Drug Class Review

Quick-relief Medications for Asthma

Final Report Update 1

October 2008

The purpose of this report is to make available information regarding the comparative effectiveness and safety profiles of different drugs within pharmaceutical classes. Reports are not usage guidelines, nor should they be read as an endorsement of, or recommendation for, any particular drug, use or approach. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.

Update 1
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TABLE OF CONTENTS

EVIDENCE TABLES

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INTRODUCTION

Asthma

Asthma is a chronic inflammatory disorder of the airways. In susceptible individuals this inflammation causes recurrent episodes of wheezing, breathlessness, cough, and other symptoms. These episodes are usually associated with widespread and variable airflow obstruction. This obstruction is often reversible, either spontaneously or with treatment. Airway inflammation also increases bronchial hyper-responsiveness to a variety of stimuli, resulting in increased susceptibility to bronchospasm. In addition to bronchospasm and inflammation, some patients also experience airway remodeling, which leads to more severe and persistent disease. Airway reversibility may be incomplete in some patients.[1, 2]

Asthma is diagnosed when 1) the patient has episodic symptoms of airflow obstruction; 2) airflow obstruction is at least partially reversible; and 3) alternative diagnoses are excluded. Asthma most often begins in childhood and in these children is frequently associated with atopy. Asthma can, however, develop at any time in life and can be related to allergens or can be nonallergic (or intrinsic).[2]

The 2004 National Health Interview Survey[3] estimated that 10.5% (30.2 million) of the United States' population have been diagnosed with asthma. These include 9.9% (21.3 million) of adults 18 years and over and 12.2% (8.9 million) of children under age 18 years. Among children in the US, 5.4% (4.0 million) had at least 1 asthma attack in the past 12 months; for adults the figure was 3.6% (7.7 million). Prevalence of asthma increased from 1980 to 1996. In 1996 new measures of asthma prevalence were adopted. These measures suggest that prevalence of asthma remained relatively stable from 1997 to 2004.[3]

Asthma medications fall into 2 general classes: medications for long-term control and medications for quick relief of airflow obstruction and symptoms.[1, 2] Persons with persistent asthma require long-term controller and quick relief medications. Long-term controller medications include corticosteroids, cromolyn sodium and nedocromil, methylxanthines, leukotriene modifiers, and long-acting beta$_2$-agonists.[1, 2] Medications for quick relief of bronchoconstriction and acute symptoms include short-acting beta$_2$-agonists and anticholinergics.

Exercise-induced asthma

Exercise-induced asthma is characterized by coughing, wheezing, shortness of breath, and chest tightness during or after exercise.[4] Exercise-induced asthma is associated with airway obstruction after exercise, as indicated by a decrease in the volume of air forcefully expired in 1 second (forced expiratory volume in 1 second, FEV_1). In exercise-induced bronchospasm exercise precipitates airway obstruction, but lung function is normal at rest.[4] The term exercise-induced asthma sometimes refers to persons who have exacerbation of their chronic asthma during exercise. We use the term exercise-induced asthma to encompass both this condition and exercise-induced bronchospasm.[1]

The mechanisms underlying exercise-induced asthma are not well understood. The hyperosmolarity hypothesis proposes that water loss from the airway causes hypertonicity of airway cells, leading to release of inflammatory mediators and subsequent bronchoconstriction.[4] Another hypothesis suggests that hyperventilation leads to cooling of airway cells, and after

exercise the rewarming process leads to dilatation of bronchiolar vessels accompanied by fluid exudation, mediator release, and bronchoconstriction.

Exercise-induced asthma can affect elite and recreational athletes. Prevalence is reported as 17% in athletes participating in winter Olympics,[4] 35% among athletes competitive in cold weather sports,[4] and 9% among school children.[4]

Treatment focuses on avoidance of the particular activities that precipitate bronchospasm, adequate warm-up periods, and pharmacologic therapy. The last of these usually consists of an inhaled short-acting beta$_2$-agonist 15 minutes prior to exercise.[4] Additional, daily therapy may be required for management of underlying chronic asthma.

Inhaled beta$_2$-agonists

Beta$_2$-agonists act mainly to relax airway smooth muscle by stimulating beta$_2$-receptors, which in turn increase cyclic AMP and produce functional antagonism to bronchoconstriction.[2] Beta$_2$-agonists may also have anti-inflammatory properties, as suggested by in vitro experiments.[5]

The short-acting beta$_2$-agonists relax airway smooth muscle and increase airflow within 30 minutes[1] and last 4 to 5 hours. They are the drug of choice for treating acute asthma symptoms and exacerbations and are used for preventing exercise-induced bronchospasm. The short-acting beta$_2$-agonists are not recommended for regularly scheduled, daily use.[1]

The United States Food and Drug Administration announced on March 31, 2005, that albuterol metered-dose inhalers using chlorofluorocarbon propellants must no longer be produced, marketed, or sold in the United States after December 31, 2008, as they deplete stratospheric ozone.[1] Numerous clinical studies have demonstrated that albuterol hydrofluoroalkane 134a formulations have safety and efficacy comparable to albuterol chlorofluorocarbon formulations.[6-8]

A hydrofluoroalkane metered-dose inhaler containing levalbuterol (Xopenex HFA®) was approved in December 2005 for the treatment or prevention of bronchospasm in adults, adolescents, and children 4 years of age and older with reversible obstructive airway disease.

Inhaled anticholinergic agents

Anticholinergic (antimuscarinic) agents such as ipratropium bromide have been used in the treatment of acute and chronic asthma. These drugs act on muscarinic receptors to inhibit the effects of acetylcholine, thus causing smooth muscle relaxation. In asthma, ipratropium bromide is less potent and its bronchodilation slower than beta$_2$-agonists, but its effects last up to 6 hours.[9] In a 2000 Cochrane review Plotnick and colleagues[10] concluded that a single dose of an anticholinergic agents is not effective in the treatment of mild and moderate asthma, and is insufficient for acute exacerbations. They noted, however, that addition of multiple doses of anticholinergic agents to beta$_2$-agonists improves lung function and avoids hospital admission in some patients.

Table 1. Pharmacokinetics, indications and dosing of included drugs[11]

Drug Trade name(s)	How supplied	Half-life and other relevant pharmacokinetic features	FDA labeled indications	Dosing (inhaled doses)	Dose adjustments for special populations
Short-acting beta-agonists					
Albuterol (salbutamol in Canada) *Ventolin HFA®, Proventil HFA® ProAir HIFA®*	Inhalation HFA aerosol powder: 0.09 mg/actuation	Absorption: Time to peak concentration: 25 minutes Elimination half-life: 3-6.5 hours	Asthma, treatment and prophylaxis Exercise-induced asthma, prophylaxis	Asthma, treatment and prophylaxis: 2 inhalations every 4-6 hours or 1 inhalation every 4 hours Exercise-induced asthma, prophylaxis: 2 inhalations 15 minutes before exercise	Pediatric patients: Asthma, treatment and prophylaxis: 4 years and older, 2 inhalations every 4-6 hours or 1 inhalation every 4 hours ProAir HIFA® is not indicated in children < 4 years Exercise-induced asthma, prophylaxis: > 4 years: 2 inhalations 15 to 30 minutes before exercise
Fenoterol (not available in the US) *Berotec*™ in Canada	Inhalation aerosol: 100ug/ inhalation	Absorption: Time to peak concentration, 2-3 hours Elimination half-life: 7 hours (parent compound)	Asthma Exercise-induced asthma, prophylaxis	Inhalation aerosol: 1 to 2 inhalations (100 ug /inhalation) 3 to 4 times daily	Pediatric patients: > 6 years, one inhalation (100 ug) 3 times daily
Levalbuterol *Xopenex® Xopenex HFA®*	Inhalation solution (nebulizer): 0.31 mg/3 mL, 0.63 mg/3 mL, 1.25 mg/3 mL, 1.25 mg/0.5 mL; Inhalation aerosol: 45 ug/ inhalation	Absorption: Time to peak concentration, 12 minutes (inhalation aerosol) Elimination half-life: 4.0 hours (± 1.1 hour)	Treatment or prevention of bronchospasm in adults, adolescents and children ≥ 4 years with reversible obstructive airway disease	Inhalation solution (nebulizer): 0.31 mg/3 mL TID; Inhalation aerosol: 2 inhalations (45 ug/inhalation) every 4-6 hours	Pediatric patients > 4 years: 2 inhalations every 4-6 hours, 1 inhalation every 4 hours may be sufficient
Pirbuterol *Exirel®, Maxair®*	Inhalation aerosol powder: 0.2 mg/actuation	Elimination half-life: about 2 hours	Asthma	Asthma: 1-2 puffs every 4-6 hours, up to 12 puffs/day	Not FDA-approved in children under 12 years of age
Terbutaline (not available in inhaled form in the US) *Bricanyl*™	Inhalation aerosol: 250 ug/inhalation; MDI powder 500ug/	Time to peak concentration: 0.5-1 hours Elimination half-life:	Asthma - Bronchospasm Other bronchopulmonary	Bronchospasm: (aerosol) 2 puffs (200 µg per puff delivered) every 4-6 hours; MDI	Not approved in children < 12 years 12 years and

Drug Trade name(s)	How supplied	Half-life and other relevant pharmacokinetic features	FDA labeled indications	Dosing (inhaled doses)	Dose adjustments for special populations
in Canada	inhalation	11-26 hours	disorders in which bronchospasm or reversible airways obstruction is a complicating factor	(powder): maximum of 4 inhalations in 24 hours	older: 2 puffs (400 µg) every 4-6 hours
Anticholinergic drugs					
Ipratropium bromide *Atrovent HFA®*	Inhalation aerosol: 17 µg delivered per inhalation	Elimination half-life: 2 hours	Aerosol or solution: long-term treatment of bronchospasm associated with COPD, including chronic bronchitis and emphysema	Bronchospasm associated with COPD: 2 puffs, 4 times a day, up to 12 puffs/day	Aerosol and solution not approved for use in children < 12 years
Combination drugs					
Ipratropium bromide and albuterol sulfate *Combivent®*	Inhalation aerosol 200 µg inhalation unit: 21 µg of ipratropium bromide and 120 µg of albuterol sulfate per actuation	Ipratropium bromide elimination half-life: 2 hours Albuterol sulfate elimination half-life: 3-6.5 hours	Patients with COPD on a regular aerosol bronchodilator who continue to have evidence of bronchospasm and who require a second bronchodilator	Bronchospasm: 2 inhalations 4 times a day or more as needed up to 12 inhalations in 24 hours	Safety and effectiveness not established in children

Abbreviations: COPD, chronic obstructive pulmonary disease; FDA, United States Food and Drug Administration; HFA, hydrofluoroalkane 134a; MDI, metered dose inhaler.

