiotropium, contain a quaternary ammonium that is responsible for the lack of penetration of the blood-brain barrier, lower systemic absorption, and a longer duration of action than their predecessor, the tertiary amine, atropine.<sup>18,19</sup> Atropine and scopolamine are the most important pharmacologically active and naturally occurring anticholinergic alkaloids.<sup>20,21</sup> In COPD, bronchoconstriction and mucus secretion are caused mostly by increased parasympathetic nerve activity, mediated by muscarinic receptors. Anticholinergic agents compete with acetylcholine at these receptors on airway smooth muscle, decreasing the intracellular concentration of cyclic guanosine monophosphate (cGMP) and inhibiting tonic cholinergic activity.<sup>22,23</sup>

There are at least 5 subtypes of muscarinic receptors.<sup>24</sup> At least 3 of these are expressed in the lung: M1 receptors are present on peribronchial ganglion cells, where the preganglionic nerves transmit to the postganglionic nerves; M2 receptors are present on the postganglionic nerves; and M3 receptors are present on smooth muscle. M1 and M3 receptors mediate the parasympathetic bronchoconstrictive effect of the vagus nerve. The submucosal glands are also innervated by parasympathetic neurons and have predominantly M3 receptors. The activation of M1 and M3 receptors by acetylcholine and its analogs stimulates secretion by tracheobronchial glands and causes bronchoconstriction. On the other hand, activation of M2 receptors

limits further production of acetylcholine and protects against parasympathetic-mediated bronchoconstriction.<sup>21,24</sup> An ideal anticholinergic agent would inhibit only the M1 and M3 receptors and spare the M2 receptors. Currently available anticholinergic agents, however, inhibit all 3 receptor subtypes.<sup>21,24</sup>

**Short-Acting Anticholinergics.** Among the anticholinergic agents, ipratropium has probably been the most widely administered therapy for COPD, alone or in combination.<sup>9</sup> Ipratropium (Atrovent, Boehringer Ingelheim, Ridgefield, Connecticut) is an anticholinergic bronchodilator that is a synthetic quaternary ammonium compound chemically related to atropine.<sup>22</sup> Ipratropium is poorly absorbed into the circulation from either the nasal mucosa or from the airway, and its half-life of elimination is about 1.6 hours after inhalation administration.<sup>21,25</sup> Ipratropium is a non-selective antagonist of M1, M2, and M3 receptors. The blockade of the M2 receptor subtype allows further release of presynaptic acetylcholine and may antagonize the bronchodilatory effect of blocking the M3 receptor.

Ipratropium is available as a nebulizable solution of 0.02% concentration in a 2.5-mL vial, and as a nasal spray of 0.03% and 0.06% strength. Each actuation of the MDI delivers 18  $\mu\text{g}$  of ipratropium from the mouthpiece. In controlled studies of patients with bronchospasm associated with COPD, ipratropium has been associated with significant improvements in pulmonary function within 15 min. Its peak of action is reached in 1–2 hours and persists for periods of 3–4 hours in the majority of patients, both as monotherapy and as a combination with SABA, and up to 6 hours in some patients.<sup>23,26,27</sup> The recommended doses of the MDI and the nebulizable solutions are 36  $\mu\text{g}$  4 times a day, and 2.5 mL vial (500  $\mu\text{g}$ ) 3–4 times a day, respectively. Although higher doses may be required to obtain a maximal effect in patients with more severe airway disease, tachyphylaxis to ipratropium has not been demonstrated.<sup>28</sup> Combinations of ipratropium with albuterol are also available in MDI form, as Combivent (Boehringer Ingelheim), and in nebulizer form, as DuoNeb (Dey, Napa, California). The use of these combinations in stable COPD is described later in this section.

Ipratropium has been shown to decrease dyspnea, increase exercise tolerance, and improve gas exchange in patients with stable COPD.<sup>29</sup> However, it does not have anti-inflammatory properties and does not change the natural history of COPD or its mortality.<sup>9,30</sup> In a landmark study, the Lung Health Study,<sup>9</sup> ipratropium was the bronchodilator of choice in patients with COPD, because of its low frequency of adverse effects, relatively long duration of action, and demonstrated bronchodilator effect. However, the investigators supported the use of bronchodilators only for symptomatic benefit, including relief of dyspnea and improvement in exercise tolerance.<sup>9</sup> Ipratro-

pium has been shown to be at least similar to or better than SABA in relieving bronchospasm in patients with stable COPD and at producing bronchodilation in patients who lacked prior response to SABAs.<sup>9,29,31</sup> Several randomized controlled trials (RCTs) compared at least 4 weeks of treatment with ipratropium alone or in combination with SABAs in almost 4,000 patients with stable COPD.<sup>15,32-39</sup> Ipratropium showed a small benefit over SABAs on lung-function outcomes, improvement in health-related quality of life (HRQL), and reduction in the requirement for oral steroids.<sup>40</sup> No significant changes in electrocardiographic and hemodynamic assessment were observed when combination therapy with SABAs was compared with SABA therapy alone over 85 days of evaluation.<sup>41</sup>

While both SAACs and SABAs are effective bronchodilator agents, inhaled SAACs have been preferred by many over SABAs in patients with stable COPD, because of its minimal cardiac stimulatory effects and its greater effectiveness than SABAs.<sup>16</sup> Ipratropium is the only SAAC currently available for the management of patients with COPD.

**Long-Acting Anticholinergics.** The only inhaled long-acting anticholinergic (LAAC) currently available to manage patients who suffer from COPD is tiotropium. Tiotropium is a second-generation quaternary ammonium compound introduced in the early 2000s, which is structurally related to ipratropium. Although most of the pharmacologic features and adverse effects are similar in all quaternary ammoniums, tiotropium differs from other anticholinergics in its functional relative selectivity and higher affinity for muscarinic receptor subtypes. It displays a 6–20-fold higher affinity for muscarinic receptors when compared with ipratropium.<sup>42</sup> Although tiotropium binds to all 3 muscarinic receptors, it dissociates much faster from the M2 receptors, resulting in a more selective antagonist action for M1 and M3 muscarinic receptor subtypes.<sup>43,44</sup> Its prolonged pharmacologic activity is the result of its slow dissociation from M1 and M3 receptors. The half-life of the tiotropium-M3 receptor complex is approximately 35 hours, compared with 0.3 hours for ipratropium (Fig. 2).<sup>18,42,44,45</sup>

Tiotropium is available as a DPI (Spiriva HandiHaler, Boehringer Ingelheim). The capsule contains 18  $\mu\text{g}$  of tiotropium (equivalent to 22.5  $\mu\text{g}$  of tiotropium). A “soft mist” form delivered by the Respimat device (Boehringer Ingelheim) is also available in some countries. Commercial combinations of tiotropium and other bronchodilator agents are not currently available. After the recommended dose of 18  $\mu\text{g}$ , mean time to onset of effect is 30 min and mean time to peak effect is about 3 hours. Subsequent doses increase efficacy until maximum effect is obtained after 1 week.<sup>46-49</sup> Tiotropium gives a prolonged, dose-dependent protection against inhaled methacholine challenge.<sup>46</sup>

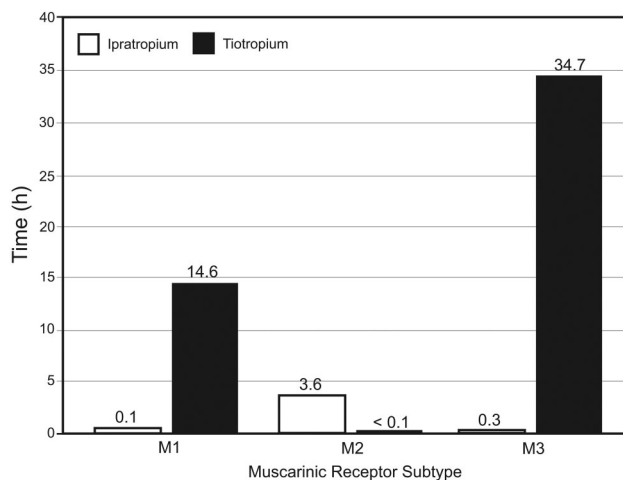


Fig. 2. Half-life muscarinic receptor complex comparison between ipratropium and tiotropium. Although tiotropium binds to all 3 muscarinic receptors, it dissociates much faster from the M2 receptors, resulting in a more selective antagonist action for M1 and M3 muscarinic receptor subtypes. (Data from References 18 and 45.)

Recent systematic reviews by Barr et al<sup>50</sup> and by Rodrigo and Nannini<sup>51</sup> have reported the results of several RCTs where tiotropium was compared to placebo<sup>52-56</sup> and ipratropium<sup>57</sup> in the treatment of patients with stable COPD. The mean duration of the trials was 7 months. The severity of COPD was generally moderate to severe; 38–80% of patients were taking ipratropium at enrollment, 32–50% were taking long-acting  $\beta_2$  adrenergic agents (LABAs), and 42–80% were taking inhaled corticosteroids (ICSs). Tiotropium, 18  $\mu\text{g}$  once daily, resulted in significantly better improvement in lung function studies than either ipratropium 36  $\mu\text{g}$  4 times daily or salmeterol 42  $\mu\text{g}$  twice daily.<sup>57</sup> Treatment with tiotropium was associated with increases in FEV<sub>1</sub> and FVC from baseline up to a year, when compared with placebo, and ipratropium. The rate of decline in FEV<sub>1</sub> was significantly slower with tiotropium versus placebo and ipratropium.<sup>57</sup>

It has been suggested that use of tiotropium increases endurance and improves symptom-limited exercise performance by reducing hyperinflation.<sup>58,59</sup> Tiotropium has been associated with significantly reduced rescue inhaler use,<sup>60</sup> reduced risk of a COPD exacerbation, and delayed time to an exacerbation, compared with both placebo and ipratropium. Dusser et al<sup>55</sup> also found that tiotropium was not associated with statistically significant differences in cardiovascular mortality, cancer mortality, or mortality from other causes. No significant differences were found in all-cause mortality between tiotropium and placebo, ipratropium, or salmeterol. The mean change in Saint George's Respiratory Questionnaire (SGRQ) score over the course of the trials was larger with tiotropium than with placebo or with ipratropium. Results of a study by Adams et al<sup>61</sup> suggest that maintenance therapy with tiotropium improves

