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Long-acting β_2-agonists for the Maintenance Treatment of Chronic Obstructive Pulmonary Disease in Patients with Reversible and Non-reversible Airflow Obstruction: A Systematic Review of Clinical Effectiveness

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CCOHTA
600-865 Carling Avenue
Ottawa ON Canada K1S 5S8
Tel. (613) 226-2553
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This report and the French version entitled *Étude méthodique de l'efficacité clinique des agonistes ß$_2$ à longue durée d'action dans le traitement d'entretien de la maladie pulmonaire obstructive chronique avec et sans réversibilité de la maladie* are available on CCOHTA's web site.

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Long-acting β_2-agonists for the Maintenance Treatment of Chronic Obstructive Pulmonary Disease in Patients with Reversible and Non-reversible Airflow Obstruction: A Systematic Review of Clinical Effectiveness

Vijay K. Shukla BPharm MSc PhD[1]
Stella Chen MD MSc[1]
Michel Boucher BPharm MSc[1]
Shaila Mensinkai MA MLIS[1]
Robert Dales MD MSc[2]

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[1] Canadian Coordinating Office for Health Technology Assessment, Ottawa ON
[2] University of Ottawa, and Ottawa Hospital, Ottawa ON

Reviewers

These individuals kindly provided comments on this report.

External Reviewers

James A. Hanley, PhD
Professor, Department of Epidemiology and Biostatistics
McGill University
Montreal QC

Brian Smith, MBBS FRACP Diploma
Clinical Epidemiology and Biostatistics, PhD
Associate Professor,
Director Respiratory Medicine
Director Clinical Epidemiology
University of Adelaide
Adelaide, Australia

George A. Fox, MD, MSc, FRCPC, FCCP
Associate Professor
Memorial University of Newfoundland
St. John's NF

CCOHTA Scientific Advisory Panel Reviewers

Ruth L. Collins-Nakai, MD MBA FRCPC FACC
Cardiologist
Edmonton AB

George A. Wells, MSc PhD
Director
Cardiovascular Research Centre
Heart Institute
University of Ottawa
Ottawa ON

This report is a review of existing literature, studies, materials and other information and documentation (collectively the "source documentation") that are available to CCOHTA. The accuracy of the contents of the source documentation on which this report is based is not warranted, assured or represented in any way by CCOHTA and CCOHTA does not assume responsibility for the quality, propriety, inaccuracies or reasonableness of any statements, information or conclusions contained in the source documentation.

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 reviewers or Scientific Advisory Panel members.

Authorship

Vijay K. Shukla led the development of the research protocol, supervised the literature review process, and summarized results in the clinical draft document. Vijay K. Shukla and Stella Chen were responsible for reviewing articles, judging their relevance, assessing their quality, and extracting and synthesizing data. Michel Boucher assisted in developing the research protocol, resolving conflicts in the study selection process, addressing external reviewers' comments, and incorporating data from new studies identified through alerts. He critically reviewed drafts, and

responded to questions from copy editors and report formatters regarding the final version. Shaila Mensinkai designed and conducted the electronic searches, provided expertise regarding information sciences, and contributed to the writing of the report. Robert Dales assisted in developing the protocol, provided clinical expertise, and reviewed drafts.

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Conflicts of Interest

Vijay Shukla, Stella Chen, Michel Boucher, and Shaila Mensinkai declared no conflicts of interest.

Robert Dales received money for continuing medical education talks from GlaxoSmithKline (manufacturer of the long-acting ß$_2$-agonist salmeterol), Boehringer Ingelheim (manufacturer of the anticholinergic agents, tiotropium and ipratropium), and Merck Frosst.

In the past five years, Dr. Fox has received financial sponsorship, hospitality, and honoraria from Actelion, AstraZeneca, Bayer HealthCare, Boehringer Ingelheim, Bristol-Meyers Squibb, Eli Lilly, GlaxoSmithKline, Janssen-Ortho, Merck Frosst, and Pfizer.

REPORT *IN BRIEF*

March 2006

Long-acting β_2-agonists for the Maintenance Treatment of Chronic Obstructive Pulmonary Disease in Patients with Reversible and Non-reversible Airflow Obstruction

Technology
Salmeterol xinafoate and formoterol fumarate (long-acting β_2-agonists)

Condition
Patients with mild to severe chronic obstructive pulmonary disease (COPD) that is defined as symptomatic, progressive chronic airflow obstruction, in a clinically stable state, without recent exacerbations, hospitalizations, or need for antibiotics, or oral and parenteral corticosteroids.

Issue
The diagnostic criteria for COPD are evolving, and newer, more expensive technologies are available for this condition, including long-acting β_2-agonists. Potential funders should understand the health impact associated with the use of these technologies.

Methods and Results
Relevant literature was identified by two reviewers working independently who systematically applied selection criteria to bibliographic citations generated from a comprehensive search of available data sources. Among the 33 unique trials that were identified, 64% were of higher quality. Long-acting β_2-agonists did not demonstrate a significant advantage over the anticholinergic agents ipratropium or tiotropium in most of the health outcome measures. Compared with placebo, long-acting β_2-agonists have a demonstrated effect in reducing COPD exacerbations and hospitalizations. More robust data on these outcome measures were available for salmeterol than for formoterol. Salmeterol was not as well tolerated as tiotropium.

Implications for Decision Making
- **Compared to no therapy, long-acting β_2-agonists improve health outcomes.** There is evidence that LABAs reduce reduce hospitalizations and disease exacerbations in patients with mild to severe COPD, compared to placebo. These outcomes can offset the direct costs of therapy.
- **Long-acting β_2-agonists have no demonstrated health benefits over ipratropium or tiotropium**. Despite eight clinical trials with over 3,500 participants, no consistent or overall improvements in health outcomes were observed with long-acting β_2-agonists, compared with anticholinergic agents. Decision makers will need to consider other factors such as tolerability, ease of use, price, and individual responsiveness when choosing between these agents.
- **Salmeterol is not as well tolerated as tiotropium.** A larger proportion of salmeterol recipients were observed to be intolerant to therapy. This could reduce the effective management of illness and have cost implications to patients and funders in terms of additional physician visits. No data were available to compare the tolerability of formoterol with tiotropium.

This summary is based on a comprehensive health technology assessment available from CCOHTA's web site (www.ccohta.ca): Shukla VK, Chen S, Boucher M, Mensinkai S, Dales R. *Long-acting β_2-agonists for the maintenance treatment of chronic obstructive pulmonary disease in patients with reversible and non-reversible airflow obstruction: a systematic review of clinical effectiveness.*

Canadian Coordinating Office for Health Technology Assessment (CCOHTA)
600-865 Carling Avenue, Ottawa ON Canada K1S 5S8 Tel: 613-226-2553 Fax: 613-226-5392 www.ccohta.ca

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EXECUTIVE SUMMARY

The Issue

Long-acting β_2-agonists have been approved for the management of patients with chronic obstructive pulmonary disease (COPD). The diagnostic criteria for COPD are evolving, and as many as 30% of patients with COPD may have airway obstruction that is measured with forced expiratory volume in one second (FEV_1) and that may be alleviated with bronchodilator therapy (i.e., reversibility). In clinical practice, it may be difficult to separate patients with COPD who respond to bronchodilator therapy from those who do not. In addition, the reversibility status for many patients with COPD fluctuates over time.

Potential funders of these drugs should understand the health impact associated with their use in patients who are diagnosed with COPD. This report will review the clinical implications of using long-acting β_2-agonists in patients with reversible and non-reversible stable COPD.

Objectives

The objective of this report is to critically examine the clinical effectiveness, through a systematic review of the literature, of inhaled long-acting β_2-agonists in patients with stable COPD and reversible or non-reversible airway obstruction. The report will address the following research questions:

- What is the effectiveness of inhaled long-acting β_2-agonists versus inhaled anticholinergics (ipratropium and tiotropium), with or without short-acting β_2-agonist aerosol agents taken on an as-needed basis, for the maintenance treatment of patients with stable COPD irrespective of the degree of airway reversibility?
- What is the effectiveness of inhaled long-acting β_2-agonists versus placebo, with or without short-acting β_2-agonist aerosol agents taken on an as-needed basis, for the maintenance treatment of patients with stable COPD irrespective of the degree of airway reversibility?

Methods

Published and unpublished literature was obtained by searching multiple databases; hand-searching selected journals, documents, and the bibliographies of selected papers; and by contacting manufacturers. Included were all published and unpublished randomized controlled trials (RCTs) of one or more weeks' duration, of parallel or crossover design, enrolling patients with a FEV_1 of 75% or less than the predicted value, and a ratio of FEV_1/forced vital capacity (FVC) of less than 70% of the predicted value. Two reviewers independently selected studies; assessed trial quality; extracted key data including deaths, serious or life threatening adverse events, COPD exacerbations, upper respiratory tract infections (URTIs) during treatment, hospitalizations during treatment, rescue short-acting β_2-agonist use for acute symptomatic relief, symptom-free days, dyspnea, lung function tests, walk tests, and quality of life measures.

Results

Of the 150 potentially relevant reports identified, 54 summarizing the results of 33 unique RCTs satisfied the inclusion criteria for this review. Of these, 20 trials compared salmeterol and placebo; two compared salmeterol, ipratropium bromide, and placebo; two compared salmeterol,

tiotropium; and placebo; and one compared salmeterol and tiotropium. Five RCTs compared formoterol and placebo; two compared formoterol, ipratropium, and placebo; and one compared formoterol and tiotropium. Overall, more robust data were available for salmeterol than formoterol.

Based on the Jadad scale, the quality assessment of these trials showed that 21 (64%) were of higher quality (quality score ≥3) and 12 (36%) were of lower quality (quality scores of 1 to 2). Higher quality studies are associated with less exaggerated estimates of effectiveness.

No significant differences were observed between long-acting β_2-agonists and ipratropium bromide or tiotropium in the outcome measures assessed with the exception of symptom-free days. For this outcome measure, one study reported a significant advantage of formoterol over ipratropium, and better improvement in lung function with tiotropium over salmeterol (FVC) and formoterol (FEV_1), but this was not supported by other evidence. Based on two studies, withdrawal due to adverse events occurred more often in salmeterol recipients compared with tiotropium recipients [odds ratio (OR) 2.16, 95% confidence interval (CI): 1.36 to 3.43].

Compared with placebo, long-acting β_2-agonists reduced COPD exacerbations [OR 0.74 (95% CI: 0.64; 0.87)] and hospitalizations [OR 0.62 (95% CI: 0.40; 0.96)]. Most studies indicate that long-acting β_2-agonists are better than placebo in reducing the use of rescue inhalers, and improving the number of symptom-free days, the level of dyspnea, and the measures of lung function (FEV_1, FVC, peak expiratory flows). Their effect on measures of quality of life was inconsistent across studies. Long-acting β_2-agonists did not demonstrate detectable differences on mortality, withdrawals due to adverse events, URTIs, or exercise capacity as measured by the walk test, compared with placebo.

Conclusions

This review examined the clinical implications of using the long-acting β_2-agonists, salmeterol and formoterol, in the management of patients with stable COPD. The review evaluated the literature comparing these drugs to the anticholinergic agents (ipratropium bromide, tiotropium) and to placebo.

Long-acting β_2-agonists were significantly more effective than placebo in reducing COPD exacerbations and hospitalizations. Improvement in the use of rescue inhalers, symptom-free days, dyspnea, and lung function were also observed, although confirmation through further study may be required. Long-acting β_2-agonists did not have any significant advantages over placebo in reducing mortality and URTIs, or improving exercise capacity and tolerability.

Long-acting β_2-agonists did not demonstrate a significant advantage compared with either anticholinergic agent in most functional outcome measures. Salmeterol is not as well tolerated as tiotropium. No data were available to compare the tolerability of formoterol with tiotropium.

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ABBREVIATIONS

AE	adverse event
ATS	American Thoracic Society
AUC	area under the curve
β_2-agonist	beta$_2$ agonist
BDI	baseline dyspnea index
BTS	British Thoracic Society
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CRDQ	Chronic Respiratory Disease Questionnaire
CTS	Canadian Thoracic Society
DB	double-blind
ERS	European Respiratory Society
FDA	Food and Drug Administration
FEV_1	forced expiry volume in one second
FVC	forced vital capacity
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HRQL	health-related quality of life
MD	mean difference
OR	odds ratio
PEF	peak expiratory flow
PEFR	peak expiratory flow rate
QoL	quality of life
RCT	randomized controlled trial
RV	residual volume
SAM	salmeterol
SF-36	Short Form Health survey 36-item
SGRQ	St. George's Respiratory Questionnaire
SWT	shuttle walking test
TDI	transitional dyspnea index
TLC	total lung capacity
URTI	upper respiratory tract infection
VC	vital capacity

1 INTRODUCTION

1.1 Background in Canada

1.1.1 Disease

As defined by the 2003 Canadian Thoracic Society (CTS), "chronic obstructive pulmonary disease (COPD) is a respiratory disorder largely caused by smoking, which is characterized by progressive, partially reversible airway obstruction, systemic manifestation and increasing frequency and severity of exacerbations."[1] Symptoms, which include shortness of breath and exercise intolerance, are usually insidious in onset, typically progressive, and characterized by frequent exacerbations. During exacerbations, there is a worsening of symptoms that generally requires a change in drug therapy. In advanced disease, patients with COPD become immobilized because of difficulty in breathing. This leads to measurable systemic manifestations, such as metabolic and structural abnormalities of peripheral locomotor muscles.

