

# The effect of inhaled $\beta_2$ -agonists on clinical outcomes in chronic obstructive pulmonary disease

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The major clinical outcomes measured in evaluating the responses to pharmacotherapy in patients with chronic obstructive pulmonary disease (COPD) include the severity of dyspnea, exercise capacity, exacerbations, and health status. Various studies have demonstrated that testing for acute bronchodilator reversibility in the pulmonary function laboratory does not predict the clinical responses to a trial of bronchodilator therapy in patients with COPD. Separate studies have shown that inhaled albuterol, both a single dose (300  $\mu$ g) and 2 weeks of therapy (200  $\mu$ g/4 $\times$ /day), reduces dyspnea. There is more published information available about the effects of long-acting ( $\geq 12$  hours' duration of action) inhaled  $\beta_2$ -agonists because of greater interest in considering clinical outcomes at the time of drug testing. In one randomized clinical trial, formoterol reduced symptoms (as recorded in a home diary) and improved health status. Nine clinical studies have examined the effects of salmeterol on clinical outcomes. Salmeterol reduced the perception of breathlessness (in 6 of 9 studies) and improved health status (in 3 of 4 studies). These results collectively demonstrate that long-acting inhaled  $\beta_2$ -agonists not only relax bronchial smooth muscle but also provide important clinical benefits in symptomatic patients with COPD. (*J Allergy Clin Immunol* 2002;110:S298-303.)

**Key words:** Inhaled  $\beta_2$ -agonists, clinical outcomes, dyspnea, chronic obstructive pulmonary disease

The usual course of chronic obstructive pulmonary disease (COPD) is a slow deterioration of lung function leading to progressive breathlessness with daily activities. Previous studies have shown that supplemental oxygen is the only treatment that can prolong survival in hypoxemic patients with COPD.<sup>1-2</sup> Furthermore, smoking cessation,<sup>3</sup> but not inhaled ipratropium bromide<sup>3</sup> or inhaled corticosteroid therapy,<sup>4-6</sup> can slow the accelerated decline in respiratory function. On the basis of this information, the published guidelines of the Global Initiative for Chronic Obstructive Lung Disease recommend that bronchodilator medications be prescribed for those with COPD *for relief of symptoms*.<sup>7</sup> The overall goals for improving clinical outcomes are to:

- Reduce symptoms, especially dyspnea
- Improve exercise capacity

## Abbreviations used

$\beta$ AR:  $\beta$ -Adrenergic receptor  
COPD: Chronic obstructive pulmonary disease  
FEV<sub>1</sub>: Forced expiratory volume in one second  
FVC: Forced vital capacity  
LABA: Long-acting  $\beta$ -agonist  
SABA: Short-acting  $\beta$ -agonist

- Reduce exacerbations and the possible need for hospitalization
- Enhance health status

This article reviews the efficacy (as related to these 4 clinical outcomes) and safety of short-acting  $\beta$ -agonists (SABAs) and long-acting  $\beta$ -agonists (LABAs).

## OUTCOMES MEASUREMENT

The different instruments used to measure the 4 clinical outcomes are listed in Table I. This review includes only methods published in randomized controlled trials that examined the effects of inhaled  $\beta$ -agonist medications in patients with COPD.

### Measurement of dyspnea

Like any sensory experience, dyspnea, or breathlessness, can be quantified by using a stimulus-response relationship. Although the precise stimulus and the exact mechanism(s) contributing to dyspnea have not been completely identified, it is possible to consider likely or putative stimuli for causing dyspnea by using different approaches. For example, activities of daily living are used as the basis for measuring dyspnea using the Baseline and Transition Dyspnea Indexes<sup>8</sup> and the dyspnea component of the Chronic Respiratory Disease Questionnaire.<sup>9</sup> Another approach is to consider that an exercise task (eg, 6-minute walking test or cycle ergometry) is the stimulus, and the individual patient can provide ratings of dyspnea on the 0 to 10 category-ratio scale developed by Borg.<sup>10</sup>

### Measurement of exercise capacity

The 6-minute walking distance has been used as a relatively simple test to evaluate possible benefits of inhaled  $\beta$ -agonist therapy. A more standardized stimulus is to have the subject walk at a specific speed on the treadmill or perform cycle ergometry. Exercise duration, power output (watts), and oxygen consumption (mL/kg/min) are standard measures of exercise capacity.