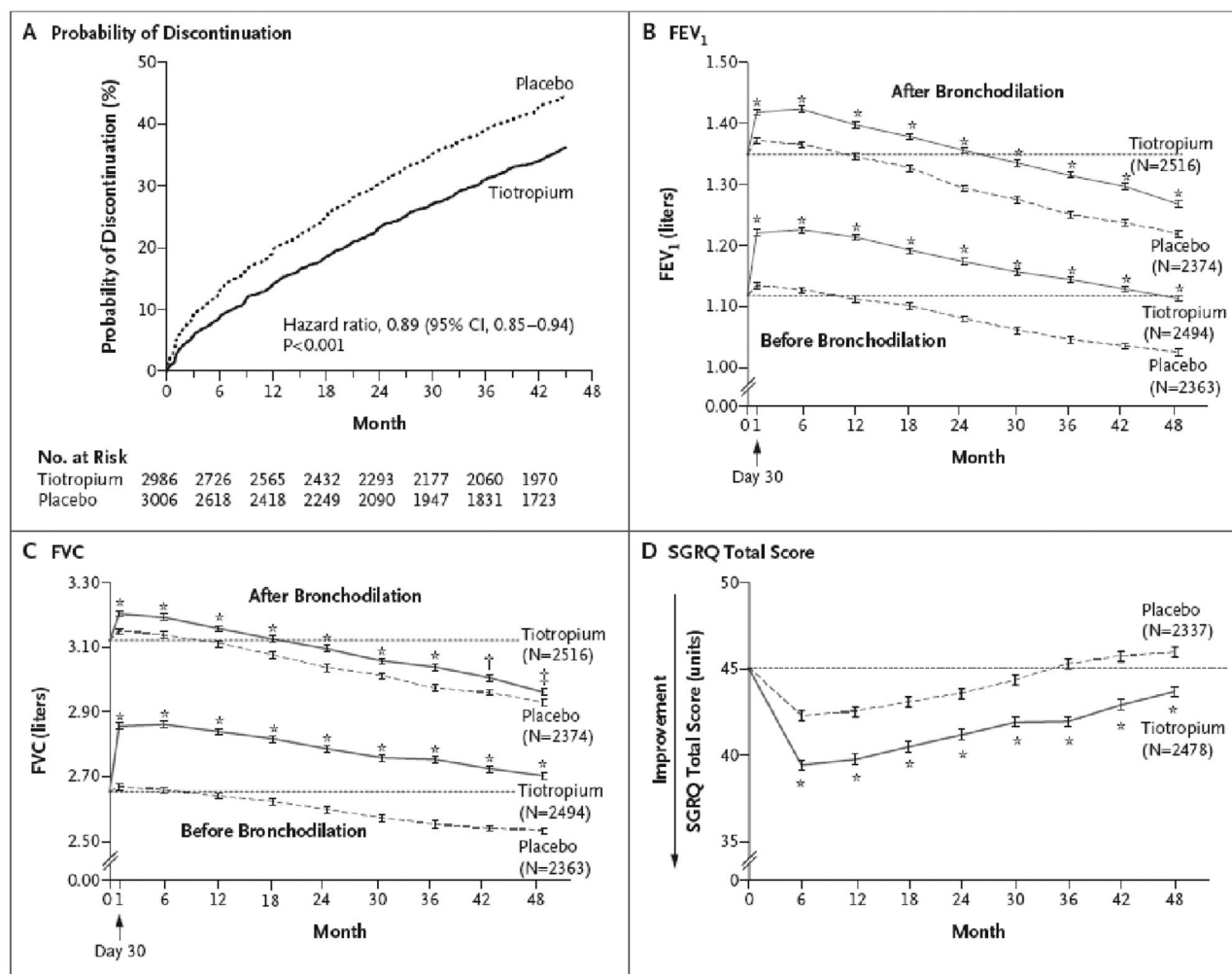


Fig. 3. A: Probability of treatment discontinuation in the tiotropium group and the placebo group. B: Estimated mean forced expiratory volume in the first second (FEV<sub>1</sub>) before and after bronchodilation from day 30 to the end of the study. Before bronchodilation the annual rates of decline were the same in the tiotropium group and the placebo group: 30 ± 1 mL/y. After bronchodilation the annual rate of decline was 40 ± 1 mL/y in the tiotropium group, as compared with 42 ± 1 mL/y in the placebo group. C: Mean forced vital capacity (FVC) before and after bronchodilation from day 30 to the end of the study. Before bronchodilation the annual rate of decline was 43 ± 3 mL/y in the tiotropium group and 39 ± 3 mL/y in the placebo group. After bronchodilation the annual rates of decline were the same in the tiotropium group and the placebo group: 61 ± 3 mL/y. D: Health-related quality of life score from month 6 to the end of the study, as measured on the Saint George's Respiratory Questionnaire (SGRQ), which ranges from 0 to 100, with lower scores indicating improvement. The annual rate of change was 1.25 ± 0.09 units per year in the tiotropium group, as compared with 1.21 ± 0.09 units in the placebo group. Repeated-measures analysis of variance was used to estimate means. Means are adjusted for baseline measurements. For FEV<sub>1</sub> and FVC, patients with 3 or more acceptable pulmonary function tests after day 30 and no missing baseline values were included in the analysis. For the SGRQ total score, patients with 2 or more acceptable scores after month 6 and no missing baseline values were included in the analysis. The I bars represent standard errors, and the horizontal dashed lines represent baseline levels. \* P < .001. † P = .002. ‡ P = .04. (From Reference 62, with permission.)

lung function and health status in patients previously naïve to COPD maintenance therapy.

Based on the previous favorable clinical outcomes, Tashkin et al<sup>62</sup> conducted the Understanding Potential Long-Term Impacts on Function with Tiotropium (UPLIFT) trial. They prospectively enrolled 5,993 patients with COPD in a 4-year randomized double-blind parallel-group trial comparing therapy with either tiotropium or placebo: one of the largest COPD studies ever undertaken. These patients

were allowed to use all respiratory medications except inhaled anticholinergic drugs. Although previous reports had suggested that tiotropium may be associated with a significant reduction in the rate of decline in lung function, compared with placebo,<sup>63,64</sup> the UPLIFT trial showed no treatment differences in the rate of decline of trough or postbronchodilator FEV<sub>1</sub> (Fig. 3).<sup>62</sup> Tiotropium reduced the risk of COPD exacerbations by 14%, the risk of respiratory failure by 33%, and all-cause mortality during the

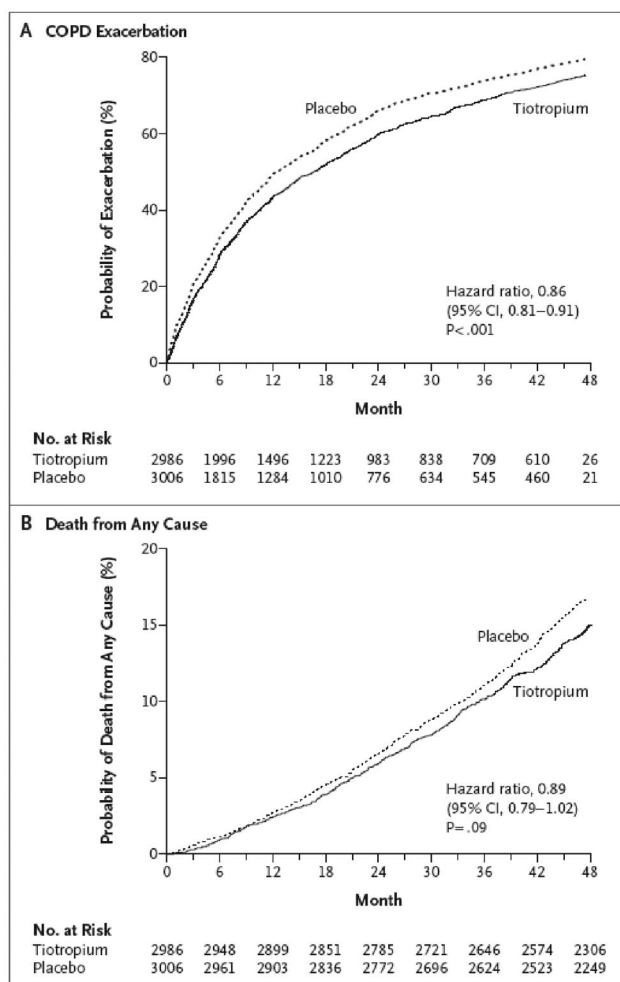


Fig. 4. Kaplan-Meier estimates of (A) the probability of chronic obstructive pulmonary disease (COPD) exacerbation, and (B) death from any cause at month 48 for all patients for whom data were available. *P* values were calculated with use of the log-rank test. CI (From Reference 62, with permission.)

treatment period by 16% (Fig. 4). The improvements of lung function and health status, the reduced exacerbations, and the decreased reports of respiratory failure were maintained over the 4-year treatment period.<sup>62</sup>

Since LAACs maintain a sustained bronchodilatory effect that is twice as long as that of LABAs, several studies have attempted to determine which pharmacologic group would be most effective in improving bronchodilation in patients with COPD.<sup>52,65-69</sup> The LABAs salmeterol and formoterol provide a faster onset of bronchodilation and trend toward greater peak effect, versus tiotropium.<sup>66-68</sup> Donohue et al<sup>68</sup> compared the effects of tiotropium and salmeterol in 623 patients with COPD during a 6-month placebo-controlled study. While tiotropium provided significantly superior bronchodilation, versus both placebo and salmeterol, the improvement in the total dyspnea index was not statistically significant. Brusasco et al<sup>52</sup> found

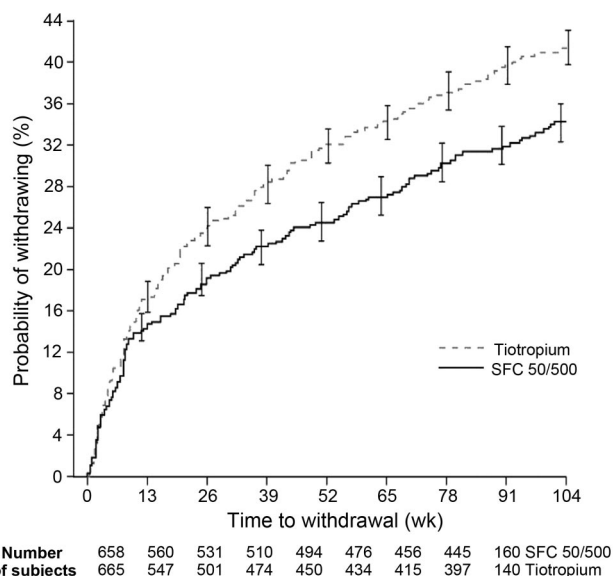


Fig. 5. Time to withdrawal on treatment in the salmeterol-plus-fluticasone propionate (SFC) and tiotropium treatment groups. (From Reference 71, with permission.)

that tiotropium had greater improvement in peak, trough, and mean FEV<sub>1</sub>, versus both salmeterol and placebo. Although tiotropium did not statistically differ from salmeterol in terms of outcomes other than bronchodilation, tiotropium did perform statistically and clinically better than placebo.<sup>52</sup> A 12-week study by Briggs et al<sup>69</sup> found that tiotropium was associated with a better mean peak and average FEV<sub>1</sub> response than salmeterol; however, data regarding exacerbations and incidence of adverse effects were not significantly different between the 2 groups.

A 6-week multicenter randomized double-blind triple-dummy pilot study by Bateman et al<sup>70</sup> compared the bronchodilator effects of tiotropium 18 μg once daily versus combination of salmeterol 50 μg plus fluticasone 250 μg twice daily in 107 patients with moderate to very severe COPD. At the end of the study period both groups of patients had a similar spirometric profile. In the INSPIRE trial, Wedzicha et al<sup>71</sup> randomized 1,323 patients with severe and very severe COPD during a 2-year period to salmeterol plus fluticasone (50 μg/500 μg) twice daily or tiotropium 18 μg once daily. They found no difference in exacerbation rate between salmeterol/fluticasone and tiotropium. More patients failed to complete the study while receiving tiotropium (Fig. 5). A small, statistically significant beneficial effect was found on health status and risk of mortality in the salmeterol/fluticasone-treated patients (Fig. 6).

