Long-acting β₂-agonists for Maintenance Therapy of Stable Chronic Obstructive Pulmonary Disease: A Systematic Review

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Long-acting $\beta_2$-agonists for Maintenance Therapy of Stable Chronic Obstructive Pulmonary Disease: A Systematic Review

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CCOHTA takes sole responsibility for the final form and content of this report. The statements and conclusions in this report are those of CCOHTA and not of its Panel members or reviewers.

Authorship

Vijay Shukla led the development of the research protocol, supervised the literature review process and summarized results in the clinical draft document through to its final version. Vijay Shukla and Donald Husereau were responsible for reviewing articles, judging their relevance, assessing their quality, and extracting data. Michel Boucher assisted in developing the research protocol, assisted with conflict resolution in the study selection process and reviewed drafts. Robert Dales assisted in developing the research protocol and provided clinical expertise, including reviewing of drafts. Shaila Mensinkai designed and conducted the electronic searches, provided expertise in the area of information science and contributed to the writing of the report.

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Disclosure of Conflicts of Interest

Vijay Shukla, Donald Husereau, Michel Boucher, Shaila Mensinkai – none

Robert Dales sits on advisory committees for GlaxoSmithKlein (makers of the long-acting beta agonist, salmeterol), and Boehringer Ingleheim (makers of the anticholinergic agent, ipratropium bromide).
Long-acting \( \beta_2 \)-agonists for Maintenance Therapy of Stable Chronic Obstructive Pulmonary Disease: A Systematic Review

**Technology Name**
- Salmeterol (Serevent\textsuperscript{®})
- Formoterol (Foradil\textsuperscript{®})

**Technology Description**
Salmeterol and formoterol are bronchodilators administered by inhaler. Bronchodilators are used to treat people with conditions such as chronic obstructive pulmonary disease or asthma by opening their airways, making it easier for them to breathe. There are two main classes of inhaled bronchodilators: anticholinergics, which block the chemical that causes airways to contract; and \( \beta_2 \)-agonists, which relax the muscles surrounding the airways. Both salmeterol and formoterol are \( \beta_2 \)-agonists. They are considered long-acting because they work for 12 hours or longer.

**Disease/Condition**
Chronic obstructive pulmonary disease (COPD) is the term for progressive chronic airflow obstruction associated with emphysema and chronic bronchitis. Cigarette smoking is the number one risk factor for COPD. According to the Ontario Lung Association, COPD is the fourth leading cause of death for men and seventh for women, and killed 9,618 Canadians in 1997.

**The Issue**
In Canada, the anticholinergic ipratropium bromide is considered the first line of treatment for regularly symptomatic COPD patients. It is used three to four times daily, with or without a short-acting \( \beta_2 \)-agonist such as salbutamol, on an as-needed basis. Several recent studies have shown the usefulness of salmeterol and formoterol for the management of COPD. However, these long-acting \( \beta_2 \)-agonists are more expensive than ipratropium bromide.

**Assessment Objectives**
To determine, through a systematic review of the literature, the efficacy and safety of salmeterol and formoterol for patients with stable non-reversible COPD as compared to:
- placebo with or without the additional use of short-acting \( \beta_2 \)-agonists; and
- anticholinergics with or without the additional use of short-acting \( \beta_2 \)-agonists

For the purpose of this assessment, COPD was considered stable if there had been no infections, flare-ups or hospitalizations in the past month.

**Methodology**
All reports describing prospective, randomized, controlled trials of both parallel and cross-over designs regardless of language or publication status were considered. Trials based on asthmatic subjects were excluded since the efficacy of bronchodilators is much greater in asthma than in COPD and this could have influenced the findings. Outcomes considered included: impact on lung function, walk test results and the need for rescue inhalers. The systematic review of the literature identified 58 potentially relevant reports. Nine reports were accepted for final inclusion by two reviewers. All nine reports were of moderate or low quality.

**Conclusions**
The review found that, compared to placebo, the long-acting \( \beta_2 \)-agonists are superior in decreasing the use of rescue inhalers. However, they did not improve functional outcomes, such as distance travelled in a six-minute walk test. Two reports identified in the literature search compared the efficacy of long-acting \( \beta_2 \)-agonists with ipratropium bromide. Neither report showed salmeterol or formoterol to be more efficacious in the patient group studied.

This summary is based on a comprehensive health technology assessment report available from CCOHTA’s web site (www.ccohta.ca): Shukla VK, Husereau D, Boucher M, Mensinkai S, Dales R. Long-acting \( \beta_2 \)-agonists for Maintenance Therapy of Stable Chronic Obstructive Pulmonary Disease: A Systematic Review.
EXECUTIVE SUMMARY

The Issue
The long-acting $\beta_2$-agonists, salmeterol and formoterol, have been recommended by some as first line maintenance therapy for stable chronic obstructive pulmonary disease (COPD), as an alternative to the anticholinergic agent ipratropium bromide, a less expensive drug. The present study was undertaken to provide information on the efficacy and safety of these long-acting $\beta_2$-agonists for this patient group.

Objectives
To critically examine, through a systematic review of the literature, the evidence from randomized controlled trials:

1) related to the efficacy and safety of long-acting $\beta_2$-agonist agents versus placebo, with or without the additional use of short-acting $\beta_2$-agonist agents, for the maintenance treatment of patients with stable COPD; and

2) related to the efficacy and safety of long-acting $\beta_2$-agonists versus anticholinergic agents, with or without the additional use of short-acting $\beta_2$-agonist agents, for the maintenance treatment of patients with stable COPD.

Methods
Published and unpublished literature was obtained by searching multiple databases, web sites, hand searching selected journals, documents and the bibliographies of selected papers, and by contacting drug manufacturers. All published and unpublished prospective studies four weeks or longer in duration, of both parallel and cross-over designs, were included in the review if patients had (a) an FEV$_1$ of 75% or less than predicted; (b) an FEV$_1$/FVC ratio less than 70% predicted; and (c) less than 15% reversibility of FEV$_1$ after a dose of short or long-acting $\beta_2$-agonist. Two independent reviewers made the decisions about the inclusion of studies and assessed trial quality. Two reviewers independently extracted data including FEV$_1$, peak expiratory flow rates (PEFR), the six-minute walk test, quality of life, dyspnea measurements, number of COPD exacerbations and rescue salbutamol use.

Results
The systematic review identified 58 potentially relevant reports, with nine reports describing eight unique trials satisfying the eligibility criteria. Five reports described four trials that compared salmeterol and placebo, two trials compared salmeterol, ipratropium bromide and placebo, one trial compared formoterol, theophylline and placebo and one trial compared formoterol, ipratropium bromide and placebo. A quality assessment of the trials, using the Jadad scale, determined that six were of moderate quality (quality score 3/5) and three were of low quality (quality score 2/5). The outcome measure data were not suitable for pooling. Compared to placebo, salmeterol significantly increased FEV$_1$ in four studies and formoterol significantly increased FEV$_1$ in two studies. A significant decrease when comparing salmeterol to placebo in
additional day-time and night-time rescue bronchodilator usage (using short-acting $\beta_2$-agonists) was observed in two studies. No significant improvements in PEFR, distance travelled in a six-minute walk test, transition dyspnea index (TDI) scores or incidence of exacerbations of COPD were observed with salmeterol versus placebo in any of the studies. Significant improvements in FVC, PEFR, and patients’ self-assessed dyspnea scores were observed with formoterol versus placebo in one study. A study comparing salmeterol and ipratropium bromide did not show any significant changes in FEV$_1$ and TDI scores. Formoterol, compared to ipratropium did not show significant improvement in any of the outcome measures (shuttle walking test, FEV$_1$, FVC, breathlessness, SGRQ total scores) with the exception of one outcome measure (PEFR) in one study. Safety data on outcomes of interest such as the incidence of tachycardia, the incidence of hypokalemia or any other serious adverse events were not reported in any of the included studies.

**Conclusions**

This review examined the efficacy of the new long-acting $\beta_2$-agonist agents salmeterol and formoterol in the management of a specific patient group, defined as those with stable COPD without a significant reversible component (less than 15% improvement in FEV$_1$ after a single dose of short or long-acting bronchodilator). The review examined literature comparing these drugs both to placebo and to the older alternative agent, ipratropium bromide. Among these patients, the review found that the long-acting $\beta_2$-agonist agents are superior to placebo in decreasing the use of a rescue inhaler. However, although an increase in FEV$_1$ was also observed, no improvement in functional outcomes such as distance travelled in a six-minute walk test were observed between long-acting $\beta_2$-agonists and placebo. There was little evidence surrounding the effects of these agents on COPD exacerbations and on health-related quality of life (HRQoL). The literature retrieved reporting on comparisons between these two new agents and ipratropium bromide included two studies, both judged to be of moderate quality; these do not show salmeterol and formoterol to be more efficacious in the patient group studied.
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1 INTRODUCTION

1.1 Background

1.1.1 Disease

Chronic obstructive pulmonary disease (COPD) refers to a spectrum of respiratory diseases that are characterized by some mixture of chronic cough, increased sputum production, dyspnea, airflow limitation and impaired gas exchange. The major characteristic of COPD is the presence of chronic airflow limitation that slowly and irreversibly progresses over a period of years. The airflow limitation is usually associated with an abnormal inflammatory response. The natural course of COPD can span 20 to 40 years. The signs and symptoms of COPD vary, depending upon the severity of the disease. Early detection and intervention may help slow the progression of disease. The primary risk factor for COPD in industrialized countries is cigarette smoking.