The major characteristic of COPD is the presence of a chronic airflow limitation that slowly and irreversibly progresses over several years.[2] Pulmonary function testing is helpful to determine the severity, prognosis, and reversibility of the obstruction in COPD patients. The two primary spirometric indicators of obstructive lung disease are a decrease in the forced expiratory volume in one second (FEV_1) and a reduction in the ratio of FEV_1 to the forced vital capacity (FVC) to <75%.[3] While spirometric testing requires specialized technology, peak expiratory flow rates (PEFR) can be measured at home using a handheld peak flow meter. PEFR roughly correlate with FEV_1, but may be less reliable in advanced disease.[3]

The classical epidemiologic studies of Fletcher and Peto showed that death and disability from COPD were related to an accelerated decline in lung function over time, with a loss of >50 mL per year in FEV_1, as compared with a normal loss of 20 mL per year.[2] This airflow limitation is usually associated with an abnormal inflammatory response.[4] The natural course of COPD can span 20 to 40 years. The signs and symptoms of COPD vary, depending on 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.[5,6]

The severity of disease can be assessed by a combination of information about symptoms and evidence of impairment of physiological functions (Table 1).[1] In most cases, COPD can be differentiated from asthma by clinical characteristics (Table 2).[1] In many patients, the symptoms of asthma and COPD overlap. The prevalence of concurrent asthma and COPD is unknown. Many guidelines state that patients with COPD have an incomplete response to salbutamol (e.g., change in FEV_1 <200 mL and 12% of predicted value).[7,8] Depending on the criteria used, between 23% and 42% of patients with COPD are responsive to bronchodilators.[9] The differentiation of COPD from asthma often requires careful integration of spirometric criteria, epidemiologic risk factors, clinical status (including the indolent and progressive nature of the symptoms), and a knowledge of the distribution and potential overlap of physiological disturbances.

Table 1: CTS classification of COPD by symptoms, disability and lung function[1]

COPD Stage	Symptoms and Disability	Lung Function (post-bronchodilator)
At risk (does not yet fulfil diagnosis of COPD)	Asymptomatic smoker, ex-smoker, or chronic cough and sputum	Normal spirometry $FEV_1/FVC \geq 0.7$ and $FEV_1 \geq 80\%$ of predicted value
Mild	**Shortness of breath from COPD when hurrying on the level or walking up slight hill**	FEV_1 60% to 79% of predicted value, $FEV_1/FVC < 0.7$
Moderate	Shortness of breath from COPD causing patient to stop after walking about 100 metres (or after a few minutes)	FEV_1 40% to 59% of predicted value, $FEV_1/FVC < 0.7$
Severe	Shortness of breath from COPD resulting in patient too breathless to leave house, breathlessness after undressing, or presence of chronic respiratory failure or clinical signs of right heart failure	$FEV_1 < 40\%$ of predicted value, $FEV_1/FVC < 0.7$

COPD=chronic obstructive pulmonary disease, CTS=Canadian Thoracic Society, FEV_1=forced expiratory volume in one second, FVC=forced vital capacity.

Table 2: Clinical characteristics of asthma and COPD[1]

Characteristic	Asthma	COPD
Age of onset	Usually <40 years	**Usually >40 years**
Smoking history	Not causal	Usually >10 pack-years
Sputum production	Infrequent	Often
Allergies	Often	Infrequent
Disease course	**Stable (with exacerbations)**	Progressive worsening (with exacerbations)
Spirometry	Often normalizes	Never normalizes
Clinical symptoms	Intermittent and variable	Persistent

COPD=chronic obstructive pulmonary disease.

1.1.2 Prevalence in Canada

From 1978-1979 to 1998-1999, the prevalence of COPD decreased in Canada.[10] During this period, the incidence of bronchitis and emphysema decreased from 4.4% to 2.4% in individuals 45 to 64 years of age, and from 6.3% to 5.8% in those 65 years and older. In spite of this decrease, COPD still imposes a high burden of illness on the Canadian health care system.[11] In 1997, the average length of stay in hospital for an exacerbation of COPD was 10.5 days.[12] Since the early 1990s, hospitalization rates have increased among women but not men. Projections indicate that the hospitalization rate of women with COPD reached the hospitalization rate of men with COPD in 2000, affecting 30,000 individuals in each group. Data from 1987 to 1998 indicate that the number of women dying from COPD has increased faster than for men. Projections indicate that the number of COPD deaths became equal for both groups in 2004, affecting an estimated 6,000 men and 6,000 women. These trends are expected to continue in the future.[12]

1.1.3 Current clinical practice in Canada

The CTS's recommendations for the management of COPD specify six goals: prevent disease progression; alleviate breathlessness and other respiratory symptoms; improve exercise tolerance; prevent and treat exacerbations; improve health status; and reduce mortality rate.[1] An integrated approach to treatment combines health care maintenance, and the use of drug and supplemental therapies in a stepwise fashion as the disease progresses.[1] Smoking cessation, and education that incorporates a self-management plan should be offered to all patients.

The bronchodilator therapy for COPD includes inhaled β_2-agonists, inhaled anticholinergics, and oral methylxanthines. All three classes include drugs that are short-acting or long-acting. Inhaled bronchodilators are the primary pharmacological therapy used in the management of COPD to achieve maximum symptom control. They produce modest improvements in FEV_1 and reduce dynamic hyperinflation. Breathlessness and exercise tolerance may improve despite little improvement in spirometric measurements.[13]

According to the CTS's recommendations, patients with COPD who have symptoms that are only noticeable with exertion and who have little disability should be offered an inhaled short-acting β_2-agonist on an as-needed basis. If the clinical response is unsatisfactory, an anticholinergic aerosol, or a combination of an anticholinergic and short-acting β_2-agonist, can be used.[1] The choice of first-line therapy in patients with mild symptomatic COPD should be individualized, and based on clinical response and tolerance to side effects. If symptoms persist despite short-acting bronchodilator therapy, a long-acting bronchodilator should be used. Recommended long-acting bronchodilators include the anticholinergic preparation tiotropium (18 µg once daily) or the long-acting β_2-agonists formoterol (12 µg twice daily) or salmeterol (50 µg twice daily). Short-acting β_2-agonists may continue to be used as needed for immediate symptom relief. Some specialists recommend the use of long-acting β_2-agonists as first-line agents for patients with regularly symptomatic COPD.[14-18]

1.2 Overview of the Technology

Salmeterol xinafoate and formoterol fumarate are the two inhaled long-acting β_2-agonists that are available in Canada (Table 3). The appropriate comparators identified in this review are the two inhaled anticholinergic agents, ipratropium bromide and tiotropium bromide monohydrate (Table 3).

1.2.1 Salmeterol xinafoate

In Canada, salmeterol is indicated for long-term bronchodilator maintenance therapy, and relief of dyspnea in patients with COPD, including those with chronic bronchitis and emphysema. It is also indicated for long-term maintenance treatment of asthma in patients ≥4 years of age with reversible obstructive airway disease, including patients with nocturnal asthma, who are using optimal corticosteroid treatment and experiencing breakthrough symptoms requiring the regular use of a short-acting bronchodilator.[19]

Table 3: Drugs available in the Canadian market

Generic Name	Trade name, Manufacturer	Dosage Form	Cost per Unit	Approved Dosages
Salmeterol xinafoate	Serevent® inhaler (Serevent aerosol), GlaxoSmithKline Inc.	25 µg salmeterol/ actuation	$52.04 for 120 doses; $26.02 for 60 doses	50 µg twice daily
	Serevent® Diskhaler® disks, GlaxoSmithKline Inc.	50 µg salmeterol/ dose	$52.04 for 60 doses	50 µg twice daily
	Serevent® Diskus®, GlaxoSmithKline Inc.	50 µg salmeterol/ dose	$52.04 for 60 doses	50 µg twice daily
Formoterol fumarate	Foradil® inhalation capsule, Novartis	12 µg formoterol/ capsule	$42.30 for 1 carton (60 capsules)	12 µg or 24 µg twice daily
	Oxeze® Turbuhaler®, AstraZeneca	6 µg or 12 µg formoterol/ metered dose	$44.63 and $33.50 for 60 doses of 12 µg and 6 µg respectively	6 µg or 12 µg twice daily
Ipratropium bromide	Atrovent®, Boehringer Ingelheim	20 µg ipratropium/ actuation	$18.64 for 200 doses	40 µg 3 to 4 times per day
Tiotropium bromide monohydrate	Spiriva®, Boehringer Ingelheim	18 µg/tiotropium capsule	$63.00 for 30 capsules	18 µg once daily

Cost information was obtained from the September 2003 Ontario Drug Benefit formulary.[20] For Oxeze® Turbuhaler® and Atrovent®, prices were obtained from October 2004 wholesaler catologues.[21]

Salmeterol is available for inhalation in three dosage forms: Serevent® inhalation aerosol, Serevent® Diskhaler® disk, and Serevent® Diskus®. Serevent® aerosol is a pressurized metered-dose inhaler therapy containing a non-aqueous suspension of microfine salmeterol xinafoate and soya lecithin. Serevent® is available in 60 and 120 metered-dose (25 µg salmeterol/actuation) formats. The recommended daily dose for this formulation is two inhalations twice daily.

Serevent® Diskhaler® disks are circular, double-foil blister packs with four regularly distributed blisters, each containing a dry powder blend of microfine salmeterol xinafoate and lactose. Each blister contains 50 µg salmeterol. The disk blister packs are available in cartons of 15 disks (four blisters/disk). Serevent® Diskhaler® disks are also available individually. Disks are used with the Serevent® Diskhaler® device. The recommended daily dose for this formulation is one blister twice daily.

Serevent® Diskus® is a dry powder presentation of microfine salmeterol xinafoate with the non-medicinal ingredient lactose for inhalation. The product consists of 60 doses, each containing the equivalent of 50 µg of salmeterol per dose. The recommended daily dose for this formulation is one blister twice daily.

1.2.2 Formoterol fumarate

Foradil® inhalation capsules contain 12 µg of formoterol fumarate, with non-medicinal ingredients. It is supplied as a free flowing powder. An Aerolizer™ device is supplied so that the capsule contents can be inhaled. Capsules are marketed in cartons of 60 with one Aerolizer™ inhalation device. The Foradil® inhalation capsule is indicated for the maintenance treatment of asthma and COPD in patients who are ≥6 years of age. The recommended daily dose for adults with COPD is one or two capsules (12 µg or 24 µg) twice daily (morning and evening) by inhalation. For the maintenance treatment of asthma in adults and children of ≥6 years of age, the recommended daily dose is one capsule twice daily (morning and evening) by inhalation. In severe cases, the dose may be increased to two capsules twice daily.[22]

The Oxeze® Turbuhaler® consists of formoterol fumarate dihydrate with non-medicinal ingredients. It is available in two strengths, 6 µg/inhalation or 12 µg/inhalation. Oxeze® Turbuhaler® is indicated for the treatment and prevention of symptoms of reversible obstructive airway disease, including asthma in patients ≥6 years of age. The recommended daily dose is 6 µg or 12 µg twice daily by inhalation, at 12-hour intervals. In adults, the maximum recommended dose is 24 µg twice daily. In children (six to 16 years old), the maximum recommended dose is 12 µg twice daily.[23]

1.2.3 Ipratropium bromide

Ipratropium bromide is available in Canada as an inhalation aerosol (Atrovent®) and as an inhalation solution (Atrovent® and generics). Atrovent® is indicated for bronchodilator maintenance therapy in patients with COPD, including those with chronic bronchitis and emphysema.[24,25]

Ipratropium bromide inhalation aerosol is supplied in a metered-dose inhaler with a mouthpiece (oral adaptor) containing 140 or 200 doses of ipratropium bromide with non-medicinal ingredients. Each valve depression delivers 20 µg of ipratropium bromide. The recommended dosage is two metered doses (actuations) (40 µg) three or four times daily. Some patients may need up to four metered doses (actuations), (80 µg) at a time to obtain maximum benefit during early treatment. The maximum daily dose is 12 metered doses (240 µg), and the minimum interval between the doses should be >4 hours.

