RESEARCH LETTER

Megatrials for Bronchodilators in Chronic Obstructive Pulmonary Disease (COPD) Treatment: Time to Reflect

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Introduction: Chronic obstructive pulmonary disease (COPD) is an important cause of morbidity and mortality worldwide. Although (long-acting) bronchodilators are used to relieve symptoms, the impact of bronchodilators on COPD mortality remains an unresolved issue. Our aim was to explore the results and the interpretations of the results of studies of bronchodilator treatment from high-impact COPD trials.

Methods: We searched PubMed and Embase for primary publications of randomized controlled trials with more than 1000 participants with COPD and that studied the effectiveness of long-acting bronchodilator treatment. We assessed population characteristics, primary outcomes, focus of outcomes, and possible bias from concomitant pulmonary medication.

Results: We retrieved 5 primary publications of large trials. Participants tended to be patients with rather severe COPD who were cared for at a hospital. Only half of the primary outcomes were statistically significant. Reports tended to focus on statically significant outcomes and not necessarily on primary outcomes or outcomes of the whole study population. The relevance of study outcomes was rarely discussed.

Discussion: The rather small effects of bronchodilators in a COPD population that is not representative for daily care, together with the tendency of relying on statistical rather than clinical significance, hampers translation to the large number of patients with COPD in the community. (J Am Board Fam Med 2013;26:221–224.)

Keywords: Bronchodilators, Chronic Disease, Chronic Obstructive Pulmonary Disease (COPD), Pharmacotherapy, Respiratory Tract Diseases

Chronic obstructive pulmonary disease (COPD) is a progressive chronic disease characterized by not fully reversible airflow obstruction. It is one of the most important causes of morbidity and mortality worldwide, directly related to cigarette smoking. Indeed, cessation of cigarette smoking is the single-most efficient intervention to prevent both disease development and progression. In addition, (long-acting) bronchodilators are used to relieve symptoms. An unresolved question is the impact of bronchodilators on COPD mortality, in part by attenuation of pulmonary function decline and exacerbations, independent from desired symptom relief. The last decade, a number of large studies on the effectiveness of long-acting bronchodilators received extensive attention in leading medical journals. Calverley observed that “ensuring that these expensive studies are done objectively to the highest standard is an important goal”. For that reason, the quality of these large trials, their external validity, and what they add to the current clinical practice, are of importance. We systematically reviewed the results and the interpretations of these results of megatrials on long-acting bronchodilators in COPD patients that were published in high impact journals.
### Table 1. Large Bronchodilator Trials According to Factors For Interpreting Good Clinical Practice on Design, Results, and Translation