1.1.2 Prevalence in Canada

In Canada, the incidence of COPD decreased slightly from 1978-1979 to 1998-1999. During this period, the incidence of bronchitis and emphysema decreased from 4.4% to 2.4% in individuals 45-64 years of age and 6.3% to 5.8% in those ≥65 years. In spite of this decrease, COPD still imposes a high burden of illness on the Canadian health care system. In 1997, the average length of stay in hospital for an exacerbation of COPD was 10.5 days. Since the early 1990’s hospitalization rates have increased among women but not men (Fig 1). If this trend were to continue, hospitalization rates in women would be expected to overtake those in men by 2003. Data from 1987 to 1998 indicate that the number of people dying from COPD has also risen (Fig 2). This rate of increase is larger in women than in men.

Figure 1: Number of individuals hospitalized with chronic obstructive pulmonary disease actual and projected, Canada excluding territories, 1985-2016.
1.1.3 Current clinical practice in Canada

Bronchodilators are the primary pharmacological therapy used in the management of COPD. They afford modest improvements in forced expiratory volume in one second (FEV$_1$) and reduce dynamic hyperinflation. Breathlessness and exercise tolerance may improve despite little improvement in spirometric measurements. Currently available bronchodilator therapy for COPD includes $\beta_2$-agonists (e.g. salbutamol, terbutaline), anticholinergics (e.g. ipratropium bromide) and methylxanthines (e.g. theophylline).

According to the Canadian guidelines for the treatment of COPD, the combination of ipratropium bromide, at two to four doses three to four times daily, plus a short-acting $\beta_2$-agonist on an as-needed basis, is considered the first line of treatment for regularly symptomatic patients. If the patients are using substantial amounts of short-acting $\beta_2$-agonists on an as-needed basis or if the symptoms are greater at night than in the early morning, a twice-daily long-acting $\beta_2$-agonist (salmeterol or formoterol) is added. However, long-acting $\beta_2$-agonists have recently been recommended by some as first line agents for regularly symptomatic COPD patients.

1.1.4 Drug utilization trends

The Montreal office of International Medical Services (IMS) was contacted to provide the most recent data available (1997 to 2001) on the utilization of ipratropium bromide, salmeterol and formoterol in Canada. Using continuous surveys of pharmacists and prescribing physicians, IMS collects information on current Canadian patterns of drug prescribing and utilization. IMS provided CCOHTA with three kinds of data and described their methods of data collection (Appendix 1).
IMS data from 1997 to 2001 reporting on Canadian drug store and hospital purchases and the estimated prescriptions dispensed, indicated there has been a marked increase in utilization of both salmeterol and formoterol and a decrease in utilization of ipratropium bromide during this period (Figures 3, 4 and 5).

**Figure 3:** Estimated number of prescriptions dispensed for ipratropium bromide (IPRA), salmeterol (SALM) and formoterol (FOMO) in Canadian drug stores from 1997 to 2001, for all clinical indications

**Figure 4:** Canadian drug store and hospital purchases of ipratropium bromide (IPRA), salmeterol (SALM) and formoterol (FOMO) from 1997 to 2001, for all clinical indications
IMS data reporting the number of times a drug was prescribed for COPD indicate that the utilization of salmeterol and formoterol for this indication increased 1,150% and 1,975% respectively, over the time period from 1997 to 2001, whereas utilization of ipratropium bromide for COPD decreased by 37%. These data do not distinguish between COPD with a reversible component and COPD with little or no reversible component.

**Figure 5:** Estimated number of ‘drug uses’ of ipratropium bromide (IPRA), salmeterol (SALM) and formoterol (FORM), specifically for COPD, from 1997 to 2001

![Graph showing drug uses over years](image)

### 1.1.5 Rationale for this review

Several studies have demonstrated the usefulness of the long-acting $\beta_2$-agonists salmeterol and formoterol for the management of COPD.\textsuperscript{16-19} According to a 1998 meta-analysis by the Cochrane Collaboration, the use of long-acting $\beta_2$-agonists in patients with non-reversible COPD produces small increases in FEV\textsubscript{1};\textsuperscript{20} however, changes in FEV\textsubscript{1} alone may not correlate highly with symptoms.\textsuperscript{21} The authors of the Cochrane review suggested that these drugs should be prescribed only for those patients who report a definite clinical improvement, in terms of better exercise capacity or reduced breathlessness. All the studies included in the Cochrane meta-analysis compared long-acting $\beta_2$-agonists with placebo. The comparative efficacy of long-acting $\beta_2$-agonists versus anticholinergics in COPD was not assessed in this meta-analysis. A number of new studies describing the use of long-acting $\beta_2$-agonists in COPD patients appeared in the literature after the publication of the Cochrane meta-analysis, including studies comparing long-acting $\beta_2$-agonists with anticholinergics.\textsuperscript{16,19}

In light of this new evidence, our systematic review of the literature sought to evaluate the evidence of efficacy and safety of long-acting $\beta_2$-agonist agents when compared to placebo or compared to anticholinergic agents (with or without additional short-acting $\beta_2$-agonists) in patients with stable COPD.
2 OBJECTIVES

To critically examine, using best evidence synthesis methodology, the evidence from randomized controlled trials:

1) related to the efficacy and safety of long-acting β\textsubscript{2}-agonist agents versus placebo, with or without the additional use of short-acting β\textsubscript{2}-agonist agents, for the maintenance treatment of patients with stable COPD; and

2) related to the efficacy and safety of long-acting β\textsubscript{2}-agonists versus anticholinergic agents, with or without the additional use of short-acting β\textsubscript{2}-agonist agents, for the maintenance treatment of patients with stable COPD.
3 METHODS

3.1 Literature Search

Published literature and conference abstracts were obtained by searching electronic databases using a well-defined search strategy (Appendix 2). On the DIALOG® system, MEDLINE®, EMBASE®, HealthSTAR® and Biosis Previews® were searched using MeSH headings, descriptors and text words for the disease and drugs. Generic and trade names as well as registry numbers for long-acting \( \beta_2 \)-agonists were used in the strategy. Unique references retrieved totaled 504. The Cochrane library on CD-ROM was also searched. Database alerts were established on MEDLINE®, EMBASE®, HealthSTAR®, Biosis Previews® using the same headings and keywords as the full search. A PUBMED update was performed in January 2002 to capture additional studies. Health Technology Assessment (HTA) websites, near-HTA websites, as well as clinical trial registries were searched. A Google™ search was performed to retrieve meeting/conference abstracts of major respiratory associations. These searches were supplemented by hand searching of selected journals and documents in the CCOHTA library collection and the bibliographies of selected papers. In addition, manufacturers of the two long-acting \( \beta_2 \)-agonists under consideration were contacted for information regarding unpublished studies, provided these were not confidential.

3.2 Inclusion Criteria

3.2.1 Types of trials

All reports describing prospective, randomized, controlled trials, of both parallel and cross-over designs, regardless of language or publication status, were included.

3.2.2 Types of participants

The eligibility criteria for trial participants are:

- non-asthmatic subjects;
- stable COPD (no recent infections, exacerbations, or hospitalizations in the past month);
- an \( FEV_1 \) of 75% or less than predicted;
- an \( FEV_1/FVC \) (forced vital capacity) ratio less than 70% predicted; and
- less than 15% improvement in \( FEV_1 \) after a dose of a short or a long-acting \( \beta_2 \)-agonist.

Since the efficacy of bronchodilator medication, including \( \beta_2 \)-agonists (long and short-acting), is much greater in asthma than in COPD, including patients with asthma in this review would have influenced the findings. In cases of chronic airflow obstruction with relatively large bronchodilator responses to short-acting \( \beta_2 \)-agonist agonists it may be difficult to determine if this represents COPD with reversibility or asthma with incomplete reversibility. To minimize the chance of including asthma cases in our review, we excluded patients with an \( FEV_1 \) response to bronchodilator of at least 15% or greater.
3.2.3 Types of interventions
Trials were included if they compared the long-acting β2-agonists salmeterol or formoterol with placebo or with an anticholinergic agent, with or without the additional use of short-acting β2-agonists. No restrictions were placed on dosage. Trials were only considered if the duration of therapy was at least four weeks.