Ipratropium bromide inhalation solution is indicated for bronchodilator maintenance therapy in patients with COPD, including those with chronic bronchitis and emphysema, and for the therapy of acute exacerbations of COPD. It is also indicated for acute asthmatic attacks. Ipratropium solution is administered by compressed air or oxygen-driven nebulizer. The solution is available in multi-dose bottles and unit dose vials. Multi-dose bottles contain 20 mL of a 0.025% (250 µg/mL) solution of ipratropium bromide with non-medicinal ingredients. Unit dose plastic vials are available as 2 mL of 0.0125% (125 µg/mL) and as 1 mL and 2 mL of 0.025% (250 µg/mL) of ipratropium bromide. For children between the ages of five and 12 years old, the recommended dose is 125 µg to 250 µg of ipratropium bromide by nebulizer. For adults, the average dose is 250 µg to 500 µg of ipratropium by nebulizer. Treatment with the ipratropium solution may be repeated every four to six hours as necessary. Nebulization should occur with a gas flow (oxygen or compressed air) of 6 L to 10 L per minute. The solution should be nebulized to dryness over 10 to 15 minutes. The Hudson Updraft, Bennett Twin Jet, DeVilbiss, Pari Compressor, and Inspiron Mini Neb nebulizers, with a face mask or mouthpiece, have been used to administer the ipratropium solution.

1.2.4 Tiotropium bromide monohydrate

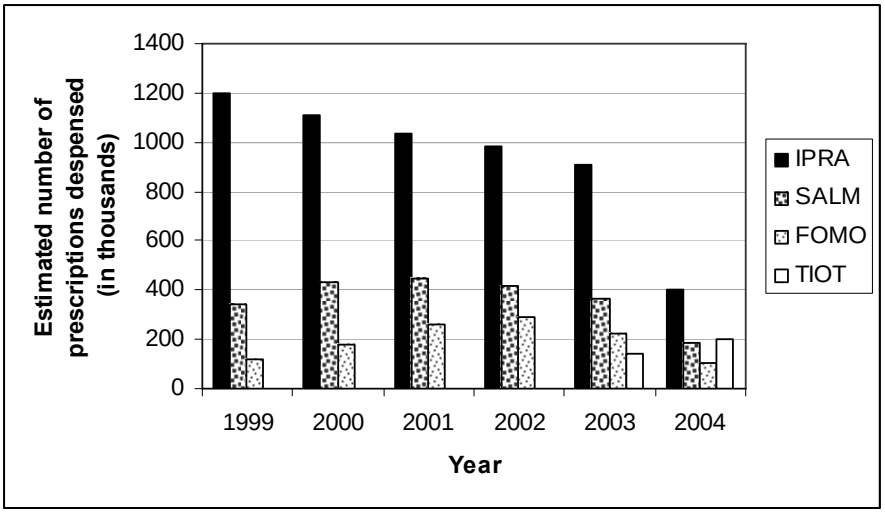
Tiotropium bromide monohydrate is indicated in Canada for long-term bronchodilator maintenance therapy in patients with COPD, including those with chronic bronchitis and emphysema. Spiriva® is available as capsules containing 18 µg of tiotropium per capsule with non-medicinal ingredients for oral inhalation. The capsules are used only with the supplied HandiHaler® inhalation device. Ten tiotropium capsules are packaged in an aluminum PVC blister card. One blister card consists of two five-cavity strips joined along a perforated line. A carton of 30 or 10 tiotropium capsules is sold with one HandiHaler® device. The recommended dosage of tiotropium is inhalation of the content of one capsule (18 µg) once daily using a HandiHaler® inhalation device.[26]

1.3 Drug Utilization Trends

The Montreal office of IMS Health, Canada (Dorothy Rhodes, IMS Health, Kirkland, QC: personal communication, 2004 Aug 18) was contacted by CCOHTA to obtain recent utilization information on salmeterol, formoterol, tiotropium and ipratropium in Canada. IMS uses continuous surveys of pharmacists and physicians to collect information on Canadian patterns of drug prescribing and utilization. IMS provided CCOHTA with two types of data, and described the methods of data collection (Appendix 1).[27]

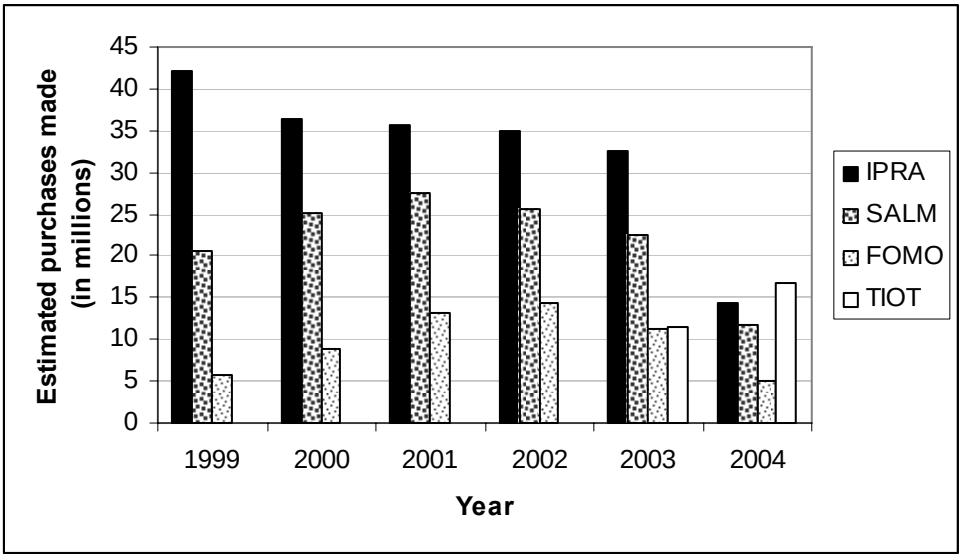
IMS data from 1999 to June 2004 indicated there was an increase in the use of salmeterol and formoterol until 2003, followed by a steady decrease to June 2004 (Figures 1 and 2). From the time that it was introduced to the Canadian market in 2003, there was a steady increase in the use of tiotropium.

Figure 1: Estimated number of prescriptions dispensed for ipratropium bromide (IPRA), tiotropium (TIOT), salmeterol (SALM), and formoterol (FOMO) in Canadian drug stores from 1999 to June 2004, for all clinical indications



Source: IMS Health, Canada, CompuScript, 2004. 2004 data provided from January to June only.

Figure 2: Canadian drug store and hospital purchases of ipratropium bromide (IPRA), tiotropium (TIOT), salmeterol (SALM), and formoterol (FOMO) from 1999 to June 2004, for all clinical indications



Source: IMS Health, Canada, Compuscript, 2004. 2004 data provided from January to June only.

2 THE ISSUE

In September 2002, CCOHTA performed a systematic review to evaluate the efficacy of long-acting β_2-agonist agents in the management of patients with stable COPD and poor reversibility (defined as <15% improvement in FEV_1 after one dose of a short- or long-acting bronchodilator).[28,29] The 2002 review found that the long-acting β_2-agonist agents were superior to placebo in decreasing the use of a rescue inhaler. Although an increase in FEV_1 was also observed, no improvement in functional outcomes such as distance travelled in a six-minute walk test was observed when long-acting β_2-agonists were compared with placebo. The systematic review also found no evidence of differences between long-acting β_2-agonists and ipratropium bromide in improving the symptoms of COPD in patients with non-reversible disease.

Similar results were reported in a 1998 Cochrane Collaboration meta-analysis examining the use of long-acting β_2-agonists in patients with non-reversible COPD <15% improvement in FEV_1 after one dose of a short- or long-acting bronchodilator).[30] In the Cochrane review, improvements in FEV_1 alone did not correlate highly with symptom improvement.

The main limitation of the CCOHTA and Cochrane reviews is that they excluded studies conducted in patients with reversible disease. These could represent up to 30% of all patients with COPD according to the 1995 American Thoracic Society (ATS) diagnosis and treatment guidelines.[31] While the intention was to minimize the chance of including asthma cases in these reviews, for many patients with COPD, the reversibility component of FEV_1 may not be associated with asthma.[32] According to a study using the ATS criteria to diagnose airway

obstruction reversibility (an increase in FEV_1 of ≥15% after inhalation of a bronchodilator aerosol), 52.1% of patients changed reversibility status when they were tested three times during the two-month study period.[9] Clinically, it may be difficult to separate patients with COPD who respond to bronchodilator therapy from those who do not, at least on the basis of one test of FEV_1 reversibility.[32]

Since the release of a previous review,[28,29] a long-acting anticholinergic, tiotropium, for the treatment of COPD, has become available. As the cost of this medication is similar to that of more expensive long-acting β_2-agonists, it is important to assess how it compares to long-acting β_2-agonists.

This study was undertaken to critically review the outcomes related to the clinical effectiveness of choosing long-acting β_2-agonists or anticholinergics (with or without short-acting β_2-agonists on an as-needed basis) in all patients with COPD, irrespective of airway reversibility.

3 OBJECTIVES

The objective of this report is to critically examine the clinical effectiveness, through a systematic review of the literature, of inhaled long-acting β_2-agonists in patients with stable COPD and reversible or non-reversible airway obstruction. The report will address the following research questions:

- What is the effectiveness of inhaled long-acting β_2-agonists versus inhaled anticholinergics (ipratropium and tiotropium), with or without short-acting β_2-agonist aerosol agents taken on an as-needed basis, for the maintenance treatment of patients with stable COPD irrespective of the degree of airway reversibility?
- What is the effectiveness of inhaled long-acting β_2-agonists versus placebo, with or without short-acting β_2-agonist aerosol agents taken on an as-needed basis, for the maintenance treatment of patients with stable COPD irrespective of the degree of airway reversibility?

4 METHODS

A protocol for the review was written a priori and followed throughout the review.

4.1 Literature Search Strategy

Published literature was identified by searching electronic databases on DIALOG® using the system's OneSearch feature. The search covered the period from 1992 onward and included the following databases: MEDLINE®, EMBASE®, BIOSIS Previews®, PASCAL, SciSearch,® and ToxFile. The search strategy (Appendix 2) included MeSH headings, descriptors and keywords for the disease and drugs. Generic and trade names, and registry numbers for long-acting ß$_2$-agonists were also used. There were no language restrictions. Retrieval was limited to human studies. Trial reports published as abstracts were also included. Parallel searches were run and updated on PubMed and the Cochrane Library. The original search was performed in December

2002. Monthly alerts were set up on MEDLINE®, EMBASE®, BIOSIS Previews®, Pharmaceutical News Index,® and Adis Clinical Trials Insight databases, and ran until December 1, 2005.

Grey literature was obtained by searching the web sites of health technology assessment (HTA) and related agencies, and clinical trial registers. The web sites of American and European respiratory and thoracic associations were searched for meeting and conference abstracts. These searches were supplemented by hand-searching selected bibliographies and documents. IMS Health, Canada was contacted to obtain drug utilization data. The Canadian affiliates of the manufacturers of the two long-acting ß$_2$-agonists that were evaluated in this review were invited to submit relevant information.

4.2 Selection Criteria

4.2.1 Study design

Randomized controlled trials (RCTs) of parallel and crossover designs were included irrespective of language, publication status, and blinding.

4.2.2 Population

Patients included were those with COPD defined as symptomatic, with progressive chronic airflow obstruction (FEV_1 <75%), who were in a clinically stable state without recent exacerbations, hospitalizations, or need for antibiotics or oral and parenteral corticosteroids. Patients could be receiving inhaled corticosteriods. Trials were only included if patients demonstrated an $FEV_1/FVC \leq 70\%$ of the predicted value at baseline.

4.2.3 Interventions

Trials were included if they compared long-acting β_2-agonists (salmeterol or formoterol) with placebo or with an anticholinergic agent (ipratropium or tiotropium), with or without short-acting inhaled β_2-agonists on an as-needed basis. No restrictions were placed on dosage. Trials were only considered if the duration of the treatment was at least one week.

4.2.4 Outcome measures

- Death
- Serious or life-threatening adverse events
- COPD exacerbations (see Appendix 3 for definitions by study)
- URTIs during the treatment (see Appendix 3 for definitions by study)
- Hospitalizations during treatment
- Inhaled rescue short-acting β_2-agonist used for acute symptomatic relief
- Symptom-free days (see Appendix 3 for definitions by study)
- Dyspnea measurements including symptom diary scores, Transitional Dyspnea Index (TDI), or Borg dyspnea scores (see Appendix 3 for definitions by study)
- Lung function including measurements of FEV_1, FVC, and PEFR

- Six-minute walk test (distance walked in six minutes) or shuttle walking test (SWT)
- Quality of life as measured by the St. George's Respiratory Questionnaire (SGRQ), Chronic Respiratory Disease Questionnaire (CRDQ), or Short-Form health Survey 36 item (SF-36) questionnaire (see Appendix 3 for description of scales and use by study).

4.3 Selection Method

4.3.1 Potentially relevant articles

Two reviewers (VS and DH) independently reviewed citations and abstracts, and applied the selection criteria. Alerts were reviewed by one of three co-authors (VS, SC, MB). All reports that were considered as potentially relevant by at least one reviewer were acquired from library resources.