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## Assessment of exacerbations

Two general approaches used to define exacerbations of COPD are symptoms and healthcare utilization. An increase in dyspnea, an increase in sputum volume, and purulence or discoloration of the sputum are the usual symptoms considered. For healthcare utilization the severity can be defined according to the need for use of an antibiotic (mild), the need for systemic corticosteroid therapy (moderate), and the need for hospitalization (severe). In 2000, an international workshop proposed a definition of an exacerbation based on a combination of symptoms and healthcare utilization.<sup>11</sup>

## Measurement of health status

Both generic and disease-specific instruments have been used to quantify health status in patients with COPD. However, the Chronic Respiratory Disease Questionnaire<sup>9</sup> and the St George's Respiratory Questionnaire,<sup>12</sup> disease-specific measurement tools used widely in clinical trials, are better able to document change with therapy compared with generic health status questionnaires.

## Should COPD patients be tested for acute bronchodilator responsiveness?

Although the post-bronchodilator forced expiratory volume in one second (FEV<sub>1</sub>) is considered the best currently available predictor of long-term prognosis, there is disagreement among professional organizations whether acute bronchodilator testing for responsiveness should be performed.<sup>13,14</sup> The key issues are the reliability and predictive value of testing for bronchodilator reversibility.

Guyatt et al<sup>15</sup> studied bronchodilator responsiveness at three different visits, each one week apart, in 23 patients with COPD. The intraclass coefficient correlation was only 0.17 for the changes in FEV<sub>1</sub> after inhalation of albuterol. Moreover, the post-bronchodilator FEV<sub>1</sub> was a poor predictor of the subsequent clinical response to either albuterol or theophylline over a 2-week trial of these medications.<sup>16</sup> Teale et al<sup>17</sup> concluded that it is not appropriate to base longer-term treatment with a bronchodilator on the results of a single test of reversibility in the laboratory.

In a recent study, O'Donnell et al<sup>18</sup> evaluated bronchodilator responses in 84 patients with stable COPD that were considered "irreversible" based on a change in FEV<sub>1</sub> <10% predicted after inhalation of 200 µg albuterol. However, the majority (83%) had significant improvements in one or more lung volumes, with the greatest changes being in residual volume and functional residual capacity. Thus, there may be significant reductions in lung hyperinflation even in the absence of a change in FEV<sub>1</sub> after bronchodilator therapy.<sup>18,19</sup> A decrease in hyperinflation allows the vertical muscle fibers of the diaphragm to increase in length and reduces the elastic recoil of the lung. Both of these changes have been associated with an improvement in dyspnea.<sup>20</sup>

In a randomized controlled trial comparing salmeterol with ipratropium bromide and placebo therapies for COPD, Mahler et al<sup>21</sup> showed improvements in lung

**TABLE I.** Standard instruments used to measure clinical outcomes in patients with COPD\*

### Dyspnea

Baseline and Transition Dyspnea Indexes (based on activities of daily living)

0-10 category scale by Borg (based on an exercise task)

### Exercise capacity

6-Minute walking distance

Treadmill walking

Cycle ergometry

Exacerbations

Symptoms (increases in dyspnea and sputum volume as well as purulence of sputum)

Health care utilization (need for antibiotics, corticosteroids, and/or hospitalization)

### Health status

Chronic Respiratory Disease Questionnaire

St George's Respiratory Questionnaire

\*These outcome measures have been used in published randomized controlled trials that evaluated bronchodilator therapy in patients with COPD.

function and reductions in the severity of dyspnea, even in the subgroup of patients who exhibited irreversibility (defined as a change in FEV<sub>1</sub> <12% predicted and/or <200 mL after inhalation of albuterol).