3.2.4 Types of outcome measures
Trials that investigated the following outcomes were considered for review:

- lung function, including FEV$_1$ and peak expiratory flow rates (PEFR)
- six-minute walk test and/or shuttle walking test (SWT)
- health related quality of life (QoL) scores
- dyspnea measurements, including symptoms diary scores
- number of exacerbations
- rescue use of a short-acting β2-agonist agent (salbutamol)
- incidences of tachycardia, hypokalemia and dry mouth

3.3 Method of the Review
3.3.1 Selection process
Two reviewers (VS and DH) independently reviewed citations and discarded irrelevant ones, based on their titles and/or abstracts. Reports considered irrelevant included case reports, review articles and studies unrelated to the use of β2-agonists for maintenance treatment of stable COPD.

3.3.2 Selection of relevant studies
Potentially relevant reports were identified and retrieved. Two reviewers (VS and DH) independently made the final selection of the relevant reports to be included in this review. Disagreement regarding inclusion of any report was resolved by discussion and forced consensus.

3.3.3 Assessment of quality
The quality of the included studies was assessed using the Jadad scale, which assesses the appropriateness of randomization and double blinding, as well as withdrawals and dropouts (Appendix 3). The concealment of allocation to treatment was also judged. Two reviewers (VS and DH) assessed the quality of the studies independently.

3.3.4 Data extraction
Two reviewers (VS and DH) independently extracted data concerning the participant characteristics, intervention details and outcome measures from the included studies (Appendix 4). Where outcome data were only available graphically, both reviewers independently estimated the value of the outcome from the figure. The mean of the two estimated values obtained by each reviewer is reported in the results.
3.3.5 Statistical analysis

Where possible, mean differences (MD) with 95% confidence intervals (95% CI) for continuous outcomes, and odds ratios (OR) with 95% CI for binary outcomes were calculated for individual trial data using the “Statistics with Confidence” software package (second edition program).\textsuperscript{22} Intention-to-treat data (ITT) were used when available. Where not available, end-point data for persons completing the trials were used. Qualitative data were presented descriptively. The decision not to conduct a meta-analysis was based on the “Guidelines for Authors of CCOHTA Health Technology Assessment Reports”.\textsuperscript{23} These guidelines suggest meta-analysis is appropriate if pool-able data on outcomes of interest are found, from a clinically homogeneous set of randomized controlled trials.

3.3.6 Disagreement

Disagreement between reviewers during quality assessment, selection of studies, and data extraction was resolved by discussion and consensus. When consensus could not be reached between reviewers, a neutral third party (MB) was available.
4 RESULTS

4.1 Quantity and Quality of Selected Reports

After reviewing the titles and abstracts of citations obtained, two reviewers (VS and DH) identified 58 potentially relevant studies. Both reviewers (VS and DH) independently reviewed potentially relevant studies in various stages of the selection process to check whether they met all of the *a priori* inclusion criteria. After reviewing the abstracts and titles of these 58 potentially relevant reports, both reviewers agreed to accept 35 of them, pending further evaluation, and reject 23 others (Appendix 5). Of the 35 potentially relevant reports, one reviewer agreed (VS) and the other disagreed (DH) with inclusion of 14 of them. This resulted in a level of agreement between reviewers that was only moderate ($6 = 0.58$ with 95% CI 0.39; 0.78). Upon further discussion, it appeared this difference related entirely to confusion surrounding the interpretation of one of the criteria for eligibility (i.e. less than 15% improvement in FEV$_1$ after a dose of a short-acting $\beta_2$-agonist). Ultimately both reviewers agreed to reject these 14 reports. The reviewers then independently evaluated the remaining studies, rejected five and selected nine reports for final inclusion. The agreement between reviewers at this point was 100%. See Figure 6 for the flow diagram describing the study inclusion process.

Figure 6: Progress through selection of potentially relevant studies
Out of these nine reports, eight were journal-published trials\textsuperscript{16,18,24-29} and one was a conference abstract\textsuperscript{30} (Table 1). Six were of parallel design\textsuperscript{16,18,24,25,28,29} and three were of cross-over design.\textsuperscript{26,27,30} Five studies compared salmeterol and placebo,\textsuperscript{18,25-27,30} two compared salmeterol, ipratropium bromide and placebo,\textsuperscript{16,28} one compared formoterol, ipratropium bromide and placebo\textsuperscript{24} and one compared formoterol, theophylline and placebo.\textsuperscript{29}

Quality assessment of these studies using the Jadad scale showed that six were of moderate quality (all with scores = 3)\textsuperscript{16,24,26-29} and three were of low quality (scores = 2).\textsuperscript{18,25,30} Concealment was unclear in all the studies. Both evaluators were in complete agreement when assessing the quality of these trials.

4.2 Assessment of Clinical Effectiveness

4.2.1 Studies comparing long-acting $\beta_2$-agonists with placebo

Seven studies had salmeterol and placebo treatment arms \textsuperscript{16,18,25-28,30} and two studies had formoterol and placebo treatment arms (Table 1, Table 2a and 2b).\textsuperscript{24,29}

a) Changes in FEV$_1$

Four reports of three trials describe changes from baseline to an endpoint of FEV$_1$ measurements between salmeterol and placebo (with or without a measure of dispersion).\textsuperscript{16,18,25,26} One report\textsuperscript{25} describes outcomes from a subset of patients in a trial fully described in another report.\textsuperscript{18} In the latter large, parallel-design, 16-week study, salmeterol 100 and 50 $\mu$g twice daily produced significant improvements in FEV$_1$ compared to placebo.\textsuperscript{18} The mean differences (MD) (with 95\% CI) for improvement in FEV$_1$ between the salmeterol 100 $\mu$g group and placebo recipients, and the salmeterol 50 $\mu$g and placebo recipients were 117.6 ml (67.88; 167.32) and 97.80 (55.61; 139.99), respectively.

In a 4+4 week cross-over study, FEV$_1$ changed from baseline to endpoint after four weeks of treatment (maintenance treatment). The change in FEV$_1$ in the salmeterol 50 $\mu$g BID group (n=24) was described as significantly higher compared to the FEV$_1$ of the placebo group (salmeterol 120 ml versus placebo 10 ml).\textsuperscript{26}

In a 12-week study comparing salmeterol (42 $\mu$g BID), ipratropium bromide (36 $\mu$g QID) and placebo, the impact on FEV$_1$ (change from baseline to different time points after administration of last dose of salmeterol) was available only as a figure for the subset of patients meeting our inclusion criteria.\textsuperscript{16} Peak improvements in FEV$_1$ in salmeterol recipients (n=50) and placebo recipients (n=47) were 155 ml (two hours after administration) and 24 ml (six hours after administration), respectively.

One 8+8 week crossover-design trial in 42 COPD patients comparing salmeterol (100 $\mu$g, BID) and placebo was published as a conference abstract.\textsuperscript{30} This abstract reported that no significant differences were observed in lung function measurements between the salmeterol and placebo groups, although no data were provided.
Formoterol compared to placebo showed improvement in FEV₁ (changes from baseline to endpoint) in two trials. In one 3-month trial comparing formoterol (18 µg BID, n=61), ipratropium bromide (80 µg TID, n=62), and placebo (n=60), improvement in percent predicted of normal FEV₁ was estimated in different treatment groups. Improvements in FEV₁ (percent predicted) in the formoterol and placebo groups were 13% and 6%, respectively, (p<0.001) after three months of treatment in this trial. In the other trial which compared formoterol (12 µg BID and 24 µg BID), theophylline and placebo, and which was 12 months in duration, data were analyzed using an Area Under Curve analysis for FEV₁ measurements over a 12-hour period (AUC-FEV₁), for a subset of patients that met our inclusion criteria. Formoterol produced an improvement in AUC-FEV₁, compared to placebo. After 12 months of treatment, the estimated AUC-FEV₁ difference between formoterol (12 µg BID, n=118) and placebo (n=117) was 145 ml (p=0.002). For the formoterol 24 µg BID dose (n=96), this difference was 141 ml (p=0.003). The individual FEV₁ values for different treatment groups were not available from this report.

b) Changes in FVC

Two studies reported on the impact of long-acting β₂-agonists on FVC. In one trial of cross-over design comparing the efficacy of salmeterol (50 µg, BID) with placebo, the increase in FVC (change in FVC from baseline to endpoint) was larger following salmeterol treatment, compared with placebo, six hours after a single dose (salmeterol 200 ml versus placebo 0.03 L) and with chronic dosing (salmeterol 150 ml versus placebo 130 ml). The latter difference was reported as non-significant. In other 3-month trial comparing formoterol (18 µg BID, n=61), ipratropium bromide (80 µg TID, n=62) and placebo (n=60), improvements in percent predicted FVC were 8%, 8% and –0.4% , respectively (formoterol versus placebo p=0.02 and ipratropium bromide versus placebo p=0.01).