4.3.2 Relevant studies

The full reports of citations identified in the broad screening procedure were acquired, and two reviewers (VS and DH, or SC and MB) independently applied the selection criteria to select the relevant articles to be included in the review.

4.3.3 Assessment of quality

Two reviewers (VS and SC) independently scored the quality of the included trial reports using a five-point scale described by Jadad (Appendix 4). Zero to two points were assigned for each of appropriateness of randomization and double blinding, and zero to one point was assigned for reporting on withdrawals and dropouts. Lower scores (≤2) were associated with exaggerated estimates of benefit. Concealment of allocation to treatment was also categorized as adequate, inadequate, or unclear. Studies that reported inadequate methods for the patient allocation sequence, or were unclear in doing so were associated with exaggerated estimates of benefit.[33]

4.3.4 Data extraction

Two reviewers (VS and SC, or SC and MB) independently abstracted data about the details of the study, participant characteristics, intervention details, and outcome measures from the included studies using a standard form (Appendix 5).

4.3.5 Statistical analysis

Data analyses were done using Cochrane Review Manager 4.1.1. For continuously distributed outcomes, weighted mean differences (MD) were calculated. For binary outcomes, pooled odds ratios (OR) were calculated. The precision of the results was expressed by 95% confidence intervals (CI) whenever possible. Data were analyzed according to the intention-to-treat principle (i.e., those who were randomized to treatment with or without receiving treatment) where possible. Data unsuitable for pooling were presented descriptively. The presence or absence of statistical heterogeneity for pooled outcomes was detected using a chi-square test procedure and a threshold of p=0.1.

4.3.6 Disagreement

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

5 RESULTS

5.1 Quantity and Quality of Selected Reports

From a total of 150 potentially relevant reports identified and screened for retrieval, 54 reports regarding 33 unique trials were included in this systematic review (Figure 3). Of the 33 trials, 26 were journal-published trials, one was a Food and Drug Administration (FDA) document, and six were conference abstracts (Appendix 6).

Of the 33 unique trials;

- 14 (42%) trials were published once as a full report[34-47]
- five (15%) trials were published once as abstract(s) or conference proceeding(s)[48-52]
- 10 (30%) trials were published as a full report, and as abstract(s) or conference proceeding(s) elsewhere[53-62]
- one was published as a full report in two journals with different first authors[63,64]
- one was published twice as an abstract by different first authors[65,66]
- one was published twice as a full report in different languages,[55,67] and as an abstract[68]
- one was published as a full report,[69] and as an abstract elsewhere;[70] it was combined with another trial[71,72] in two publications: one was a full report by Brusasco *et al.*;[73] the other one was an abstract by Friedman *et al.*[74]
- one was retrieved from an FDA document;[71,72] this trial was combined with a study by Donohue *et al.*[69] in two publications: one was a full report by Brusasco *et al.*;[73] the other one was an abstract by Friedman *et al.* [74]

Twenty-one (64%) studies were of higher quality (Jadad score ≥3), with three studies (9.7%) receiving the highest score (Jadad score=5). Twelve (36%) were of lower quality (Jadad score ≤2).

5.2 Trial Characteristics

Nine of the 33 studies were of crossover design,[45-49,53-55,57] and 24 were of parallel design.[34-44,50-52,56,58-65,69,71,72] Twenty studies compared salmeterol and placebo;[34,35,37,39-41,43,45,46,48-51,53,55-58,61,62] two compared salmeterol, ipratropium bromide, and placebo;[36,38] two compared salmeterol, tiotropium, and placebo;[69,71,72] one compared salmeterol and tiotropium;[52] five compared formoterol and placebo;[42,44,47,60,65] two compared formoterol, ipratropium bromide, and placebo;[59,63,64] and one compared formoterol and tiotropium.[54] Details of each study, including the design, quality assessment scores, participant characteristics, interventions, and outcomes are presented in Appendix 6.

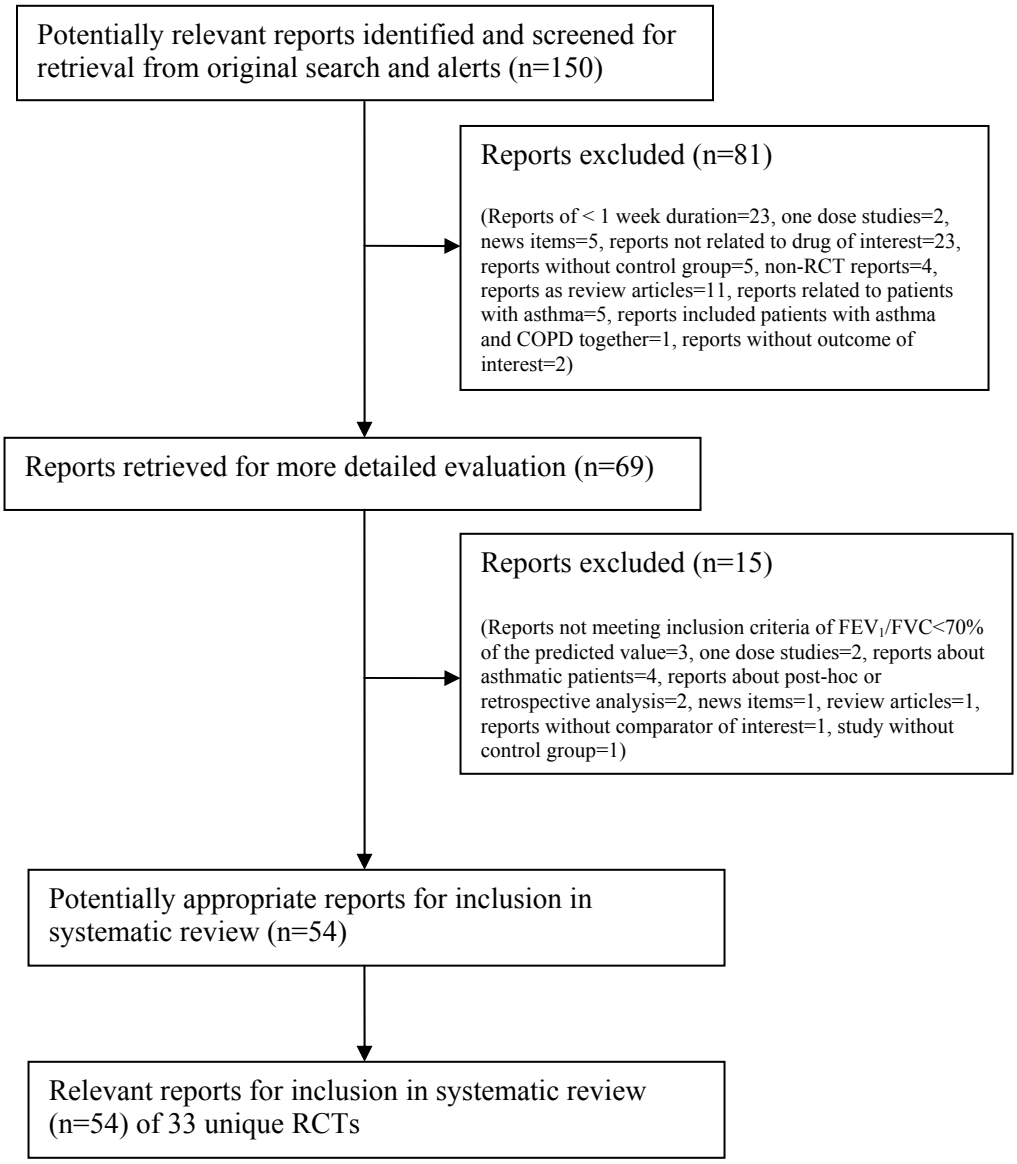
Of the 33 trials, eight adopted the ATS 1995 diagnostic criteria to define COPD;[36-38,41,43,58-60] one used the criteria from ATS 1987;[57] one adopted the criteria from ATS 1962;[39] one used criteria from ATS (year not specified);[52] three used criteria from the British Thoracic Society (BTS 1997),[40,45,47] one used the criteria from ATS 1995 and BTS 1997;[61] one used the criteria from the European Respiratory Society (ERS 1995);[63,64] and three trials used the criteria from the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guideline.[42,44,62] The diagnostic criteria for each are outlined in Appendix 7. The investigators of three reports defined patient population on the basis of clinical history, smoking habits, lung function and radiological examinations, without referring to any available guidelines.[35,46,49] The remaining reports did not specify their diagnostic criteria of COPD.

Similarly, a variety of definitions were used among the 33 studies to define the primary and secondary outcome measures.

- "Symptom-free days" was defined as number of days or nights without symptoms, percentage of nights without rescue medication use, percentage of days or nights with rescue medications use, night-time awakening changed from baseline, awakenings per week, or percentage of "bad" days.
- "Rescue salbutamol use" was measured by doses during day or night, puffs of salbutamol per week or day, or decrease of puffs per day from baseline.
- "Quality of life" was measured by SGRQ, CRDQ, or SF-36. Investigators reported the difference of quality of life scores, changed from baseline, end-point values of quality of life scores, or percentage of patients that gained a clinically meaningful improvement in quality of life outcome.
- "Improvement in dyspnea" was evaluated by patient self-rating daytime and night-time symptom scores (different definition provided by different authors), Borg scores, and TDI. Different measurements were used, including end-point values symptom scores, change in symptom scores from baseline, percentage of patients with better night-time symptom scores, or percentage of patients who gained a clinically meaningful improvement in TDI.
- "FEV_1" was presented as improvement from baseline (actual value or percentage of change), end-point values in the last visit, end-point values, or area under the curve (AUC) of FEV_1.
- "FVC" was presented as improvement from baseline (actual value or percentage of change), or AUC of FVC.
- "PEFR" was presented as improvement from baseline, or end-point values.
- "COPD exacerbation" was defined in eight ways based on the literature search.
- "URTI" was not clearly defined in the selected articles. When no data were provided for "patients with URTI," "patients need antibiotics," or "patients with candidosis in unspecified site, or throat infection, or hoarseness" were used to compute number of patients with URTI.

The definitions used for COPD exacerbations, URTIs, CRDQ scores, SGRQ scores, symptom-free days, and dyspnea are presented by study in Appendix 3.

Figure 3: Report screening and selection procedure



5.3 Data Analyses and Synthesis

The meta-analyses of long-acting β_2-agonists versus placebo, and long-acting β_2-agonists versus anticholinergics were performed for the outcomes of death, withdrawal due to an adverse event, exacerbation of COPD, URTI, hospitalization, and clinically meaningful improvements in SGRQ, CRDQ, and TDI. These meta-analyses are summarized in Tables 4 and 5; forest plots are presented in Appendices 8 to 13.

There were either insufficient data, or a lack of uniformity in the reporting of the data available, to perform meta-analyses for the outcomes of symptom-free days, rescue bronchodilator use, distance covered in walk tests, quality of life measures (other than SGRQ and CRDQ), dyspnea measures (other than TDI), and the lung function measures of FEV_1, FVC, and PEFR. Comparative data for these outcomes are presented by study in Appendix 14.