Scope and Key Questions

The purpose of this review is to compare the benefits and harms of short-acting beta$_2$-agonists and ipratropium bromide used for quick relief of asthma symptoms. For the original report we included long- and short-acting beta$_2$-agonists for the treatment of asthma (including exercise-induced asthma) and chronic obstructive pulmonary disease. For Update 1 we were asked to focus only on short-acting drugs for quick relief of asthma symptoms (quick-relief medications for asthma). Therefore, for this report we included from the original report only sections that relate to short-acting beta$_2$-agonists. We included short-acting beta$_2$-agonists used on a regular basis in the original report, and we also updated that information in Update 1. We added ipratropium bromide to the review, and we did not include studies of chronic obstructive pulmonary disease. We also did not update metaproterenol for Update 1, per the request of our participating organizations.

The Oregon Evidence-based Practice Center wrote preliminary key questions, identifying the populations, interventions, and outcomes of interest, and, based on these, the eligibility criteria for studies. These preliminary questions were reviewed and revised by representatives of organizations participating in the Drug Effectiveness Review Project. The participating organizations of the Drug Effectiveness Review Project are responsible for ensuring that the

scope of the review reflects the populations, drugs, and outcome measures of interest to clinicians and patients. The participating organizations approved the following key questions to guide this review:

Key Questions

1. What are the comparative efficacy and effectiveness of quick-relief medications used to treat outpatients with bronchospasm due to asthma or to prevent or treat exercise-induced bronchospasm?
2. What are the comparative incidence and severity of adverse events reported from using quick-relief medications to treat outpatients with bronchospasm due to asthma or to prevent or treat exercise-induced bronchospasm?
3. Are there subgroups of patients for which quick-relief medications used to treat outpatients with bronchospasm due to asthma or to prevent or treat exercise-induced bronchospasm differ in efficacy, effectiveness, or frequency and severity of adverse events?

METHODS

Literature Search

To identify relevant citations, 2 independent reviewers identified potentially relevant titles and abstracts from the Cochrane Central Register of Controlled Trials (Issue 1, 2006), Cochrane Database of Systematic Reviews, DARE, and MEDLINE (1966 to February, week 4, 2006). For Update 1 we searched these databases until June 2, 2008. Search terms included drug names and indications (see Appendix A for complete search strategies). To identify additional studies, we also searched reference lists of included studies and reviews and we reviewed dossiers submitted by pharmaceutical companies. All citations were imported into an electronic database (EndNote 9.0.0, Thomson Scientific).

Articles deemed potentially relevant after review of titles and abstracts were retrieved in full-text form. Two independent reviewers achieved consensus on all included and excluded articles. Excluded articles were coded in the EndNote database with the reason for exclusion.

Study Selection

We reviewed a selection of drugs currently available in the United States and of interest to the organizations participating in the Drug Effectiveness Review Project (Table 1). In addition, we were asked to review 2 drugs available only in Canada: terbutaline (Bricanyl™) and fenoterol (Berotec™).

We excluded studies that examined mixed populations where outcomes were not presented for subgroups of interest to us.

We examined studies that present 1 or more of the primary outcomes of interest to this review, effectiveness outcomes and outcomes related to safety and harms. For effectiveness and safety, published and as well as unpublished English-language reports in any geographic setting were included if they had a total sample size ≥ 10. We included letters if primary data were presented and there was sufficient detail to evaluate quality. We excluded abstracts and conference proceedings, as these publications generally do not have sufficient detail to assess

internal or external validity. Theses were not included as the full-text is frequently difficult to retrieve.

For the assessment of efficacy and effectiveness we included reports of randomized controlled trials and controlled clinical trials that directly compared the drugs of interest to us (that is, head-to-head trials). For the assessment of adverse effects we examined studies with head-to-head comparisons only, but we included a broad range of study designs: observational studies, before-after studies, case series with a sample size ≥ 10, randomized controlled trials, and controlled clinical trials. Clinical trials often are not designed to assess adverse events, may select low-risk patients (in order to minimize drop-out rates), or may have too short a follow-up period in which to adequately assess safety. Observational studies designed to assess adverse event rates may include broader populations, carry out observations over a longer period, use higher quality methods for assessing adverse events, or examine larger sample sizes.

The important differences between the original report and this update with respect to scope are as follows:

1. The original report focused only on $beta_2$-agonists. This update includes short-acting anticholinergic drugs and the combination of short-acting $beta_2$-agonist and short-acting anticholinergic agents.
2. The original report included short-acting and long-acting $beta_2$-agonists. This update includes only short-acting $beta_2$-agonists, as it is focused on quick-relief medications for asthma.
3. The original report included chronic obstructive pulmonary disease as well as asthma (including exercise-induced asthma); this update examined only asthma (including exercise-induced asthma).

The addition of short-acting anticholinergic drugs in Update 1 necessitated a completely new review of ipratropium bromide. We identified 2 recent high-quality Cochrane systematic reviews of anticholinergic therapy for chronic asthma in children over 2 years of age[9] and in adults.[12] We used these 2 reviews as the basis for our review of ipratropium bromide. These reviews focused on chronic asthma. The review in children included studies in which the anticholinergic agent was used for more than 1 week and the review in adults[12] included only studies with follow-up of greater than 24 hours. The last search date for the review by McDonald and colleagues[9] was February 2007 and for the review by Westby and colleagues,[12] May 2004. We updated the searches, adding relevant studies of both acute and chronic asthma. Thus we did not examine the effectiveness or safety of ipratropium bromide in acute asthma in studies published prior to 2004.

Because the use of ipratropium bromide in exercise-induced bronchospasm was not reviewed in these 2 Cochrane reviews, we searched specifically for this drug-indication combination, with no restriction on search dates (see Appendix A).

Inclusion and exclusion criteria: Update 1

Included populations

1. Adults or children with asthma including those with exercise-induced bronchospasm

Excluded populations

1. Persons with chronic obstructive pulmonary disease

2. Persons with acute bronchitis
3. Persons with bronchiectasis
4. Children less than 2 years old with recurrent or persistent wheezing
5. Persons with cystic fibrosis
6. Persons with high-altitude pulmonary edema

Included interventions

1. Inhaled short-acting $beta_2$-agonists
   a. Albuterol (salbutamol in Canada) metered dose inhaler and nebulizer solution
   b. Levalbuterol (that is, (R)-albuterol; not available in Canada) metered dose inhaler and nebulizer solution
   c. Pirbuterol (not available in Canada)
   d. Terbutaline: available only in Canada
   e. Fenoterol: available only in Canada
2. Short-acting anticholinergics
   a. Ipratropium bromide metered dose inhaler and nebulizer solution
3. Combination products
   a. Ipratropium bromide with albuterol metered dose inhaler (Combivent®) or ipratropium bromide with albuterol nebulizer solution

Excluded interventions

1. Systemic corticosteroids
   a. Prednisone
   b. Methylprednisolone
   c. Prednisolone
2. Salmeterol
3. Long-acting anticholinergics: tiotropium
4. Studies in which bronchospasm was induced by methacholine, histamine, or cold
5. Combination products that include a quick-relief agent and another agent not included in this review
6. Formoterol
7. Metaproterenol

Included comparisons

1. Head-to-head studies examining the above bronchodilators

Excluded comparisons

1. Comparisons to other drugs or to placebo (to achieve indirect comparisons)

Included effectiveness outcomes

1. Symptoms such as cough, wheezing, shortness of breath
2. Change in treatment regimen for the exacerbation
3. Healthcare utilization (length of stay in the emergency department or other clinical facility, need for re-treatment within 24 hours, number of hospital admissions, length of hospital stay)
4. For exercise-induced bronchospasm: exercise tolerance, symptoms

5. Mortality

Included safety outcomes
1. Overall adverse events
2. Withdrawals due to adverse events
3. Serious adverse events

Included settings
1. Outpatient settings including urgent care facilities and the emergency department

Included study designs
1. For effectiveness, head-to-head randomized controlled trials or controlled clinical trials with total sample size ≥ 20; No minimum duration of follow-up
2. For adverse events, head-to-head randomized controlled trials, controlled clinical trials, or observational studies with sample size ≥ 10; no minimum duration of follow-up

Data Abstraction

We abstracted relevant descriptive and outcomes data into a relational database developed for this review. We recorded results of intention-to-treat analyses, when reported. If only per protocol results were reported, we specified the nature of these results and reported them. In trials with crossover, outcomes for the first intervention were recorded if available. Results of the first intervention would avoid the potential for bias due to differential withdrawal before crossover, a "carryover effect" (from the first treatment) in studies lacking a washout period, and a "rebound" effect from withdrawal of the first intervention.

Quality Assessment

We assessed the internal validity (quality) of controlled clinical trials using the predefined criteria listed in the quality assessment tool found in Appendix B. These criteria are based on those used by the United States Preventive Services Task Force and the National Health Service Centre for Reviews and Dissemination. For each included trial we assessed the following features: methods used for randomization, for allocation concealment, and for blinding of participants, investigators, and assessors of outcomes; the similarity of comparison groups at baseline; adequacy of reporting of attrition, crossover, adherence, and contamination; presence of post-allocation exclusions; and the use of intention-to-treat analysis.

We assessed observational and other study designs with adverse event data on the basis of unbiased selection of patients, attrition, unbiased and accurate ascertainment of events, and control for potential confounders (Appendix B).

These criteria were then used to categorize studies into good-, fair-, and poor-quality studies. Studies that had a significant flaw in design or implementation such that the results were potentially not valid were categorized as "poor". Studies which met all quality criteria were rated good-quality; the remainder were rated fair. As the "fair-quality" category is broad, studies with this rating vary in their strengths and weaknesses. Studies rated poor are presented in the in-text tables and the evidence tables, and may be referenced in the text, but do not contribute to the conclusions of this report.

External validity of studies was assessed by examining the following: whether the study population was adequately described; inclusion and exclusion criteria; and whether the treatment received by the comparison group was reasonably representative of standard practice.

Systematic reviews that fulfilled inclusion criteria were rated for quality using pre-defined criteria (see Appendix B): clearly stated questions and inclusion criteria, adequate search strategy, quality assessment of individual trials, provision of adequate information, and appropriate methods of synthesis.

