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Comparison of Efficacy and Safety Outcomes in Randomized Trials of Long-Acting and Short-Acting B_2-Agonists for Chronic Obstructive Pulmonary Disease: A Review

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Abstract

Limited information is available comparing the efficacy and safety of Short-Acting β_2-agonists (SABAs) versus long-acting β_2-agonists (LABAs) for maintenance therapy in Chronic Obstructive Pulmonary Disease (COPD). The objective of this research was to conduct a systematic literature review and evaluate COPD-related outcomes in a meta-analysis. The literature review identified randomized clinical trials of LABAs and SABAs as maintenance therapy in adults with stable COPD. PubMed/Medline, Embase, and the Cochrane Library were searched for reports published between January 1, 1990 and July 16, 2010. Only studies of at least 2 weeks in duration were included. Few studies directly comparing LABAs and SABAs were expected; therefore, studies with placebo or ipratropium were included for a potential indirect-comparison.

A total of 938 studies were identified with 62 meeting all inclusion criteria. Only one study directly compared outcomes for LABA versus SABA. This study reported significantly better airflow and greater reduction in symptoms for the LABA treatment. Twelve studies evaluated a SABA with a shared common comparator, but indirect meta-analysis was not tenable due to different outcome variables.

The efficacy and safety of LABAs and SABAs in patients with COPD has been demonstrated, but only LABAs have supporting data for maintenance treatment. In usual clinical care, SABAs appear to be used in place of LABAs for long-term therapy, despite the lack of any empirical support. This review supports the current evidence-based guidelines that recommend LABAs for maintenance therapy in adults with stable COPD and reserves SABAs for use as rescue medications.

Keywords: Pulmonary disease; Chronic obstructive; Adrenergic beta-agonists; Randomized controlled trials; Bronchodilators

Abbreviations: COPD: Chronic Obstructive Pulmonary Disease; LABA: Long Acting Beta Agonist; SABA: Short Acting Beta Agonist; FEV_1: Forced Expiratory Volume (in 1 second); BDI: Baseline Dyspnea Index; TDI: Transitional Dyspnea Index; SGRQ: St. George's Respiratory Questionnaire; CRDQ: Chronic Respiratory Disease Questionnaire

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a progressive disease affecting more than 24 million people in the United States [1,2]. It is the fourth-leading cause of death in the United States, with more than 121,000 deaths due to COPD reported in 2009 [3]. In 2002, the direct costs to treat COPD in the United States were estimated at $18 billion and this value has been projected to climb to $29.5 billion in 2010 [4]. Some of the burden of COPD is related to certain comorbid conditions such as cardiovascular disease, respiratory infections, and osteoporosis. In addition, COPD reduces quality of life by limiting the functional and exercise capacity of affected individuals.

Because no medications have been shown to alter the progression of COPD, the aims of current pharmacotherapy are to decrease symptoms, reduce the incidence and severity of exacerbations, and improve quality of life and exercise tolerance [5]. Inhaled bronchodilator medications constitute the cornerstone of symptom management in COPD. Inhaled β_2-agonists work by activating the β_2-adrenoceptor which relaxes the smooth muscle cells of airways. These agents are further classified based on duration of action into short-acting β_2-agonists (SABAs) (e.g., levalbuterol, albuterol) and Long-Acting β_2-Agonists (LABAs) (e.g., formoterol, arformoterol, indacaterol, and salmeterol). The duration of action for most SABAs is 4 to 6 hours (for levalbuterol, up to 8 hours for some patients), whereas the duration for LABAs is 12 or more hours.

For maintenance therapy in patients with moderate to severe COPD, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines recommend the use of long-acting bronchodilators (including LABAs) because they are effective and convenient [6]. However, research has shown that many patients do not receive maintenance therapies and primary care physicians are often unfamiliar with the guidelines [7,8]. Some physicians or payers may consider LABAs and SABAs to be functionally equivalent and interchangeable as maintenance therapies.

Randomized Controlled Trials (RCTs) of COPD treatments differ in study design depending on the outcome variables. For RCTS examining maintenance outcomes in COPD, the primary outcome variables are related to the prevention of exacerbations or altering disease progression. However, most COPD RCTsexamine improvement in airflow obstruction and symptom relief (chronic cough, excess sputum, and dyspnea). The Food and Drug Administration (FDA) in the United States has offered guidance on primary outcome measures and study durations depending on the indication sought for a COPD

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treatment. For studies measuring improvement in airflow, the recommended primary outcome variable is post-dose FEV_1 (forced expiratory volume in 1 second) and the recommended study duration is 3 to 6 months. For studies assessing the prevention of exacerbations, whether based on severity, duration, frequency of exacerbations or time to first exacerbation, the recommended study duration is 1 year. Finally, for studies examining disease progression alteration the recommend outcome variable is the reduced trajectory of serial FEV_1 measured over a 3-year period [9].