c) Changes in PEFR

Two trial reports contained data describing changes in PEFR after the use of long-acting β₂-agonists. In one 4-week trial of cross-over design comparing salmeterol and placebo in 66 current smokers with COPD, the morning PEFR values during the salmeterol and placebo periods were 238±[Standard Error (SE)] 10 L/min and 226±(SE) 10 L/min, respectively. The corresponding evening PEFR values for salmeterol and placebo were 242±(SE) 10 L/min and 237±(SE) 10 L/min, respectively. The reported magnitude of the mean treatment difference between salmeterol and placebo for PEF was 7.0±(SE) 2 L/min. Another 12-week parallel design trial in 183 COPD patients comparing formoterol, ipratropium bromide and placebo reported changes in morning PEFR without reporting a measure of dispersion. In this study, changes from baseline to endpoint in the morning PEFR in the formoterol and placebo groups were 15.3 L/min and –0.9 L/min, respectively (p<0.001).

d) Walk test

Results of six-minute walk tests, with or without post-walk breathlessness tests, are reported in four trials. One 16-week trial involving 674 COPD patients observed no significant difference between the salmeterol 100 µg BID group, the salmeterol 50 µg BID group, and the placebo group in the distance walked in six minutes at any time-point during the study. Data on mean distance travelled in six-minutes in the different treatment groups were not available from the report. Breathlessness was evaluated using a ten-point Borg scale. (See Appendix 6 for
descriptions of the scales used for different outcome measures). The incidence of breathlessness (Borg scores >3) in the salmeterol 50\text{\textg BID} group compared to the placebo group was decreased [OR 0.62 (95\% CI 0.42; 0.91)]. No difference was observed between the salmeterol 100\text{\textg BID} group and the placebo group.

In a 4+4 week cross-over trial of 29 COPD patients, no increases in distances walked in six minutes were observed after chronic dosing with salmeterol (50\text{\textg BID}), when compared with placebo. The median (interquartile range) values for the distance travelled in six minutes was 450 (371-491) metres for placebo and 425 (392-473) metres for salmeterol recipients.

An 8+8 week cross-over design trial in 42 COPD patients comparing salmeterol (100\text{\textg, BID}) and placebo was published as a conference abstract. This trial concluded that no significant differences between salmeterol and placebo were observed in the distance walked in six minutes or in breathlessness scores (Borg Scale) before and after a six-minute walk. However, quantitative data were not provided for these outcomes.

One study comparing formoterol, ipratropium bromide and placebo reported data on changes from baseline to end point (without a measure of dispersion) in walking distance measured with the Shuttle Walking Test (SWT). Mean changes in SWT distance in the formoterol and placebo groups were 19.2 m and 5.1 meters, respectively (p=not significant).

e) Dyspnea measurement

In two trials comparing salmeterol and placebo, patients self-assessed the severity of their day-time and night-time symptoms every day by using 0-5 and 0-4 ordinal symptom severity scales, respectively (Appendix 6). Low scores represent better outcomes. Both the day-time and night-time symptom scores were reduced during the salmeterol (50\text{\textg, BID}) period when compared with the placebo period in a 4+4 week cross-over study. The median (with range) day-time scores in the salmeterol and placebo groups were 1.0 (0-3.4) and 1.8 (0.1-4.0), respectively. The median (with range) night-time scores for these groups were 0.9 (0-3.4) and 1.6 (0.1-4.0), respectively. In a second 16-week study comparing salmeterol 100\text{\textg BID}, salmeterol 50\text{\textg BID}, and placebo, the median day-time scores between weeks 9 and 16 were 1, 1 and 2 respectively. The difference between active treatment arms and placebo was reported to be statistically significant. The median night-time score reported in all three groups was 0 between weeks 5 and 16.

A 12-week trial comparing salmeterol (42\text{\textg BID}, n=48), ipratropium bromide (36\text{\textg QID, n=47}), and placebo (n=50), measured the severity of dyspnea at baseline with a multi-dimensional baseline dyspnea index (BDI), and changes in the severity of dyspnea were assessed every two weeks with a transition dyspnea index (TDI). No significant difference was observed in TDI scores at any time point between patients using salmeterol and patients using placebo. TDI scores in the salmeterol and placebo groups at 12 weeks were 0.35 and 0.48, respectively.

An 8+8 week cross-over design trial comparing salmeterol 100\text{\textg BID} and placebo, published as an abstract, concluded that salmeterol significantly reduced patients’ self-assessed night-time symptoms compared to placebo. The details about the scale used and median values of the scores in the control and treatment groups were not available in this abstract.
In one study comparing formoterol, ipratropium bromide and placebo, patients self-assessed the severity of their morning and evening breathlessness using a single 0-4 ordinal symptoms severity scale. Low scores represent better outcomes. The changes in breathlessness scores from baseline to end-point in the formoterol and placebo groups were –0.21 and 0.00, respectively (p=0.040). A measure of dispersion was not reported in the study.

f) Additional bronchodilator usage

Four trials, with or without quantitative data, provided information on the additional use of bronchodilators. In three trials, salmeterol was reported to be associated with less rescue salbutamol inhaler use, compared with placebo treatment. The median (range) values for day-time rescue salbutamol doses in the salmeterol and placebo groups were 1.7 (0-6.1) and 2.6 (0-7.9), respectively, and the median values for night-time rescue salbutamol doses were 0 (0-4.2) and 0.3 (0-5.0), in a 4+4 week cross-over study. In the other two studies, the number of day-time and night-time rescue doses of salbutamol used in the treatment and control groups were not reported.

In a trial comparing salmeterol, ipratropium bromide and placebo, no difference was observed in additional bronchodilator use, between the placebo and salmeterol groups, in patients satisfying our inclusion criteria.

g) Quality of life

Changes in health-related quality of life (HRQoL) were evaluated in two trials, one comparing salmeterol 100 μg BID, salmeterol 50 μg BID and placebo, and the other comparing formoterol 18 μg BID, ipratropium bromide 80 μg TID and placebo. The salmeterol study analyzed a subset of a patient group reported in a separately published trial. In this study evaluating HRQoL, patients were asked to complete the disease-specific St. George’s Respiratory Questionnaire (SGRQ, see Appendix 6 for a description) and the Medical Outcomes Study Short Form 36 (SF-36) at baseline and after 16 weeks of treatment. HRQoL data were obtained for 326 patients at baseline. Data from 283 patients (95 patients in the placebo group and 94 in each salmeterol group) were used for the final HRQoL analysis. Data from 43 patients were rejected due to non-completion of one or both questionnaires at 16 weeks and/or an inability to meet pre-set quality control criteria. Compared to placebo, salmeterol 50 μg BID was associated with an improvement (changes from baseline to endpoint score; negative changes represent better outcomes) in SGRQ total scores [salmeterol 50 μg BID: -6.8 (SD) 13.2 versus placebo: -1.4 (SD) 11.7]. Total scores represent the sum of the three components of the SGRQ including distress due to respiratory symptoms, effect of disturbances on mobility and physical activity and psychosocial impact of the disease. No statistically significant differences between placebo and either dose of salmeterol were observed in any of the domains of the SF-36 with the exception of the “role-emotional”. These scores were observed to be worse for the salmeterol 100 μg group than for placebo recipients (p=0.027).

In the trial comparing formoterol, ipratropium bromide and placebo, HRQoL was evaluated using disease-specific SGRQ. Out of the 183 patients randomized, 144 patients completed the SGRQ assessment. Information on the number of patients in individual treatment groups who were unable to complete the assessment and reasons for not doing so were not reported. SGRQ
total scores were almost unchanged in all three groups during the treatment period. The mean changes in SGRQ total scores from baseline to endpoint in the formoterol and placebo groups were 0 and 1.5, respectively.

h) COPD exacerbations
Two studies reported information on COPD exacerbations, without providing any definition of the term “COPD exacerbation”. In one 16-week trial, a similar incidence of COPD exacerbations was observed among patients on salmeterol 100 μg BID, patients on salmeterol 50 μg BID, and patients on placebo. The numbers of exacerbations in these groups were 91, 75 and 98, respectively. Another 8+8 week cross-over trial reported that lower incidences of COPD exacerbations were observed with salmeterol 100 μg BID treatment compared with placebo treatment.

Safety data of interest were not available in any of the studies.