Data Analysis and Synthesis

For Update 1 we compared short-acting beta$_2$-agonists, ipratropium bromide, and combinations of these 2 drugs/classes to each other. We did not include a review of the long-acting beta$_2$-agonist formoterol because although it has a more rapid onset of action than salmeterol,[1] it is not indicated as a rescue medication for asthma.[1]

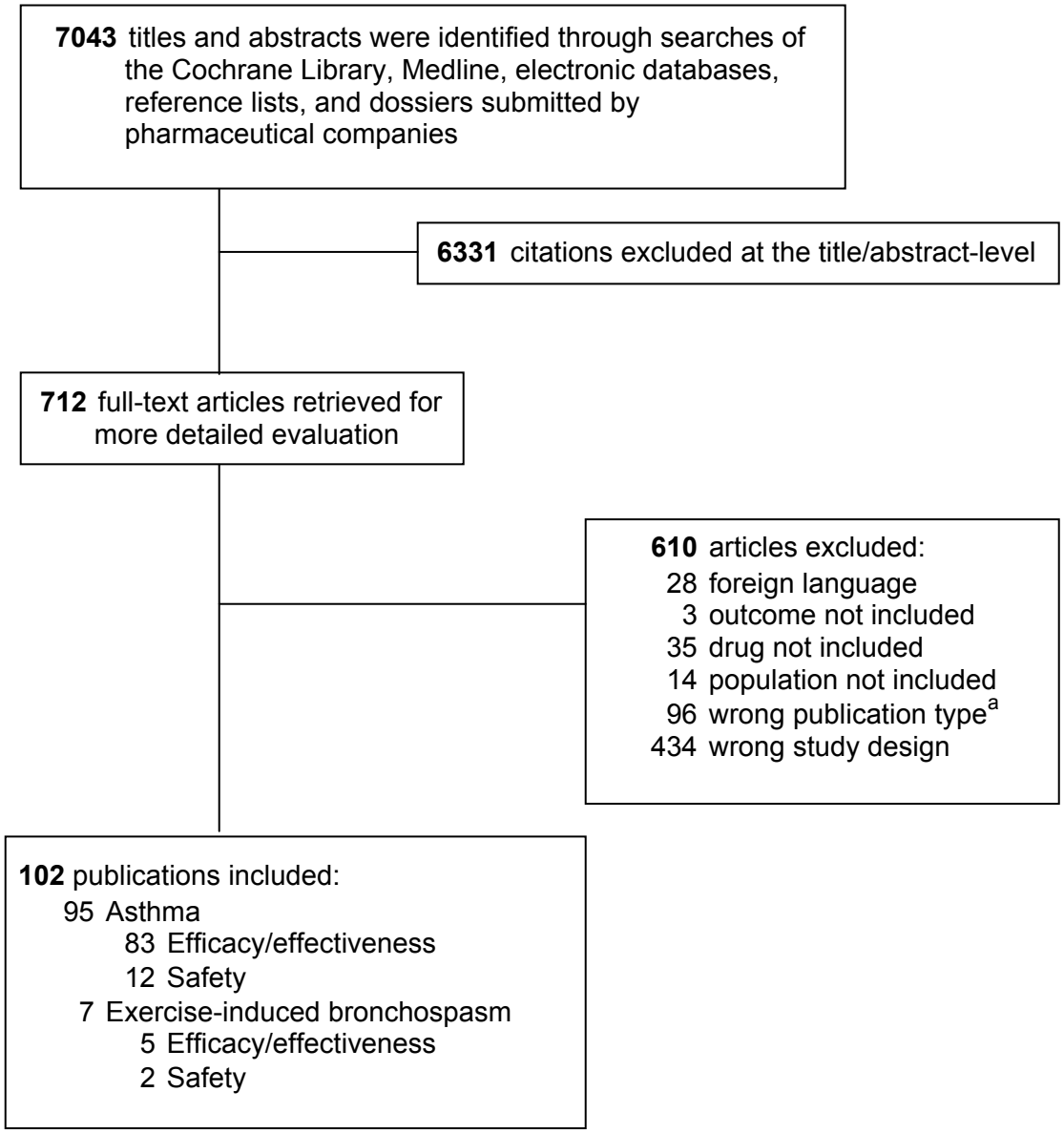
Important descriptive information about population, setting, intervention, and quality of studies is presented in tables. Data were synthesized and are presented in a narrative, as there was too much clinical and methodologic diversity to pool the data in a meta-analysis.

RESULTS

For the original report database searches identified 6629 citations. After inclusion and exclusion criteria were applied, 104 studies were included in this review (Figure 1). Included studies for each between-drug comparison are shown in Table 2. We identified 1 or more studies for all comparisons of interest except for levalbuterol. Available studies compared it to albuterol but not to any other drugs. Of the 104 included studies, 9 studies were poor quality for measures of effectiveness and are not discussed.[13-22]

For Update 1 we identified 510 new citations, of which 10 were included in the update, plus the 2 systematic reviews used as the basis for the review of ipratropium bromide.[9, 12]

Figure 1. Literature search results



[a] Wrong publication types included letters with insufficient information, editorials, non-systematic reviews, case reports, and case series with fewer than 10 patients.

Table 2. Quick-relief medications for asthma: included citations: efficacy, effectiveness, and safety

	Fenoterol[a]	Levalbuterol	Metaproterenol (original report only)	Pirbuterol	Terbutaline[a]	Ipratropium bromide
Albuterol	24 (24)[21, 23-45]	14 (15)[18, 46-60, 61, 102]	5 (6)[62-67]	3 (4)[14, 15, 67, 68]	23 (22)[13, 16, 19, 22, 34, 37, 44, 67, 69-82]	Wraight 2004[83] (IB vs. IB+albuterol) Salo 06,[84] Charakaborti 06,[85] Sharma 04,[86] Watanasmsiri 06,[87] Ranston 2005[88] (albuterol vs. IB+albuterol)
Fenoterol[a]			1 (1)[89]		12 (11)[34, 37, 44, 90-97]	
Levalbuterol						Ralston 2005[88] (levalbuterol vs. albuterol+IB)
Metaproterenol				3 (3)[67, 98, 99]	3 (3)[67, 100, 101]	
Pirbuterol					1 (1)[67]	

Studies identified for Update1 are represented by the first author's last name and year of publication, and are highlighted.
Abbreviations: IB, ipratropium bromide.
[a] Available in Canada only.

Systematic reviews

The original report identified no systematic reviews of head-to-head comparisons of interest. In the Cochrane Database of Systematic Reviews there are a number of reviews related to inhaled $beta_2$-agonists. None of these reviews fulfilled our inclusion criteria; the most common reason was a focus on placebo-controlled trials (and not head-to-head trials). Since these reviews provide additional background and useful information, we have briefly summarized their scope and conclusions in Appendix C.

We used 2 recent systematic reviews as the basis for our review of ipratropium bromide for Update 1.[9, 12] Both of these reviews focused on chronic asthma; 1 review was of children more than 2 years of age with anticholinergic agent use for more than 1 week,[9] the other review was of adults with anticholinergic use for more than 24 hours.[12] The results of these reviews are summarized below in the relevant section for each drug comparison.

Efficacy and effectiveness

Key Question 1.

What are the comparative efficacy and effectiveness of quick-relief medications used to treat outpatients with bronchospasm due to asthma or to prevent or treat exercise-induced bronchospasm?

Albuterol compared with levalbuterol

Demographic and study characteristics are summarized in Tables 4 and 5 and effectiveness outcomes in Table 6.

Adult asthma

Nelson and colleagues[54] and Pleskow and others[56] examined 362 patients 12 years of age and older with moderate to severe asthma. Each participant was given a nebulizer 3 times daily of either levalbuterol (0.63 mg or 1.25 mg), racemic albuterol (1.25 mg or 2.5 mg), or placebo for 4 weeks. The mean number of puffs of rescue medication used per day decreased in all active treatment groups. The within-group change was significant for levalbuterol 1.25 mg ($P<0.001$) and of borderline significance for racemic albuterol 2.5 mg ($P=0.056$). Rescue medication use increased in the placebo group ($P=0.019$). The percentage of patients reporting "asthma" or "asthma increase" (these were not defined) appeared similar among all groups (statistics not provided). Other effectiveness measures were not reported in this study.

A pilot controlled clinical trial by Nowak and colleagues[55] (N=91) examined adults presenting to the emergency department with asthma. Treatment consisted of 3 doses of albuterol (2.5 mg and 5.0 mg) or levalbuterol (0.63 mg to 5.0 mg) delivered via nebulizer over 60 minutes. The primary outcomes of this study were pulmonary function measures and the study was not powered to examine healthcare utilization. In the discussion section of the paper, however, the authors indicate that patients treated with levalbuterol required less additional therapy, and a greater percentage were discharged after 3 doses than after treatment with albuterol. However, hospitalization rates were similar between the 2 drugs for matched dosages. Rate for levalbuterol 0.63 mg was 0%; for 1.25 mg, 7%; for 2.5 mg, 8%; for 3.75 mg, 29%; and for 5.0 mg, 8%. Rate for albuterol 2.5 mg was 7%; and for 5.0mg, 0%. No statistical comparisons were presented for these outcomes.

Two randomized controlled trials compared racemic albuterol to levalbuterol. Nowak and colleagues[102] enrolled 627 adults with acute asthma exacerbations presenting to the emergency department or to acute care clinics. Approximately two-thirds of these patients were African American. Nebulized treatments of either levalbuterol 1.25 mg or racemic albuterol 2.5 mg were given every 20 minutes for 1 hour, then every 40 minutes for 3 additional doses, then as necessary for up to 24 hours. At the time of emergency department/clinic discharge, patients were given a 5-day course of oral corticosteroids and a blinded, nebulized study drug to be given 3 times a day for 3 days, then as needed for up to 3 times a day for 7 days. The time to meet emergency department or clinic discharge criteria (the primary outcome) did not differ between the 2 treatments: 76.0 minutes with levalbuterol and 78.5 minutes with albuterol ($P=0.74$). Hospitalization rates were similar between groups (levalbuterol 7.0% and albuterol 9.3%, $P=0.28$). Relapse rates at 7 and 30 days were also similar between groups ($P>0.05$). In the subgroup of subjects not on steroids at the time of the emergency department visit, fewer levalbuterol- than albuterol-treated patients required hospitalization (3.8% compared with 9.3%, $P=0.03$). However, there was no significant difference in admission rates for the subgroup taking steroids at baseline.

In the second randomized controlled trial, Hamilos and colleagues[60] compared regular use of levalbuterol 90 µg HFA (in 2 actuations) with racemic albuterol 180 µg HFA (also in 2 actuations) 4 times daily over 52 weeks in patients 12 years of age or older. The focus of the study was the safety of long-term, regular use of levalbuterol metered dose inhaler. Pirbuterol metered dose inhaler was used as rescue medication. The study was originally designed for 12

months of follow-up, but was modified to 6 months, with no rationale for this change provided. Attrition rates were high overall (44%) at 6-month follow-up; rates were even higher at 12 months (65% with levalbuterol and 57% with albuterol). Because of the high attrition and the change in follow-up period without provision of a rationale, this study was rated poor quality.

In this study by Hamilos and coauthors,[60] the rates of adverse events over the year follow-up were similar between treatment groups (72.0% with levalbuterol and 76.8% with albuterol, *P*=0.12). Rates of asthma adverse events and asthma attacks (the latter defined as requiring hospitalization, a visit to the emergency department or clinic, or a burst of corticosteroids) were similar between groups. Rates of rescue medication use and daytime asthma control days were similar between groups (no statistics reported). Quality of life (as measured with the Adult Asthma Quality of Life Questionnaire) improved to a similar extent in both groups. Pediatric patients did, however, demonstrate a greater improvement in quality of life (as measured with the pediatric Asthma Quality of Life Questionnaire) with levalbuterol than with albuterol. No statistics were provided for the pediatric measures and the sample size was small (N=31).