5.3.1 Incidence of death

The meta-analysis of data on the incidence of death comparing long-acting β_2-agonists and placebo (Table 4) is presented as a forest plot in Appendix 8. The comparisons between long-acting β_2-agonists and anticholinergics appear in Table 5.

a) Long-acting β_2-agonists versus placebo

Salmeterol versus placebo
A meta-analysis of data from 11 studies with 3,520 patients showed no significant difference between salmeterol and placebo in the incidence of death [OR 0.68 (95% CI: 0.27; 1.72)].[36,38-41,43,56,61,62,69,71,72]

Formoterol versus placebo
A meta-analysis of data from four studies with 2,148 patients showed no significant difference between formoterol and placebo in the incidence of death [OR 1.54 (95% CI: 0.79; 3.02)].[42,44,59,60]

Long-acting β_2-agonists as a group versus placebo
A pooled analysis of data from 15 studies with 5,668 patients showed no significant difference between long-acting β_2-agonists and placebo in the incidence of death [OR 1.16 (95% CI: 0.68; 1.98)].[36,38-44,56,59-62,69,71,72]

Table 4: Long-acting β_2-agonists versus placebo for COPD: summary of meta-analyses

Outcome Measure	Trials Reporting Outcome (% Of All Trials)	Participants Randomized (% Of All Trial Participants)	OR (95% CI)	OR P Value
Salmeterol versus placebo: 24 trials[34-41,43,45,46,48-51,53,55-58,61,62,69,71,72] with 6,548 patients				
Death	11 (46%)	3,520 (54%)	0.68 (0.27; 1.72)	0.42
Withdrawal due to AE	7 (29%)	2,786 (43%)	0.83 (0.65; 1.04)	0.11
Exacerbation of COPD	9 (38%)	3,210 (49%)	0.74 (0.62; 0.88)	0.0009
URTI	4 (17%)	1,722 (26%)	1.02 (0.71; 1.46)	0.93
Hospitalization	2 (8%)	805 (12%)	0.98 (0.52; 1.86)	0.96
Improvement* in SGRQ	2 (8%)	805 (12%)	1.18 (0.73; 1.93)	0.50
Improvement* in CRDQ	2 (8%)	545 (8%)	1.71 (1.21; 2.42)	0.002
Improvement* in TDI	2 (8%)	736 (11%)	1.70 (1.25; 2.31)	0.0008
Formoterol versus placebo: 7 trials[42,44,47,59,60,63-65] with 4,126 patients				
Death	4 (57%)	2,148 (52%)	**1.54 (0.79; 3.02)**	0.21
Withdrawal due to AE	5 (71%)	2,269 (55%)	0.91 (0.70; 1.18)	0.46
Exacerbation of COPD	3 (43%)	1,352 (33%)	0.76 (0.56; 1.02)	0.07
URTI	2 (29%)	1,231 (30%)	1.13 (0.76; 1.68)	0.55
Hospitalization	2 (29%)	1,231 (30%)	0.39 (0.21; 0.73)	0.003
Improvement* in SGRQ	-	-	-	-
Improvement* in CRDQ	-	-	-	-
Improvement* in TDI	-	-	-	-
Long-acting β_2-agonists versus placebo: 31 trials[34-51,53,55-65,69,71,72] with 10,674 patients				
Death	15 (48%)	5,668 (53%)	1.16 (0.68; 1.98)	0.58
Withdrawal due to AE	12 (39%)	5,055 (47%)	0.86 (0.72; 1.02)	0.09
Exacerbation of COPD	12 (39%)	4,562 (43%)	0.74 (0.64; 0.87)	0.0002
URTI	6 (19%)	2,953 (28%)	1.07 (0.82; 1.39)	0.64
Hospitalization	4 (13%)	2,036 (19%)	0.62 (0.40; 0.96)	0.03
Improvement* in SGRQ	2 (6%)	805 (8%)	1.18 (0.73; 1.93)	0.50
Improvement* in CRDQ	2 (6%)	545 (5%)	1.71 (1.21; 2.42)	0.002
Improvement* in TDI	2 (6%)	736 (7%)	1.70 (1.25; 2.31)	0.0008

*Clinically meaningful improvement. OR=odds ratio, CI=confidence interval, AE=adverse event, COPD=chronic obstructive pulmonary disease, URTI=upper respiratory tract infection, SGRQ=St. George's Respiratory Questionnaire, CRDQ=Chronic Respiratory Disease Questionnaire, TDI=Transitional Dyspnea Index.

Table 5: Long-acting β_2-agonists versus anticholinergics for COPD: summary of meta-analyses

Outcome Measure	Trials Reporting Outcome (% of all trials)	Participants Randomized (% of all trial participants)	OR (95% CI)	OR p Value
Salmeterol versus tiotropium: 3 trials[52,69,71,72] with 1,860 patients				
Death	2 (67%)	807 (43%)	4.36 (0.73, 25.93)	0.11
Withdrawal due to AE	2 (67%)	807 (43%)	2.16 (1.36, 3.43)	0.001
Exacerbation of COPD	2 (67%)	807 (43%)	1.08 (0.81, 1.44)	0.61
URTI	NR	NR	NR	NR
Hospitalization	NR	NR	NR	NR
Improvement* in SGRQ	2 (67%)	807 (43%)	0.79 (0.60, 1.05)	0.10
Improvement* in CRDQ	NR	NR	NR	NR
Improvement* in TDI	2 (67%)	747 (40%)	0.90 (0.68, 1.21)	0.50
Salmeterol versus ipratropium: 2 trials[36,38] with 816 patients				
Death	2 (100%)	538 (66%)	Not estimable	NR
Withdrawal due to AE	2 (100%)	538 (66%)	0.45 (0.07, 2.95)	0.40
Exacerbations of COPD	2 (100%)	538 (66%)	0.81 (0.56, 1.19)	0.29
URTI	1 (50%)	268 (33%)	1.05 (0.52, 2.14)	0.89
Hospitalization	NR	NR	NR	NR
Improvement* in SGRQ	NR	NR	NR	NR
Improvement* in CRDQ	2 (100%)	538 (66%)	1.27 (0.90, 1.79)	0.17
Improvement* in TDI	NR	NR	NR	NR
Formoterol versus tiotropium: 1 trial[54] with 74 patients				
Death	NR	NR	NR	NR
Withdrawal due to AE	NR	NR	NR	NR
Exacerbation of COPD	NR	NR	NR	NR
URTI	NR	NR	NR	NR
Hospitalization	NR	NR	NR	NR
Improvement* in SGRQ	NR	NR	NR	NR
Improvement* in CRDQ	NR	NR	NR	NR
Improvement* in TDI	NR	NR	NR	NR
Formoterol versus ipratropium: 2 trials[59,63,64] with 963 patients				
Death	1 (50%)	580 (60%)	Not estimable	NR
Withdrawal due to AE	2 (100%)	703 (73%)	1.84 (0.64; 5.31)	0.26
Exacerbation of COPD	2 (100%)	703 (73%)	0.78 (0.44; 1.37)	0.39
URTI	1 (50%)	580 (60%)	0.96 (0.58; 1.59)	0.88
Hospitalization	NR	NR	NR	NR
Improvement* in SGRQ	NR	NR	NR	NR
Improvement* in CRDQ	NR	NR	NR	NR
Improvement* in TDI	NR	NR	NR	NR
Long-acting β_2-agonists versus anticholinergics: 8 trials[36,38,52,54,59,63,64,69,71,72] with 3,713 patients				
Death	5 (63%)	1,925 (52%)	4.36 (0.73; 25.93)	0.11
Withdrawal due to AE	6 (75%)	2,048 (55%)	1.53 (0.88; 2.64)	0.13

Outcome Measure	Trials Reporting Outcome (% of all trials)	Participants Randomized (% of all trial participants)	OR (95% CI)	OR p Value
Exacerbation of COPD	6 (75%)	2,048 (55%)	0.94 (0.76; 1.17)	0.59
Hospitalization	NR	NR	NR	NR
URTI	2 (25%)	848 (23%)	0.99 (0.66; 1.49)	0.97
Improvement* in SGRQ	2 (25%)	807 (22%)	0.79 (0.60; 1.05)	0.10
Improvement* in CRDQ	2 (25%)	538 (14%)	1.27 (0.90; 1.79)	0.17
Improvement* in TDI	2 (25%)	747 (20%)	0.90 (0.68; 1.21)	0.50

* Clinically meaningful improvement, OR=odds ratio, CI=confidence interval, AE=adverse event, COPD=chronic obstructive pulmonary disease, URTI=upper respiratory tract infection, SGRQ=St. George's Respiratory Questionnaire, CRDQ=Chronic Respiratory Disease Questionnaire, TDI=Transitional Dyspnea Index, NR=not reported.

b) Long-acting β_2-agonists versus anticholinergics

Salmeterol versus ipratropium
No deaths were reported in two studies comparing salmeterol and ipratropium.[36,38]

Salmeterol versus tiotropium
A meta-analysis of data from two studies did not show a significant difference in the incidence of death when salmeterol groups were compared with tiotropium groups [OR 4.36 (95% CI: 0.73; 25.93)].[69,71,72]

Formoterol versus ipratropium
One study by Dahl reported no deaths in formoterol and ipratropium groups.[75]

Formoterol and tiotropium
No data were available on death as an outcome.

5.3.2 Patients withdrawn due to adverse events

The meta-analysis of data on the number of patients who withdrew because of adverse events when long-acting β_2-agonists are compared with placebo is shown in Table 4; comparisons between long-acting β_2-agonists and anticholinergics in Table 5. These data are presented as forest plots in Appendices 9 and 10 respectively.

a) Long-acting β_2-agonists versus placebo

Salmeterol versus placebo
A meta-analysis of data from seven studies with 2,786 patients did not show a significant difference between salmeterol and placebo in the number of patients who withdrew because of adverse events [OR 0.83 (95% CI: 0.65; 1.04)].[36,38,41,43,61,69,71,72]

Formoterol versus placebo
A meta-analysis of data from five studies with 2,269 patients showed no significant difference between formoterol and placebo groups in the number of patients who withdrew because of adverse events [OR 0.91 (95% CI: 0.70; 1.18)].[42,44,59,60,63]

Long-acting β_2-agonist as group versus placebo
A meta-analysis of data from 12 studies with 5,055 patients showed no significant difference in the number of patient withdrawals due to adverse events from the long-acting β_2-agonists group compared with the placebo group [OR 0.86 (95% CI: 0.72; 1.02)].[36,38,41-44,59-61,63,69,71,72]

b) Long-acting β_2-agonists versus anticholinergics

Salmeterol versus ipratropium
A meta-analysis of data on the number of patients who withdrew because of adverse events from two studies with 538 patients showed no significant difference between salmeterol and ipratropium [OR 0.45 (95% CI: 0.07; 2.95)].[36,38]

Salmeterol versus tiotropium
A meta-analysis of data from two studies with 807 patients showed a significantly higher number of patients who withdrew from the salmeterol group because of adverse events compared with the tiotropium group [OR 2.16 (95% CI: 1.36; 3.43)].[69,71,72]

Formoterol versus ipratropium
A meta-analysis of the data from two studies with 703 patients showed no significant difference in the number of patients who withdrew from the formoterol group because of adverse events compared with the ipratropium group [OR 1.84 (95% CI: 0.64; 5.31)].[59,63]

Formoterol versus tiotropium
There were no data available on the number of patients who withdrew because of adverse events.

Long-acting β_2-agonists as a group versus anticholinergics as a group
A meta-analysis of data from six studies with 2,048 patients showed no significant difference in the number of patients who withdrew because of adverse events when the long-acting β_2-agonists group was compared with the anticholinergics group [OR 1.53 (95% CI: 0.88; 2.64)].[36,38,59,63,69,71,72]

5.3.3 Patients with exacerbations of COPD

The meta-analysis of data on the number of patients with exacerbations when long-acting β_2-agonists were compared with placebo appears in Table 4; comparisons between long-acting β_2-agonists and anticholinergics are shown in Table 5. These data are presented as forest plots in Appendices 11 and 12 respectively.

a) Long-acting β_2-agonists versus placebo

Salmeterol versus placebo
A meta-analysis of data on the number of patients with exacerbations from nine studies with 3,210 patients showed a significant reduction in the number of patients with exacerbations in the salmeterol group compared with the placebo group [OR 0.74 (95% CI: 0.62; 0.88)].[36,38,41,56,58,61,62,69,71,72]

Formoterol versus placebo
A meta-analysis of data from three studies with 1,352 patients showed no significant difference between formoterol and placebo in the number of patients with exacerbations [OR 0.76 (95% CI: 0.56; 1.02)].[59,60,63]

Long-acting β_2-agonists as a group versus placebo
A meta-analysis of data from 12 studies with 4,562 patients compared long-acting β_2-agonists and placebo.[36,38,41,56,58-63,69,71,72] Treatment with long-acting β_2-agonists reduced the number of patients with exacerbations [OR 0.74 (95% CI: 0.64; 0.87)].

b) Long-acting β_2-agonists versus anticholinergics

Salmeterol versus ipratropium
A meta-analysis of data from two studies with 538 patients showed no significant difference between salmeterol and ipratropium in the number of patients with exacerbations [OR 0.81 (95% CI: 0.56; 1.19)].[36,38]

Salmeterol versus tiotropium
A meta-analysis of data from two studies with 807 patients showed no significant difference between salmeterol and tiotropium in the number of patients with exacerbations [OR 1.08 (95% CI: 0.81; 1.44)].[69,71,72]

Formoterol versus ipratropium
A meta-analysis of data from two studies with 703 patients showed no significant difference between formoterol and ipratropium in the number of patients with exacerbations [OR 0.78 (95% CI: 0.44; 1.37)].[59,63]

Formoterol and tiotropium
The study by van Noord *et al*. reported that four (5.7%) patients in the tiotropium group and 14 (20.3%) patients in the formoterol group had COPD exacerbation. The 95% CI or p value was not reported for these findings.[54]

Long-acting β_2-agonists as a group versus anticholinergics as a group
A meta-analysis of data from six trials with 2,048 patients showed no significant difference between β_2-agonists and anticholinergics in the number of patients with exacerbation [OR 0.94 (95% CI: 0.76; 1.17)]. [36,38,59,63,69,71,72] Data that were unsuitable for pooling, from a small study, indicated that tiotropium led to fewer COPD exacerbations than formoterol.[54]

5.3.4 Incidence of URTI

The meta-analysis of data on the number of patients with URTIs when long-acting β_2-agonists were compared with placebo appears in Table 4; these data are presented as a forest plot in Appendix 13. Comparisons between long-acting β_2-agonists and anticholinergics are shown in Table 5.

a) Long-acting β_2-agonists versus placebo

Salmeterol versus placebo
A meta-analysis of data from four studies with 1,722 patients showed no significant difference between salmeterol and placebo in the incidence of URTI [OR 1.02 (95% CI: 0.71; 1.46)].[36,41,43,61]

Formoterol versus placebo
A meta-analysis of data from two studies with 1,231 patients showed no significant difference between formoterol and placebo in the incidence of URTI [OR 1.13 (95% CI: 0.76; 1.68)].[59,60]

Long-acting β_2-agonists as a group versus placebo
A meta-analysis of data from six studies with 2,953 patients showed no significant difference between long-acting β_2-agonists and placebo in the incidence of URTI [OR 1.07 (95% CI: 0.82; 1.39)].[36,41,43,59-61]

b) Long-acting β_2-agonists versus anticholinergics

Salmeterol versus ipratropium
One study found no significant difference between salmeterol and ipratropium in the incidence of URTI [OR 1.05 (95% CI: 0.52; 2.14)].[36]

Salmeterol versus tiotropium
No data were available on the incidence of URTI from any of the studies comparing salmeterol with tiotropium.