#### Adverse Events of Anticholinergic Agents

Adverse drug effects play a critical role on patient's adherence to inhaled pharmacotherapy in stable COPD.<sup>72</sup>

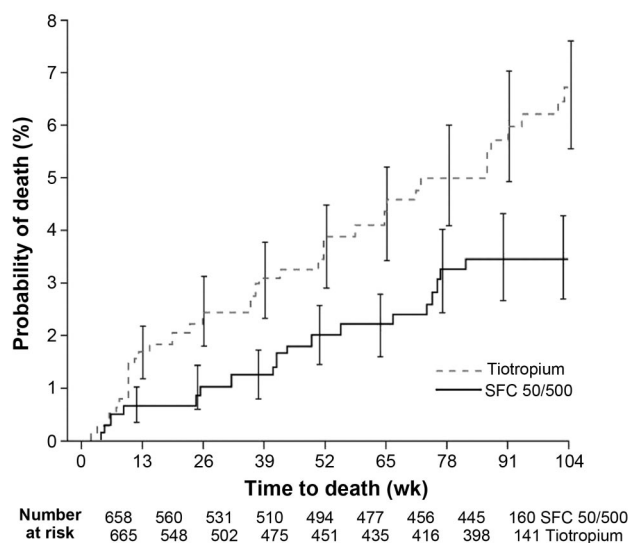


Fig. 6. Time to death on treatment in the salmeterol-plus-fluticasone propionate (SFC) and tiotropium treatment groups. (From Reference 71, with permission.)

Although maintenance therapy for COPD is generally well tolerated, adverse events have been reported in all long-term clinical studies of COPD. This is a combination of the adverse effects associated with pharmacotherapy plus the inherent severity of disease and the presence of comorbidities.

The actions and adverse effects of each of the anticholinergic agents are very similar. Since they are very poorly absorbed, all of the currently approved inhaled anticholinergic agents have a very wide therapeutic margin and are very well tolerated. Ipratropium and tiotropium have been studied for the well known adverse effects of atropine on pulmonary mucociliary clearance, increased intraocular pressure, and urinary outflow.<sup>26,73</sup> Unlike atropine, ipratropium and tiotropium lack appreciable effect on the central nervous system and do not inhibit mucociliary clearance.<sup>16</sup> If any of these agents have inadvertent contact with the eye, they can cause pupillary dilatation and blurred vision. Several case reports have correlated the use of a loose-fitting mask while administering ipratropium with anisocoria due to unilateral mydriasis.<sup>74,75</sup> The presence of acute anisocoria is clinically relevant, since its workup proves to be costly and sometimes invasive. This effect on the eye is particularly important in the case of tiotropium, since its prolonged duration of action may precipitate acute glaucoma. Dryness of the mouth is a common adverse effect of all anticholinergic agents<sup>76,77</sup>; however, it is rarely enough reason for the patient to discontinue therapy.

A recent meta-analysis by Barr et al<sup>50</sup> reported that dry mouth was significantly increased with tiotropium, compared with placebo, ipratropium, and salmeterol, and urinary tract infections were significantly increased, com-

pared with placebo and ipratropium. Bad taste and a brief coughing spell are occasional complaints. When comparing individual adverse effects of anticholinergics with placebo, there is not a statistically significant difference between groups.<sup>78</sup> While several studies have reported that at recommended doses ipratropium does not produce clinically important changes in pulse rate or blood pressure,<sup>79,80</sup> the Lung Health Study showed that after 5 years of follow-up, ipratropium was associated with hospitalizations for supraventricular tachycardia, and with overall cardiovascular disease morbidity and mortality.<sup>9</sup>

By contrast, in a pooled analysis of placebo-controlled trials of patients receiving tiotropium conducted by Kesten et al,<sup>81</sup> it was found that cardiovascular mortality, cardiac arrest, and myocardial infarction did not occur more frequently than in patients receiving placebo. There was no apparent excess of other arrhythmias classified as serious and left-heart failure, compared with patients receiving placebo. Since tiotropium may worsen signs and symptoms associated with prostatic hyperplasia, narrow-angle glaucoma, or bladder-neck obstruction, it should be used with caution in patients with any of these conditions. Some other reactions reported in individual patients include constipation, increased heart rate, blurred vision, glaucoma, urinary difficulty, and urinary retention.<sup>82</sup> Patients with moderate to severe renal impairment (creatinine clearance of  $\leq 50$  mL/min) should be closely monitored, since tiotropium is predominantly excreted by the kidneys through active secretion.<sup>82</sup> With the exception of dry mouth, the tolerability profile of tiotropium seems similar to that with placebo, ipratropium, or salmeterol.

At the end of 2008, the Food and Drug Administration reported a possible increased incidence of stroke in users of tiotropium,<sup>83</sup> and, shortly after, a meta-analysis by Singh et al<sup>84</sup> concluded that inhaled anticholinergics were associated with a significantly higher risk of cardiovascular death, myocardial infarction, or stroke among patients with COPD. Their conclusions were the result of studies following up patients from 6 weeks to 5 years. Among the individual cardiovascular adverse events, inhaled anticholinergics appeared to significantly increase the risk of myocardial infarction and cardiovascular death, without a statistically significant increase in the risk of stroke. A sensitivity analysis restricted to 5 long-term trials ( $> 6$  mo) confirmed the significantly increased risk of cardiovascular death, myocardial infarction, or stroke (2.9%) in patients treated with anticholinergics, versus 1.8% of the control patients. Both preliminary data received by the Food and Drug Administration from the UPLIFT trial<sup>63</sup> and the final analysis of the trial reported no increased risk of stroke with tiotropium, versus placebo. In fact, Decramer and colleagues<sup>63</sup> concluded that use of tiotropium was associated with a reduction of respiratory morbidity as well as a reduced cardiac morbidity.

## $\beta_2$ Adrenergic Agents

These highly selective  $\beta_2$  adrenergic agents stimulate intracellular adenylyl cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic adenosine-3',5'-monophosphate (cAMP). Increased levels of cAMP are associated with bronchial smooth muscle relaxation and inhibition of release of mediators of cellular hypersensitivity, especially from mast cells.<sup>85</sup>

SABAs are one of the mainstays of bronchodilator strategy for acute, symptomatic COPD. These agents are known to alleviate symptoms and improve airflow obstruction when rescue bronchodilation is needed.<sup>86</sup> However, routine use of SABAs in patients with symptomatic COPD has been associated with a higher risk of adverse effects and overuse due to the submaximal bronchodilation achieved with typically prescribed doses.<sup>87</sup>

**Albuterol Sulfate.** Albuterol (Proventil, Schering-Plough, Kenilworth, New Jersey; Ventolin, GlaxoSmith-Kline, Philadelphia, Pennsylvania; ProAir, Teva Specialty Pharmaceuticals, North Wales, Pennsylvania) also known as albuterol, is a hydrophilic molecule that accesses the  $\beta_2$  receptor from the extracellular compartment.<sup>85</sup> Albuterol is available as a nebulizable solution of 0.63, 1.25, or 2.5 mg/3 mL, and also 5 mg/mL. Albuterol is also supplied as MDI in an 18-g canister that contains 200 actuations and an 8-g canister with 60 actuations. Each actuation delivers 120  $\mu$ g of albuterol from the valve, and 90  $\mu$ g from the mouthpiece. A capsule is available for use with a Rotahaler (GlaxoSmithKline) inhalation device. Each capsule contains 200  $\mu$ g. Combinations of albuterol plus ipratropium are also available in MDI and nebulizable solution. The usual dose is 2.5 mg of the nebulizable solution, 2 puffs of the MDI, or one capsule with the Rotahaler every 4–6 hours. In controlled clinical trials, the onset of improvement in pulmonary function was within 5–15 min, its peak occurs within 60–90 min, and the duration of action is 4–6 hours. This limited duration at the active site is due to its low affinity, when compared to that of the LABAs.<sup>85</sup>

Most randomized clinical trials that compared regularly scheduled versus as-needed use of SABAs have reported no difference between the 2 regimens.<sup>88</sup> Cook et al<sup>89</sup> found that patients with regularly scheduled SABAs used as much as twice the amount of drug received without a clinically important impact on symptoms, dyspnea scores, or exercise tolerance, compared with as-needed use of SABA. Balkissoon and Make<sup>90</sup> recently conducted a double-blind crossover study comparing the safety and efficacy of 3 weeks of fluticasone/salmeterol (250  $\mu$ g/50  $\mu$ g) twice a day plus albuterol 180  $\mu$ g as needed every 4 hours to fluticasone/salmeterol (250  $\mu$ g/50  $\mu$ g) twice a day plus albuterol/ipratropium (90  $\mu$ g/18  $\mu$ g) 2 puffs as needed

every 4 hours in 20 patients. There were no statistically significant differences between either rescue inhaler formulation with regard to measures either of lung function or dyspnea or in terms of safety parameters of cardiac monitoring, glucose and potassium levels, and other adverse events. SABA and SABA/SAAC appeared to be equally safe and efficacious as rescue inhalers for patients with COPD on combination therapy of ICS/LABA.

A meta-analysis by Appleton et al<sup>91</sup> reported the results of comparing ipratropium with salmeterol and formoterol in a total of 7 studies with 2,652 patients.<sup>92–99</sup> Although salmeterol<sup>92–95</sup> and formoterol<sup>96,97</sup> were associated with a significantly greater change of morning peak expiratory flow and FEV<sub>1</sub>, there were no significant differences in HRQL, risk of exacerbations, exercise capacity, rescue bronchodilator use, adverse effects, or any of the symptom scores, over monotherapy with ipratropium. Evaluation of combination therapy with LABAs resulted in a significant improvement in post-bronchodilator lung function, supplemental SABA use, and HRQL, over therapy with a LABA alone, by evaluating the Chronic Respiratory Questionnaire and the SGRQ.<sup>94,95,98</sup>

Yildiz<sup>100</sup> evaluated 12 weeks of therapy with ipratropium plus theophylline, formoterol plus theophylline, or ipratropium plus formoterol in patients with COPD and found that there was not a significant difference in the mean change in symptom scores, the number of subjects experiencing an exacerbation, or the rate of adverse effects between the combinations. All combinations had a positive impact on HRQL.

**Levalbuterol Tartrate.** Levalbuterol (Xopenex, Sepracor, Marlborough, Massachusetts), also known as R albuterol or levosalbutamol, is the single R-enantiomer isomer of the racemic albuterol. Levalbuterol inhalation solution is supplied in 3-mL unit-dose vials that contain 0.31 mg of levalbuterol (as 0.36 mg of levalbuterol HCl), or 0.63 mg of levalbuterol (as 0.73 mg of levalbuterol HCl), or 1.25 mg of levalbuterol (as 1.44 mg of levalbuterol HCl). It is also available in individually pouched 0.5-mL unit-dose vials containing 1.25 mg of levalbuterol. Each 15-g canister of the MDI provides 200 actuations and each 8.4-g canister provides 80 actuations. Each actuation delivers 45  $\mu$ g of levalbuterol base from the mouthpiece. The recommended dose of levalbuterol is 1.25 mg 3 times a day of nebulizer solution or 2 puffs (90  $\mu$ g) every 4–6 hours. The mean time to onset of action is 5–15 min, and the duration of action is 5–8 hours.