Pediatric asthma

Symptoms and use of rescue medication did not differ between drugs in the 5 pediatric studies that compared albuterol and levalbuterol.[51, 53, 57, 59, 61] Two of these studies took place in the emergency department. Qureshi and colleagues[57] examined children aged 2 to 14 years (N=129) upon presentation to a pediatric emergency department with a moderate to severe acute asthma exacerbation (asthma score >8 out of a possible score of 15 or FEV1). These children were given 3 nebulized treatments of either albuterol 2.5 mg or 5.0 mg (depending on weight) or levalbuterol 1.25 mg or 2.5 mg at 20-minute intervals, with subsequent treatments given at 30- and 60-minute intervals based on clinical assessment, pulmonary function testing, and the discretion of the attending physician. There were no significant differences between groups after the first, third, and fifth nebulizer treatments for the primary outcome of improvement in asthma score (validated score based on respiratory rate, auscultation, retractions, dyspnea, and oxygen requirement) or percentage of predicted FEV_1.

Hardasmalani and colleagues[51] (N=70) randomized patients aged 5 to 21 upon presentation to the emergency department to levalbuterol 1.25 mg or albuterol 2.5 mg via nebulization, along with ipratropium bromide 250 µg in children <30 kg and 500 µg in children >30 kg. Three treatments were given as needed at 20-minute intervals, along with oral steroids after the second treatment. There were no differences among groups for oxygen saturation, respiratory rate, peak flow rates, or the need for extra treatments.

Three studies examined regular daily use of levalbuterol and albuterol. Milgrom and colleagues[53] examined 338 children aged 4 to 11 years with at least mild asthma for ≥ 60 days before screening and randomized them to receive 21 days of three-times-a-day levalbuterol 0.31 mg, levalbuterol 0.63 mg, albuterol 1.25 mg, albuterol 2.5 mg, or placebo via nebulizer in a double-blind fashion. No significant differences were noted among the treatment groups for overall asthma symptom score, number of symptom-free days, quality of life, or use of rescue medication. Asthma control days were not different among groups for the first 14 days of treatment; however, from day 14 to 21, levalbuterol 0.31 mg was associated with significantly greater improvement in asthma control days than levalbuterol 0.63 mg and albuterol 1.25 mg (*P*<0.04 for both comparisons).

Skoner and colleagues[59] randomized asthmatic children age 2 to 5 years to albuterol (1.25 mg or 2.5 mg, depending on weight), levalbuterol (0.31 mg or 0.63 mg, independent of weight),

or placebo each given 3 times a day over 21 days via nebulizer. Symptom score improved in all groups over the 3 weeks, with no significant difference among groups. There were also no differences among groups for use of rescue medications, the number of uncontrolled asthma days, functional status score, or Child Health Status Questionnaire responses. The Pediatric Asthma Caregiver's Quality of Life Questionnaire improved more for the levalbuterol groups, although between-group differences were not significant. In a subgroup analysis of patients less than 33 pounds, overall Questionnaire score was significantly improved after levalbuterol 0.63 mg compared to albuterol (P=0.016). This study was of fair quality: Although it reported using intention-to-treat analyses for efficacy and effectiveness measures, the number of subjects actually analyzed was unclear. Study completion rate was 83.4%.

In a fair-quality randomized controlled trial Berger and colleagues[61] compared levalbuterol 90 µg HFA metered dose inhaler to racemic albuterol 180 µg HFA metered dose inhaler and to placebo, all administered 4 times daily on a regular basis for 28 days. The primary outcomes were spirometric measures. The use of rescue medications (days/week) decreased with both active treatments (levalbuterol compared with placebo, P<0.001; albuterol compared with placebo, P<0.01; and levalbuterol compared with albuterol, P>0.05).

Healthcare utilization outcomes varied among the 3 studies that examined them.[46, 51, 57] These trials all took place in the emergency department and were similarly designed randomized controlled trials, with blinding of the patient and treating physician.

Qureshi and colleagues[57] reported a per protocol analysis of 129 mostly African American children. Ten patients were excluded from analysis, including 6 due to protocol violation. The authors noted no differences in the secondary outcomes of percent of patients hospitalized from the emergency department, length of care in the emergency department, median number of nebulizations, or rate of adverse events. In the levalbuterol group 11% of patients were hospitalized; in the albuterol group the rate was 13%. The baseline rate of hospitalization was 13%. The authors indicate that their study was underpowered to detect a possible difference in rates between groups.

Similar results were reported by Hardasmalani and colleagues,[51] who also examined hospital admission rates as a secondary outcome after treatment of children and adolescents in the emergency department. In the albuterol group 2 of 34 patients (2.9%) were admitted compared with 3 of 36 children (4.3%) in the levalbuterol group (between-group, P=0.528).

In contrast to the 2 studies just discussed, a significant decrease in hospital admission rate was noted with the use of levalbuterol in the emergency department in a study by Carl and associates.[46] This study (N=547) of predominantly African American boys with moderate to severe chronic asthma randomized children aged 1 to 18 years upon presentation to the emergency department. Patients received nebulized treatment at 20-minute intervals of 1.25 mg levalbuterol or 2.5 mg of albuterol until they either met discharge criteria or reached the maximum of six treatments within 2 hours. The average hospital admission rate for the last 5 years was 42% for this study setting, and this study was powered to examine hospital admission rates as a primary outcome.

Carl and colleagues[46] noted a hospital admission rate of 122/269 (45%) with albuterol and 101/278 (36%) with levalbuterol (between-group, P=0.02). The use of albuterol in the 24 hours prior to the emergency department visit correlated with hospital admissions (P=0.002). After controlling for age, treatment with >3 aerosols in the last 12 hours and oral corticosteroid use in the previous 24 hours, investigators found that levalbuterol was still associated with a lower admission rate, 43% compared with 53% for albuterol (relative risk 1.25; 95% CI 1.01 to

1.51, *P*=0.04). Emergency department length of stay (*P*=0.25), mean number of aerosols in the emergency department (*P*=0.08), and hospital length of stay for those admitted (*P*=0.63) did not differ between groups.

Exercise-induced asthma

No studies compared albuterol with levalbuterol in persons with exercise-induced asthma.

Levalbuterol compared with albuterol plus ipratropium bromide

Adult asthma

No studies reported this combination of drugs.

Pediatric asthma

Ralston and colleagues[88] compared levalbuterol to the combination of racemic albuterol plus ipratropium bromide in 140 children age 6 to 18 years seen in the emergency department with acute asthma in a fair-quality study. For the study's primary outcome of length of stay in the emergency department or the hospital (if admitted), the median value was comparable between the 2 study groups (*P*=0.130). The groups were also comparable for the number of nebulization treatments in the emergency department and the time between treatments. Fewer patients were given adjunct medications (including steroids) in the levalbuterol group than in the albuterol-plus-ipratropium bromide group (*P*=0.022).

Albuterol compared with albuterol plus ipratropium bromide

Adult asthma

The Cochrane systematic review by Westby and colleagues[12] was used as the basis for this drug comparison. This review examined the effectiveness of anticholinergic agents compared with placebo and compared with beta$_2$-agonists, or as adjuncts to beta$_2$-agonists. These authors searched multiple bibliographic databases up to August 2004 and identified 9 studies with follow-up greater than 24 hours involving 440 patients in comparing anticholinergic drug plus beta$_2$-agonist combination therapy with beta$_2$-agonist monotherapy. One of the studies examined CR terbutaline and 2 other studies did not provide sufficient data for inclusion in the reviewers' meta-analysis. These reviewers noted heterogeneity across the remaining studies for follow-up intervals, dosing, and study design (parallel and crossover). They found no significant difference in any of the symptom scores between treatments. Overall there were fewer withdrawals with beta$_2$-agonist monotherapy. Two studies looked at the number of patients with exacerbations and found no significant differences between treatments. There was also little difference in adverse effects between the 2 treatments.

We identified 1 additional study in our update of the review by Westby et al.[12] In a good-quality trial of adults (89% African American) presenting to an emergency department with acute asthma, Salo and colleagues[84] randomized 66 patients to either albuterol 7.5 mg/h plus ipratropium bromide 1.0 mg/h or albuterol alone via continuous nebulization over 120 minutes. Oral prednisone was given at 1 mg/kg. There was no significant difference in hospital admission rates between the combination therapy (25%) and albuterol monotherapy groups (16.7%) (*P* not reported). The odds ratio for hospital admissions in the combination group was 1.66 (95% CI 0.48 to 5.8, *P*=0.62).

Pediatric asthma

The Cochrane review by McDonald and colleagues[9] included studies of children using an anticholinergic drug for more than 1 week. One very small trial compared ipratropium bromide plus salbutamol with placebo plus salbutamol, both delivered by metered aerosol 4 times daily. A second trial compared ipratropium bromide plus fenoterol with placebo plus fenoterol delivered via nebulizer 3 times daily. Both trials failed to show any significant benefit with respect to symptom scores from the addition of anticholinergic drugs to beta$_2$-agonist monotherapy.

For this update we reviewed studies from 2004 to mid 2008 involving ipratropium bromide, including 3 studies treating acute asthma in children. In a fair-quality trial set in India,[85] children age 5 to 15 years with mild to moderate acute exacerbation of asthma were randomized to either 4 actuations of ipratropium bromide (80 µg total) or placebo given with a metered dose inhaler using a spacer. All children were first given 4 actuations of salbutamol (400 mcg total) via a metered dose inhaler and spacer, then the study drug. Thirty minutes after treatment there was no significant difference between treatments in scores for wheezing or for use of accessory muscles.

In the second fair-quality trial, Watanasomsiri and colleagues[87] randomized 74 children age 3 through 15 years who presented to an emergency department in Thailand to either salbutamol 1.2 mg to 2.5 mg (depending on weight) plus ipratropium bromide 250 µg or salbutamol monotherapy. For both therapies, 3 doses were delivered by nebulizer at 20-minute intervals. Oral corticosteroids were administered to all children, and additional doses of salbutamol were administered for incomplete response. There were no significant differences (P>0.05) between groups in the rate of hospital admissions (5% with combination therapy and 9% with monotherapy). Follow-up by mail showed that the groups had similar rates of a "close secondary attack that required rescue medication" (9% with combination therapy and 21% with monotherapy). Data were available for 85% of randomized subjects, and "close" was not defined. Subgroup analyses based on age and severity "showed no statistically significant differences between the 2 groups at any time," but it was unclear which outcomes were examined for these analyses.

In a small, poor-quality, open-label trial set in India,[86] children age 6 to 14 years who reported to the emergency department with an acute exacerbation of asthma were randomized to salbutamol sulfate 150 µg/kg/dose or to a combination of salbutamol plus ipratropium bromide 250 µg/kg/dose. Both therapies were delivered by nebulization every 20 minutes for 3 doses. Oxygen was administered; there was no mention of corticosteroids. Dyspnea, wheeze, and accessory muscle scores decreased from baseline more with combination therapy than with monotherapy (between-group P<0.05), although decreases were seen with both groups. Hospitalization occurred in 1 patient in the combination therapy group and 4 subjects in monotherapy.