<table>
<thead>
<tr>
<th>Study (trial registry; funding)</th>
<th>Patients (n)</th>
<th>Length of Follow-up</th>
<th>Selection Criteria (Part)</th>
<th>Population</th>
<th>Interventions</th>
<th>Rescue</th>
<th>Prohibited medication</th>
<th>Allowed bias medication</th>
<th>Primary outcome</th>
<th>Results</th>
<th>Significance</th>
<th>Focus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calverley, 2007&lt;sup&gt;6&lt;/sup&gt; (registered; funding from GSK)</td>
<td>6112</td>
<td>3 years</td>
<td>40-80 years old, COPD diagnosis, FEV&lt;sub&gt;1&lt;/sub&gt;: &lt;60%, FER: &lt;0.70 before BD, Reversibility: &lt;10% No respiratory disease, use of oxygen</td>
<td>65 years 75% male 43% smoker FEV&lt;sub&gt;1&lt;/sub&gt; 44% predicated value</td>
<td>Salmeterol/ Fluticasone, Salmeterol Fluticasone Placebo</td>
<td>Albuterol</td>
<td>Long-acting BD, steroids</td>
<td>Short-acting and other BD</td>
<td>Mortality</td>
<td>12.6% vs 13.5% vs 16.0% vs 15.2%</td>
<td>NS</td>
<td>A</td>
</tr>
<tr>
<td>Calverley et al, 2003 (not registered; funding from GSK)</td>
<td>1465</td>
<td>1 year</td>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;: 25% to 70% before BD, FER: &lt;0.70 before BD, Reversibility: &lt;10% 1 exac/year 3 years No respiratory disease, use of oxygen</td>
<td>63.5 years 72.5% male 51% smoker FEV&lt;sub&gt;1&lt;/sub&gt; 49% predicated value</td>
<td>Salmeterol/ Fluticasone, Salmeterol Fluticasone Placebo</td>
<td>Albuterol</td>
<td>Long-acting β-agonist, steroids</td>
<td>Anticholinergics and theophyllin</td>
<td>FEV&lt;sub&gt;1&lt;/sub&gt; before BD</td>
<td>10% vs 2% vs 2% vs 3%</td>
<td>P &lt; .01</td>
<td>B</td>
</tr>
<tr>
<td>Tashkin et al, 2008 (registered; funded by BI and Pfizer)</td>
<td>5993</td>
<td>4 years</td>
<td>&gt;40 years, FEV&lt;sub&gt;1&lt;/sub&gt;: &gt;70%, FER: &lt;0.70 No respiratory disease, use of oxygen Myocardial infarction during last 6 months, unstable arrhythmia</td>
<td>64.5 years 75% male 30% smoker FEV&lt;sub&gt;1&lt;/sub&gt; 48% predicated value</td>
<td>Spiriva Placebo</td>
<td>—</td>
<td>Short-acting anticholinergics</td>
<td>All nonanticholinergics</td>
<td>FEV&lt;sub&gt;1&lt;/sub&gt; decline before and after BD</td>
<td>Before BD: 30 vs 30 mL/yr After BD: 40 vs 42 mL/yr</td>
<td>NS</td>
<td>C</td>
</tr>
<tr>
<td>Niewoehner et al, 2005 (not registered; funded by BI and Pfizer)</td>
<td>1829</td>
<td>6 months</td>
<td>&gt;40 years, COPD diagnosis, FEV&lt;sub&gt;1&lt;/sub&gt;: &lt;60%, FER: &lt;0.70 No asthma Myocardial infarction during past 6 months, cardiac hospital during past year</td>
<td>67.8 years 99% male 30% smoker FEV&lt;sub&gt;1&lt;/sub&gt; 36% predicated value 29% oxygen</td>
<td>Spiriva Placebo</td>
<td>—</td>
<td>Short-acting anticholinergics</td>
<td>All nonanticholinergics</td>
<td>%Exacerbation</td>
<td>32.3% vs 27.9%</td>
<td>P = .037</td>
<td>D</td>
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Continued
Methods

WD and LB conducted a search in both PubMed and Embase until 2011, July 31st, containing terms of COPD and bronchodilators. We included primary publications in leading journals with an impact factor >15 in 2011 of randomized controlled trials with more than 1000 participants with COPD, that studied the effectiveness of long-acting bronchodilator treatment. WD and LB independently and systematically assessed population characteristics, primary outcomes, focus of subgroup analyses, and possible bias from concomitant pulmonary medication.

Results

We reviewed five primary publications of large trials on bronchodilator effect in COPD patients. We included primary publications in leading journals with an impact factor >15 in 2011 of randomized controlled trials with more than 1000 participants with COPD, that studied the effectiveness of long-acting bronchodilator treatment.
always correctly stated the population key characteristics, whereas another used pre-bronchodilator values as primary outcome.

**Discussion**

Despite the positive tone in the reports of large trials on long-acting bronchodilator therapy in COPD patients, only half of the primary outcomes were statistically significant. Next, reports tend to focus on statically significant outcomes and not necessarily on primary outcomes or outcomes of the whole study population.

Compared with combining results of smaller rigorous trials into meta-analyses, megatrials could provide a small advantage on minimizing confounding by change. However, since large trials increase their participant numbers by reducing protocol rigidness, bias can be introduced that weakens causative interpretations. For instance, in these COPD megatrials, various co-medications were allowed during the study without proper adjustments for it in the analyses. On the other hand, decreased rigidity may provide a generalization of results in daily practice, but only if the study population is representative of the target population to which its results will be applied. Moreover, the clinical relevance of the rather small effects in a possibly biased COPD population that is not representative for daily care should be debated, in particular as meta-analyses rate these trials on their patient numbers mostly.

Most patients with COPD are treated in the community, while the selection of patients for large trials is biased toward referred, hospital cared patients. This, together with the tendency of relying on statistical rather than clinical significance, hampers translation to the large number of patients with COPD in the community. Independent from symptom relief, we would therefore plea for some precaution on the customary prescription of long-acting bronchodilators for the COPD population at large.

**References**

3. Calverley PM, Rennard SI. What have we learned from large drug treatment trials in COPD? Lancet 2007;370:774–85.