Although it has been suggested that levalbuterol produces less direct effect on  $\beta_1$  adrenergic receptors and/or fewer cardiac adverse effects than albuterol, this difference has not been consistently demonstrated by long-term well-designed randomized clinical trials. The effectiveness of nebulized levalbuterol in stable COPD has received



little attention, as compared to racemic albuterol. In a small randomized double-blind placebo-controlled trial, Datta et al<sup>101</sup> compared nebulized levalbuterol to racemic albuterol, combined racemic albuterol and ipratropium, and placebo in a group of 30 patients with moderate to severe stable COPD. Treatment with levalbuterol resulted in a similar spirometric profile to that of racemic albuterol or the combination of racemic albuterol and ipratropium. According to that study, for single-dose, as-needed use in COPD there appeared to be no clinical advantage in using levalbuterol over conventional nebulized bronchodilators. On the other hand, in a larger and more recent multicenter randomized double-blind study of 209 patients with COPD who received levalbuterol or albuterol for 6 weeks, Donohue et al<sup>102</sup> found that levalbuterol was associated with significant bronchodilation, compared with placebo, and improved clinical control of COPD, as evidenced by reductions in rescue-medication use, compared with placebo and/or comparable doses of racemic albuterol.

The inhaled LABAs include salmeterol, formoterol, and arformoterol. LABAs are recommended in the GOLD guidelines for long-term prevention and reduction of COPD-related symptoms. Since they have a longer half-life than SABAs, dosing only twice a day may provide continuous daytime and nighttime bronchodilation and symptom control. Compared with SABAs, LABAs are associated with greater improvement of symptoms, fewer numbers of exacerbations, a reduction in the need for rescue medications, and improvements in overall health status in patients with stable COPD.<sup>13,93</sup>

**Salmeterol Xinafoate.** Salmeterol (Serevent Diskus, GlaxoSmithKline) inhalation aerosol contains salmeterol as the racemic form of the acid salt of salmeterol. It was the first inhaled LABA approved by the Food and Drug Administration. Its active component is salmeterol base, a highly selective  $\beta_2$  adrenergic bronchodilator. In vitro studies show salmeterol to be at least 50 times more selective for  $\beta_2$  adrenoceptors than albuterol. The Diskus is a specially designed plastic inhalation delivery system with a dose indicator that contains a double-foil blister strip of a powder formulation of salmeterol, intended for oral inhalation only. Each unit contains 60 blisters, and each blister contains 50  $\mu\text{g}$  of salmeterol. The usual dose is one inhalation of 50  $\mu\text{g}$  twice daily.

Salmeterol has been combined with fluticasone propionate in an MDI (Advair HFA, GlaxoSmithKline) and a DPI (Advair Diskus, GlaxoSmithKline) formulation. Advair HFA (fluticasone/salmeterol) is available in 3 strengths: 45  $\mu\text{g}/21 \mu\text{g}$ , 115  $\mu\text{g}/21 \mu\text{g}$ , and 230  $\mu\text{g}/21 \mu\text{g}$ . Each inhaler provides 120 metered inhalations. The usual dose is 1–2 inhalations twice daily. Advair Diskus (fluticasone/salmeterol) is also available in 3 strengths: 100  $\mu\text{g}/50 \mu\text{g}$ , 250  $\mu\text{g}/50 \mu\text{g}$ , and 500  $\mu\text{g}/50 \mu\text{g}$ . The usual dose is one

inhalation twice daily. Although onset of action typically starts after 10–15 min post-dose, the median time to onset of clinically important bronchodilation ranges from 30 min to 45 min, peaks at 120 min, and lasts 12 hours in most patients.<sup>103</sup>

Treatment with salmeterol has been shown to significantly improve and maintain bronchodilation,<sup>104</sup> as well as improve airway obstruction, decrease the use of rescue medication, and improve quality of life in patients with COPD.<sup>96</sup> Ferguson et al<sup>105</sup> recently evaluated the effect of salmeterol 50  $\mu\text{g}$  versus fluticasone/salmeterol (250  $\mu\text{g}/50 \mu\text{g}$ ) on the rate of exacerbations in 782 patients with COPD exacerbations. Treatment with salmeterol alone was associated with a 31% higher risk of exacerbations, a 25% higher risk of time to first exacerbation, and 40% higher annual rate of exacerbations requiring oral corticosteroids than combination therapy.

**Formoterol Fumarate.** Formoterol (Foradil Aerolizer, Schering-Plough) is also a racemic LABA. Formoterol comes in a blister-packaged capsule that contains 12  $\mu\text{g}$  of formoterol that is used with a single-dose DPI called an Aerolizer. Formoterol is a selective LABA that provides substantial and sustained bronchodilatory effect for up to 12 hours following a single dose. Treatment with formoterol is associated with an onset of action that is comparable to that of albuterol,<sup>106</sup> usually within 5 min of administration, and faster than that of salmeterol.<sup>103,107</sup> Peak bronchodilation is achieved within 60–120 min after administration of the recommended 12- $\mu\text{g}$  dose. Its clinical efficacy and duration of action are comparable to those of salmeterol. It also provides additional benefit when administered in combination with other bronchodilators or ICSs.

Formoterol has been combined with budesonide propionate in an MDI. Symbicort HFA (AstraZeneca) (budesonide/formoterol) is available in 2 strengths: 80  $\mu\text{g}/4.5 \mu\text{g}$  and 160  $\mu\text{g}/4.5 \mu\text{g}$ . Each inhaler provides 120 metered inhalations. The usual dose is 1–2 inhalations twice daily.

When compared to salmeterol, the first difference is the relative degree of  $\beta_2$  adrenergic receptor activation. Results from methacholine-challenge studies have shown that formoterol elicits a dose-dependent protective response, whereas salmeterol is associated with both a flatter dose-response curve and significantly weaker protection against bronchoconstriction. Formoterol has a faster onset of action and a greater peak bronchodilatory effect, compared with salmeterol, as a result of a higher selectivity for the  $\beta_2$  receptor,<sup>108-111</sup> and its lower lipophilicity. A 12- $\mu\text{g}$  dose of formoterol is equivalent to a 50- $\mu\text{g}$  dose of salmeterol.

In several clinical studies formoterol had a tolerability similar to albuterol, salmeterol, and ipratropium, and the same adverse-event profile as that of other  $\beta_2$  adrenergic

agents.<sup>106,112-114</sup> At least 4 large placebo-controlled clinical trials, with almost 3,000 patients with stable COPD, have reported that formoterol significantly reduced daytime and nighttime symptoms of COPD, use of rescue medication, exacerbations of COPD, and exacerbation-related hospitalizations. In addition, its bronchodilatory effect maintained for up to 12 months and reduced dynamic hyperinflation better than other bronchodilators.<sup>100,115-117</sup> Its use has also been associated with decreased SABA use and improvement of patients' quality of life.<sup>118</sup> In one of the most comprehensive reviews, Berger and Nadel<sup>113</sup> summarized the data obtained from 13 crossover trials. The conclusion of their analysis provides confirmation of the results already presented on the efficacy and safety of formoterol.

**Arformoterol Tartrate.** Arformoterol (Brovana, Sepacor, Marlborough, Massachusetts) is the (R,R)-enantiomer of formoterol that has 2-fold greater potency than racemic formoterol (which contains both the (S,S) and (R,R)-enantiomers). Each unit-dose vial of 2 mL contains 15  $\mu\text{g}$  of arformoterol. The recommended dose is one 15- $\mu\text{g}$  unit dose twice daily. Treatment with arformoterol is associated with an onset of significant bronchodilation after 7 min. Peak bronchodilation is achieved within 60–180 min after administration, and it is sustained for up to 12 hours following a single dose.

In a recent prospective multicenter open-label 12-month trial conducted by Donohue et al,<sup>119</sup> 793 patients with COPD were randomized to receive nebulized arformoterol 50  $\mu\text{g}$  once daily ( $n = 528$ ) or MDI salmeterol 42  $\mu\text{g}$  twice daily ( $n = 265$ ). Both LABAs were well tolerated, produced effective bronchodilation, and their use was not associated with the development of clinically meaningful tolerance over the treatment period in these patients with severe to very severe COPD. Hanania et al<sup>120</sup> evaluated the long-term safety and efficacy of arformoterol 15  $\mu\text{g}$  or 25  $\mu\text{g}$  and formoterol 12  $\mu\text{g}$  twice daily in patients with COPD in a multicenter, 6-month randomized double-blind double-dummy clinical trial. In all groups, exacerbations occurred with less frequency after 6 months of treatment, compared with the first 3 months. Improvement of lung function and reduction of use of the short-acting bronchodilators ipratropium and albuterol were sustained at 6-months in all treatment groups.

### Adverse Events of $\beta_2$ Adrenergic Agents

Although the adverse effects of inhaled  $\beta_2$  adrenergic agents are generally minor, they may be important in the dosages required to produce bronchodilation in patients with COPD. Most  $\beta_2$  adrenergic agents have the potential to increase cardiac contractility, decrease peripheral vascular resistance, increase pulse pressure, increase cardiac

output, and change serum potassium and magnesium. While it is recognized that  $\beta_2$  adrenergic receptors are the predominant receptors in bronchial smooth muscle, data indicate that there is a concentration of  $\beta_2$  receptors in the human heart that could be as high as 50%. The precise function of these receptors has not been established. In addition, use of  $\beta_2$  adrenergic agents in patients with COPD may be accompanied by pulmonary vasodilation, which may worsen ventilation-perfusion matching and result in a slight fall in  $P_{aO_2}$ .<sup>121</sup> A study by Polverino et al<sup>122</sup> reported that, in patients with severe COPD exacerbations, the underlying pulmonary gas-exchange abnormalities remain essentially unchanged after albuterol nebulization. However, while in convalescence, the pulmonary gas-exchange response to albuterol was deleterious, resulting in small decrements in  $P_{aO_2}$  due to further ventilation-perfusion worsening. One possible explanation for the variability in response to therapeutic doses of SABAs in patients with COPD is the effect of the adrenergic  $\beta_2$  receptor (ADRB2) gene polymorphisms.<sup>123</sup>

Other adverse events may include tremors, sleep disturbance, hypokalemia, immediate hypersensitivity reactions, bronchospasm, tachycardia, palpitations, and supraventricular arrhythmias,<sup>124-128</sup> These events are generally less pronounced with LABAs than with SABAs. The presence of hypokalemia and preexisting heart disease effects should be carefully considered when choosing LABAs to treat elderly patients with stable COPD.<sup>129</sup>

A meta-analysis by Salpeter et al<sup>130</sup> of 20 RCTs assessed the cardiovascular effects of inhaled LABAs in patients with asthma or COPD. LABAs were associated with a 4-fold increase in cardiovascular events, compared with placebo. However, most of these events were due to sinus tachycardia. While major cardiovascular events were higher, compared with placebo, they did not reach statistical difference. The cardiac safety of formoterol and nebulized formoterol has been evaluated by 2 more recent studies that found no clinically important cardiac adverse events.<sup>131,132</sup> A recent comparative analysis of over 2,000 patients with COPD by Jara et al<sup>133</sup> concluded that risk of total mortality and cardiac end-points were similar for users of tiotropium and LABAs. While adverse events appear to be dose-related,<sup>134</sup> large clinical trials have documented the safety of LABAs in COPD, when administered at therapeutic doses.<sup>66</sup> The risk for respiratory infections, pneumonia in particular, seems to be similar to that of placebo.<sup>116,135-137</sup>

Although results from the Salmeterol Multicenter Asthma Research Trial (SMART)<sup>138</sup> found a small, but statistically significant, increase in the number of asthma-related deaths in patients treated with salmeterol, compared with those receiving placebo, that finding has only been reported in patients with COPD by Salpeter et al,<sup>139</sup> in a pooled analysis. However, their conclusions were based

on very few events, which have not been verified in recent reviews of the literature.<sup>140</sup> In the Toward a Revolution in COPD Health (TORCH) study, adverse events were reported by 90% of patients, and serious adverse events by 40%; there was no significant difference in deaths due to pulmonary causes between placebo and salmeterol.<sup>141</sup> As a result, the Food and Drug Administration has not mandated label warnings for formoterol and salmeterol concerning the possibility of an increase in risk for serious COPD exacerbations and COPD-related deaths in patients with COPD who receive regular treatment with LABAs.