Ipratropium bromide compared with ipratropium bromide plus albuterol

Adult asthma

In a small, fair- to poor-quality trial in New Zealand,[103] 36 adults with mild to moderate asthma using inhaled corticosteroids were randomized to 4 puffs three times daily of salbutamol 100 µg/ipratropium bromide 20 µg daily via a metered dose inhaler (Combivent®) or ipratropium bromide 20 µg 4 puffs 3 times daily (Atrovent®). Both groups used ipratropium bromide 40

µg/puff for symptom relief. After 2 weeks of the assigned treatment drug (Phase 1), the inhaled steroids were withdrawn from both groups (Phase 2). Patients were then observed until one of the following predetermined criteria for loss of control of asthma were met: mean morning peak expiratory flow rates <90%, mean run-in values in 2 consecutive morning peak flow rates <80% of mean values during the run-in period; night wakening occurring 2 or more nights per week more often than during run-in; or distressing or intolerable symptoms. The mean time to loss of control was shorter in the salbutamol/ipratropium bromide group (8.9 days; 95% CI, 4.5 to 13.3) than with ipratropium bromide alone (16.8 days; 95% CI, 12.2 to 21.4; between-group *P*=0.03). Because at baseline the 2 treatment groups differed nonsignificantly (at alpha=0.05) on days to loss of control, a post hoc analysis was done. This post hoc analysis of subjects matched by FEV_1 (% predicted) showed no significant difference in days to loss of control (*P*>0.05).

The systematic review of chronic ipratropium bromide use in adults by Westby and colleagues[12] did not discuss this comparison explicitly, although this comparison was compatible with their inclusion criteria. It is unclear if they did not identify studies comparing ipratropium bromide plus albuterol with ipratropium bromide, or if they did not include this comparison.

Pediatric asthma

We identified no studies comparing the effect of ipratropium bromide with and without albuterol on control of asthma in children.

Albuterol compared with pirbuterol

Demographic and study characteristics are summarized in Table 7.

Of the 3 studies (in 4 publications) that provided direct comparative data on these drugs,[14, 15, 67, 68] 2 were of poor quality,[14, 15] and 1 was of fair quality.[67] None of these studies provided data on effectiveness outcomes.

Albuterol compared with fenoterol: Comparisons relevant to Canada

Only 1 of the 24 head-to-head studies identified comparing albuterol with fenoterol reported effectiveness outcomes for asthma. The study was of poor quality.[21]

Albuterol compared with terbutaline: Comparisons relevant to Canada

Adult asthma

Demographic and study characteristics are summarized in Table 10 and effectiveness outcomes in Table 11.

Use of rescue medications was examined and found to be similar in 2 poor-quality trials. Lindsay and colleagues[22] found that in 46 subjects over the age of 7 years, the mean number of doses of $beta_2$-agonists taken over 24 hours was 3.2 (SD 1.6) for terbutaline 1.6 mg and 5.8 (SD 2.3) for salbutamol 0.58 µg (no between-group comparisons). In an adult asthma population Gioulekas and others[19] did not find a significant difference in use of rescue medication.

In adults with asthma, symptom scores did not differ between albuterol and terbutaline in 3 studies (2 poor- and 1 fair-quality).[13, 19, 22] In a fourth (poor-quality) randomized controlled trial of 159 adults with asthma,[80] the mean daytime asthma symptom score (*P*<0.001) and the mean nighttime score (*P*<0.05) were lower with terbutaline 0.5 mg twice daily than albuterol 0.1 mg 2 puffs twice daily. No rescue medications were used during this study.

Pediatric asthma

In pediatric asthma there was no significant difference in symptoms between the 2 drugs[70, 77, 79] and respiratory rate decreased after both treatments.[77]

In exercise-induced asthma in a pediatric population, the only effectiveness outcome reported was the need for aminophylline treatment. Of patients receiving albuterol 0.2 mg, 21% needed aminophylline; of patients treated with terbutaline 0.25 mg, 8% required aminophylline[78] (no between-group statistics).

Fenoterol compared with terbutaline: Comparisons relevant to Canada

Adult asthma

Demographic and study characteristics are summarized in Table 12. Effectiveness outcomes are summarized in Table 13.

Anderson and colleagues[90] found no significant difference between fenoterol 0.4 mg and terbutaline 0.5 mg in symptom scores in adults with asthma. There was no difference in patient preference between the 2 drugs in another study.[97]

Pediatric asthma

There were no data in children.

Fenoterol compared with ipratropium bromide: Comparisons relevant to Canada

Adult asthma

There were no data in adults.

Pediatric asthma

The Cochrane review by McDonald and colleagues[9] included a study comparing fenoterol 0.2 mg to ipratropium bromide 40 µg, each drug given 3 times daily via inhaler. After more than 1 week no significant difference in symptom scores was seen in children with mild stable asthma.[104] We did not identify any additional studies for this comparison.

Fenoterol plus ipratropium bromide compared with fenoterol: Comparisons relevant to Canada

Adult asthma

There were no data in adults.

Pediatric asthma

The Cochrane review by McDonald and colleagues[9] included 1 small trial that compared fenoterol plus ipratropium bromide with fenoterol monotherapy.[105] However, McDonald and colleagues did not identify sufficient data in the primary study to draw conclusions on comparative effectiveness.

Pirbuterol compared with terbutaline: Comparisons relevant to Canada

We identified no studies comparing pirbuterol with terbutaline in asthma.

Safety

Key Question 2.

What are the comparative incidence and severity of adverse events reported from using quick-relief medications to treat outpatients with bronchospasm due to asthma or to prevent or treat exercise-induced bronchospasm?

Overview of adverse events

Withdrawal rates are presented in Table 14. Adverse events related to sympathomimetic side effects are expected with these medications and are discussed below. There was also a broad range of gastrointestinal, musculoskeletal, and other miscellaneous adverse events. There were no apparent differences in the rates and severity of adverse events between the various drugs compared in this review.

Albuterol compared with levalbuterol

Adult asthma

Total withdrawal rates in studies comparing albuterol with levalbuterol ranged from 0% to 11.0% (the latter rate with levalbuterol 1.25 mg in adult asthmatic patients over 4 weeks[54]) among the 4 studies reporting these data.[49, 54, 55, 106] Withdrawal rates were similar between the 2 drugs with neither drug consistently reporting higher rates. These studies reported several dosages for each drug; no relationship between dose and withdrawal rate was noted.

Available data indicate that heart rate increased 5 to 15 beats per minute 30 minutes after treatment with either albuterol or levalbuterol.[47, 57, 106] Between-group statistical comparisons were rarely reported; in 1 study of adults with asthma who were treated 3 times daily over 4 weeks, the increase in pulse rate 15 minutes after treatment with racemic albuterol 2.5 mg/dose was significantly greater than with levalbuterol 0.63 mg/dose (4.8 beats per minute compared with 2.4; data estimated from graph) ($P<0.05$).[54]

In the only study examining blood pressure, there were no significant changes with treatment in either group.[47] Palpitations[106] and tachycardia[54] were reported in a similar percentage of patients for the two drugs.

Light-headedness, dizziness, nervousness, anxiety, and restlessness were reported in a number of studies. Rates were similar for albuterol 1.25 mg to 2.5 mg and levalbuterol 0.63 mg to 1.25 mg.[47, 54, 57] There appeared to be slightly higher rates of these symptoms with the higher dosages, but between-group statistical comparisons were not provided in most studies. Tremor was reported in 3 studies, with comparable rates between treatment drugs.[48, 54, 106]

Blood glucose increased 3 hours after 4 doses of albuterol 2.5 mg and levalbuterol 1.25 mg with no significant difference between the 2 drugs ($P=0.70$).[49] An increase in mean serum glucose was noted for levalbuterol 0.63 mg (2.4 mg/dL) and albuterol 2.5 mg (4.4 mg/dL) 15 minutes after treatment at day 28 of 3 times daily dosing.[54] Maximum changes in glucose ranged from 15.9 to 62.4 mg/dL for levalbuterol and 46.4 to 57.1 mg/dL for albuterol 60 minutes after dosing in adult asthma.[55]

In an adult asthma population, potassium was noted to decrease 3 hours after 4 doses of albuterol 2.5 mg or levalbuterol 1.25 mg with no significant difference between the 2 drugs ($P=0.17$).[49] Three other studies also recorded a dose-dependent decrease in potassium 1-10 hours

after both levalbuterol and albuterol, with no significant difference between the 2 drugs for comparable dosages.[49, 55, 57]

Nowak and colleagues[102] examined adults with acute asthma exacerbations presenting to the emergency department or to acute care clinics. Nebulized treatments of either levalbuterol 1.25 mg or racemic albuterol 2.5 mg were given every 20 minutes for 1 hour, then every 40 minutes for 3 additional doses, then as necessary for up to 24 hours. The frequency of adverse events during the acute, consecutive treatment period in the emergency department was similar between groups, and events were largely related to stimulation of $beta_2$-receptors: headache, nervousness, tremor, and tachycardia (no statistics provided). Rates for serious adverse events (not defined) were also reported as similar between groups. Serum potassium concentration was also similar in the 2 groups (data not published).

A randomized controlled trial[60] that was rated poor quality, as noted earlier, compared regular use of levalbuterol 90 µg (in 2 actuations) with racemic albuterol 180 µg (also in 2 actuations) 4 times daily over 52 weeks in patients 12 years of age or older. Rates of potentially $beta_2$-receptor-mediated adverse events were similar between the 2 groups (for a composite outcome of tachycardia, palpitations, chest pain, hypertension, nausea, nervousness, and others, $P>0.05$). There was little change in serum potassium or glucose levels, heart rate, or QTc interval over the course of the study and no significant difference ($P>0.05$) between treatment groups for any of these outcomes.

Pediatric asthma

The rate of withdrawal from pediatric studies was inconsistent in the 2 studies that reported these data,[53, 59] but the overall rate of adverse events was generally similar for treatment groups (placebo 52%, levalbuterol 0.31 mg 53.4%, levalbuterol 0.63 mg 60.8%, and albuterol 1.25 mg 53.8%).[59]

Heart rate increased 30 minutes after treatment with albuterol 2.5 mg or levalbuterol 0.63 mg.[18, 53, 59] The increase was approximately 5 to 15 beats per minute in both treatment groups,[18, 53] with a lesser increase noted in the third study.[59] After regular use three times daily for 21 days, the heart rate increase was still noted, but was less marked in one study (e.g., 6 beats per minute with albuterol 2.5mg)[53] and slightly more marked in a second study[59] (up to 6 beats per minute). Note that changes in heart rate are likely dose dependent, and the dose equivalent of albuterol 1.25 mg is levalbuterol 0.63 mg.

Light-headedness, tremor, and headache were reported with similar rates for up to 5 doses of albuterol 2.5 mg and levalbuterol 1.25 mg.[57] Tremulousness was reported in 37% and 33% of pediatric patients using levalbuterol and racemic albuterol, respectively,[57] with no significant difference between groups.