These data collectively demonstrate that acute bronchodilator testing in the pulmonary function laboratory based on changes in FEV<sub>1</sub> has little, if any, value in predicting the clinical response to one or more bronchodilator medications for the treatment of patients with COPD.

## EFFICACY OF SABAs

SABAs (4- to 6-hour duration of action) have been used for more than 3 decades in the treatment of COPD. However, the majority of studies evaluating the effects of the SABAs have focused on changes in lung function as the primary outcome measure. Accordingly, there is limited information available on the benefits of these agents on clinical aspects.

### Metaproterenol

Although Berger and Smith<sup>22</sup> found no change in lung function after inhalation of metaproterenol, subjects increased both their treadmill and hall-walking distances significantly with the SABA compared with placebo. It is conceivable that the enhanced exercise capacity was the result of reduced lung hyperinflation.

### Albuterol

Guyatt et al<sup>16</sup> examined the effects of 2 weeks of inhaled albuterol (200 µg/4×/day) in 19 patients with COPD who had <25% change in FEV<sub>1</sub> 30 minutes after albuterol as an inclusion criterion. The results showed significant improvements not only in FEV<sub>1</sub> (+140 mL), forced vital capacity (FVC) (+450 mL), and maximal inspiratory mouth pressure (+3.5 cm water), but also in measures of dyspnea and health status.<sup>16,23</sup> Belman et al<sup>19</sup> evaluated the acute effects

of albuterol (300 µg) compared with placebo on dynamic hyperinflation during exercise in 13 patients with moderate-to-severe COPD. In addition to inducing significant increases in FEV<sub>1</sub> (+230 mL) and FVC (+510 mL), albuterol improved both dynamic hyperinflation and dyspnea ratings during exercise. Furthermore, there were significant correlations between the changes in dyspnea and the changes in end-inspiratory lung volume (a measure of dynamic hyperinflation) ( $r = 0.77$ ;  $P < .01$ ).<sup>19</sup> The results of these two studies support general clinical experience that albuterol is an effective short-acting bronchodilator that reduces dyspnea. This benefit may be because of its effect on reducing hyperinflation (at rest and/or during exertion) and may not be reflected by changes in spirometry.

### Terbutaline

Pino-Garcia et al<sup>24</sup> showed that inhaled terbutaline (500 µg) resulted in significant decreases in dyspnea, as measured on the Borg scale, and central inspiratory drive, as measured by the mouth pressure at 0.1 seconds after airway occlusion, but no change in the pattern of breathing in 25 patients with irreversible COPD.

## EFFICACY OF LABAs

Formoterol and salmeterol are the two LABAs currently approved for the treatment of COPD. Although these agents are newer than the SABAs, there is more information available about their clinical benefits because of the greater recent interest in considering such outcomes at the time of drug testing.

### Formoterol

The approved dose of formoterol dry powder inhalation capsules is 12 µg twice daily.

**Lung function.** Formoterol has an acute onset of bronchodilation (within 5 minutes) and a duration of ≥12 hours. Cazzola et al<sup>25</sup> found a dose-dependent increase in the spirometric parameters with formoterol (12, 24, and 36 µg), and the mean peak bronchodilation was more rapid than that observed with salmeterol.

**Dyspnea.** Dahl et al<sup>26</sup> reported that formoterol dry powder 12 and 24 µg twice daily provided statistically significant improvements in the mean total diary symptom score compared with placebo during a 12-week period, along with a concurrent reduction in the rescue use of albuterol.

**Exercise performance.** A review of the literature did not reveal any published information about the effect of formoterol on exercise performance.

**Exacerbations.** Dahl et al<sup>26</sup> reported there were no significant differences between formoterol and placebo treatment groups in the number of days of additional therapy required for exacerbations of COPD.