### Inhaled Corticosteroids

Although ICSs are employed to reduce inflammation in patients with severe and very severe COPD, their role as monotherapy in COPD has not only been well defined but also discouraged. Fluticasone plus salmeterol (Advair) and budesonide plus formoterol (Symbicort) are the only ICS plus LABA combinations that have been approved to treat COPD. If something is clear regarding ICSs, it is that they represent the most controversial group of inhaled drugs in the management of patients with severe to very severe COPD. For dosing schedule and formulations, please review the previous section on LABAs.

The rationale behind combination using ICS plus LABA is the existing evidence that both groups may have complementary and synergistic effects when delivered from a single inhaler. Several large-scale studies in patients with moderate to severe COPD have demonstrated that treatment with ICS/LABA is associated with significantly greater improvements in lung function, exacerbations, health status, and breathlessness, compared with placebo or monotherapy. Perng et al<sup>142</sup> recently evaluated the effect of salmeterol/fluticasone (100 µg/1,000 µg daily), tiotropium/fluticasone (18 µg/1,000 µg daily), and tiotropium (18 µg daily) alone for 12 weeks on the inflammatory cells and mediators in sputum induced from patients with COPD who were newly-diagnosed or had not taken any medication for 3 months prior to the study. The results showed that salmeterol/fluticasone was associated with a significant reduction in interleukin-8 (IL-8) and matrix metalloproteinase 9 (MMP-9), as compared to tiotropium alone. There were no treatment differences between the salmeterol/fluticasone and tiotropium/fluticasone groups in decreasing IL-8 and MMP-9 levels. All treatment groups failed to significantly reduce the numbers of total inflammatory cells in induced sputum. Furthermore, there were no significant differences in terms of improvement of FEV<sub>1</sub>, FVC, C-reactive protein, or HRQL between treatment groups.

Choudhury et al<sup>143</sup> conducted an RCT to evaluate the effect of withdrawing ICS from 260 patients with COPD. After follow-up assessments at 3-month intervals for a

year, it was found that withdrawal of long-term ICS in patients with COPD was associated with a significantly higher risk of exacerbation, shorter time to exacerbation, and symptom deterioration.

**Adverse Events of Inhaled Corticosteroids.** It is unclear whether the risk of pneumonia in patients with COPD has a direct association with ICS or occurs as a consequence of an interaction with LABAs when used in combination. In the most current meta-analysis conducted at the time this paper was submitted, Singh et al<sup>144</sup> evaluated long-term use of ICS alone or in combination and the risk of pneumonia in COPD. In their analysis of 18 RCTs including a total of 16,996 patients, ICS alone or in combination with LABAs was associated with a significantly higher risk of any pneumonia, and serious pneumonia, but without a significantly increased risk of pneumonia-related mortality, when compared to placebo or LABAs. According to their risk analysis, about one in every 47 patients with COPD using ICS for a year is likely to develop pneumonia. Inhaled corticosteroids are also associated with an increased frequency of oropharyngeal candidiasis,<sup>135,145-148</sup> pharyngitis,<sup>135,144-146</sup> and a moderate to severe degree of easy bruising.<sup>135,145,146</sup> Use of inhaled triamcinolone has been associated with reduction of bone mineral density and osteoporosis in patients with COPD.<sup>149</sup> While bone mineral density and incidence of fracture were similar for ICS used alone or in combination with LABAs for up to 3 years, versus placebo, in more recent studies,<sup>140,146,147</sup> adding ICS must be balanced against the potential risk for more complications in patients with an already complex treatment regimen.

Although one can argue that combination therapy is unquestionably associated with improved clinical outcomes, concerns for safety and adverse events associated with long-term use of LABAs and ICSs exist and impact the routine management of patients with stable COPD. In an RCT of 449 patients with moderate or severe COPD, Aaron et al evaluated all 3 classes of long-acting inhaled therapies. Forty-seven percent of patients in the tiotropium-plus-placebo group discontinued study medications, compared with 43% in the tiotropium-plus-salmeterol group and 26% in the tiotropium-plus-salmeterol-fluticasone group.<sup>150</sup> Combination of tiotropium plus fluticasone-salmeterol was not associated with higher mortality or more adverse events than the therapy with tiotropium plus placebo. Serious adverse events were similar for monotherapy and combination therapy.

### Emerging Pharmacotherapy

Despite the global impact of COPD and a better understanding of its pathophysiology, the advance in pharmacotherapy has been limited to the development of longer-

acting inhaled bronchodilators. Nevertheless, simplifying COPD management is of paramount importance to improving adherence to prescribed therapy.<sup>76,151</sup>

Some of the ultra-long-acting  $\beta_2$  adrenergic agents in clinical development and under different phases of study are indacaterol (phase III), carmoterol (phase III), GSK-159797 (phase IIb), GSK-642444 (phase IIb), GSK-597901, GSK-159802, and GSK-678007.<sup>152,153</sup> Indacaterol appears to be a very effective bronchodilator, as measured by videomicroscopy in a precision-cut lung slice preparation.<sup>154</sup> It has an onset of action as fast as albuterol,<sup>155</sup> a longer than 24-hour duration of action in patients with mild to moderate COPD,<sup>156,157</sup> and no evidence of tolerance or important adverse effects.<sup>158</sup> Preclinical data suggest that indacaterol has a greater cardiovascular safety margin than formoterol or salmeterol. In 635 patients with moderate to severe COPD, a single DPI dose of indacaterol was associated with statistically significant improvements in FEV<sub>1</sub> and significant reduction of rescue medication use, compared with placebo. The effects of indacaterol on FEV<sub>1</sub> were similar to those of tiotropium.<sup>158</sup>

Bauwens et al<sup>159</sup> recently assessed the bronchodilator efficacy, safety, and tolerability of indacaterol in 51 patients with moderate to severe COPD. Single doses of indacaterol (150  $\mu$ g, 300  $\mu$ g, and 600  $\mu$ g) were given in the morning and compared with placebo and with formoterol 12  $\mu$ g twice daily. All doses of indacaterol provided a 24-hour bronchodilation, were well tolerated, and were at least as efficacious as formoterol 12  $\mu$ g twice daily. Carmoterol (CHF-4226) has a high selectivity as well as a high affinity for the  $\beta_2$  adrenoceptor. It displays a fast onset of action and duration of activity of approximately 30 hours.

Several other long-acting inhaled anticholinergics, such as aclidinium (phase III), NVA-237 (glycopyrrolate) (phase III), OrM3 (phase IIb), GSK-233705 (phase II) LAS-35201, CHF5407 (phase I), and GSK-656398, are now in development.<sup>160-162</sup> A phase IIa trial of single doses of inhaled aclidinium in 17 patients with COPD reported a significant bronchodilatory response. Its onset of significant bronchodilation was observed as early as 15 min after administration, and this effect was sustained for at least 24 hours.<sup>161</sup> Glycopyrrolate has been associated with a significantly lower effect on cardiovascular parameters than tiotropium,<sup>163</sup> and lack of dry mouth.<sup>164</sup> Results of studies in patients with COPD have shown that a single dose of 480  $\mu$ g was associated with a bronchodilatory effect up to 32 hours, and exhibited a rapid onset of action (5 min post-dose). The improvements in lung function appeared comparable with those of tiotropium.<sup>165</sup>

Combination of ultra-long-acting bronchodilators seems to be the next logical generation of agents in the management of patients with moderate to severe COPD, since once-a-day seems to be the regimen preferred by most

patients.<sup>166</sup> Formoterol plus tiotropium (phase III), salmeterol plus tiotropium (phase III), carmoterol plus tiotropium (preclinical phase), and indacaterol plus glycopyrrolate (phase II) are among the combinations undergoing clinical investigation.

Novel formulations also known as M3 antagonist  $\beta_2$  agonist bronchodilators have a dimer molecule with a bi-functional mechanism of action. These agents have entered phase II of clinical trials. If effective, this approach will for sure revolutionize the management of patients with COPD.<sup>162,167,168</sup>

Some of the formulations with an ICS and an ultra-LABA undergoing clinical trials include carmoterol plus budesonide (preclinical phase), and indacaterol plus mometasone (phase III).<sup>162</sup>

The development of once-daily triple therapy is expected to be part of the future arsenal of agents. Combinations with novel anti-inflammatory compounds, such as inhaled phosphodiesterase 4 inhibitors, could deliver 3 complementary therapeutic effects for patients with stable COPD. A combination of inhaled phosphodiesterase 4 inhibitor (tofigilast, phase II) plus a LAAC, and potentially with a LABA or an M3 antagonist  $\beta_2$  agonist is anticipated.<sup>169</sup>

### Pharmacoeconomics

The financial burden of treating COPD not only relates to direct medical costs such as drug acquisition, but also indirect medical costs such as time lost from work or due to disability, caregiver costs, and premature mortality. In 2004 COPD consumed \$37.2 billion, of which \$21 billion were direct health-care-cost-related.<sup>170,171</sup>

The cost of ipratropium and its combination with SABAs is higher than SABAs alone. Friedman et al<sup>172</sup> conducted pharmacoeconomic evaluations of health-care resource utilization to determine the costs associated with COPD exacerbations. Their analysis showed that combination therapy was associated with a 20% reduction in COPD exacerbations, a 44% reduction in hospitalizations, and a 50% reduction in hospital days, compared to therapy with SABA alone. The cost of hospital admissions accounted for 48% of the total direct medical costs in that trial. The length of hospital stay (and cost per medication per patient) was 103 days (\$269) for albuterol, 20 days (\$156) for ipratropium, and 46 days (\$197) for combination therapy. Although SABA therapy was more expensive, there was no significant difference in the costs between the ipratropium and combination-therapy groups. The mean difference in the cost of hospitalization (resulting from all causes, including COPD) between treatment groups was \$1,056, and the difference in total health-care costs (excluding study drug acquisition cost) was \$1,043 in favor of tiotropium. Whether or not levalbuterol

is more cost-effective than racemic albuterol for patients with COPD is still an unresolved issue.<sup>173,174</sup>

Oostenbrink et al conducted a one-year cost-effectiveness analysis of the substitution of tiotropium for ipratropium in patients with COPD. Therapy with tiotropium was associated with a significant improvement on the SGRQ (ipratropium 34.6% vs tiotropium 51.2%). The number of hospital admissions (46%), hospital days (42%), and unscheduled visits to health-care providers (36%) was significantly reduced with tiotropium therapy. Mean annual health-care costs, including the acquisition cost of the study drugs, were 1,721 euros in the tiotropium group and 1,541 euros in the ipratropium group (difference 180 euros). Incremental cost-effectiveness ratios were 667 euros per exacerbation avoided and 1,084 euros per patient with a relevant improvement on the SGRQ. Substituting tiotropium for ipratropium in that trial resulted in improved health outcomes and was associated with increased acquisition costs of 180 euros (\$233) per patient per year.<sup>175</sup> A similar cost-effective analysis in Spain revealed that tiotropium was more cost-effective than ipratropium, and to a lesser extent to salmeterol, as measured by objective clinical variables.<sup>176</sup>

Oba conducted a direct cost-effectiveness evaluation of long-acting bronchodilators in the treatment of COPD.<sup>171</sup> Newer long-acting agents are often more expensive, and they are typically associated with a higher insurance co-payment. Tiotropium was associated with significantly fewer hospitalizations per patient-year, versus placebo and salmeterol. The cost-effectiveness ratio per quality-adjusted life years (QALYs) gained was almost \$15,000 lower for tiotropium than that for salmeterol (\$26,094 vs \$41,000, respectively). These findings have been supported by several trials outside the United States, where the higher acquisition cost of tiotropium was offset by the overall reduced health-care costs.<sup>177,178</sup> Combination therapy with anticholinergics plus LABAs is more expensive. In Australia, for example, the predicted government cost of supplying salmeterol and ipratropium MDIs is 8-fold and 7-fold, respectively, over the cost of one month's albuterol supply.<sup>179</sup> This analysis highlights the need to identify patients who benefit from combination therapy to assure that cost matches clinical benefit.