4.2.2 Studies comparing long-acting β2-agonists and anticholinergic agents
Two 12-week studies comparing salmeterol, anticholinergic agents and placebo; however, only one study separately reported quantitative data related to FEV1 and TDI (as figures) for the subset of COPD patients that met our inclusion criteria (Table 2a and 2b). No significant differences between the salmeterol and ipratropium groups in FEV1 (change from baseline) were observed at any time-point in these studies. Peak improvements in FEV1 from baseline in salmeterol (n=48) and ipratropium recipients (n=47) were 155 ml (two hours after treatment) and 165 ml (one hour after treatment), respectively. No statistically significant difference in TDI scores was reported between the two groups at any time-point during the study (salmeterol TDI score 0.35 versus ipratropium TDI score 0.98 at week 12). This study also reported that, in three treatment groups, no significant differences were observed in salbutamol use as a rescue medication.

In a 3-month trial comparing formoterol, ipratropium bromide and placebo, formoterol produced significantly (p=0.040) greater improvement (change from baseline to endpoint) than ipratropium bromide in PEFR (15.3 L/min versus 7.1 L/min) (Tables 2a and 2b). However, the observed difference was reported not to be statistically significant between formoterol and ipratropium bromide for the percent predicted FEV1 (13% versus 7%), the percent predicted FVC (8% versus 8%), improvement in breathlessness scores (-0.21 versus -0.29) and improvement in SGRQ total scores (0.0 versus -0.5).

Safety data of interest were not available from these trials.
5 DISCUSSION

Long-acting $\beta_2$-agonists are recommended by some as primary maintenance therapy for stable COPD patients, potentially replacing the less expensive alternative, ipratropium bromide. Canadian provincial drug plan managers have observed that the use of salmeterol and formoterol has increased substantially in recent years, a finding supported by data supplied by IMS and reported in this paper (Figures 3, 4 and 5). The present study was undertaken to provide information on the efficacy of long-acting $\beta_2$-agonists for patients with stable COPD, specifically in light of recent changes in prescribing practices.

To minimize the chance of inadvertently including cases of asthma in our analysis, we included cases of COPD only if the acute FEV$_1$ response to bronchodilator was less than 15%. Inadvertently including cases of asthma could have altered our findings, since beta-agonists tend to be much more effective in asthma than COPD due to the larger bronchodilator response in asthma. The advantage of excluding COPD cases with significant reversibility is that asthma cases were unlikely to have been included. A disadvantage is that the results of this study may not extrapolate to patients with COPD who have a reversible component to their disease, as measured by at least a 15% improvement in FEV$_1$ following inhalation of a short- or long-acting bronchodilator.

Nine studies describing eight unique trials met our inclusion criteria; these measured a wide variety of subjective and objective outcomes. It is not clear from these studies whether they are powered sufficiently to detect significant changes between treatment and control groups for the multiple different outcome measures under consideration. A meta-analysis approach is useful when sample sizes of individual studies are too small to detect an effect, and when results from several studies disagree with regard to magnitude and direction of effect. Our original intent was to carry out a meta-analysis of quantitative outcome measures. However, after a careful consideration of differences in trial design and reporting, we determined that meta-analysis was not possible. Study authors were contacted for more descriptive quantitative data, without success. Due to these limitations, a best-evidence-synthesis approach was used.

When conducting a meta-analysis it is necessary to investigate possible publication and language biases, as well as assessment of trial quality and heterogeneity. We have sought to minimize selection bias by systematically reviewing all published and unpublished randomized controlled studies, without imposing any language restrictions on the literature retrieval, and with the use of two independent reviewers. We included all randomized studies meeting our inclusion criteria, irrespective of their quality. Six studies included in our review were of moderate quality and three were of poor quality (using the Jadad scale).

We originally hoped to perform a sensitivity analysis, based on the quality of trial reporting. However, since data were not pooled by meta-analysis, we were not able to conduct such a sensitivity analysis. Accordingly it was not possible for us to comment on the influence of quality on the effect size of different outcome measures. Like many other systematic reviews, clinical heterogeneity between trials limits a proper assessment of the overall effect of the
intervention being examined. Since we have not performed a meta-analysis, the issue of statistical heterogeneity is not applicable here.

Findings related to the drugs being reviewed:

**Salmeterol:** Compared to placebo, salmeterol improved night-time\textsuperscript{27,30} and day-time\textsuperscript{18,27} dyspnea, and FEV\textsubscript{1}, and reduced the use of short-acting \( \beta \textsubscript{2} \)-agonists as rescue therapy.\textsuperscript{18} Salmeterol was not shown to increase the distance walked in six-minutes\textsuperscript{18}. The one placebo-controlled study of salmeterol’s effect on outcomes related to HRQoL\textsuperscript{25} found that salmeterol improved disease-specific quality of life as measured by an SGRQ. (In this study, data from 13% of patients were not included in the final analysis for various reasons.) However, when salmeterol was compared to ipratropium, there was no significant improvement found in FEV\textsubscript{1} and TDI.

**Formoterol:** Compared to placebo, formoterol improved the severity of patients’ self assessment of morning and evening dyspnea\textsuperscript{24} and FEV\textsubscript{1}\textsuperscript{29} but not SGRQ scores or distance walked as measured with the SWT.\textsuperscript{24} Only one study compared the efficacy of formoterol with ipratropium bromide and this study reported no significant difference in any of the outcome measures, with the exception of one (improvement in PEFR).\textsuperscript{24}

Our results are similar to those of an earlier review conducted by the Cochrane Collaboration in 1998.\textsuperscript{20} All of the studies included in Cochrane review (four placebo controlled studies) were also included in our review;\textsuperscript{18,25-27} in addition, we identified five new studies.\textsuperscript{16,24,28-30} We would like to point out several differences between our analysis and that of Cochrane. In the Cochrane review, FEV\textsubscript{1} endpoint data from the placebo and salmeterol groups in two cross-over trials were pooled to calculate a weighted mean difference. The Cochrane analysis found no difference between the placebo and treatment groups.\textsuperscript{26,27} We preferred to analyze the net improvement (i.e. the difference from the baseline to endpoint in treatment arms), as we felt it more accurately reflects the impact of maintenance therapy on the true improvement in FEV\textsubscript{1}. Another difference between the two reviews is that no studies comparing long-acting \( \beta \textsubscript{2} \)-agonists and ipratropium bromide were available for inclusion at the time of the Cochrane review.
6 CONCLUSIONS

This review examined the efficacy of the new long-acting $\beta_2$-agonist agents salmeterol and formoterol in the management of a specific patient group, defined as those with stable COPD without a significant reversible component (less than 15% improvement in FEV$_1$ after a single dose of short- or long-acting bronchodilator). The review examined literature comparing these drugs both to placebo and to the older alternative agent, ipratropium bromide.

Among these patients, the review found that the long-acting $\beta_2$-agonist agents are superior to placebo in decreasing the use of a rescue inhaler. However, although an increase in FEV$_1$ was also observed, no improvement in functional outcomes such as distance travelled in a six-minute walk test were observed between long-acting $\beta_2$-agonists and placebo. There was little evidence surrounding the effects of these agents on COPD exacerbations and on health-related quality of life (HRQoL).

The literature retrieved reporting on comparisons between these two new agents and ipratropium bromide included two studies, both judged to be of moderate quality; these do not show salmeterol and formoterol to be more efficacious in the patient group studied.
7 REFERENCES


Appendix 1: Methods of IMS Data Collection

1. **Estimate of the number of prescriptions dispensed in Canadian retail pharmacies:**
The IMS HEALTH “CompuScript” database estimates the number of prescriptions dispensed by Canadian retail pharmacies. The CompuScript sample is drawn from IMS’s panel of over 4,700 pharmacies that represent approximately two-thirds of all retail pharmacies in Canada. The sample is stratified by province, store type (chain or independent), and store size (large or small), comprises over 2,000 stores and is a representative sample of stores in Canada. Records are collected electronically each month from the pharmacies. After passing through various quality control checks, the sample data are projected to populations in each province and provincial totals are added together to provide a national estimate.

2. **Estimate of the number of purchases made by Canadian drug stores and hospitals:**
The Canadian Drug Store and Hospital Purchases Audit estimates dollar values and unit volumes of pharmaceutical products purchased by retail pharmacies and hospitals in Canada. Data from purchase invoices are collected on a monthly basis from samples of drug stores and hospitals that are representative of the Canadian universe of drug stores and hospitals. The drug store sample consists of 210 drug stores stratified by region and store size (large or small). The hospital sample comprises 87 hospitals stratified by region and type; the general hospitals being further stratified by number of beds (small vs. large). Projection factors are applied to the raw data to obtain estimates of purchases for the whole of Canada.