**Health status.** The 12-µg dose of formoterol produced statistically and clinically significant improvements (5.1 U) in the total score on the St George's Respiratory Questionnaire compared with placebo. Although the 24-

µg dose also achieved significant benefits, the magnitude of change was not as great as with the 12-µg dose.<sup>26</sup>

### Salmeterol xinafoate

The recommended dose of salmeterol delivered by metered dose inhaler or diskus is 50 µg twice daily.

**Lung function.** The peak effect of salmeterol on lung function in patients with COPD is approximately 2 hours and the duration is ≥12 hours.<sup>21,27</sup> Cazzola et al<sup>25</sup> found that acute reversibility to albuterol did not reliably predict the response to inhaled salmeterol in individual patients. Ramirez-Venegas et al<sup>28</sup> demonstrated that salmeterol reduced lung hyperinflation compared with placebo therapy, with significant decreases in functional residual capacity (−546 mL) and residual volume (−516 mL) at 4 hours after salmeterol.

**Dyspnea.** Ramirez-Venegas et al<sup>28</sup> examined the acute effects of salmeterol in response to breathing through inspiratory resistances of 5, 15, and 30 cm water/L/second for 1 minute each. Dyspnea ratings were better at 0.5, 2, and 4 hours after salmeterol compared with placebo ( $P = .002$ ). By using a multidimensional instrument to measure changes in dyspnea based on activities of daily living, Mahler et al<sup>21</sup> showed that salmeterol reduced dyspnea on the Transition Dyspnea Index after 2, 4, 8, and 10 weeks of treatment compared with placebo therapy. However, in a similarly designed study, Rennard et al<sup>27</sup> observed no statistical differences in the Transition Dyspnea Index scores between salmeterol and placebo treatment groups.

The effect of salmeterol on dyspnea has also been examined in two studies evaluating salmeterol alone against combination therapy (salmeterol plus another bronchodilator) in addition to placebo. ZuWallack et al<sup>29</sup> showed an improvement of +1.3 units on the Transition Dyspnea Index with salmeterol at 12 weeks compared with +1.1 with theophylline and +1.9 with salmeterol and theophylline combination therapy. Van Noord et al<sup>30</sup> reported that salmeterol provided a greater percentage of days with ≤1 symptom compared with placebo (49% ± 3% vs 34% ± 4%;  $P < .05$ ).

Although Boyd et al<sup>31</sup> reported no difference in the 6-minute distance walked between salmeterol and placebo groups, patients treated with salmeterol were significantly less breathless at the end of the walking test after 8 weeks ( $P = .02$ ) and 16 weeks ( $P = .004$ ) of therapy. Similarly, Grove et al<sup>32</sup> found that patient ratings of perceived exertion on the Borg scale at the end of the 6-minute walking test were better with salmeterol compared with placebo after 4 weeks of therapy. In contrast, patient ratings of dyspnea at the end of the 6-minute walking test did not differ with salmeterol compared with placebo treatment.<sup>21,27</sup>

**Exercise performance.** Patakas et al<sup>33</sup> showed that 15 patients with COPD were able to walk a significantly greater distance on the treadmill after salmeterol compared with placebo. In contrast, Mahler et al,<sup>21</sup> Rennard et al,<sup>27</sup> Boyd et al,<sup>31</sup> and Grove et al<sup>32</sup> found no differences in the 6-minute walking distance with salmeterol compared with placebo therapy.

**Exacerbations.** In 3 separate 12-week trials, there was no consistent effect of salmeterol on exacerbations of COPD compared with placebo.<sup>21,27,30</sup> Of interest, Dowling et al<sup>34,35</sup> reported that salmeterol reduced respiratory epithelial damage induced by *Haemophilus influenzae* and by *Pseudomonas aeruginosa*, probably by maintaining intracellular concentrations of cyclic adenosine monophosphate. However, the clinical impact of this “cytoprotection” on the respiratory tract requires further investigation.