Formoterol versus ipratropium
One study found no significant difference between formoterol and ipratropium in the incidence of URTI [OR 0.96 (95% CI: 0.58; 1.59)].[59]

Formoterol versus tiotropium
No data were available on the incidence of URTI from any of the studies comparing formoterol with tiotropium.

5.3.5 Incidence of hospitalization

The meta-analysis of data on the number of patients who were hospitalized when long-acting β_2-agonists were compared with placebo appears in Table 4; comparisons between long-acting β_2-agonists and anticholinergics are shown in Table 5.

a) Long-acting β_2-agonists versus placebo

Salmeterol versus placebo
Two studies found no significant difference in the incidence of hospitalization between salmeterol and placebo groups [OR 0.98 (95% CI: 0.52; 1.86)].[69,72]

Formoterol versus placebo
A meta-analysis of data from two studies showed a significant reduction in the hospitalization incidence with formoterol compared with placebo [OR 0.39 (95% CI: 0.21; 0.73)].[59,60]

Long-acting β_2-agonists as a group versus placebo
Four studies comparing long-acting β_2-agonists and placebo showed that long-acting β_2-agonists significantly reduced the hospitalization incidence [OR 0.62 (95% CI: 0.40; 0.96)].[59,60,69,72]

b) Long-acting β_2-agonists versus anticholinergics
No data were available comparing long-acting β_2-agonists with anticholinergics for this outcome measure.

5.3.6 Symptom-free days and nights

There was no uniform standard of data reporting on symptom-free days, hence a meta-analysis could not be performed for this outcome measure. Comparative data by study are presented in Appendix 14.

a) Long-acting β_2-agonists versus placebo

Salmeterol versus placebo
A study by Mahler reported a significant increase in the mean percentage of days without rescue albuterol (also known as salbutamol) use, and the mean percentage of nights with no awakening requiring salbutamol, in the salmeterol group compared with the placebo group.[41] The Rennard study observed no significant difference between salmeterol and placebo groups in the mean number of night-time awakenings over the treatment period.[38] van Noord reported a significant decrease in the mean percentage of days with the additional use of a salbutamol inhaler in the salmeterol group compared with the placebo group.[58] The Calverley study reported no significant difference between salmeterol and placebo in the mean number of awakenings per week.[61] One crossover trial published as an abstract reported a significant improvement (p=0.029) in night-time symptoms with salmeterol (28% of patients) versus placebo (6% of patients), and in the median percentage of nights without the use of rescue salbutamol (48% for salmeterol versus 37% for placebo, p=0.012).[48]

Formoterol versus placebo
A study by Rossi reported that the median percentage of days without the use of rescue medication was significantly higher in the formoterol 12 µg and 24 µg groups compared with the placebo group.[60] One study, published as a conference abstract by Eliraz, reported a significantly higher percentage of rescue reliever-free days in the formoterol group compared with the placebo group.[65] A study by Dahl reported that patients in the formoterol 12 µg and 24 µg groups had fewer "bad" days compared with the placebo group, although data were not shown.[76]

b) Long-acting β_2-agonists versus anticholinergics

Salmeterol versus ipratropium bromide
A study by Rennard reported no significant difference between salmeterol and ipratropium groups in the mean number of night-time awakenings over the treatment period.[38]

Formoterol versus ipratropium bromide
A study by Dahl reported a significantly lower percentage of "bad" days in formoterol 12 μg and 24 μg groups, compared with the ipratropium bromide group.[76]

Salmeterol versus tiotropium
Data on symptom-free days were not reported in any of the included studies.

Formoterol versus tiotropium
Data on symptom-free days were not reported in any of the included studies.

5.3.7 Rescue inhaler use

Data available from different studies on rescue inhaler use did not have a uniform standard of reporting, and hence a meta-analysis on this outcome measure was impossible. Comparative data by study are presented in Appendix 14.

a) Long-acting β_2-agonists versus placebo

Salmeterol versus placebo
Twelve studies reported a decreased use of rescue inhalers in the salmeterol group compared with the placebo group.[36,38,40,41,48,55-57,61,62,69,71,72]

Formoterol versus placebo
Four studies reported a decreased use of rescue inhaler in the formoterol group compared with the placebo group.[42,59,60,63] One study by Smith *et al*. did not find a significant difference between the two groups [mean difference(MD) −0.17, (95% CI: −0.45; 0.11)].[47]

b) Long-acting β_2-agonists versus anticholinergics

Salmeterol versus ipratropium
One study by Mahler and one by Rennard reported no difference between salmeterol and ipratropium in decreasing the use of rescue salbutamol.[36,38]

Formoterol versus ipratropium
A study by Dahl reported that formoterol at 12 μg and 24 μg doses significantly reduced the use of rescue medication compared with ipratropium.[75] A study by Wadbo reported no difference between formoterol and ipratropium in reducing relief consumption of short-acting β_2-agonists.[63]

Salmeterol versus tiotropium
Two studies reported information on the use of rescue salbutamol. A study by Briggs reported that more rescue medications were used in the tiotropium group than in the salmeterol group.[52] The FDA file also reported an increasing use of rescue inhaler in the tiotropium group after 24 weeks of treatment (0.13 puff per day increased from baseline), compared with a reduction in rescue inhaler use in the salmeterol group (0.26 puff per day decreased from baseline).[72]

Formoterol versus tiotropium
A study by van Noord reported no difference between formoterol and tiotropium in the mean number of daytime [tiotropium 2.41±0.14(SE), formoterol 2.37±0.14(SE)] and night-time rescue salbutamol inhalations [tiotropium 0.56±0.05(SE), formoterol 0.52±0.05(SE)].[54]

5.3.8 Distance covered in walk tests

Comparative data by study are presented in Appendix 14.

a) Long-acting β_2-agonists versus placebo

Salmeterol versus placebo
Four studies, without reporting any data, stated that there was no significant difference in the six-minute walk test between salmeterol and placebo groups.[36,38,48,56] In the study by Gupta, a MD of 31.56 metres (m) (95% CI: −46.35; 109.47) covered in the six-minute walk test was reported between salmeterol and placebo groups.[40] In a crossover study by Melani and Di Gregorio, the MD for the distance covered in a 12-minute walk was 41m (95% CI: −21.18; 103.18).[57]

Formoterol versus placebo
In a study by Wadbo, no significant change from baseline was observed between formoterol and placebo in the distance covered in the shuttle walking test [MD 14.10 m (95% CI: −8.51; 36.71)].[63] The study by Smith *et al*. did not find a significant difference between the two groups in the six-minute walk test [MD −3.54 m, (95% CI: −21.48; 14.40)].[47]

b) Long-acting β_2-agonists versus anticholinergics

Salmeterol versus ipratropium
One study by Mahler and one by Rennard observed no significant difference between salmeterol and ipratropium in the six-minute walk test.[36,38]

Formoterol versus ipratropium
In the study by Wadbo, no significant change from baseline was observed between formoterol and ipratropium in the shuttle walking test [MD 1.7 m (95% CI: −20.45; 23.85)].[63]

Salmeterol versus tiotropium
No data were available on this outcome.

Formoterol versus tiotropium
No data were available on this outcome.

5.3.9 Quality of life

The meta-analyses of data on quality of life as measured by the improvement in SGRQ and CRDQ are presented in Tables 4 and 5. Comparative data for all quality of life outcomes by study are presented in Appendix 14.

a) Long-acting β_2-agonists versus placebo

Salmeterol versus placebo
Four studies used SGRQ,[34,61,69,72] four studies used CRDQ,[36,38,41,43] and one study used SF-36 for the quality of life assessment.[40]

A meta-analysis of data on the number of patients with a clinically significant improvement in SGRQ scores (defined as a four-point improvement) using data from the Donohue study[69] and the FDA study[72] did not show any significant difference between salmeterol and placebo in terms of quality of life [OR 1.18 (95% CI: 0.73; 1.93)]. In the study by Donohue, the difference in SGRQ scores between salmeterol and placebo groups was −1.11.[69] In another study, Jones *et al*. observed a significant improvement from baseline in SGRQ scores with the salmeterol 50 µg twice daily dose [MD −5.4 (95% CI: −8.98; −1.82)], whereas no significant difference was observed with the salmeterol 100 µg twice daily dose [MD −0.90 (95% CI: −4.24; 2.44)], compared with placebo.[34] In the study by Calverley, a significant reduction from baseline in SGRQ scores was observed in the placebo group [MD −2.2 (95% CI: −3.3; −1.0)], while the reduction was not statistically different from the baseline for the salmeterol group.[61] Neither difference was clinically significant, as the score improvement was <4 points in both groups.

An improvement in CRDQ scores was observed in two studies.[36,38] In the study by Mahler, the MD in CRDQ scores between salmeterol and placebo was 5 (95% CI: 1.24; 8.76),[36] while Rennard reported a non-statistically significant difference [MD 3.5 (95% CI: −0.67; 7.67)].[38] In one study by Hanania and one by Mahler, the measure of dispersion around mean values for improvement in CRDQ scores was not reported; hence, the MD with 95% CI could not be calculated.[41,43] A meta-analysis of the data from these two studies was done using the number of patients with a clinically significant improvement in CRDQ scores (defined as a 10-point improvement). This analysis showed a significant improvement in quality of life with salmeterol compared with placebo [OR 1.71 (95% CI: 1.21; 2.42].[41,43]

In the study by Gupta, salmeterol showed significantly improved scores in the role physical domain [MD 23.53 (95% CI: 1.22; 45.84)]; and vitality, energy, and fatigue domain [MD 16.69 (95% CI: 6.39; 27)] of SF-36, compared with placebo.[40] In other domains of SF-36, no significant differences were observed between salmeterol and placebo.

Formoterol versus placebo
Six studies reported SGRQ score results as end-point scores or improvement in SGRQ scores from baseline.[42,44,59,60,63-65] In the study by Dahl, formoterol 12 µg twice daily produced a significant improvement in SGRQ scores [MD −5.10 (95% CI: −8.52; −1.68)], compared with placebo, while no improvement was observed with the 24 µg dose of formoterol [MD −3.30 (95% CI: −6.99; 0.39)].[59] In the study by Wadbo, the use of formoterol did not result in significant improvement in SGRQ scores, compared with placebo [MD −1.5 (95% CI: −4.69; 1.69)].[63] In the study by Rossi, a significant improvement was observed in SGRQ scores with formoterol 12 µg [MD −4.4 (95% CI: −7.87; −0.93)], but not with formoterol 24 µg [MD −3 (95% CI: −6.58; 0.58)], compared with placebo.[60] In other studies, the measure of dispersion was unavailable to calculate the MD with 95% CI.[42,44,65]

In a crossover study, Smith *et al*. reported no significant difference in the CRDQ-dyspnea score between formoterol and placebo [MD −0.02, (95% CI: −0.36; 0.32)]. [47]

b) Long-acting β_2-agonist versus anticholinergics

Salmeterol versus ipratropium
Pooled data from two studies showed no significant differences between salmeterol and ipratropium in either CRDQ scores [MD 0.8 (95% CI: −5.86; 4.26)] or number of patients with significant improvement in CRDQ scores [OR 1.27 (95% CI: 0.90; 1.79)] [36,38]

Formoterol versus ipratropium
Two studies reported data on SGRQ scores.[59,63] In the study by Dahl, formoterol 12 µg produced a significant improvement in SGRQ scores compared with ipratropium [MD −5.5 (95% CI: −8.96; −2.04)], whereas no significant difference was observed with formoterol 24 µg [MD −3.7 (95% CI: −7.43; 0.03)].[59] In the second study by Wadbo, no significant difference was observed between formoterol and ipratropium groups in the percent change in baseline SGRQ scores [MD 0.5 (95% CI: −2.68; 3.68)].[63]

Salmeterol versus tiotropium
One study reported no significant difference between salmeterol and tiotropium in SGRQ total score improvement (MD 1.6).[69] Another study reported no significant difference between salmeterol and tiotropium in SGRQ scores.[72] In the pooled analysis of data from two studies on the number of patients showing a four-point improvement in SGRQ scores, tiotropium did not show a significant advantage over salmeterol [OR 0.79 (95% CI: 0.60; 1.05)].[69,72]

Formoterol versus tiotropium
No data were available on this outcome.