3. **Estimates of drug use by diagnosis:**
The Canadian Disease and Therapeutic Index (CDTI) identifies drug usage and treatment patterns by physician speciality. A representative sample of 652 Canadian office-based physicians, stratified by geographic region and representing all major specialties, report for each of four consecutive quarters. Each physician submits a case record book, detailing information on diagnosis made and treatment recommended for all patients (excluding patient identity) seen over a 48-hour reporting period during the quarter. The data are then validated and coded, and processed to obtain estimates for the whole of Canada. Where use of a drug is associated with a particular diagnosis, the unit of measurement is the “drug use” and is interpreted as the estimated number of times that a particular drug is recommended for particular diagnosis.
Appendix 2: Literature Search

Guide to Search Syntax (DIALOG®, Cochrane Library)

! Explode the search term. Retrieve the search concept plus all narrower terms.
? Truncation symbol, single character. Retrieve plural and variant ending of search terms.
* Truncation symbol, any number of characters.
“ “ Search phrases.
(w) Proximity operator. Words must be adjacent.
() Proximity operator. Words must be adjacent.
(n) Proximity operator. Words must be near each other in any order.
ab Search in article abstract.
de Descriptor i.e., subject heading (a controlled, thesaurus term)
ME Medical subject heading
RN Registry number (i.e., CAS)
ti Search in titles
tw Text word

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AND

Human OR people OR person? ?

Performed 25/06/2001
Total = 504 unique hits
EMBASE® = 122 hits
MEDLINE® = 323 hits
HealthSTAR® = 54 hits
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## Appendix 3: Quality Assessment Form

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<td>A trial reporting that it is “randomized” is to receive one point. Trials describing an appropriate method of randomization (table of random numbers, computer generated) receive an additional point. However, if the report describes the trial as randomized and uses an inappropriate method of randomization (date of birth, hospital numbers) a point is deducted.</td>
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<tr>
<td><strong>Double-blindling:</strong> Total Points: □ 0 □ 1 □ 2</td>
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<td>A trial reporting that it is “double blind”, it is to receive one point. Trials that describe an appropriate method of double blinding (identical placebo, active placebo) are to receive an additional point. However, if the report describes the trial as double blind and uses an inappropriate method (e.g. comparison of tablets versus injection with no double dummy), a point is deducted.</td>
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<td><strong>Withdrawals and dropouts:</strong> Total Points: □ 0 □ 1</td>
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<td>A trial reporting the number and reason for withdrawals is to receive one point. If there is no statement, no point is given.</td>
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<tr>
<td>TOTAL Score □ Low (0-2 pts) □ Moderate (3-4 pts) □ High (5 pts)</td>
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**Allocation concealment** □ Adequate □ Inadequate □ Unclear

**Adequate:** Central randomization; numbered or coded bottles or containers; drugs prepared by a pharmacy, serially numbered, opaque, sealed envelopes, etc.

**Inadequate:** Alternation; reference to case record # or date of birth, etc.

**Unclear:** Allocation concealment approach is not reported or fits neither of the above categories.
## Appendix 4: Data Extraction Form

**EFFICACY STUDY RESULTS : ACUTE/MAINTENANCE**

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### Industry sponsorship:
- Yes / No / no info

### Are the patients randomly assigned to the treatment conditions:
- Yes / No

### Is the study double blinded:
- Yes / No
- Parallel / Crossover

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### Age (years)

### Weight

### COPD type
- Chronic bronchitis
- Emphysema
- Mixed

### Smokers
- Mild (<10/day)
- Moderate (10-20/day)
- Heavy (>20/day)

### Mean duration of disease

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</tr>
</tbody>
</table>

### Other variables:
- COPD type
- Smokers
- Mean duration of disease
- Mean FEV₁ (75% or less than predicted)
- FEV₁/FVC (<70% predicted)
- FEV₁ reversibility after short-acting beta-agonists (<15%)
- No of pts improving > 20% in FEV₁
- PEFR
### Dyspnea

O₂ Consumption L/min

### SYMPTOM RESOLUTION

<table>
<thead>
<tr>
<th>Metric</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improvement in FEV₁ (absolute value)</td>
<td></td>
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<tr>
<td>Improvement in FEV₁ (% predicted)</td>
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<tr>
<td>Improvement in FVC (absolute value)</td>
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<tr>
<td>Improvement in oxygen consumption</td>
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<tr>
<td>Peak expiratory flow (PEF)</td>
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<tr>
<td>Improvement in dyspnea</td>
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<tr>
<td>COPD exacerbations</td>
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<tr>
<td>Symptom-free days</td>
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<tr>
<td>Quality of life</td>
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<tr>
<td>Distance on 6 minute walk test</td>
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<tr>
<td>Distance on 12 minute walk test</td>
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<tr>
<td>Reduction in rescue inhaler use</td>
<td></td>
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<tr>
<td>Hospitalization</td>
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<tr>
<td>Visits to emergency rooms</td>
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<tr>
<td>Visits to doctor for lung problems</td>
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</tbody>
</table>

### ADVERSE EFFECTS

<table>
<thead>
<tr>
<th>Effect</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence of tachycardia</td>
<td></td>
</tr>
<tr>
<td>Incidence of hypoklemia</td>
<td></td>
</tr>
<tr>
<td>Dry mouth</td>
<td></td>
</tr>
</tbody>
</table>
Appendix 5: List of Excluded Studies

Studies related to reversible obstructive airway disease


Studies do not satisfy less than 15% reversibility in FEV₁ after short-acting β₂-agonist 1-5


Studies of less than four-week duration 1-13


**Drug not compared with comparator of interest** 1-5


**Studies without control group** 1-3


3. Shima K, Takenaka S. [The clinical evaluation of formoterol (BD 40A) in bronchial asthma with long term administration and in chronic obstructive pulmonary disease with short term administration]. *Yakuri to Chiryo* 1983;11(9):3935-42.
Duplicate studies


Retrospective studies


Economic evaluation studies without data of clinical interest

Appendix 6: Scales Used for Different Outcome Measures

Baseline dyspnea index (BDI) and transition dyspnea index (TDI): BDI is used to rate the severity of dyspnea at a single state and TDI is used for measuring the changes from that single state (baseline). The scores of both indices depend upon the rating of three different categories: functional impairment, magnitude of task and magnitude of effort. At baseline state dyspnea is rated in five grades from 0 (severe) to 4 (unimpaired) for each category. The ratings from each of the three categories are added to form a baseline focal score (range 0 to 12). At the transition period, changes in dyspnea are rated by seven grades, ranging from –3 (major deterioration), to 3 (major improvement). The rating for each of the three categories was added to form a transition focal score (range –9 to +9).

Borg dyspnea scale: The Borg dyspnea scale is a subjective assessment scale for assessing the intensity of breathlessness. Intensity of breathlessness is scored from 0 to 10. Zero is equivalent to no breathlessness and 10 is equivalent to maximum breathlessness. When using this scale, decimal values may be awarded.

Day-time night-time symptom scores scale: This ordinal scale is used by the patient for self-assessment of respiratory symptoms. Night-time symptoms are scored as:
0= no symptoms during the night;
1= symptoms causing you to wake once or to wake early;
2= symptoms causing you to wake twice or more (including waking early);
3= symptoms causing you to awake most of the night;
4= symptoms so severe that you did not sleep at all.

Day-time symptoms are scored as:
0= no symptoms during the day;
1= symptoms for one short period during the day;
2= symptoms for two or more short periods during the day;
3= symptoms for most of the day that did not affect your daily activities;
4= symptoms for most of the day that did affect your daily activities;
5= symptoms so severe that you could not go to work or perform daily activities.

Morning and evening symptom score scale: This ordinal scale is similar to the day-time night-time symptom score scale. Here, the same scale is used to assess the severity of respiratory symptoms for morning and evening. Symptoms are scored as:
0= no symptoms;
1= slight symptoms during one or several periods;
2= slight symptoms most of the day, well tolerated;
3= moderate symptoms, affected daily routines;
4= severe symptoms; inability to perform daily routines.

Short Form Health Survey 36-Item (SF-36): The SF-36 is one of the most commonly used measures of quality of life. The SF-36 was designed to understand the burden of chronic disease and the effect of treatments on general health status. It has eight dimensions measuring physical functioning, role functioning (work or other activities) affected by both physical and emotional symptoms, pain, general health, vitality, social functioning and mental health. These eight
subscales may be collapsed into two domain scores reflecting physical and mental components of quality of life. The SF-36 dimensions are scored separately and transformed to a 0-100 scale. Each scale is scored positively, which means that higher scores indicate better health related quality of life (HRQoL) and lower scores indicate worse HRQoL.

**Shuttle walking test (SWT):** The SWT requires the patient to walk up and down a 10 metre course. Each minute the speed of walking is increased. The test is discontinued if the patient is too breathless to continue or fails to reach the next cone in the designated time.