**Health status.** Jones et al<sup>36</sup> reported that salmeterol 50 µg twice daily was associated with significant improvements in “Total” and “Impacts” scores on the St George’s Respiratory Questionnaire compared with placebo in a 16-week clinical trial. These scores exceeded the threshold for a “clinically important difference” ( $\geq 4$  U).

In a 12-week trial, the total score on the Chronic Respiratory Disease Questionnaire was higher (better) for the salmeterol-treated group ( $7.1 \pm 1.4$ ) compared with the placebo group ( $2.1 \pm 1.3$ ) ( $P = .007$ ).<sup>21</sup> Furthermore, the proportion of patients who achieved increases of  $\geq 10$  points in overall score (the minimal important clinical difference) was significantly higher at week 12 with salmeterol (46%) than in the placebo group (27%). However, in another study of identical design, the difference between the total score on the Chronic Respiratory Disease Questionnaire for salmeterol (10.3) and placebo (6.8) approached statistical significance ( $P = .078$ ).<sup>27</sup>

## SIDE EFFECTS OF $\beta$ -AGONISTS

Side effects of inhaled  $\beta$ -agonists are generally dose-related and the result of activation of extrapulmonary  $\beta$ -adrenergic receptors ( $\beta$ ARs). Cardiovascular adverse events are potentially the most serious. These may include an increase in blood pressure, tachycardia, cardiac arrhythmias, and palpitations as a result of direct stimulation of  $\beta_2$ ARs in the atria and possibly  $\beta_1$ ARs with higher doses of inhaled medication.<sup>37,38</sup> However, recent studies have shown that salmeterol does not cause significant differences in resting 12-lead or 24-hour electrocardiography in patients with symptomatic COPD.<sup>21,27,29</sup>

Cazzola et al<sup>39</sup> examined the acute effects of a single dose of salmeterol (50 µg) and two doses of formoterol (12 and 24 µg) in 12 patients with COPD who had pre-existing cardiac arrhythmias and hypoxemia. They found slight increases in heart rate and in ventricular premature contractions with the LABAs compared with placebo. Moreover, the frequency of these cardiac effects was higher with the 24-µg dose of formoterol. The investigators concluded that “salmeterol, 50 µg, is more favorable than formoterol, 12 µg, when we consider the bronchodilating effect and formoterol, 24 µg, when we consider the effect on the heart.”<sup>39</sup>

Tremor can be induced by stimulation of  $\beta_2$ ARs found in skeletal muscles. However, tremor did not occur more frequently with salmeterol compared with placebo in multicenter trials,<sup>21,27,29</sup> although the 100-µg dose (not

recommended for use) was associated with a significantly higher incidence of tremor than the 50-µg dose.<sup>36</sup>

$\beta$ -Agonists can also cause hypokalemia because of shifting of potassium within cells.<sup>40</sup> In addition, these agents may increase levels of serum glucose, insulin, lactate, pyruvate, and free fatty acids when used in higher doses.

## CONCLUSIONS

More published investigations are available that evaluate the clinical outcomes associated with the LABAs compared with SABAs. This reflects an emerging interest in considering and measuring dyspnea, exercise performance, exacerbations, and health status that coincides with the development and testing of both formoterol and salmeterol.

Nonetheless, there is only one published study examining clinical outcomes of formoterol therapy in patients with COPD. In this randomized controlled trial, formoterol improved the “mean total diary symptom score” and health status compared with placebo therapy.<sup>26</sup>

In contrast, 9 published clinical trials have evaluated salmeterol in patients with COPD. Most of these studies (6 of 9) showed that salmeterol reduced the perception of dyspnea under various conditions (eg, added respiratory load, activities of daily living, and exercise). However, 3 of 4 studies showed no improvement in exercise capacity (6-minute walking distance) with salmeterol compared with placebo. Although there are conflicting data on the effect of salmeterol in reducing exacerbations of COPD, improvements in health status have been observed (in 3 of 4 trials) with salmeterol.

