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.[1,2] 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".[3] 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.

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Table 1. Large Bronchodilator Trials According to Factors For Interpreting Good Clinical Practice on Design, Results, and Translation

	Characteristics				Medication Protocol				Effect			
Study (trial registry; funding)	Patients (n)	Length of Follow-up	Selection Criteria (Part)	Population	Interventions	Rescue	Prohibited medication	Allowed bias medication	Primary outcome	Results	Significance	Focus*
Calverley, 2007[6] (registered; funding from GSK)	6112	3 years	40–80 years old, COPD diagnosis FEV_1: <60% FER: <0.70 before BD Reversibility: <10% No respiratory disease, use of oxygen	65 years 75% male 43% smoker FEV_1 44% predicated value	Salmeterol/ Fluticason Salmeterol Fluticason Placebo	Albuterol	Long-acting BD, steroids	Short-acting and other BD	Mortality	12.6% vs 13.5% vs 16.0% vs 15.2%	NS	A
Calverley et al,[4] 2003 (not registered; funding from GSK)	1465	1 year	FEV_1: 25% to 70% before BD FER: <0.70 before BD Reversibility: <10% ≥1 exac/year 3 years No respiratory disease, use of oxygen	63.5 years 72.5% male 51% smoker FEV_1 49% predicted value	Salmeterol/ Fluticason Salmeterol Fluticason Placebo	Albuterol	Long-acting β-agonist, steroids	Anticholinergics and theophillin	FEV_1 before BD	10% vs 2% vs 2% vs −3%	$P < .01$	B
Tashkin et al,[7] 2008 (registered; funded by BI and Pfizer)	5993	4 years	>40 years FEV_1: <70%, FER: <0.70 No respiratory disease, use of oxygen Myocardial infarction during last 6 months, unstable arrhythmia	64.5 years 75% male 30% smoker FEV_1 48% predicted value	Spiriva Placebo	—	Short-acting anticholinergics	All nonanticholinergics	FEV_1 decline before and after BD	Before BD: 30 vs 30 mL/yr After BD: 40 vs 42 mL/yr	NS	C
Niewoehner et al,[5] 2005 (not registered; funded by BI and Pfizer)	1829	6 months	>40 years COPD diagnosis FEV_1: <60% FER: <0.70 No asthma Myocardial infarction during past 6 months, cardiac hospital during past year	67.8 years 99% male 30% smoker FEV_1 36% predicted value 29% oxygen	Spiriva Placebo	—	Short-acting anticholinergics	All nonanticholinergics	%Exacerbation %Exacerbation hospitalization	32.3% vs 27.9% 9.5% vs 7.0%	$P = .037$ NS	D

Continued

Table 1. Continued

Study (trial registry; funding)	Characteristics				Medication Protocol				Effect			Focus*
	Patients (n)	Length of Follow-up	Selection Criteria (Part)	Population	Interventions	Rescue	Prohibited medication	Allowed bias medication	Primary outcome	Results	Significance	
Vogelmeier et al,[8] 2011 (registered; funded by BI and Pfizer)	7376	1 year	>40 years FEV_1: <70%, FER: <0.70 ≥1 exacerbation during past year No asthma CVD	62.9 years 74.7% male 48% smoker FEV_1 49% predicted value	Spiriva Salmeterol	Albuterol	Anticholinergics, long-acting β-agonist	Short-acting β-agonist	Time to first exacerbation	187 vs 145 days (first fourth of patients)	$P < .001$	E

*A: Acknowledge statistically nonsignificant results for primary outcome, but the focus is on beneficial effect and secondary outcome in main text discussion and conclusion. They claim the study is underpowered. B: Focus is on secondary outcomes in main text discussion. C: Focus is on secondary outcome in result and discussion section of both abstract and main text. Of many nonsignificant post hoc subgroup analyses, they only state the significant one. D: Acknowledge statistically nonsignificant results for the primary outcome (called "borderline significant"), but focus is on beneficial effect in the abstract and main text results. E: Focus is on an exaggerated effect on one fourth of all patients (a third had an exacerbation), which is not stated in the abstract. Focus is on inaccurate description of population in main text discussion and conclusion.

BD, bronchodilator; BI, Boehringer Ingelheim; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; FER, forced expiratory ratio; FEV_1, forced expiratory volume in first second; GSK, GlaxoSmithKline; NS, not significant.

Methods

WD and LB conducted a search in both PubMed and Embase until 2011, July 31st, containing (Mesh) 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 outcomes, and possible bias from concomitant pulmonary medication.

Results

We retrieved five primary publications of large trials on bronchodilator effect in COPD patients, including 1465 to 7376 patients with a mean follow-up between 6 and 48 months (Table 1).[4–8] Mean COPD severity as measured by percentage of predicted forced expiratory volumes ranged from 36% to 49% at baseline. The mean proportion of males was 77%. All studies included patients with at least 10 pack-years smoking history only, and patients with co-prevalence of asthma were excluded. Certain types of pulmonary co-medication were allowed during all studies, but none of the analyses were adjusted for these co-medications during follow-up. Table 1 also summarizes the various effects of bronchodilators on primary outcomes. Primary outcomes were mortality,[6] exacerbations[5,8] and lung function decline.[4,7] Although all studies report positive outcomes for the study medication of interest in general, only three of six primary outcomes of the studies were statistically significant.[4,5,8] Clinical significance was discussed in two trials only.[4,5] The statistically significant primary outcomes include pre-bronchodilator FEV_1 change (post-bronchodilator FEV_1 was not statistically significant in this study),[4] percentage of patients with exacerbations (the other primary outcome: number of hospitalizations for exacerbations, did not statistically differ significantly between groups),[5] and time to exacerbations (a statistically significant modified population of analyses).[8] Studies focused on statistically significant secondary outcomes,[4,7] and statistically significant subgroup analyses.[7] Although two studies acknowledged statistically non-significant results for the primary outcome they focused on its beneficial effect,[6,7] and on the secondary outcome.[6] One study did not always correctly stated the population key characteristics,[8] whereas another used pre-bronchodilator values as primary outcome.[4]

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.[9] However, since large trials increase their participant numbers by reducing protocol rigidness, bias can be introduced that weakens causative interpretations.[10] 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 rigidness 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.[9] 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.

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