Milgrom and colleagues[53] noted a larger increase in serum glucose 60 minutes after albuterol 2.5 mg than after levalbuterol 0.63 mg on both day 0 and day 21 of treatment 3 times a day ($P\leq0.043$) in children. Among children age 2 to 5 years, Skoner and colleagues[59] noted an increase in serum glucose 30-60 minutes after the last dose in all groups, including the placebo group, with the greatest increase after albuterol 1.25 mg (no data presented). In a poor-quality study of children aged 3 to 11 years,[18] blood glucose increased 60 minutes after treatment with levalbuterol 0.16 mg, 0.63 mg, and 1.25 mg (and not with 0.31 mg). The largest increase was 30.5 mg/dL (with levalbuterol 1.25 mg). Increases were also seen after racemic albuterol 1.25 and 2.5 mg (16 and 20 mg/dL, respectively). Again, the dose equivalence of albuterol 1.25 mg to levalbuterol 0.63 mg must be noted.

A decrease in serum potassium was noted 1-10 hours after levalbuterol and albuterol, with no significant difference between the 2 drugs.[57] In a study of albuterol and levalbuterol given 3 times daily, potassium decreased more with albuterol 2.5 mg than with levalbuterol 0.63 mg and 0.31 mg ($P<0.05$) at day 0; there was no significant difference between the 2 drugs at day 21.[53] Skoner and colleagues[59] noted a reduction in serum potassium 30-60 minutes after the last dose in all groups, including the placebo group, with the greatest reduction after albuterol 1.25 mg (no data presented). In a poor-quality study, serum potassium levels decreased in a pediatric population 60 minutes after treatment with levalbuterol 0.63 mg (-0.5 meq/L), levalbuterol 1.25 mg (-0.5 meq/L), racemic albuterol 1.25 mg (-0.4 meq/L), and albuterol 2.5 mg (-0.6 meq/L).[18]

In Update1, an additional randomized controlled trial compared regular-use levalbuterol 90 µg with albuterol 180 µg and placebo, all administered 4 times daily on a regular basis for 28 days.[61] The rates of any adverse event were highest with racemic albuterol (56.4% compared with 51.4% for placebo and 43.4% for levalbuterol). The rate of discontinuation due to adverse events was lower with levalbuterol (1.3%) than with albuterol (2.6%) or placebo (8.6%). Changes in heart rate, plasma potassium, and plasma glucose were similar among groups including placebo at day 28 (data not provided in the paper).

Albuterol compared with pirbuterol

No comparative data on withdrawals or cardiovascular, metabolic, or neurologic adverse events were provided in the included studies for either adults or children. One comparative study in a pediatric population reported no "cardiac side effects" in 17 patients.[68]

Levalbuterol compared with albuterol plus ipratropium bromide

Adult asthma

No studies reported this combination of drugs.

Pediatric asthma

Ralston and colleagues[88] compared levalbuterol with the combination of racemic albuterol plus ipratropium bromide in 140 children age 6 to 18 years seen in the emergency department for acute asthma. No serious adverse events occurred in either treatment group, and the rates of development of new tremor, nervousness, nausea, palpitations, and headache were similar between groups ($P>0.05$). Heart rate increased more with albuterol 5.0 mg plus ipratropium bromide 0.25 mg (increase 26 beats per minute) than with levalbuterol 1.25 mg (increase 11 beats per minute, between-group $P=0.003$). Maximal heart rate was also higher with albuterol plus ipratropium bromide (between-group $P=0.019$).

Albuterol compared with albuterol plus ipratropium bromide

Adult asthma

The Cochrane review by Westby and colleagues[12] reported fewer withdrawals with beta$_2$-agonist monotherapy than with beta$_2$-agonist plus an anticholinergic agent, but none of the 7 studies providing these data demonstrated statistically significant differences. In our review, data on adverse events were not provided in the only additional study that we identified examining this drug comparison.[84]

Pediatric asthma

The Cochrane review of use of anticholinergic drugs in children[9] identified only 1 study comparing albuterol with albuterol plus ipratropium bromide. It found no significant difference in the rates of tremor and palpitations between groups.

As mentioned earlier, we identified a fair-quality trial set in India[85] with children age 5 to 15 years with mild-to-moderate acute exacerbation of asthma. In this study patients were randomized to receive either ipratropium bromide (80 µg total) or placebo after initial treatment with salbutamol (400 µg total), all via a metered dose inhaler and spacer. At 30 minutes after treatment there was no significant difference between treatments in heart rate, which increased in both groups (7 beats per minute with combined therapy and 9 beats per minute with monotherapy, *P*=0.38). No specific adverse events were reported.

Watanasomsiri and colleagues[87] randomized 74 children age 3 through 15 years who presented to an emergency department in Thailand to either salbutamol 1.2 mg to 2.5 mg (depending on weight) plus ipratropium bromide 250 µg or salbutamol monotherapy, delivered by nebulizer for 3 doses at 20-minute intervals. In the combined therapy group 1 patient had headache and 1 had nausea; no other adverse events were reported.

In a small, poor-quality, open-label trial set in India,[86] children age 6 to 14 year who reported to the emergency department with an acute exacerbation of asthma were randomized to salbutamol sulfate 150 µg/kg/dose or to a combination of salbutamol plus ipratropium bromide 250 µg/kg/dose, both delivered by nebulization every 20 minutes for 3 doses. Tremors (monotherapy 32%, combined therapy 16%) and vomiting (monotherapy 12%, combined therapy 4%) were more frequent in the salbutamol-only group, and cough and transient eye irritation more frequent with combination therapy.

Ipratropium bromide compared with ipratropium bromide plus albuterol

Adult asthma

Adverse events were not reported in the only study comparing these drugs.[103]

Pediatric asthma

We identified no studies comparing ipratropium bromide (as monotherapy) with ipratropium bromide plus albuterol (a combination therapy) in children.

Fenoterol compared with terbutaline: Comparisons relevant to Canada

Data on withdrawal rates was limited, reported in only 3 studies.[92, 95, 97] In a study of pediatric asthma patients, 2 of 38 participants using terbutaline withdrew due to worsening asthma; none withdrew from the fenoterol group.[95] The other studies reporting these data were also very small sample sizes.[92, 97]

Pirbuterol compared with terbutaline: Comparisons relevant to Canada

No data on withdrawals or adverse events were provided in the included studies.

Albuterol compared with terbutaline: Comparisons relevant to Canada

Adult asthma

Total withdrawals ranged from 0% to 15.6% and withdrawals due to adverse events from 0% to 6.3% in the 6 studies reporting these data. Rates were similar for albuterol and terbutaline. The high rate of total withdrawals occurred in an adult asthmatic population using albuterol 0.4 mg 3 times daily over 3 weeks; none of the withdrawals in this study were felt to be due to adverse events.[19]

Effects on systolic blood pressure and diastolic blood pressure were similar for albuterol and terbutaline in the only study reporting these data.[69] Heart rates generally increased 5 to 10 beats per minute from 15 minutes to 2 hours after treatment for both drugs. Palpitations were noted in a small number of patients with both drugs.[13, 44, 76] A small decrease in potassium was noted after terbutaline and albuterol 26 puffs each.[44] Headache was reported in 20%-30% of patients taking either terbutaline or albuterol in 2 small studies.[44, 76]

Pediatric asthma

Potassium decreased 0.48 meq/L after terbutaline 0.125 mg/kg and 0.85 meq/L after albuterol 0.125 mg/kg 30 minutes after treatment (within-group $P<0.05$ for both groups; no between-group P values reported).[73] Palpitations were noted in a small number of children.[70]

Fenoterol compared with terbutaline compared with albuterol: Comparisons relevant to Canada

In a small crossover study[44] of 8 men and 2 women with asthma, fenoterol, salbutamol, and terbutaline all produced similar bronchodilation. However, the increase in heart rate, QTc interval, and tremor and the fall in plasma potassium were greater after fenoterol than after salbutamol or terbutaline.

Albuterol compared with fenoterol: Comparisons relevant to Canada

Adult asthma

The only trial reporting withdrawals from a study of albuterol and fenoterol treated adults with acute asthma in the emergency department.[35] Here the only "withdrawal" was 1 death from asthma among 128 study participants receiving fenoterol. Other studies comparing albuterol and fenoterol were cohort[26] or case control[38, 40] studies and rate of withdrawal from these studies was not provided.

Blood pressure in adult patients decreased by 1 to 6 mm Hg for both drugs 1-2 hours after treatment. Between-group comparisons were not reported, but both drugs appeared to have similar effects in all studies. Heart rate response was variable with a decrease of 6 beats per minute to an increase of 18 beats per minute between 15 minutes and 2 hours after treatment. Palpitations were occasionally reported with both drugs[28, 44] with no difference between groups.

A minor decrease in serum potassium was reported in 2 studies,[43, 44] with a greater decline with higher dosage: 26 puffs of terbutaline 250 µg was associated with a decrease in potassium of 0.52 mmol/L, fenoterol 200 µg with a decrease of 0.76 mmol/L, and albuterol 100 µg with a decrease of 0.46 mmol/L.[44]

Data were not available on the comparative effect of these drugs on blood glucose or gastrointestinal adverse events. Headache was noted in a small study (N=10) in 2 patients with terbutaline 250 µg, 3 patients with albuterol 100 µg, and 5 patients with fenoterol 200 µg.[44]

We identified 1 case-control examining the predictors for severe life-threatening asthma in a tertiary care hospital in South Africa.[108] Thirty consecutive patients aged 13 to 45 years with severe life-threatening asthma admitted to the intensive care unit were compared with 60 patients with chronic asthma who attended an outpatient respiratory clinic. The odds ratio for severe life-threatening asthma with the use of inhaled fenoterol (200 µg metered dose inhaler) compared to the use of albuterol was 6.8 (95% CI, 2.2 to 16.2; *P*=0.0004).

Pediatric asthma

There was minimal reporting of adverse events in these studies. Tremor was noted to be more marked with salbutamol than with terbulatine or fenoterol.[37] Onset for all three drugs was within 5 minutes with a later peak with salbutamol (at 15 minutes)[37] heart rate increased more with salbutamol and fenoterol than with terbutaline ($P<0.05$). In this same study there were no differences in blood pressure between the drugs.

Among children with chronic asthma age 7 to 13 years (15 of 16 were male), no significant differences were noted between salbutamol and fenoterol for the time of response to the medications, maximal effect, and duration. There was no increase in heart rate and no adverse events reported.[27]

Subpopulations

Key Question 3.

Are there subgroups of patients for which quick-relief medications used to treat outpatients with bronchospasm due to asthma or to prevent or treat exercise-induced bronchospasm differ in efficacy, effectiveness, or frequency and severity of adverse events?

Age and sex

No study specifically examined an older (>65 years of age) population. Several trials examined mostly male patients with asthma.[27, 31, 44] No study examined a predominantly female population either as part of the main study or as a subgroup. No studies stratified results by sex. One study examined outcomes based on age,[87]comparing salbutamol plus ipratropium bromide to salbutamol monotherapy. Subgroup analyses based on age and severity "showed no statistically significant differences between the 2 groups at any time," but it is unclear exactly which outcomes were examined for these analyses.