These results collectively demonstrate that LABAs not only improve lung function by relaxing bronchial smooth muscle but also provide clinical benefits that are important to symptomatic patients with COPD.

## DISCUSSION SESSION

**Question:** How do most of the outcomes you measure correlate with the effect on FEV<sub>1</sub>?

**Dr Mahler:** At baseline, the correlations are a little better, maybe .3 or .4. When we look at the changes in dyspnea and the changes in FEV<sub>1</sub>, the correlation is approximately .15 or .12 at least. Most people believe that these are different constructs. That is why it is important not only to measure FEV<sub>1</sub> to show some bronchodilation but to look at these clinical outcomes, which clearly represent different measures that are not redundant.

**Question:** One of the problems that we have in treating COPD is to try to find something effective for the patients who do not bronchodilate, which is a substantial portion of that group. Will we be able to address issues like dyspnea, or perceptual issues related to COPD, without having to demonstrate to the FDA that there is a conventional change in FEV<sub>1</sub>, particularly since some of these patients for whom we want these therapies do not respond with an improvement in FEV<sub>1</sub>? Is there recognition now that this is an unmet need? Will we be able to obtain approval for new drugs using outcome measures other than FEV<sub>1</sub>?

**Comment:** I know that the FDA is interested in clinical outcomes. It is very difficult in a therapeutic drug trial in COPD patients to be consistently successful with the secondary outcomes, whether it is the 6-minute walk or the various dyspnea indices. So I think that is a very discouraging note in new drug development, that the

FDA really does require primarily a mechanical lung function change.

*Question:* How does the action of a bronchodilator compare with primarily psychotropic medicines such as opiates in the management of COPD?

*Dr Mahler:* There have been trials, both acute and chronic, looking at opiates on perception of dyspnea. In the randomized controlled trials, there is no consistent reduction in dyspnea with narcotic medications. That is surprising because we use opiates in end-of-life care. However, in symptomatic, moderate-to-severe COPD patients using the inhaled route, there is no clear or consistent benefit. With oral medications, side effects such as constipation and sleepiness seem to outweigh the potential benefits in relief of breathlessness. I am not aware of any head-to-head comparisons between opiates and bronchodilators. Generally, we can say that the bronchodilators do improve dyspnea in a large group of people. To determine whether they work in single patients we have to try it. In contrast, narcotics generally work in relieving dyspnea. However, all of us use them for end-of-life care and perhaps in select cases where nothing else seems to be working.

*Question:* Can you explain how bronchodilators decrease FRC at rest? In theory, at rest, shouldn't the FRC be the same independent of any partial narrowing of airways? At equilibrium, airway resistance should not make a difference, and the very clear effects that you showed in your study ought to be due to some other effect of drugs on lung function.

*Dr Mahler:* It has been my assumption that it is just better, emptying of airways on exhalation allowing these changes in FRC. We did not measure more sophisticated ways to look at respiratory muscle function or compliance of the lung during these studies.

*Comment:* People have not really considered changes in lung vascular volume. If one thinks of the chest as a closed compartment, the blood volume in the lung takes up space. If the bronchodilators are improving the emptying of the lung vessels, then there is more volume in the lung. So, some of these nonbronchodilator effects could be due to changes in lung volume that might have a physiologic effect.

*Comment:* I would think that most of these patients are flow-limited during their tidal breathing. If that is true, I would not expect them to come to an equilibrium. Only those patients who are not breathing on their flow volume curve would be expected to come to some type of mechanical equilibrium, which would be independent of their resistance. For most of these patients, then, it is straightforward as to why the lung volumes are affected by bronchodilators.

*Dr Mahler:* We did not measure flow limitation in our subjects. We see major changes in lung volumes without any changes in flow rates, which would be advantageous.

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