**St. George’s Respiratory Questionnaire (SGRQ):** The SGRQ is a disease-specific instrument in which items are weighed using empirically derived weights. It has three components: “Symptoms,” measuring the distress due to respiratory symptoms; “Activity,” measuring the effect of disturbances to mobility and physical activity; and “Impacts,” quantifying the psychosocial impact of the disease. A number of items in the symptom component relate to the frequency of symptoms over the previous year. Each component is scored using a 0-100 scale, with the highest scores indicating the poorest level of health.
<table>
<thead>
<tr>
<th>Study &amp; Funding</th>
<th>Quality Assessment Score</th>
<th>Participants</th>
<th>Interventions</th>
<th>Outcomes</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ulrik, 199527</td>
<td>RCT, DB, crossover design</td>
<td>3 66 current smokers with COPD, FEV₁ values of 1-2 L, and &lt; 60% of predicted values, FEV₁/FVC &lt; 60%, &lt; 15% increase in FEV₁ after inhalation of 0.4 mg salbutamol</td>
<td>Salmeterol (50 :g BID) or placebo for 4+4 weeks, no washout period at crossover point</td>
<td>PEFR, day-time and night-time symptom scores, and use of rescue salbutamol</td>
<td>2-week run-in period, methylxantine and/or short courses of corticosteroids allowed</td>
</tr>
<tr>
<td>Newman et al., 199630 (available only as an abstract)</td>
<td>RCT, DB, crossover design</td>
<td>2 42 patients with COPD, lack of response to oral steroids, less than 15% reversibility to salbutamol, mean FEV₁ 0.93 L (35% of predicted)</td>
<td>Salmeterol 100 :g BID or placebo (both via diskhaler) for 8+8 weeks</td>
<td>Day-time night-time symptom scores, use of rescue salbutamol, percentage of days unable to perform normal activity, 6-minute walking distance, breathlessness after 6-minute walk (Borg scale), lung function test results, incidence of adverse events and COPD exacerbations</td>
<td>2-week run-in period, salbutamol allowed as rescue medication</td>
</tr>
<tr>
<td>Grove et al., 199626</td>
<td>RCT, DB, crossover design</td>
<td>3 29 COPD patients with FEV₁ values 25-75% of predicted normal and 5-15% reversibility of FEV₁ with salbutamol 200 :g</td>
<td>Salmeterol 50 :g BID (metered dose inhaler) or matching placebo for 4+4 weeks, 1 week washout period between crossover periods</td>
<td>Changes in FEV₁, FVC, TLC and RV from baseline, 6-minute walking distance, changes in oxygen uptake compared to resting values</td>
<td>At least 1-week run-in period, inhaled corticosteroids, anticholinergics and oral theophylline allowed</td>
</tr>
<tr>
<td>Boyd et al., 199718</td>
<td>RCT, DB, parallel design</td>
<td>2 674 COPD patients with FEV₁ values ≥ 70% of predicted normal, FEV₁/FVC ratios of ≥ 60% and increases in FEV₁ of 5-15% after inhalation of a single dose (400 or 800) of salbutamol</td>
<td>Salmeterol 50 :g BID, 100 :g BID or placebo from a metered dose inhaler for 16 weeks</td>
<td>Day-time night-time symptom scores, changes in FEV₁ and FVC from baseline and 6-minute walking distance</td>
<td>2-week run-in period, patients were allowed to take non-3₂-agonist medication during the trial</td>
</tr>
</tbody>
</table>

AUC: area under the curve; DB: double blind; COPD: chronic obstructive pulmonary disease; CRDQ: chronic respiratory disease questionnaire; FEV₁: forced expiratory volume in one second; FVC: forced vital capacity; PEFR: peak expiratory flow rate; RCT: randomized controlled trial; RV: residual volume; TLC: total lung capacity
<table>
<thead>
<tr>
<th>Study &amp; Funding Source</th>
<th>Method</th>
<th>Quality Assessment Score</th>
<th>Participants</th>
<th>Interventions</th>
<th>Outcomes</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jones and Bosh, 1997²⁵</td>
<td>RCT, DB, parallel group study</td>
<td>2</td>
<td>283 COPD patients with FEV₁ values # 70% of predicted normal, FEV₁/FVC ratios of # 60% and an increase in FEV₁ of 5-15% after inhalation of single dose (400 or 800) of salbutamol</td>
<td>Salmeterol 50 :g BID or 100 :g BID or placebo from a metered dose inhaler for 16 weeks</td>
<td>Health related quality of life using St. George’s Respiratory Questionnaire (SGRQ) and the Short Form 36 questionnaire (SF-36)</td>
<td>2-week run-in period, patients were allowed to take non-³₂-agonist medication during the trial</td>
</tr>
<tr>
<td>Mahler et al., 1999¹⁶</td>
<td>RCT, DB, parallel group study</td>
<td>3</td>
<td>Trial was done on a mixed population; included only 145 COPD patients with FEV₁ values # 65% of the predicted normal values, FEV₁/FVC ratios of # 70%, FEV₁ reversibility with short-acting ³₂-agonist of # 15% and baseline severity of breathlessness of grade I</td>
<td>Salmeterol 42 :g BID or ipratropium bromide 36 :g QID or placebo for 12 weeks</td>
<td>FEV₁ AUC, baseline dyspnea index, transition dyspnea index, 6-minute walking distance, day-time night-time symptom scores, health related quality of life using CRDQ, supplemental salbuterol use, and COPD exacerbations</td>
<td>Run-in periods from 6 hours to 3 days, # 10 mg of prednisone or equivalent or inhaled corticosteroids were allowed during the trial</td>
</tr>
<tr>
<td>Rennard et al., 2001²⁸</td>
<td>RCT, DB, parallel group study</td>
<td>3</td>
<td>179 COPD patients with FEV₁ values # 65%, FEV₁/FVC ratios of # 70%, FEV₁ reversibility after salbutamol of # 12%, and score of 1 on MMRC five point dyspnea scale</td>
<td>Salmeterol 42 :g BID, ipratropium bromide 36 :g QID, or placebo for 12 weeks</td>
<td>FEV₁ AUC, baseline dyspnea index/ transitional dyspnea index assessment, 6-minute walking distance and Borg dyspnea assessment, symptoms scores, quality of life using CRDQ and COPD exacerbations</td>
<td>Corticosteroids, inhaled and oral (&lt; 10 mg/day), allowed</td>
</tr>
<tr>
<td>Rossi et al., 2002²⁹</td>
<td>RCT, DB, parallel group study</td>
<td>3</td>
<td>Trial was done in a mixed population; included were only 418 COPD patients with FEV₁ values &lt; 70% of the predicted normal values, FEV₁/FVC ratios # 88%, FEV₁ reversibility with short-acting ³₂-agonists &lt; 15% and baseline severity of breathlessness of grade I</td>
<td>Formoterol 12 or 24 :g BID or matching placebo or oral slow release theophylline for 12 months</td>
<td>FEV₁ AUC</td>
<td>Inhaled corticosteroids and rescue salbutamol allowed</td>
</tr>
</tbody>
</table>

AUC: area under the curve; DB: double blind; COPD: chronic obstructive pulmonary disease; CRDQ: chronic respiratory disease questionnaire; FEV₁: forced expiratory volume in one second; FVC: forced vital capacity; PEFR: peak expiratory flow rate; RCT: randomized controlled trial; RV: residual volume; TLC: total lung capacity; MMRC = Modified Medical Research Council
<table>
<thead>
<tr>
<th>Study &amp; Funding Source</th>
<th>Method</th>
<th>Quality Assessment Score</th>
<th>Participants</th>
<th>Interventions</th>
<th>Outcomes</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stahl et al., 2002&lt;sup&gt;24&lt;/sup&gt; Industry</td>
<td>RCT, DB, parallel group study</td>
<td>3</td>
<td>183 COPD patients with FEV&lt;sub&gt;1&lt;/sub&gt; &lt; 60% of predicted normal, FEV&lt;sub&gt;1&lt;/sub&gt;/FVC &lt; 70% and FEV&lt;sub&gt;1&lt;/sub&gt; reversibility after single dose of formoterol &lt; 12%</td>
<td>Formoterol 18 g, BID, ipratropium bromide 80 g TID, or placebo for 12 weeks</td>
<td>Health related quality of life using St. George’s Respiratory Questionnaire (SGRQ), morning and evening symptom scores, walking distance in shuttle walking test, PEFR, and changes in FEV&lt;sub&gt;1&lt;/sub&gt; and FVC from baseline</td>
<td>Inhaled corticosteroids at constant doses and rescue short-acting &lt;sub&gt;2&lt;/sub&gt;-agonists were allowed</td>
</tr>
</tbody>
</table>