For the combination therapies of ICS/LABA there are potential cost savings with the use of combination inhalers, compared with separate inhalers. However, the only exception to this cost saving is with budesonide/formoterol at doses higher than 1,200  $\mu\text{g}/\text{d}$ , where separate inhaler devices can become equivalent to or cheaper than combination inhalers. A low-dose fluticasone/salmeterol delivered via an MDI is currently the cheapest combination inhaler but only marginally cheaper than budesonide/formoterol delivered as a DPI. At higher doses, both fluticasone/salmeterol inhalers are marginally cheaper than the budes-

onide/formoterol inhaler.<sup>180</sup> In a recent evaluation of the lifetime cost-effectiveness of treatment with fluticasone/salmeterol (500  $\mu\text{g}/50 \mu\text{g}$ ), compared with no maintenance treatment in COPD in the United States, cost-effectiveness was defined as  $\leq$  \$50,000 per QALY. Treatment with fluticasone/salmeterol resulted in a lifetime incremental cost-effectiveness ratio of \$33,865/QALY. Treatment with salmeterol 50  $\mu\text{g}$  alone was found to have an incremental cost-effectiveness ratio of \$20,797/QALY. Although fluticasone 500  $\mu\text{g}$  was effective in reducing the number of exacerbations, there was not a significant difference in mortality, when compared to no maintenance treatment.<sup>181</sup>

### Stage-Guided Approach to Inhaled Pharmacotherapy

Post-bronchodilator forced expiratory volume in the first second ( $\text{FEV}_1$ ) has been recommended by the GOLD guidelines for the diagnosis and assessment of the severity of COPD (see Fig. 1).<sup>3</sup> The following section summarizes some of the most current evidence supporting inhaled pharmacotherapy at different stages of severity.

#### Mild COPD (Stage I)

For patients with mild COPD (stage I), bronchodilator therapy should be administered only as needed to relieve acute, intermittent symptoms.<sup>3</sup> Use of short-acting bronchodilators has substantial implications, since management of acute symptoms accounts for a significant portion of health-care utilization and expenditures in patients with COPD. Short-acting bronchodilators, such as albuterol and ipratropium, are appropriate, and may be administered either as monotherapy or together as combination bronchodilator therapy.<sup>3,102</sup>

The synergistic effect obtained by combining SAACs and SABAs has been based on the fact that anticholinergics seem to work predominantly on the proximal large airways, while  $\beta$  agonists work on medium to small size airways. While  $\beta_2$  adrenergic agents directly act on the smooth muscle, providing a more rapid onset of action, anticholinergics reduce the respiratory cholinergic tone and sustain activity a little longer. In other words, co-administration of these agents generally results in more bronchodilation than does the administration of each agent alone.<sup>15,37</sup> A crossover study of 863 patients found that combination of albuterol and ipratropium resulted in a 24% significantly higher peak  $\text{FEV}_1$  than that achieved by albuterol alone, and 37% greater than that achieved with ipratropium alone.<sup>37</sup> Although there is little evidence that the sequence of administration, if used in separate formulations, affects the clinical effect, current formulation with both agents obviates deciding in which sequence to give the 2 drugs. Adequate dosing with ipratropium alone may

obviate combination therapy in patients with symptoms of airway obstruction.

According to the GOLD guidelines,<sup>3</sup> SABAs remain the agents of first resort during exacerbations, and inhaled anticholinergics may be added either as soon as maximum dose of the SABA has been reached or when SABA therapy has not meet its therapeutic goal.<sup>182</sup>

### Moderate COPD (Stage II)

Nearly half of the patients newly diagnosed with COPD are in stage II.<sup>183</sup> Most patients with moderate and severe COPD experience more frequent and persistent symptoms and a progressive dyspnea that becomes refractory to short-acting bronchodilators. Inhaled long-acting bronchodilators are the mainstay of current drug therapy for COPD and are recommended as first-line therapy in symptomatic patients with moderate to severe airflow limitation (stages II and III).<sup>184</sup> They not only prevent or reduce symptoms but also maintain normal levels of activity.<sup>162</sup> Although it is not always clear which long-acting bronchodilator should be considered first, LAACs are of noteworthy value as parasympathetic cholinergic stimulation is strongly implicated in the pathophysiology of airflow obstruction in COPD.<sup>51,66,67</sup>

The choice between LABA or LAAC may depend on availability, clinical response, and adverse events experienced by the individual patient.<sup>125</sup> Since prior sections of the paper have summarized the pharmacologic and clinical profile of each long-acting bronchodilator used separately for moderate COPD, combination therapy will be discussed next.

Current guidelines advocate combining different long-acting bronchodilators in patients with moderate COPD whose airflow obstruction becomes more severe and is not sufficiently controlled by monotherapy. While combining LAAC with LABA seems a convenient way of delivering treatment and obtaining better clinical results,<sup>3,185,186</sup> more data supporting long-acting bronchodilator combination therapy are necessary.

In 2 different randomized double-blind 3-period cross-over studies, van Noord et al<sup>65,187</sup> found that tiotropium 18  $\mu\text{g}$  plus formoterol 12  $\mu\text{g}$  once or twice daily was associated with a significant improvement in airflow obstruction (Fig. 7), resting hyperinflation, and reduced daytime albuterol use, when compared with either agent alone. Interestingly, adding formoterol twice daily to tiotropium was not superior to adding formoterol once daily to tiotropium in regards to nighttime use of SABA (Fig. 8).

Similar results were obtained by Rabe et al,<sup>188</sup> who recently compared a combination of tiotropium and formoterol to fluticasone and salmeterol in 592 patients with moderate COPD for 6 weeks. After a 12-hour lung function profile was obtained, the tiotropium/formoterol was

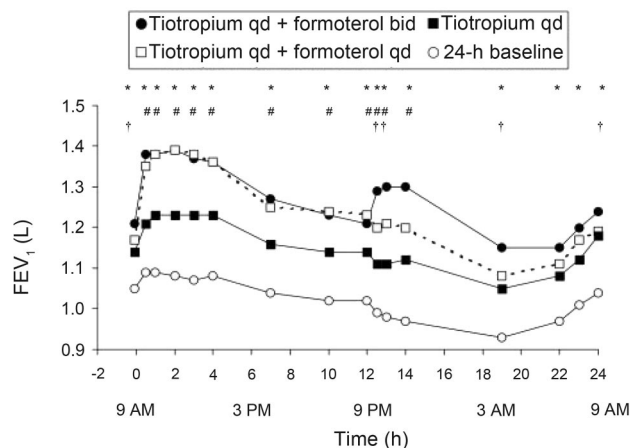


Fig. 7. Mean forced expiratory volume in the first second ( $\text{FEV}_1$ ) before and at the end of 2-week treatment periods. \*  $P < .05$  tiotropium once a day (qd) plus formoterol twice a day (bid) versus tiotropium once a day. #  $P < .005$  tiotropium once a day plus formoterol once a day versus tiotropium once a day. †  $P < .005$  tiotropium once a day plus formoterol twice a day versus tiotropium once a day plus formoterol once a day. (From Reference 187, with permission.)

associated with significantly better lung function parameters than the fluticasone/salmeterol combination.

### Severe to Very Severe COPD (Stages III and IV)

The current COPD management guidelines recommend addition of an ICS to bronchodilator therapy for patients with an  $\text{FEV}_1 < 50\%$  predicted who experience repeated exacerbations.<sup>3</sup> Some physiological and clinical data suggest that addition of ICS to LABA therapy in patients with severe to very severe COPD may be more effective than either treatment alone.<sup>189-193</sup>

In a randomized double-blind placebo-controlled parallel-group study with 1,465 patients, Calverley et al<sup>135</sup> reported that therapy with salmeterol/fluticasone for 12 months significantly improved pretreatment  $\text{FEV}_1$ , compared with placebo or either single agent alone. There was a statistically significant improvement in HRQL and a reduction in exacerbation rate with salmeterol/fluticasone, compared with placebo. Similar combination has also been associated with significant reductions in the number of inflammatory cells in biopsy specimens (CD4+, CD8+, and CD45+ cells) and induced sputum (eosinophils), compared with placebo in patients with COPD.<sup>141</sup>

The TORCH study<sup>141</sup> compared twice-daily therapy with salmeterol/fluticasone (50  $\mu\text{g}$ /500  $\mu\text{g}$ ), salmeterol 50  $\mu\text{g}$  alone, fluticasone 500  $\mu\text{g}$  alone, or placebo for 3 years in 6,112 patients with moderate to severe COPD. Although the all-cause mortality rate was lower with salmeterol/fluticasone (12.6%), versus 13.5% with salmeterol, 16.0% with fluticasone, and 15.2% with placebo, it did not reach

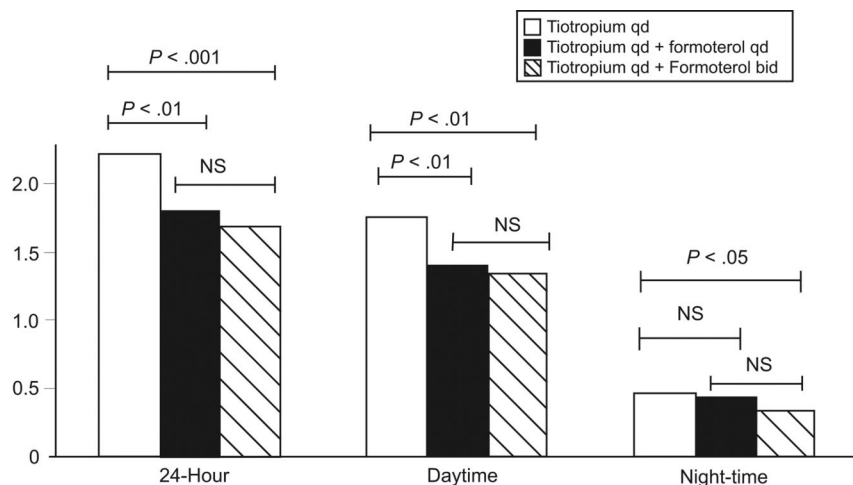


Fig. 8. Mean 2-weekly number of puffs of rescue albuterol per day. qd = once a day. bid = twice a day. NS = not significant. (From Reference 187, with permission.)