5.3.10 Improvement in dyspnea

Pooled data on dyspnea, measured by improvement in TDI, are presented in Tables 4 and 5. Comparative data for all dyspnea outcomes by study are presented in Appendix 14.

a) Long-acting β_2-agonists versus placebo

Salmeterol versus placebo
Four studies reported daytime and night-time symptom scores or daily symptom scores.[55,56,58,61] In the study by van Noord, salmeterol improved daytime symptom scores compared with placebo [MD −0.3 (95% CI: −0.58; −0.02)], but it had no effect on night-time symptom scores [MD 0.10 (95% CI: −0.18; 0.38)].[58] Two studies reported a significant improvement in median daytime and night-time scores in the salmeterol group compared with the placebo group.[55,56]

Four studies used the Borg dyspnea scale for measuring dyspnea after the six-minute walk test.[35,38,48,53] In a crossover study by Grove, the median Borg scores were significantly lower (better) with salmeterol than with placebo.[53] In three other studies, no significant differences were observed between salmeterol and placebo groups in end-point Borg scale scores after the six-minute walk test.[35,38,48] Of these three studies, one study[35] provided enough data to calculate

the MD in Borg scores between salmeterol and placebo groups. This calculation showed no statistically significant difference [MD −0.3 (95% CI: −0.71; 0.11)]. Another study measured dyspnea after exercise using the modified Borg scale.[46] In this study by O'Donnell *et al*., the salmeterol use was associated with less dyspnea (Borg scale of 2.7±0.3 SEM) than placebo (Borg scale 3.6±0.4 SEM), although the difference did not reach statistical significance (p=0.07).

Five studies used TDI scores to assess dyspnea.[36,41,43,69,71,72] Studies by Malher and Hanania reported a significant improvement in TDI scores with salmeterol, compared with placebo.[36,43] A pooled analysis of the results from the Donohue study and the findings from a study available on the FDA's web site that assessed the number of patients with at least a one-point improvement in TDI (a clinically significant improvement), also showed that salmeterol is significantly better than placebo [OR 1.70 (95% CI: 1.25; 2.31)].[69,71,72]

In the study by Corisico, visual analogue scale (VAS) scores were used for measuring the level of dyspnea.[39] In this study, no significant difference was observed between salmeterol and placebo groups [MD −0.6, (95% CI: −3.16; 1.96)]. Finally, using a breathlessness score (0=none, 4=breathless at rest), Vestbo *et al*. reported that the odds of decreasing breathlessness was higher with salmeterol compared with placebo, after two weeks of treatment [OR 1.57 (95% CI: 1.17; 2.12)].[77]

Formoterol versus placebo

In the study by Calverley, the improvement in dyspnea was statistically significant in the formoterol group compared with the placebo group.[42] Formoterol at doses of 12 µg and 24 µg twice daily produced significant improvement in daily symptom scores compared with placebo in the study by Dahl,[75] whereas no such effect was observed in the study by Rossi.[60] In both studies, the data required to calculate the MD were not reported. A study by Wadbo[63] reported that formoterol produces a significant improvement in breathlessness, compared with placebo. No effect was observed on the Borg scale score after exercise.[63] Finally, Smith *et al*. reported no significant difference between formoterol and placebo in daytime symptoms [MD 0.03 (95% CI: −0.28; 0.35)] or night-time symptoms [MD −0.14 (95% CI: −0.33; 0.04)].[47]

b) Long-acting β_2-agonists versus anticholinergics

Salmeterol versus ipratropium

Results from two studies showed that salmeterol does not have a significant advantage over ipratropium in improving TDI scores[36] or Borg scores.[38]

Formoterol versus ipratropium

The study by Dahl reported formoterol 12 µg twice daily produced a significant improvement in daily symptom scores, compared with ipratropium.[59] In the same study, formoterol 24 µg twice daily did not significantly improve daily symptom scores. The study by Wadbo reported that formoterol produced no significant improvement in breathlessness and post-exercise Borg scale scores, compared with ipratropium.[63]

Salmeterol versus tiotropium
A pooled analysis of the number of patients with a one-point improvement in TDI scores from two studies showed that salmeterol did not have any significant advantage over tiotropium in improving the level of dyspnea [OR 0.90 (95% CI: 0.68; 1.21)].[69,72]

Formoterol versus tiotropium
No data were available on this outcome.

5.3.11 Effect on FEV_1

Because data available on FEV_1 from different studies did not have a uniform standard of reporting, it was impossible to pool data from all the studies identified in the systematic review. Detailed study-specific data are presented in Appendix 15. The ATS web site[78] indicates that a 50-mL improvement in FEV_1 is clinically important, although a similar result may not be statistically significant in a large sample study.

a) Long-acting β_2-agonists versus placebo

Salmeterol versus placebo
A meta-analysis of the findings from four studies, using a random effects model, showed a significant improvement in FEV_1 from baseline with salmeterol, compared with placebo [MD 82.88 mL (95% CI: 36.89; 128.86)].[41,43,56,79] Five studies reported FEV_1 data as end-point values.[35,37,39,40,61] A pooled analysis of data from these studies, using a random effects model, did not show a significant improvement in FEV_1 with salmeterol, compared with placebo [MD −0.84 (95% CI: −143.33; 141.65)]. Data from other studies were not pooled because of their crossover design and the lack of relevant data.

In a study by Vestbo *et al*.,[77] salmeterol was associated with a better improvement in FEV_1 compared with placebo at two weeks [MD 61 mL (95% CI: 28; 94)]. Furthermore, the median change in FEV_1 after the treatment was also reported at week 2 and week 52 in this study. After two weeks, the change in FEV_1 favoured salmeterol [median 60 mL, 25th to 75th percentile: −35, 180], as compared with placebo [median 0 mL, 25th to 75th percentile: −100, 100]. After 52 weeks, the difference in median change in FEV_1 still favoured salmeterol [median 0 mL, 25th to 75th percentile: −130, 140] over placebo [median −65 mL, 25th to 75th percentile: −200, 85]. In a study by O'Donnell *et al*., which assessed the effect of salmeterol after exercise,[46] improvement of the trough FEV_1 after treatment with salmeterol was better (1.17 L ±0.09 SEM) compared with placebo (1.03 L ±0.08 SEM), $p<0.01$.

Formoterol versus placebo
Seven studies[42,44,47,59,60,63-65] compared formoterol with placebo, using FEV_1 as the outcome measure. One study was published twice.[63,64] Although a meta-analysis was impossible, all the studies except one[47] reported that formoterol was significantly better than placebo in improving FEV_1. In the study by Smith *et al*., which assessed formoterol in poorly reversible disease, there was no significant difference between formoterol and placebo in the trough FEV_1 [MD 1.01% of predicted value (95% CI: −0.74; 2.75)].[47]

b) Long-acting β_2-agonists versus anticholinergics

Salmeterol versus ipratropium
Two studies reported no significant difference between salmeterol and ipratropium in improving FEV_1.[36,38]

Formoterol versus ipratropium
A study by Dahl reported that formoterol, used at a dose of 12 µg or 24 µg twice daily, produced a significant improvement in FEV_1, compared with ipratropium.[59] A study by Wadbo reported no significant difference between formoterol and ipratropium in improving FEV_1.[63]

Salmeterol versus tiotropium
A study by Donohue, comparing the effect of salmeterol and tiotropium on the trough FEV_1, reported a MD of −52 mL ±20 SEM, p=0.0088, in favour of tiotropium (the trough FEV_1 was measured 23 to 24 hours post-dose).[69] A study in the FDA file reported no significant difference in changes from baseline in the trough FEV_1 between the two comparison groups.[71] A study by Briggs *et al.* found a significant difference in FEV_1 $AUC_{0\text{-}12\ hr}$ of 37 mL (p=0.027) in favour of tiotropium.[52]

Formoterol versus tiotropium
One crossover study by van Noord[54] compared the effect of formoterol and tiotropium on FEV_1. They reported a 0.059 L ±0.02 SEM improvement in trough FEV_1 with formoterol, compared with 0.1 L ±0.02 SEM improvement with tiotropium (p<0.05).

5.3.12 Effect on FVC

Detailed results by study are presented in Appendix 15.

a) Long-acting β_2-agonists versus placebo

Salmeterol versus placebo
Twelve studies comparing salmeterol and placebo reported data on FVC.[36,38-40,45,46,49,53,57,58,61,69] A meta-analysis of data from three studies indicates that salmeterol produced a significant improvement in FVC compared with placebo [MD 84.89 mL (95% CI: 32.71; 137.08)].[39,40,61] Data from other studies were unsuitable for meta-analysis, because necessary information for the pooling of data was not reported. A study by Donohue reported a significant improvement in FVC with salmeterol compared with placebo [MD 134 mL ±39 SE].[69] Similar studies by Mahler and Rennard also reported a significant improvement in FVC with salmeterol compared with placebo.[36,38] In a crossover study evaluating salmeterol after exercise, O'Donnell *et al*. reported a better trough FVC in the salmeterol group (2.48 L ±0.12 SEM), compared with placebo (2.25 L ±0.12 SEM), p< 0.01.[46] A study by van Noord reported no significant difference between salmeterol and placebo in improving the FVC predicted [MD 3% (95% CI: −0.37; 6.37)].[58] Three crossover studies reported no significant difference between salmeterol and placebo in improving FVC.[49,53,57]

Formoterol versus placebo
Two studies reported data on FVC.[63,65] Data from these studies were unsuitable for meta-analysis, because the measure of dispersion with mean values was unavailable. Both studies reported that formoterol produced a significant improvement in FVC compared with placebo. Data were not reported in the study by Calverley and *et al.*, but a significant improvement in FVC was noted in the formoterol group compared with the placebo group.[42]

b) Long-acting β_2-agonists versus anticholinergics

Salmeterol versus ipratropium
Two studies reported no difference between salmeterol and ipratropium in improving FVC.[36,38]

Formoterol versus ipratropium
One study reported no significant difference between formoterol and ipratropium in improving FVC.[63]

Salmeterol versus tiotropium
Two studies reported that tiotropium provides a significant improvement in FVC compared with salmeterol.[52,69] In the Donohue study,[69] the difference in the trough FVC between salmeterol and tiotropium was 112 mL (p=0.003). In the Briggs study[52], the difference in FVC $AUC_{0\text{-}12hr}$ between tiotropium and sameterol was 101 mL (p=0.0028).

Formoterol versus tiotropium
One crossover study reported that the use of tiotropium was associated with a higher trough FVC (0.157 L ±0.03 SEM) compared with formoterol (0.083 L ±0.03 SEM), although the difference was not statistically significant (p=0.054).[54]

5.3.13 Effect on PEFR

Detailed results by study are presented in Appendix 15.

a) Long-acting β_2-agonists versus placebo

Salmeterol versus placebo
Four parallel-design studies and four crossover studies reported data on PEFR.[46,49,55,57,58,62,69,77] A study by Dal Negro reported that salmeterol produces a significant improvement in PEFR compared with placebo [MD 13.3 L/min (95% CI: 3.1; 23.5)].[62] A study by van Noord reported no significant difference between salmeterol and placebo in improving morning [MD 26 L/min (95% CI: −2; 54)] and evening [MD 18 L/min (95% CI: −11; 47)] PEFR.[58] A study by Donohue reported a significant improvement in PEFR from baseline with salmeterol compared with placebo.[69] The study by Vestbo *et al*. reported a significant improvement in PEFR with salmeterol over placebo [MD 16 L/min (95% CI: 11; 21)] after two weeks of treatment. This difference was maintained over 52 weeks [MD 15 L/min (95% CI: 10; 20)].[77] In the study by O'Donnell *et al*., which assessed the effect of salmeterol after exercise, authors reported better PEFR in the salmeterol group (3.75 L/s ±0.2 SEM) compared with the placebo group (3.35 L/s ±0.23 SEM), p<0.01.[46] One crossover trial by Ulrik reported salmeterol (50 µg twice daily) produced a significant improvement in morning PEFR, compared with placebo, without showing

a significant effect on evening PEFR.[55] Another crossover trial by Broseghini reported a significant improvement in PEFR with the salmeterol 100 µg twice daily dose, while no such effect was observed with the 50 µg twice daily dose.[49] One crossover trial by Melani reported that salmeterol has no significant improvement in morning and evening PEFR, compared with placebo.[57]

Formoterol versus placebo
Five studies comparing formoterol with placebo used PEFR as an outcome measure.[42,44,60,63,65] A study by Calverley reported that formoterol was associated with a significantly higher morning and evening PEFR, compared with placebo.[42]A study by Rossi,[60] comparing formoterol with placebo, reported that formoterol 12 µg twice daily produces a significant improvement in PEFR [MD 26 L/min (95% CI: 6.45; 45.55)]. Similar results were reported when used at 24 µg twice daily [MD 27 L/min (95% CI: 7.42; 46.58)].[60] A study by Wadbo reported that formoterol produces a significant increase from baseline in morning PEFR [MD 16.2 L/min (95% CI: 8; 24)] and evening PEFR [MD 14.3 L/min (95% CI: 6; 23)], compared with placebo.[63] Two other studies reported data on PEFR, but SDs were not reported.[44,65] Of these two studies, Eliraz *et al*. reported that formoterol produces a significant improvement in PEFR compared with placebo.[65] In the second study by Szafranski, no statement was made about the comparative efficacy of formoterol and placebo.[44]

b) Long-acting β_2-agonists versus anticholinergics

Salmeterol versus ipratropium
No data are available on this outcome.