AUC: area under the curve; DB: double blind; COPD: chronic obstructive pulmonary disease; CRDQ: chronic respiratory disease questionnaire; FEV<sub>1</sub>: forced expiratory volume in one second; FVC: forced vital capacity; PEFR: peak expiratory flow rate; RCT: randomized controlled trial; RV: residual volume; TLC: total lung capacity
<table>
<thead>
<tr>
<th>Study &amp; Funding Source</th>
<th>FEV₁</th>
<th>FVC</th>
<th>PEFR</th>
<th>Walk Test</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Salmeterol versus placebo</strong></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Ulrik, 1995²⁷ Industry</td>
<td>Reversibility in mean FEV₁ (as % of predicted): 2.7% (SE) 0.4 versus 3.4% (SE) 0.4</td>
<td></td>
<td>Mean morning PEFR (L/min): 238 (SE) 10 versus 226 (SE) 10 (p&lt;0.001)</td>
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<td></td>
<td>Mean evening PEFR (L/min): 242 (SE) 10 versus 237 (SE) 10</td>
<td></td>
<td>No treatment difference was observed in 6 minute walking distance, and breathlessness after 6 minute walk (Borg scale) (actual data not reported)</td>
<td></td>
</tr>
<tr>
<td>Newman et al., 1996³⁰ Industry</td>
<td>No significant difference in lung function measurement (actual data not reported)</td>
<td></td>
<td>No treatment difference was observed in 6 minute walking distance, and breathlessness after 6 minute walk (Borg scale) (actual data not reported)</td>
<td></td>
</tr>
<tr>
<td>Grove et al., 1996²⁶ Industry</td>
<td>Mean change in FEV₁ from baseline: 120 ml versus 10 ml</td>
<td>Mean change in FVC from baseline: 150 ml versus 130 ml</td>
<td>Median distance (interquartile range) covered in 6 minute walk test: 425 m (392-473) versus 450 m (371-491)</td>
<td></td>
</tr>
<tr>
<td>Boyd et al., 1997¹⁸ Industry</td>
<td>MD with 95% CI in FEV₁ between salmeterol 50 μg and placebo group: 97.80 (55.61; 139.99)</td>
<td>MD with 95% CI in FEV₁ between salmeterol 100 μg and placebo group: 117.60 (67.88; 167.32)</td>
<td>No treatment difference was observed between salmeterol and placebo in 6 minute walking distance (actual data not reported)</td>
<td></td>
</tr>
<tr>
<td>Jones and Bosh, 1997²⁵ Industry</td>
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</table>

AUC: area under the curve; CI: confidence interval; FEV₁: forced expiratory volume in one second; FVC: forced vital capacity; PEFR: peak expiratory flow rate; SE: standard error
<table>
<thead>
<tr>
<th>Study &amp; Funding Source</th>
<th>FEV$_1$</th>
<th>FVC</th>
<th>PEFR</th>
<th>Walk Test</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Salmeterol versus ipratropium versus placebo</strong></td>
<td></td>
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<tr>
<td>Mahler et al., 1999$^{16}$ Industry</td>
<td>Peak improvement in FEV$_1$: 155 ml versus 165 ml versus 24 ml</td>
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<tr>
<td>Rennard et al., 2001$^{28}$ Industry</td>
<td>FEV$_1$ AUC 0-12 hr responses for salmeterol and ipratropium groups were significantly greater than placebo (data not reported)</td>
<td>FVC AUC 0-12 hr, responses for the salmeterol and ipratropium groups were significantly greater than placebo (data not reported)</td>
<td></td>
<td>No significant differences between salmeterol and ipratropium</td>
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<tr>
<td><strong>Formoterol versus placebo</strong></td>
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<tr>
<td>Rossi et al., 2002$^{29}$ Industry</td>
<td>Estimated FEV$_1$ AUC 0-12 hr difference between (a) formoterol 12 mg and placebo: 145 ml (b) formoterol 24 mg and placebo: 141 ml</td>
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<tr>
<td><strong>Formoterol versus ipratropium versus placebo</strong></td>
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<tr>
<td>Stahl et al., 2002$^{24}$ Industry</td>
<td>Improvement in FEV$_1$ (% predicted): 13% versus 7% versus 6%</td>
<td>Changes in PEFR (from baseline in L/min): 15.3 versus 7.1 versus –0.9</td>
<td>Mean changes from baseline in shuttle walking test distance (meters): 19.2 versus 17.5 versus 5.1</td>
<td></td>
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</tbody>
</table>

AUC: area under the curve; CI: confidence interval; FEV$_1$: forced expiratory volume in one second; FVC: forced vital capacity; PEFR: peak expiratory flow rate; SE: standard error
Table 2b: Long-acting $\exists_2$-agonists for COPD: Results of included studies

<table>
<thead>
<tr>
<th>Study &amp; Funding Source</th>
<th>Day-time Night-time Symptom Scores</th>
<th>Rescue Salbutamol Use</th>
<th>SGRQ Scores</th>
<th>SF-36 Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Salmeterol versus Placebo</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ulrik, 1995\textsuperscript{27} Industry</td>
<td>Median day-time symptom scores: 1.0 (range 0-3.4) versus 1.8 (range 0.1-4.0) (p&lt;0.001) Median night-time symptom scores: 0.9 (range 0-3.4) versus 1.6 (range 0.1-4.0) (p=0.001)</td>
<td>Median day-time rescue salbutamol doses: 1.7 (range 0-6.1) versus 2.6 (range 0-7.9) (p=0.02) Median night-time rescue salbutamol doses: 0 (range 0-4.2) versus 0.3 (range 0-5.0) (p&lt;0.001)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Newman et al., 1996\textsuperscript{30} (available only as an abstract) Industry</td>
<td>Salmeterol reduced night-time symptoms compared to placebo (symptom scores not reported)</td>
<td>Salmeterol compared to placebo reduced day-time night-time rescue salbutamol use (data not reported)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grove et al., 1996\textsuperscript{26} Industry</td>
<td></td>
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</tr>
<tr>
<td>Boyd et al., 1997\textsuperscript{18} Industry</td>
<td>Median day-time symptom scores with salmeterol 100 $\Phi$g, 50 $\Phi$g, and placebo groups were 1, 1 and 2 respectively Median night-time symptom scores with salmeterol 100 $\Phi$g, 50 $\Phi$g, and placebo groups were 0, 0 and 0, respectively</td>
<td>Salmeterol, compared to placebo, reduced median day-time and night-time use of additional bronchodilator (actual data not reported)</td>
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<tr>
<td>Jones and Bosh, 1997\textsuperscript{25} Industry</td>
<td></td>
<td></td>
<td>SGRQ total scores in salmeterol 50 $\Phi$g versus placebo group: -6.8 (SD) 13.2, versus -1.4 (SD) 11.7 SGRQ total scores in salmeterol 100 $\Phi$g versus placebo group: -2.3 (SD) 11.6 versus -1.4 (SD) 11.7</td>
<td>No statistically significant differences in any of the domains of the SF-36 with the exception of 'role emotional' SF-36 'role emotional' domain scores in salmeterol 50 $\Phi$g versus placebo group: 2.9 $\forall$ 46.8 versus $-0.0 \forall$ 46.6 SF-36 'role emotional' domain scores in salmeterol 100 $\Phi$g versus placebo group: $-12.7 \forall 43.1$ versus $-0.0 \forall 46.6$</td>
</tr>
</tbody>
</table>
SD: standard deviation; SF-36: short form 36 health questionnaire; SGRQ: St. George’s respiratory questionnaire
<table>
<thead>
<tr>
<th>Study &amp; Funding Source</th>
<th>Day-time Night-time Symptom Scores</th>
<th>Rescue Salbutamol Use</th>
<th>SGRQ Scores</th>
<th>SF-36 Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Salmeterol versus ipratropium versus placebo</strong></td>
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<td></td>
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<tr>
<td>Mahler et al., 1999\textsuperscript{16}</td>
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<tr>
<td>Industry</td>
<td>No significant differences in supplemental salbuterol use observed among the three groups (actual data not reported)</td>
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<tr>
<td><strong>Rennard et al., 2001\textsuperscript{28}</strong></td>
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<tr>
<td>Industry</td>
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<td><strong>Formoterol versus placebo</strong></td>
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<td>Stahl et al., 2002\textsuperscript{24}</td>
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</tr>
<tr>
<td>Industry</td>
<td>Mean changes in breathlessness scores from baseline: -0.21 versus –0.29 versus 0.0</td>
<td>Mean changes in SGRQ scores from baseline: 0.0 versus -0.5 versus 1.5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SD: standard deviation; SF-36: short form 36 health questionnaire; SGRQ: St. George’s respiratory questionnaire