Although both SABAs and LABAs appear to be used for long-term treatment of COPD in usual clinical care [10], there have been no comprehensive reviews or meta-analyses comparing the use of LABAs versus SABAs for maintenance therapy. The objective of this study was to summarize the evidence for LABAs and SABAs in maintenance management of patients with COPD based on available published RCTs. This review examined RCTs of LABAs and SABAs in patients with stable COPD to compare their effects on lung function (FEV_1), incidence of exacerbations, and use of rescue medications, β-mediated adverse events, and symptoms such as dyspnea and exercise-tolerance measures.

Methods

The focus of this review was published, RCTs involving adult patients with stable COPD without asthma who received a LABA or a SABA either alone or combined with other therapies. The outcomes of interest were lung function as measured by FEV_1, incidence of exacerbations, use of rescue medications, dyspnea, exercise tolerance, quality of life, and β-mediated adverse events (especially cardiovascular events).

A systematic literature search was conducted using PubMed/Medline, Embase, and the Cochrane Library to identify relevant studies published and indexed between January 1, 1990 and July 16, 2010. Multiple search terms were used and the reference sections in other literature reviews or meta-analyses were examined to identify additional studies. Maintenance therapy was broadly defined as 2 or more weeks of regular dosing of a LABA or SABA; studies with durations of less than 2 weeks were excluded. Based on a preliminary review of the literature, few direct comparative studies of SABAs versus LABAs were expected and the most common comparators for indirect meta-analysis were placebo and ipratropium. Studies that did not directly compare a LABA versus a SABA or compare a LABA or SABA with placebo or ipratropium were excluded.

Data abstraction was performed by a single investigator using a pre-specified extraction form. The following information was abstracted from each study: (1) author identification, (2) year of publication, (3) study design (parallel or crossover) and quality, (4) sample size, (5) key inclusion criteria and exclusion criteria, (6) drug and dosing for each treatment arm, and (7) baseline characteristics (mean age, gender, and predose FEV_1/forced vital capacity [FVC]). The quality assessment examined the blinding of patients, care providers, and outcome assessors; similarity of treatment groups at baseline; imbalances between treatment groups in dropout rates; completion rates; whether the analysis was on the intention-to-treat patient set; how missing data were addressed; and selective reporting of outcomes [11].

For each outcome of interest, abstracted data included the outcome definition, the analysis time point, sample size, and reported summary measures (e.g., mean, standard deviation). For the outcomes with highly variable definitions, such as FEV_1, Area Under the Curve (AUC), and rescue medication use, we extracted values for a broad range of definitions. Other outcomes extracted included: exercise tolerance and related dyspnea scores on the Borg scale [12]; dyspnea as measured by Baseline Dyspnea Index (BDI) and Transitional Dyspnea Index (TDI) [13]; incidence of exacerbations; quality of life assessments measured by the St. George's Respiratory Questionnaire (SGRQ) [14] or the Chronic Respiratory Disease Questionnaire (CRDQ) [15]; and incidence of beta-mediated adverse events, cardiac adverse events, and metabolic abnormalities.

Results

The initial search yielded 938 studies. Following abstract review, 873 studies were excluded based on criteria specified in the study protocol (Figure 1). Full-text review of the remaining 65 studies resulted in 3 additional exclusions, leaving 62 studies for data extraction. Among these 62 studies, only one study directly evaluated a SABA versus a LABA [16], 49 studies evaluated a LABA versus placebo or ipratropium [17-65], and12 evaluated a SABA versus placebo or ipratropium [66-77]. There was insufficient data to complete a direct meta-analysis of SABA versus LABA. Due to the variations in outcomes and definitions and the small number of SABA studies, there was also insufficient data to allow meaningful indirect comparisons of LABAs and SABAs on the extracted endpoints. Below is a description of the limitations for FEV_1 and exacerbations, which were the most common outcome variables. A brief summary follows for other outcome variables.

FEV_1

Thirty-one studies reported numerical FEV_1 outcomes [20,22-24,26,27,29,30,33-36,38-40,42,44-46,48,49,51,56,58,59,61,63,66,67,72-77], but only 17 studies reported change in peak FEV_1 (occurring within 1-4 hours after dosing) from baseline [16,27,34-36,40,44,45,48,58,63,66,67,70,74,77]. None of these 17 studies included an analysis of a LABA versus ipratropium, eliminating the possibility of an indirect comparison through ipratropium. Among the placebo-controlled studies, 10 LABA [34-36,45,48,58,63] studies and 5 SABA studies [66,67,74,75,77] reported change in peak FEV_1, but only 2 of the SABA studies (both 2-weeks in duration) reported the variance for the outcome variable. Similarly, for serial measurements of FEV1 after bronchodilator administration, there was only a single placebo controlled SABA study [69].