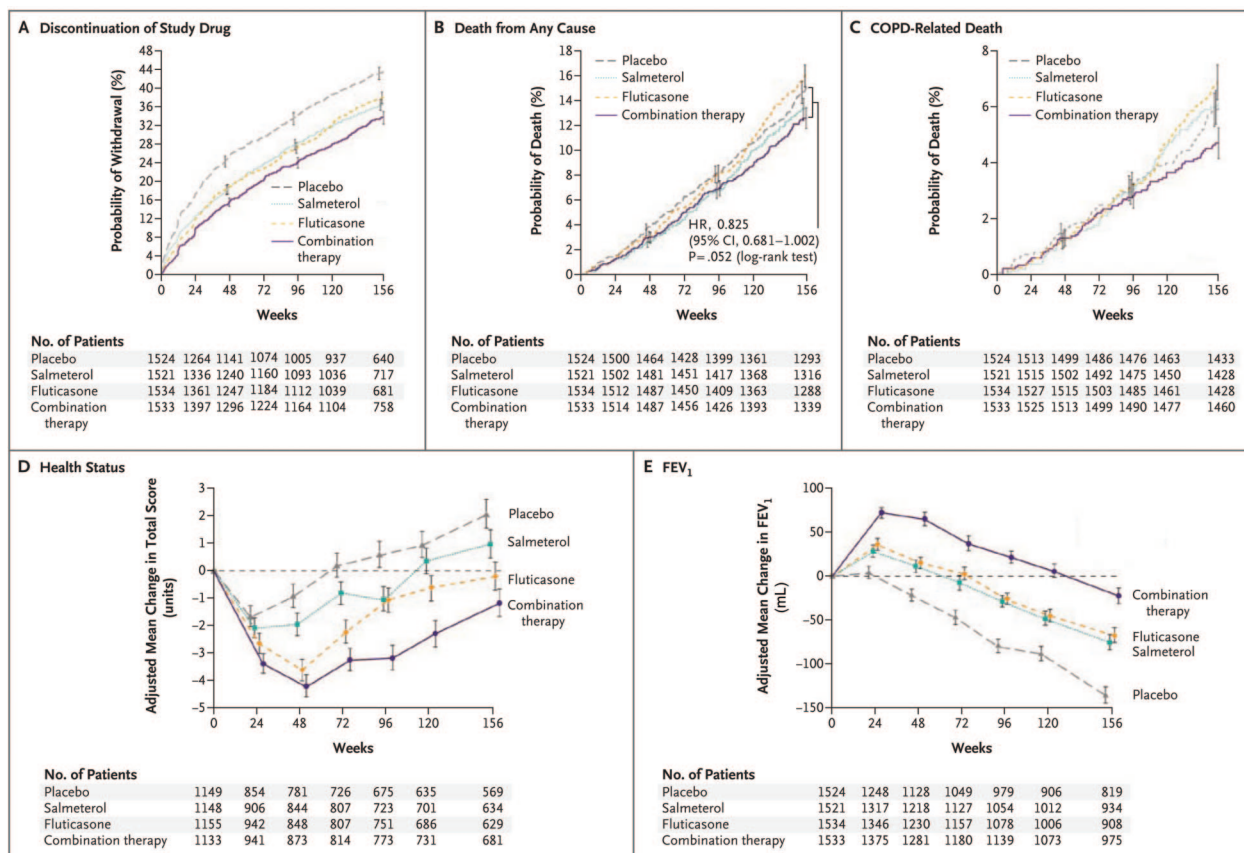


Fig. 9. Outcomes in patients with chronic obstructive pulmonary disease (COPD). A: Cumulative incidences of discontinuation of a study drug at 3 years were 43.5% in the placebo group, 36.4% in the salmeterol group, 38.1% in the fluticasone group, and 33.7% in the group receiving the combination of salmeterol plus fluticasone propionate. B: In the analysis for the primary end point of the probability of death from any cause at 3 years, the risk of death in the placebo group was 15.2%, as compared with 12.6% in the combination-therapy group. Salmeterol and fluticasone propionate in combination reduced the risk of death at any time during the 3-year study period by 17.5% ( $P = .052$ ). C: The probability of COPD-related death at 3 years was 6.0% in the placebo group, 6.1% in the salmeterol group, 6.9% in the fluticasone group, and 4.7% in the combination-therapy group. D: Effect of each study medication on health status, assessed according to changes in total score on the Saint George's Respiratory Questionnaire (SGRQ). E: Effect of each study medication on forced expiratory volume in the first second ( $FEV_1$ ). The values in the tables below the graphs represent (B) the number of patients alive, (C) the number of patients alive or dead from non-COPD-related causes, and (A, D, and E) the number of patients remaining in the study. The I bars represent standard errors (at approximately 1, 2, and 3 years in panels A, B, and C). HR = hazard ratio. (From Reference 141, with permission.)

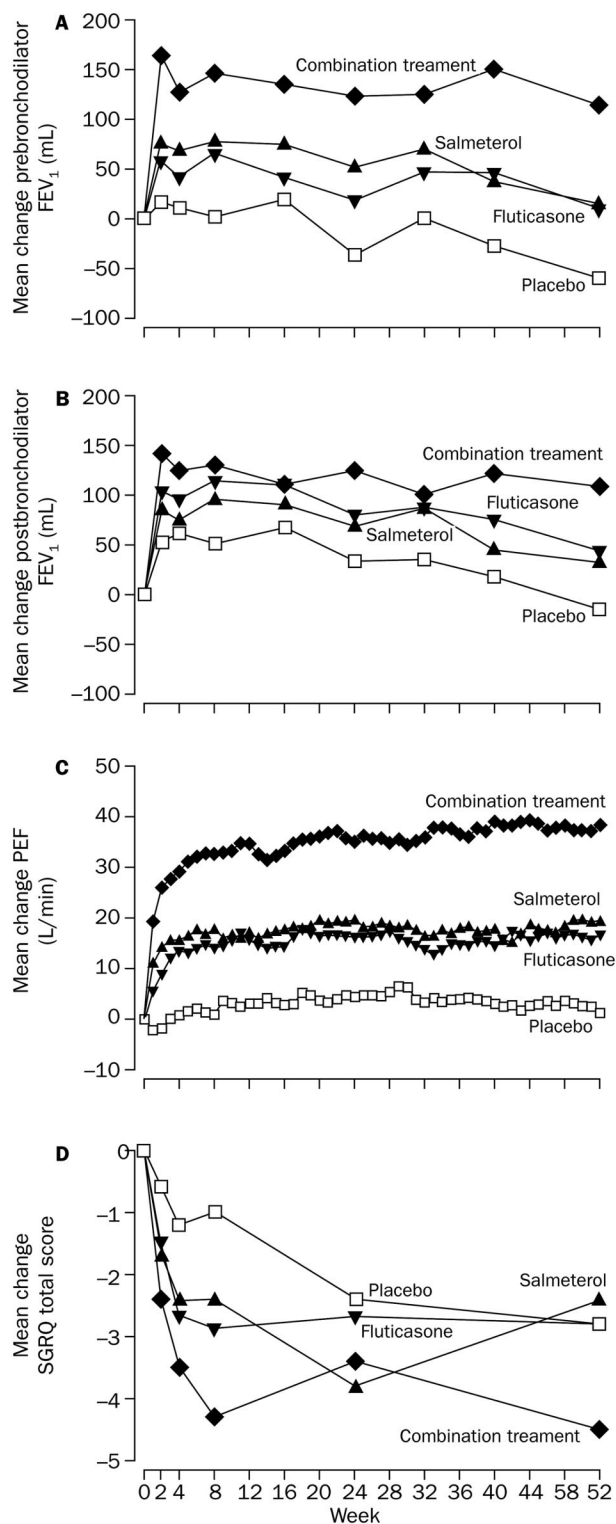
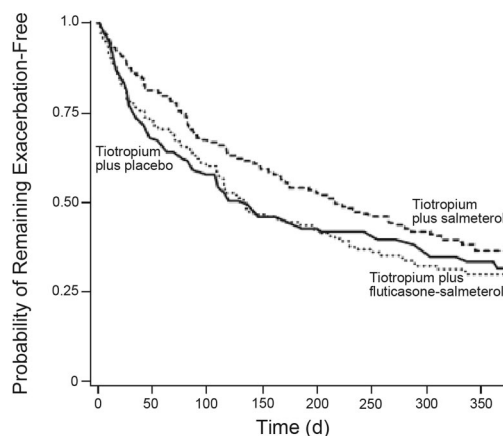


Fig. 10. Effect of treatment on lung function measurements and health status. Raw mean changes from baseline are shown. A: Pre-bronchodilator forced expiratory volume in the first second (FEV<sub>1</sub>). B: Post-bronchodilator FEV<sub>1</sub>. C: Daily peak expiratory flow. D: Health status. The fall in Saint George's Respiratory Questionnaire score represents an improvement in health status. (From Reference 145, with permission.)



Patients at risk, n	
Tiotropium plus placebo	156 102 84 65 59 57 50 45
Tiotropium plus salmeterol	148 100 81 61 55 48 41 38
Tiotropium plus fluticasone-salmeterol	145 116 94 82 72 62 55 48

Fig. 11. Kaplan-Meier estimates of the probability of remaining free of exacerbations of chronic obstructive pulmonary disease (COPD), according to treatment assignment. The unadjusted hazard ratios were 1.02 (95% confidence interval 0.77–1.37) for tiotropium plus placebo versus tiotropium plus salmeterol ( $P = .87$ ), and 0.80 (confidence interval, 0.60–1.08) for tiotropium plus placebo versus tiotropium plus fluticasone-salmeterol ( $P = .15$ ). (From Reference 150, with permission.)

statistical significance. Salmeterol/fluticasone was associated with a significant reduction in the annual rate of moderate to severe exacerbations and improvement in health status, compared with placebo, salmeterol, and fluticasone (Fig. 9).

In an effort to measure the impact of pharmacotherapy in modifying lung function decline in COPD, Celli and colleagues<sup>194</sup> conducted a detailed analysis of the TORCH trial data on FEV<sub>1</sub> decline. Using data from over 26,000 measurements of post-bronchodilator FEV<sub>1</sub> made during follow-up, they reported that the rate of decrease in FEV<sub>1</sub> between 6 months and 3 years after randomization was significantly lower with the LABA/ICS combination (39 mL/y), fluticasone alone, or salmeterol alone (42 mL/y), compared with placebo (55 mL/y). Those authors concluded by stating that, “while these results are encouraging, their validity must be judged against possible methodological limitations, which may be present even in such a large randomized trial.”<sup>194</sup>

Additional trials have examined the effects of adding formoterol to budesonide.<sup>135,191,195</sup> In a crossover of 16 patients with moderate to severe COPD on regular LABA therapy, Cazzola et al<sup>195</sup> compared the effects of single doses of formoterol/budesonide (12 μg/400 μg) with those of salmeterol/fluticasone (50 μg/250 μg). Although both groups showed similar improvements in FEV<sub>1</sub> levels over 12 hours, treatment with formoterol/budesonide resulted in faster onset of action and superior improvements in FEV<sub>1</sub>,



compared with salmeterol/fluticasone at both 2 hours and 6 hours post-treatment. Two placebo-controlled studies compared treatment with a single inhaler containing formoterol/budesonide (9 µg/320 µg) twice daily and treatment with formoterol/budesonide (9 µg/200 µg or 400 µg) twice daily administered alone.<sup>135,191</sup>

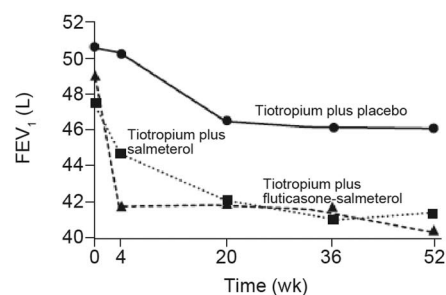
In the study of 812 patients with COPD by Szafranski et al,<sup>191</sup> treatment with formoterol/budesonide resulted in FEV<sub>1</sub> improvement similar to that achieved with formoterol alone but significantly greater than that with budesonide 200 µg alone. However, combination therapy was associated with better morning and evening peak flow and fewer mild exacerbations than either agent alone. In the largest study (*n* = 1,022), Calverley et al<sup>135</sup> showed that a similar combination was associated with effective maintenance therapy over 12 months, fewer withdrawing from the study, reduced risk of exacerbations, significant improvements in SGRQ score, less use of rescue medications, and prolonged the time to first COPD exacerbation, versus monotherapy with formoterol and budesonide (Fig. 10).