Formoterol versus ipratropium
One study reported a significant increase from baseline in morning PEFR with formoterol compared with ipratropium [MD 8.2 L/min (95% CI: 0.5; 15.8)].[64]

Salmeterol versus tiotropium
One study reported that tiotropium was superior to salmeterol in improving evening PEFR.[69] A study in the FDA file reported no significant difference in morning or evening PEFR between the two comparison groups, without providing data.[72]

Formoterol versus tiotropium
The study by van Noord *et al*. reported no significant difference between formoterol and tiotropium, on morning [tiotropium 262 L/min ±2.6 (SE), formoterol 259L/min ±2.6 (SE)] or evening [tiotropium 274 L/min ±2.8 (SE), formoterol 266 L/min ±2.8 (SE)].[54]

6 DISCUSSION

6.1 Assessment of Clinical Effectiveness

6.1.1 Salmeterol

Salmeterol was compared with placebo in 24 trials,[34-41,43,45,46,48-51,53,55-58,61,62,69,71,72] compared with ipratropium in two trials,[36,38] and compared with tiotropium in three trials.[52,69,71,72] Compared with placebo, salmeterol produced a significant reduction in COPD exacerbations (pooled analysis of nine trials) and improved dyspnea measured by TDI (pooled analysis of two trials). Although salmeterol improved the quality of life when measured by CRDQ, a pooled estimate indicates that it did not when measured by SGRQ. Contradictory results were reported in studies using other quality of life instruments. No significant differences were observed between salmeterol and placebo in the incidence of death (pooled analysis of 11 trials), in patient withdrawal due to adverse events (pooled analysis of seven trials), in the incidence of hospitalization (pooled analysis of two trials), and in the incidence of URTI (pooled analysis of four trials). For the outcome measures of symptom-free days, rescue medication use, distance covered in walk tests, improvement in dyspnea, FVC, and PEFR, pooling was impossible because of the lack of a uniform standard of reporting or non-availability of data of interest. Despite some inconsistency in study findings, most of these trials indicate that salmeterol produces a significant improvement in symptom-free days, rescue medication use, dyspnea, FVC, and PEFR, compared with placebo. Although the pooled estimates of the effect of salmeterol on FEV_1 are inconsistent, depending on the type of measurement, most trials report an improved FEV_1 with salmeterol, compared with placebo. No significant improvement is observed in the distance covered in the walk test in any of the studies (eight trials).

Comparing salmeterol with ipratropium did not reveal any significant differences in any of the outcome measures assessed. Compared with tiotropium, salmeterol did not show any significant difference in mortality, COPD exacerbations, quality of life, or dyspnea. For the outcome of rescue inhaler use, two studies indicated that salmeterol is better than tiotropium, but no p values were available. For PEFR, two studies had contradictory results. Two of three studies indicated that tiotropium is better than salmeterol for improving FEV_1. Two studies reported that tiotropium was significantly better than salmeterol in improving FVC. Compared to tiotropium, significantly more patients using salmeterol withdrew from their treatment group because of adverse events, although such findings were based on two RCTs with a total of 807 patients.

6.1.2 Formoterol

Formoterol was compared with placebo in seven trials,[42,44,47,59,60,63-65] with ipratropium in two trials[59,63,64] and with tiotropium in one trial.[54] Compared with placebo, formoterol reduces hospitalization (pooled analysis of two trials). Most studies indicated that formoterol significantly increases the number of symptom-free days and nights, improves FEV_1, FVC, and PEFR; and reduces the use of a rescue inhaler. Inconsistent results were found regarding to the effect of formoterol on quality of life and dyspnea, compared with placebo. No significant differences were observed between formoterol and placebo for the outcome measures of

incidence of death, number of study participants who withdrew because of adverse events, number of patients with COPD exacerbations, incidence of URTI, and distance covered during a walk test.

Compared with ipratropium, formoterol did not show any significant or consistent differences in most of the outcome measures assessed, with the possible exception of better improvement in symptom-free days and PEFR, although such evidence was scarce. One study compared formoterol and tiotropium.[54] In this study, tiotropium was better than formoterol in improving COPD exacerbations, trough FEV_1, and FVC, although no p value was reported for disease exacerbations, and results did not reach statistical significance for FVC. No difference was observed between formoterol and tiotropium in the use of rescue short-acting bronchodilators and PEFR.

6.1.3 Long-acting β_2-agonists as a group

Compared with placebo, long-acting β_2-agonists reduced the number of patients with COPD who experienced exacerbations and hospitalizations. The evidence indicated that reduction of disease exacerbation was mainly driven by salmeterol studies, while formoterol studies showed the decrease in hospitalizations. Long-acting β_2-agonists have yet to demonstrate an impact on mortality, the incidence of URTIs, and exercise tolerance as measured with walk tests. Although some inconsistency was observed, most studies indicated that long-acting β_2-agonists may be better than placebo in improving symptom-free days, dyspnea, and spirometric testing results; and reducing the use of rescue inhalers. Considering the ways that this outcome was measured in the included studies, we concluded that the effect of long-acting β_2-agonists on quality of life was inconsistent.

Long-acting β_2-agonists did not demonstrate a significant advantage over either of the two available anticholinergic agents in any of the functional outcome measures that were pooled in the meta-analysis. Data that were unsuitable for pooling indicated differences in symptom control: one trial showed a significant advantage of formoterol over ipratropium in augmenting the number of symptom-free days. Unpooled data also indicated better improvement in some spirometric tests with tiotropium compared with salmeterol and formoterol, although such evidence was scarce.

6.2 Study Limitations

Fifty-four reports describing 33 unique clinical trials met the inclusion criteria for this systematic review. Duplicate publications, and lack of a uniform standard of reporting were common in the selected studies. Of the included RCTs, 14 (42%) had multiple publications, and seven duplicate publications (21%) had a different primary author. These studies measured subjective and objective outcomes. Data on outcome measures such as rescue salbutamol use and FEV_1 were reported in three ways, while data on symptom-free days were reported in six ways. Because of a lack of a uniform standard of reporting for many outcome measures, the pooling of data was impossible, and the best evidence synthesis approach was used in such cases.[80] When enough data were available for pooling for an outcome measure, a meta-analysis of the data was performed.

When conducting a systematic review, it is necessary to investigate possible publication and language biases, and to assess trial quality and heterogeneity. This review sought to minimize selection bias by systematically reviewing all published and unpublished RCTs without imposing language restrictions on the literature retrieval, and with the use of two independent reviewers. This review included all RCTs meeting the inclusion criteria irrespective of their quality. Overall, 21 trials were judged to be of higher quality (Jadad score ≥3), while 12 were of lower quality (Jadad scale ≤2).

Clinical heterogeneity was a problem, as several included trials used different definitions of COPD for patient selection, different durations of run-in period, and different observation periods (one week to one year). There were also differences among included studies regarding the use of other medications permitted during the trial (Appendix 6 shows study characteristics). In the van Noord study, patients on minimal dose of oral corticosteroids were enrolled, contrary to our inclusion criteria of only accepting COPD patients on inhaled steroids. That study was included because two out of 71 patients were using oral steroids at study entry, and the dose used was within the physiological range, i.e., <10 mg of prednisone per day. Conflicting and contradictory study results for outcome measures, such as the use of rescue inhalers, changes in quality of life, and change in FEV_1, may be related to clinical heterogeneity in the included RCTs.

6.3 Comparison of Results with Other Systematic Reviews

After a search of the literature from 1992 onward, one systematic review published by Sin *et al.* in 2003 was identified in which long-acting β_2-agonists were compared with placebo in patients with COPD.[81] In the review, which was similar to this one, Sin *et al*. included patients with COPD with or without reversibility. The results of Sin's systematic review were comparable with those of this systematic review.[81] In this systematic review, 33 unique trials met the inclusion criteria, of which 31 compared a long-acting β_2-agonist to placebo, whereas nine studies were included in the systematic review by Sin *et al.* Except for two studies that did not meet the inclusion criteria for this review,[82,83] all the studies included in the Sin review were also included in this review. This difference may be related to the period of the literature search, and stricter inclusion criteria. Studies up to May 2002 were included in Sin's review, whereas this review included studies up to December 2005. Similar to this review, Sin's review showed that, compared with placebo, long-acting β_2-agonists significantly reduced the COPD exacerbation rate. Contrary to this review, however, Sin's review reported no significant improvement in FEV_1 with long-acting β_2-agonists: FEV_1 improvement from baseline was 82 mL (95% CI: −26; 190) in the Sin review versus 82.88 mL (95% CI: 36.89; 128.86) in this review. This difference in FEV_1 may be related to the smaller number of included studies (n=2) in Sin's meta-analysis compared with the number of studies (n=4) used in this meta-analysis.

The differences between this review and the 2002 CCOHTA review of COPD in non-reversible patients were related to the results of outcomes such as disease exacerbations. In non-reversible COPD patients (i.e., those included in the 2002 review), long-acting β_2-agonists did not show any significant effect on COPD exacerbations, compared with placebo.[28] This review found that in a mixed population of non-reversible and partially reversible COPD, long-acting β_2-agonists

significantly reduced COPD exacerbations, compared with placebo. This difference may be related to a difference between the patient populations included in the two systematic reviews; and to the fact that the results of the 2002 review in non-reversible COPD patients were based on data from two studies, whereas the results of this review were based on data from 12 studies for COPD exacerbations. This systematic review and the previous systematic review of non-reversible COPD patients found a significant improvement in FEV_1 from baseline with long-acting β_2-agonists, compared with placebo. No difference was observed for distance covered in walk tests. Neither systematic review observed a difference between long-acting β_2-agonists and ipratropium bromide for any of the outcome measures assessed, except for a lower number of "bad" days with formoterol in one study.[76] A small study also indicated a possible better improvement in some lung functions with tiotropium compared with formoterol.[54]

The limitations for interpreting the results of this systematic review are multiple outcome measures with some contradictory results, and multiple definitions of outcome measures such as COPD exacerbations and symptom scores. There is an urgent need for experts to set internationally accepted standards for outcome measures in COPD drug trials, and establish a minimum number of objective outcome measures to prove the efficacy and effectiveness of these drugs.

6.4 Implications for Decision Making

6.4.1 Long-acting β_2-agonists improve health outcomes

Compared with no therapy, choosing to use these agents in stable, mild to severe COPD patients can reduce hospitalizations and disease exacerbations. These outcomes can offset the direct costs of therapy.

6.4.2 Long-acting β_2-agonists have no demonstrated health advantages over ipratropium or tiotropium

Despite the availability of eight trials with over 3,500 participants, no consistent or overall improvements in health outcomes were observed with long-acting β_2-agonists, compared with anticholinergic agents. Decision makers will need to consider other factors, such as tolerability, ease of use, price, and individual responsiveness, when choosing between these agents.

6.4.3 Salmeterol is not as well tolerated as tiotropium

A larger proportion of salmeterol recipients were observed to be intolerant to therapy. This could reduce the effective management of illness and have cost implications to patients and funders in terms of additional physician visits. No data were available to compare the tolerability of formoterol with tiotropium.

7 CONCLUSIONS

This review examined the clinical implications of using the long-acting β_2-agonists, salmeterol and formoterol, in the management of patients with stable COPD. The review evaluated the literature comparing these drugs to the anticholinergic agents (ipratropium bromide, tiotropium) and to placebo.

Long-acting β_2-agonists were significantly more effective than placebo in reducing COPD exacerbations and hospitalizations. Improvement in the use of rescue inhalers, symptom-free days, dyspnea, and lung function were also observed, although confirmation through further study may be required. Long-acting β_2-agonists did not have any significant advantages over placebo in reducing mortality and URTIs, or improving exercise capacity and tolerability.

Long-acting β_2-agonists did not demonstrate a significant advantage compared with either anticholinergic agent in most functional outcome measures. Salmeterol is not as well tolerated as tiotropium. No data were available to compare the tolerability of formoterol with tiotropium.

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APPENDICES

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