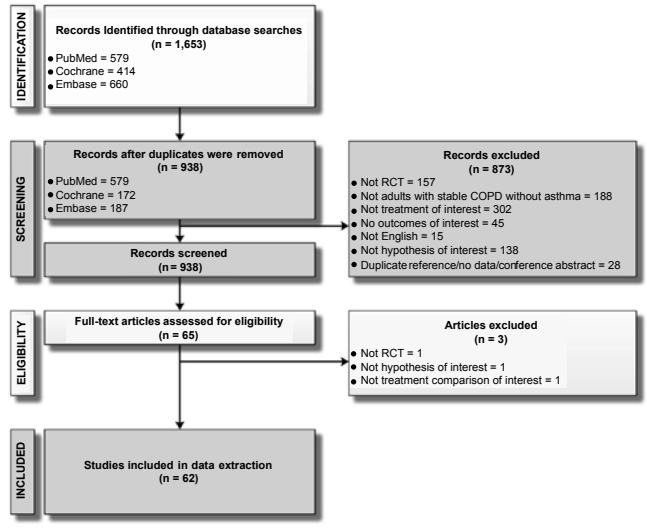

Figure 1: Study inclusion for data extract.

Exacerbations

Definitions for the incidence of exacerbations varied across the 35 studies reporting this outcome [16,19-21,23-30,32-34,37,41,43,47,49,50,52,56,58-60,62,64,66-70,74,76]. However, 33 studies included definitions of exacerbations that were moderate to severe based on the requirement for a change in the baseline medication regimen to improve respiration [16,19-21,23-30,32-34,37,41,43,47,49,50,52,58-60,62,64,66-70,74]. Among the 27 studies reporting the percentage of patients experiencing exacerbations: 21 studies evaluated LABA therapy versus placebo [19-21,23,27,29,30,32-34,37,41,43,47,49,50,52,58,60,62,64], but only 3 studies evaluated SABA therapy versus placebo [66,67,74]. The 3 SABA studies were all 12 weeks in length and changes in exacerbation frequency for studies shorter than 24 weeks in duration are not considered clinically meaningful.

Other outcome variables

Among the other outcome variables there were insufficient SABA studies for indirect comparisons. The number of SABA studies for each variable was dyspnea (1), use of rescue medications (1), tremor (2), six-minute walking test (2), CDRQ (4, but only 1 with sufficient numerical information), and SGRQ (1).

Discussion

The goal of this review was to complete a meta-analysis of published randomized clinical trials comparing LABAs and SABAs for maintenance treatment in COPD. Unfortunately, only a single study was found preventing the completion of a direct meta-analytic comparison. The single study was a 3-week randomized, double blind crossover trial comparing the addition of formoterol or salbutamol to ipratropium [16]. The primary outcome variable, peak expiratory flow, as well as post-dose FEV_1 and the SGRQ symptom score improved significantly more during the formoterol/ipratropium treatment period than the salbutamol treatment period. There were no significant differences on SGRQ total, activity, or impacts sores, exacerbation rates, rescue medication use, or adverse events. The single RCT directly comparing SABA versus LABA found better outcomes for adding LABA to ipratropium than SABA to ipratropium.

The direct meta-analytic comparison was not possible due to the lack of studies, so the possibility of an indirect comparison was examined. Indirect comparisons meta-analyses have a greater potential to produce biased results due to uncontrolled differences between patients or procedures in the different studies [78]. However, there was an insufficient number of SABA studies of two or more weeks in duration, with a placebo or ipratropium comparator, and with a relevant outcome variable reported with sufficient detail to allow for even an indirect meta-analysis. Further efforts to increase the number of SABA papers (such as including non-English publications, contacting authors to get variances or numeric estimates, adding the most recent publications) may have allowed an indirect meta-analysis on one or more outcome variables to be completed, but it is unlikely to yield particularly relevant information. In addition to the limitations of indirect comparisons, the SABA treatments were not used in any trials longer than 12 weeks rendering any findings for maintenance outcomes suspect. Because the goal of this research was to compare LABAs versus SABAs for use as maintenance therapy for COPD; we included only studies with duration of 2 weeks or longer. This restriction eliminated many of the studies of SABAs identified in the initial literature search, which were only 2- or 3-day studies.

The GOLD treatment guidelines for COPD recommend the use of long-acting bronchodilators (including LABAs) because they are effective and convenient [6]. Due to their longer duration of action, LABAs can control COPD symptoms throughout the night, whereas SABAs would lose effectiveness. In this review, we did not find any data supporting the use of SABAs for maintenance therapy. The single RCT that compared adding a LABA (formoterol) or a SABA (albuterol) to ipratropium, found better airflow outcomes for the LABA treatment [16].

Conclusions

LABAs have been studied extensively as maintenance therapies in patients with COPD and have long-term safety and efficacy evidence. Although many patients with COPD are only treated with SABAs in usual clinical care, there is an absence of empirical support for the use of SABAs as maintenance therapy. This review supports the current evidence-based guidelines for COPD, which recommend the preferential use of LABAs for maintenance treatment of COPD and reserves the use of SABAs for rescue treatment.

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