Whether addition of ICS to LAAC/LABA combination therapy provides additional benefit over LAAC/LABA or even LAAC alone is still to be clearly determined. The Canadian Thoracic Society/Canadian Respiratory Clinical Research Consortium conducted a randomized double-blind placebo-controlled trial with 449 patients with moderate or severe COPD who reported having at least one exacerbation during the previous 12-month period.<sup>150</sup> They were assigned to a 1-year treatment with tiotropium 18 µg plus placebo, tiotropium 18 µg plus salmeterol, or tiotropium 18 µg plus fluticasone/salmeterol (500 µg/50 µg). Although there was not a significant difference in the percentage of patients experiencing exacerbations with any of the regimens (63%, 65%, and 60%, respectively) sensitivity analysis shifted in the direction favoring tiotropium plus salmeterol and tiotropium plus fluticasone/salmeterol (Fig. 11). The combination tiotropium plus fluticasone/salmeterol was associated with significant improvement of lung function, disease-specific quality of life, and reduced number of hospitalizations, compared with tiotropium plus placebo. However, tiotropium plus salmeterol did not statistically improve lung function or hospitalization rate, compared with tiotropium plus placebo (Fig. 12).

To illustrate the stepwise approach to pharmacotherapy, Cooper and Tashkin<sup>13</sup> created the flow chart shown in Figure 13.

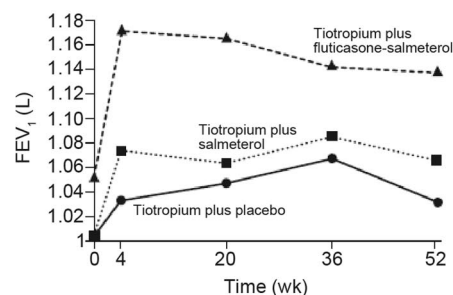
### Discussion

RTs are among the few medical professionals who receive formal training on all aerosol devices routinely used for the management of patients with stable COPD. Inhaled pharmacotherapy is as good as the instruction offered to



Patients with valid observations at each time point, n

Tiotropium plus placebo	154	147	132	126	123
Tiotropium plus salmeterol	146	134	122	122	122
Tiotropium plus fluticasone-salmeterol	145	141	131	129	124

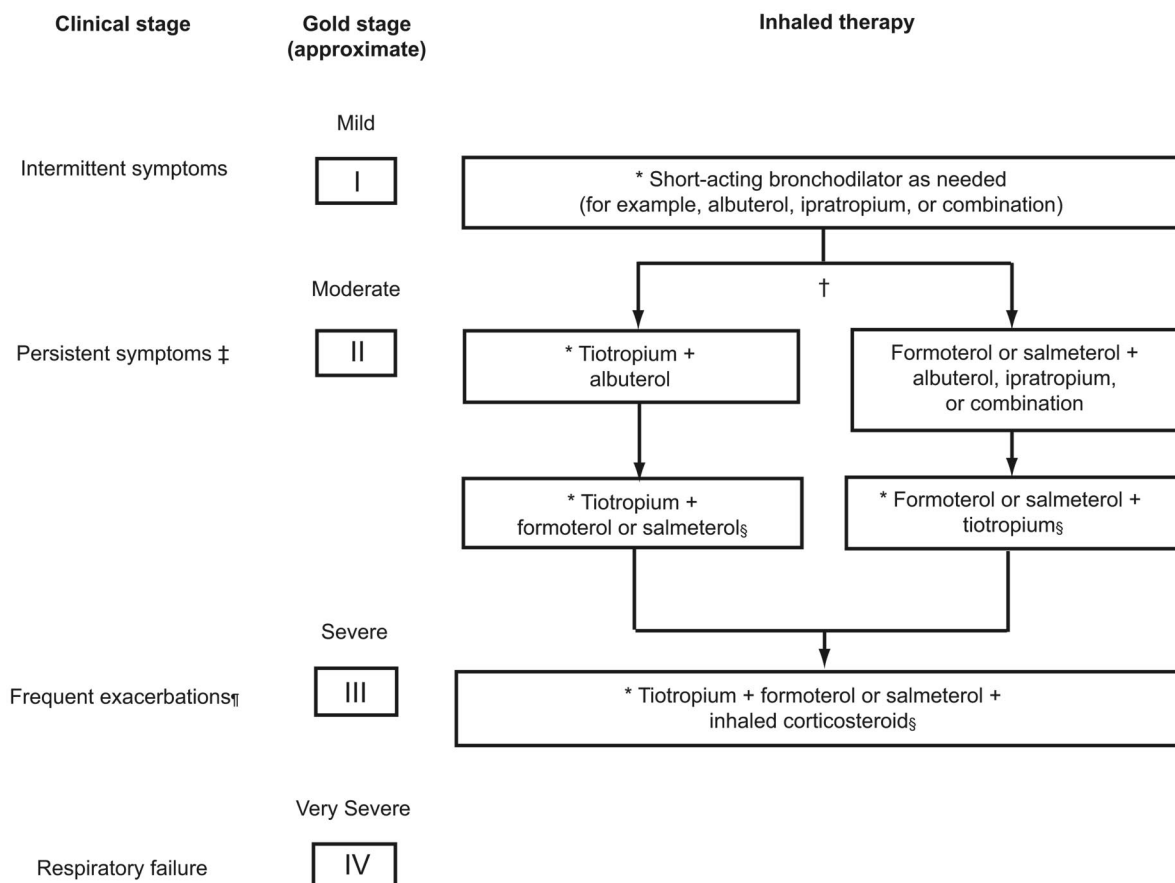


Patients with valid observations at each time point, n

Tiotropium plus placebo	152	141	128	123	120
Tiotropium plus salmeterol	146	137	117	117	115
Tiotropium plus fluticasone-salmeterol	142	141	129	125	122

Fig. 12. Changes in health-related quality of life and forced expiratory volume in the first second (FEV<sub>1</sub>) over 1 year. Top: Scores on the St George's Respiratory Questionnaire (SGRQ). Lower scores indicate improvements in quality of life. *P* = .02 for tiotropium plus placebo versus tiotropium plus salmeterol at 52 weeks; *P* = .01 for tiotropium plus placebo versus tiotropium plus fluticasone-salmeterol at 52 weeks. Bottom: Mean prebronchodilator FEV<sub>1</sub>. *P* = .87 for tiotropium plus placebo versus tiotropium plus salmeterol at 52 weeks; *P* = .049 for tiotropium plus placebo versus tiotropium plus fluticasone-salmeterol at 52 weeks. (From Reference 150, with permission.)

the patient on the use of inhalers. As such, RTs should make several attempts to guarantee that the patient is using the device that matches the ability to perform a good technique. It is the RT who most often has the prime opportunity to assess correct use of these devices in a variety of clinical settings. Some of the mistakes related to inhaled pharmacotherapy include inadequate instruction about correct inhaler technique, inadequate patient education regarding the purpose and importance of the medications, suboptimal dosing, failure to recommend administration of the medication prior to exertion, and inadequate monitoring of patient response to treatment.<sup>72</sup> These pitfalls affect therapeutic response but may be positively impacted by



\* Four-step algorithm for the implementation of inhaled treatment

† Pathway on left is recommended; pathway on right side is a valid alternative

‡ Defined as need for rescue medication on more than two occasions per week

§ A short-acting bronchodilator can be used for rescue. Low-dose methylxanthines can be prescribed if the response to inhaled bronchodilator therapy is insufficient

¶ Defined as two or more exacerbations per year

Fig. 13. Suggested strategy for the stepwise introduction of inhaled pharmacotherapy based on the clinical staging of chronic obstructive pulmonary disease (COPD). GOLD = Global Initiative for Chronic Obstructive Lung Disease. (From Reference 13, with permission.)

RTs who actively participate in the education and application of the guidelines. The RT should take the time to evaluate improvement of airflow, symptoms, exercise tolerance, the amount of rescue medication used, and the frequency of health resource utilization. The knowledge gained from this assessment, combined with the physician awareness of and compliance with the existing guidelines, are important ingredients to a good prescription for patients with COPD.

This review demonstrates the difficult task RTs and other medical professionals face when managing patients with COPD on a daily basis. Notwithstanding methodological limitations, all the studies have clearly demonstrated that no treatment is not an option for these patients. An accelerated rate of decline in lung function continues to be the landmark of this chronic illness. While one can argue that current evidence has not absolutely proven

that a single agent that dramatically improves this rate of decline exists, the results of several studies are encouraging.<sup>140,196</sup> Patients with COPD suffer from a long-lasting illness. Most studies referenced in this review failed to capture seasonal variation in patients with COPD, due to the limitation of the study periods. While results of short-term studies have been consistent with those of large and longer multicenter trials, long-term studies (> 12 months) offer the advantage of measuring frequency of exacerbations, adverse events, and health-related cost and utilization versus simply estimating risks or calculating predictions.

Despite the unquestionable role of inhaled pharmacotherapy in the management of patients with stable COPD, many researchers still have difficulty pinpointing the best parameter that correlates with clinical response to a specific pharmacologic intervention. The multifaceted

pathophysiology of COPD forces clinicians to explore new combination of agents to target specific events in the disease process.<sup>197</sup> To complicate matters, patients with COPD are heterogeneous in terms of their clinical presentation, rate of disease progression, and disease severity. The FEV<sub>1</sub> has been widely used as one of the primary outcomes in a large percentage of the studies summarized in this review.<sup>198</sup> While it provides information on the degree of airflow limitation, it appears to lack a strong correlation to the severity of symptoms or HRQL. Therefore, the favorable spirometric profile exhibited by the critically important long-acting bronchodilators may not necessarily be followed by similar improvements in HRQL.<sup>199</sup> Although adding ICS to long-acting bronchodilators remains very controversial, it seems logical to consider this option in patients with severe to very severe COPD who are refractory to combination of long-acting bronchodilators and who have frequent exacerbations. The associated improved clinical outcomes have to be weighed against concerns for safety and adverse events associated with long-term use of LABAs and ICSs. The field of inhaled pharmacotherapy for the management of chronic pulmonary illnesses is still under rigorous investigation. Time will only clarify the specific role of the available and emerging agents into the stepwise approach to managing patients with COPD.

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