Race

For the most part, data on race and ethnicity were not provided in studies. No studies were exclusively of African American or other minority populations; 2 studies compared albuterol with levalbuterol in predominantly African American pediatric patients with asthma;[46, 57] and 2 studies examined minority adult patients.[55, 102]

Albuterol compared with levalbuterol

In a randomized controlled trial set in an emergency department[46] a primarily African American population of children (86% black) age 1 to 18 years (N=482) received either albuterol 2.5 mg or levalbuterol 1.25 mg via nebulizer every 20 minutes to a maximum of 6 doses. Hospitalization rate, the primary outcome, was significantly lower in the levalbuterol group (36%) than in the albuterol group (45%, *P*=0.02). Length of hospital stay did not differ in the 2 groups (*P*=0.63), and no significant adverse events occurred in either group.

In a similar randomized controlled trial[57] in an emergency department of 129 children aged 2 to 14 years (83% African American), there were no significant differences between treatment groups for the primary outcome of clinical asthma score and FEV_1 after 1, 3, and 5 treatments. There were also no differences in the number of treatments, length of emergency department care, rate of hospitalization, and changes in heart rate, respiratory rate, and oxygen saturation. One child receiving albuterol had tachycardia >200 beats per minute. Adverse events were not significantly different in the 2 groups.

In adults 2 randomized controlled trials, both by Nowak and colleagues[55, 102] examined predominantly African American populations with acute asthma presenting to the emergency department. The pilot study[55]was only powered for pulmonary function outcomes. In the larger trial[102] (N=627), in which approximately two-thirds of enrolled patients were African American, there were no significant differences in relapse rates and hospital admission rates between albuterol and levalbuterol groups; however, outcomes were not stratified by race.

Other drug comparisons

A trial[84] in which 89% of participants were African American compared albuterol plus ipratropium bromide with albuterol alone. No significant differences were found between groups in rate of hospital admissions.

Comorbidities

No data on subgroups based on comorbidities among persons with asthma were identified.

CONCLUSIONS

Table 3. Summary of the evidence by key question

	Drugs compared: Number and quality of studies	Findings
Key Question 1.		
Adults What are the comparative efficacy and effectiveness of quick-relief medications used to treat outpatients with bronchospasm due to asthma or to prevent or treat exercise-induced bronchospasm?	Albuterol compared with levalbuterol: 3 fair, 1 poor RCT Levalbuterol compared with albuterol + IB: 0 RCTs Albuterol compared with pirbuterol: 0 RCTs Albuterol compared with albuterol + IB: Cochrane review (8 studies) and 1 good RCT IB compared with IB + albuterol: 1 fair-poor RCT	**Albuterol compared with levalbuterol:** **Regular use.** Among adults with asthma, less rescue medication was required with levalbuterol (no between-group statistics) with no apparent difference in symptoms (1 RCT). **Treatment in the ED.** A controlled clinical trial found decreased need for additional treatment with levalbuterol compared with comparable albuterol dosages, but hospital admission rates were similar. 1 RCT found no significant difference in rates of admission or relapse or time in the ED. For patients not using corticosteroids, levalbuterol decreased admissions compared with albuterol (*P*=0.03). **Albuterol compared with albuterol + IB:** **Regular use.** No significant difference in symptom scores or rates of AEs between treatments (8 studies in Cochrane review) **Treatment in ED.** No significant difference in hospital admissions (1 RCT) **IB compared with IB + albuterol:** **Regular use.** Combination better with respect to time to loss of control after withdrawal of steroids (*P*=0.03; 1 RCT) We identified no data on exercise-induced asthma in adults.
	Comparisons specific to Canada: Terbutaline compared with albuterol: 3 poor, 1 fair RCT Terbutaline compared with fenoterol: 2 fair, 1 poor RCT Fenoterol compared with albuterol: 1 poor RCT Terbutaline compared with pirbuterol: 0 RCTs Fenoterol compared with IB: 0 Pirbuterol compared with terbutaline: 0	**Comparisons of interest in Canada:** **Terbutaline compared with albuterol**: No significant difference in use of rescue medication (3 poor-quality studies) or change in symptoms (1 fair, 2 poor studies). **Terbutaline compared with fenoterol:** NSD symptom scores (1 RCT) and patient preference (1 RCT).

	Drugs compared: Number and quality of studies	Findings
Children What are the comparative efficacy and effectiveness of quick-relief medications used to treat outpatients with bronchospasm due to asthma or to prevent or treat exercise-induced bronchospasm?	Albuterol compared with levalbuterol: 1 good, 5 fair RCTs Levalbuterol compared with albuterol + IB: 1 fair RCT Albuterol compared with albuterol + IB: 1 good systematic review (1RCT) plus 2 fair and 1 poor RCT Albuterol compared with pirbuterol: 0 RCTs IB compared with IB plus albuterol: 0 RCTs	**Albuterol compared with levalbuterol**: **Regular use** (3 studies). In 1 study there was no significant difference in symptoms or use of rescue medications at 21 days, but fewer days of adequately controlled asthma with levalbuterol 0.63 mg and albuterol 1.25 mg than levalbuterol 0.31 mg on days 14-21 (P<0.04). A second study showed no significant difference in the number of days of inadequate control. The third study showed no significant difference in use of rescue medication between albuterol MDI and levalbuterol MDI administered QID for 28 days **Treatment of asthma in the ED** (3 studies). No significant difference in symptoms (2 studies), need for additional treatments (3), length of stay in ED (2). Two studies also found no difference in rates of hospital admissions, but the third found fewer hospital admissions with levalbuterol 1.25 mg 3 doses than albuterol 2.5 mg 3 doses (P=0.02). This third study was larger and was powered to detect a difference in this outcome. **Levalbuterol compared with albuterol + IB:** No significant differences in length of stay in the ED or hospital or in number of nebulization treatments. Fewer levalbuterol patients received adjunct medications (P=0.02). **Albuterol compared with albuterol + IB:** 1 RCT in the Cochrane review showed no significant difference in symptoms scores between groups with chronic asthma. For acute use, 1 RCT showed no significant difference in hospital admissions or rescue medication use; a 2nd RCT found no significant difference in symptoms 30 minutes after treatment.
	Comparisons specific to Canada: Terbutaline compared with albuterol: 1 good, 3 fair RCTs; EIA: 1 fair RCT Fenoterol compared with IB: 1 RCT in a Cochrane review Fenoterol compared with albuterol: 0 RCTs Fenoterol compared with metaproterenol: 0 RCTs Terbutaline compared with fenoterol: 0 RCTs Terbutaline compared	**Comparisons of interest in Canada:** **Terbutaline compared with albuterol:** Symptoms in pediatric asthma: NSD (3 studies) EIB: 1 RCT showed fewer patients requiring aminophylline treatment with terbutaline than with albuterol (no statistics provided) **Fenoterol compared with IB in chronic asthma:** Symptoms: NSD (1 study in Cochrane review)

	Drugs compared: Number and quality of studies	Findings
	with metaproterenol: 0 RCTs Terbutaline compared with pirbuterol: 0 RCTs Fenoterol compared with IB + fenoterol: 0 RCTs Pirbuterol compared with terbutaline: 0	
Key Question 2.		
Adults What are the comparative incidence and severity of adverse events reported from using quick-relief medications to treat outpatients with bronchospasm due to asthma or to prevent or treat exercise-induced bronchospasm?	Albuterol compared with levalbuterol: 3 fair, 1 poor RCT; 5 RCTs with AE data only Albuterol compared with albuterol + IB: Cochrane review (7 RCTs) Albuterol compared with pirbuterol: 0 RCTs	**Albuterol compared with levalbuterol:** No significant difference in withdrawal rates (3 studies). Heart rate increased with both drugs (3), greater with albuterol (1). No significant difference in BP (1), palpitations (1), tachycardia (1), increased blood glucose (1), or dizziness/nervousness/anxiety/tremor (6). In 5 studies, decrease in K+ did not differ significantly between drugs. **Albuterol compared with albuterol + IB:** In 7 RCTs in a Cochrane review, withdrawal rates were similar; no other comparative AE data.
	Comparisons specific to Canada: Fenoterol compared with albuterol: 1 poor RCT; 9 RCTs with AE data only Terbutaline compared with albuterol: 1 fair, 3 poor RCTs; 6 RCTs with AE data only Terbutaline compared with fenoterol: 2 fair, 1 poor RCTs; 3 RCTs with AE data only Terbutaline compared with pirbuterol: 0 RCTs	**Comparisons of interest in Canada:** **Fenoterol compared with albuterol:** BP decreased 1-6 mm Hg (7 studies) after both drugs; heart rate response varied (-5 to +15 BPM) (9). Decrease in K+ was not significantly different between groups (2). 1 case-control study: OR for severe life-threatening asthma with the use of inhaled fenoterol (200 µg metered dose inhaler) compared to the use of albuterol 6.8 (95% CI, 2.2 to 16.2). **Terbutaline compared with albuterol:** Similar effects on BP (1 study). Heart rate increased 5-15 BPM (NSD) (4). K+ decreased approximately 0.5 meq/L with both drugs (1). Headache rare with both drugs (2). **Terbutaline compared with fenoterol:** Sparse data on comparative safety.
Children What are the comparative incidence and severity of adverse events reported from using quick-relief medications to treat outpatients with bronchospasm due to asthma or to prevent or	Albuterol compared with levalbuterol: 1 good, 3 fair Albuterol compared with pirbuterol: 1 RCT for AEs only Levalbuterol compared with albuterol + IB: 1 fair RCT	**Albuterol compared with levalbuterol:** Withdrawal rates varied (2 studies). Increase in heart rate: NSD (3 studies). BP: no data. No significant difference between drugs for tremor (1), light-headedness (1), dizziness (1), nervousness (1). Blood glucose increased with both drugs, more with albuterol (1). Decrease in K+: NSD (2); lower K+ with albuterol (1 study at day 0, NSD day 21; 2nd study, no data). For

	Drugs compared: Number and quality of studies	Findings
treat exercise-induced bronchospasm?	Albuterol compared with albuterol + IB: 2 fair RCTs	Update1, rates of any AEs highest with albuterol, lower with placebo, and lowest with levalbuterol (1 RCT; no statistics) **Albuterol compared with pirbuterol**: No data on comparative effectiveness **Levalbuterol compared with albuterol + IB:** In the ED heart rate increased more with albuterol (*P*=0.019). Rates of tremor, nervousness, nausea, headache were not significantly different between groups. **Albuterol compared with albuterol + IB:** In two studies in the ED and one with regular use for 1 week, there were no significant differences in adverse events between treatment groups.
	Comparisons specific to Canada: Fenoterol compared with albuterol: 3 RCTs with AE data only Terbutaline compared with albuterol: 1 good, 3 fair; 2 RCTs with AE data only Terbutaline compared with fenoterol: 2 RCTs withi AE data only Terbutaline compared with pirbuterol: 0	**Comparisons of interest in Canada:** **Fenoterol compared with albuterol:** Minimal reporting of adverse events in these studies. Heart rate increased more with salbutamol and fenoterol than with terbutaline (*P*<0.05). **Terbutaline compared with albuterol:** Heart rate response varied with no significant difference between drugs (3). No BP data. K+ decreased approximately 0.5 meq/L with both drugs (1). No neurological comparative data. Fenoterol compared with terbutaline: Scant data on AEs (1 study).
Key Question 3.		
Adults and children Are there subgroups of patients for which quick-relief medications used to treat outpatients with bronchospasm due to asthma or to prevent or treat exercise-induced bronchospasm differ in efficacy, effectiveness, or frequency and severity of adverse events?	Albuterol compared with levalbuterol: Age/sex: 0 studies Race: 2 studies in children, 2 studies in adults Albuterol compared with albuterol + IB: Age: 1 fair	**Albuterol compared with levalbuterol:** 2 RCTs in children and 2 in adults were predominately African American populations seen in the ED. In children 1 study showed decreased rate of hospitalization with levalbuterol; the other showed no significant difference. In adults 1 RCT showed no significant difference in hospitalization rates. The second did not provide effectiveness outcomes. No study stratified results based on race. **Albuterol compared with albuterol + IB:** In 1 RCT with a predominately African American population, subgroup analyses based on age or disease severity revealed no significant difference between groups (specific outcomes referred to are unclear).

	Drugs compared: Number and quality of studies	Findings
	Comparisons specific to Canada: No data on subgroups identified.	**Comparisons of interest in Canada:** No data on subgroups identified.

Abbreviations: AE, adverse events; BP, blood pressure; BPM, beats per minute; EIA, exercise-induced asthma; ED, emergency department; IB, ipratropium bromide; K+, serum potassium; MDI, metered dose inhaler; NSD, no significant difference; QID, four times a day; RCT, randomized controlled trial.

Table 4. Albuterol compared with levalbuterol: Demographic and study characteristics in adults (studies with effectiveness outcomes only)

Author Year	Study duration	Intervention	N	Mean age in years (SD)	% Female	Other medications permitted during study	Quality	Funder
Hamilos 2007	6 to 12 months	Levalbuterol metered dose inhaler 90 µg QID Albuterol metered dose inhaler 180 µg QID	746	39.0 (14.8)	67	Up to three 5- to10-day courses of oral steroids	Poor	Sepracor, Inc.
Nelson 1999 Pleskew 2004	4 weeks	Albuterol 1.25 mg TID Albuterol 2.5 mg TID nebulizer Levalbuterol 0.63 mg TID nebulizer Levalbuterol 1.25 mg TID nebulizer	362	36.5 (15)	60	Medications for asthma or allergic rhinitis, including inhaled and intranasal corticosteroids, sodium cromoglycate and nedocromil sodium if withheld for a sufficient period before study visits	Fair	Sepracor, Inc.
Nowak 2004	3 doses	Albuterol 2.5 mg nebulizer Albuterol 5.0 mg nebulizer Levalbuterol 0.63 mg Levalbuterol 1.25 mg Levalbuterol 2.5 mg nebulizer Levalbuterol 3.75 mg Levalbuterol 5.0 mg nebulizer	91	33(12)	54	Medication restrictions: long-acting bronchodilators within 24 hours, ipratropium bromide and theophylline within 48 hours, astemizole within 7 days, and monoamine oxidase inhibitors, methylphenidate hydrochloride, and tricyclic antidepressants within 30 days.	Fair (controlled clinical trial)	Sepracor, Inc.
Nowak 2006	30 days	Levalbuterol 1.25 mg Albuterol 2.5 mg Drugs given every 20 min times 3, then every 40 min up to 3 doses, then as needed. Discharged home on 5-day course of oral steroids and the study drug TID for 3 days then as needed up to TID for 7 days	627	37.0 (13)	61.2	Oral prednisone 40 mg 1 dose	Fair	Sepracor, Inc.

Abbreviations: TID, three times a day; QID, four times a day.

Table 5. Albuterol compared with levalbuterol: Demographic and study characteristics in children (studies with effectiveness outcomes only)

Author Year	Study duration	Intervention	N	Mean age in years (SD)[a]	% Female	Other medications permitted during study	Quality	Funder
Berger 2006	28 days	Levalbuterol MDI 90 µg QID Albuterol MDI 180 µg QID Placebo MDI QID	150	8.6 (1.8)	37	Single 5-day course of corticosteroids	Fair	Sepracor, Inc.
Carl 2003	2 hours	Albuterol 2.5 mg or levalbuterol 1.25mg via nebulizer q20min, maximum 6 treatments	547	7.1	33	Oral prednisone single dose	Good	Not reported
Hardasmalani 2005	3 treatmentsin 1 hr	Albuterol 2.5 mg q20 minutes PRN Levalbuterol 1.25 mg q20 Minutes PRN nebulizer	70	12.3	40	Ipratropium (250 µg in children <30 kg and 500 µg for >30 kg) given with study drug via nebulizer. Oral steroids 2 mg/kg given after 2nd treatment	Fair	Not reported
Milgrom 2001	3 weeks	Albuterol 1.25 mg nebulizer Albuterol 2.5 mg nebulizer Levalbuterol 0.31 mg Levalbuterol 0.63 mg	338	8.5 (1.9)	41.7	Stable doses of inhaled corticosteroids initiated ≥60 days before randomization	Fair	Sepracor, Inc.
Qureshi 2005	Maximum of 5 treatments	Albuterol 2.5-5 mg nebulizer Levalbuterol 1.25-2.5 mg nebulizer	129	5.8	34.1	Prednisone or equivalent corticosteroid given to all children with second albuterol treatment. Ipratropium bromide therapy permitted after the third study treatment.	Fair	Sepracor, Inc.
Skoner 2005	3 weeks	Albuterol 1.25-2.5 mg TID nebulizer Levalbuterol 0.31 mg TID nebulizer Levalbuterol 0.63 mg TID nebulizer Placebo nebulizer	211	3.4 (1.1)	69.2	Patients received matching blinded medications: levalbuterol 1.25 mg for the levalbuterol groups, albuterol 2.5 mg for the albuterol group. Non-beta$_2$ agonist asthma medications including ipratropium and	Fair	Sepracor, Inc.

Author Year	Study duration	Intervention	N	Mean age in years (SD)[a]	% Female	Other medications permitted during study	Quality	Funder
						inhaled corticosteroids if taken at stable doses prior and throughout the study.		

Abbreviations: MDI, metered dose inhaler; TID, three times a day; QID, four times a day.
[a] Data are for comparison group unless otherwise indicated.

Table 6. Albuterol compared with levalbuterol: Effectiveness outcomes

Author Year	Outcome category	Outcome at time point	Intervention	Baseline N	Baseline Mean (SD) or Number (%)	Follow-up N	Follow-up Mean (SD) or Number (%)	Change from baseline, Mean (SD), *P* value	Comments
Adults									
Hamilos 2007[a]	Use of rescue medication		Levalbuterol	495	NR	171	124 (72.6%)	NR	The study protocol was amended to reduce the study period to 6 months for newly enrolled patients
			Albuterol	250	NR	108	74 (68.9%)	NR	
	Compliance		Levalbuterol	496	NR	171	163 (95.7%)	NR	
			Albuterol	250	NR	108	104 (96.1%)	NR	
	Quality of life	12 months	Levalbuterol Albuterol	Both groups improved to a similar extent on the adult AQLQ Pediatric AQLQ was greater for the levalbuterol group					
Nowak 2004	Healthcare utilization	Patients discharged after 3 doses (number)	Albuterol 2.5 mg	14	NR	14	7 (50%)	NR	Controlled clinical trial (i.e. not randomized)
			Albuterol 5.0 mg	13	NR	13	8 (62%)	NR	
			Levalbuterol 0.63 mg	12	NR	12	11 (92%)	NR	
			Levalbuterol 1.25 mg	14	NR	14	12 (86%)	NR	
			Levalbuterol 2.5 mg	12	NR	12	8 (67%)	NR	
			Levalbuterol 3.75 mg	14	NR	14	5 (36%)	NR	
			Levalbuterol 5.0 mg	12	NR	12	10 (83%)	NR	
		Patients hospitalized (number)	Albuterol 2.5 mg	14	NR	14	1 (7%)	NR	
			Albuterol 5.0 mg	13	NR	13	0 (0%)	NR	
			Levalbuterol 0.63 mg	12	NR	12	0 (0%)	NR	
			Levalbuterol 1.25 mg	14	NR	14	1 (7%)	NR	
			Levalbuterol 2.5 mg	12	NR	12	1 (8%)	NR	
			Levalbuterol 3.75 mg	14	NR	14	4 (29%)	NR	
			Levalbuterol 5.0 mg	12	NR	12	1 (8%)	NR	
		Patients requiring additional therapy after conclusion of	Albuterol 2.5 mg	14	NR	14	6 (43%)	NR	

Author Year	Outcome category	Outcome at time point	Intervention	Baseline N	Baseline Mean (SD) or Number (%)	Follow-up N	Follow-up Mean (SD) or Number (%)	Change from baseline, Mean (SD), *P* value	Comments
		the study (number)							
			Albuterol 5.0 mg	13	NR	13	4 (31%)	NR	
			Levalbuterol 0.63 mg	12	NR	12	1 (8%)	NR	
			Levalbuterol 1.25 mg	14	NR	14	1 (7%)	NR	
			Levalbuterol 2.5 mg	12	NR	12	3 (25%)	NR	
			Levalbuterol 3.75 mg	14	NR	14	5 (36%)	NR	
			Levalbuterol 5.0 mg	12	NR	12	1 (8%)	NR	
Nowak, 2006	Healthcare Utilization	Time to discharge (minutes)	Albuterol 2.5 mg	312	NR	312	78.5	NR	*P* value between albuterol and levalbuterol = 0.074
			Levalbuterol 1.25 mg	315	NR	315	76.0	NR	
		Rate of hospital admission	Albuterol 2.5 mg	312	NR		9.3 (95% CI 6.1 to 12.6)		*P* value between albuterol and levalbuterol = 0.28
			Levalbuterol 1.25 mg	315	NR		7.0 (95% CI 4.2 to 9.8)		
		Relapse rate (% returning for urgent care at 30 days)	Albuterol 2.5 mg	312			14 (5.0%)		
			Levalbuterol 1.25 mg	315			16 (5.5%)		
Nelson 1998; Pleskow 2004[a]	Rescue medication	% of patients using any rescue medication (No.) at 4 weeks	Albuterol 1.25 mg	68	NR	68	66 (97.1%)	NR *P*>0.05	
			Albuterol 2.5 mg	74	NR	74	72 (97.3%)		
			Levalbuterol 0.63 mg	72	NR	72	69 (95/8%)		
			Levalbuterol 1.25 mg	73	NR	73	70 (95.9%)		
		No. of puffs of rescue medication per day (puff/day)	Albuterol 1.25 mg	68	NR	68	3.6 (SD 3.0)	0.01, *P*=0.99	
			Albuterol 2.5 mg	74	NR	74	3.8 (SD 2.9)	-0.50, *P*=0.56	
			Levalbuterol 0.63 mg	72	NR	72	3.5 (SD 3.2)	-0.25, *P*=0.372	
			Levalbuterol 1.25 mg	73	NR	73	2.7 (SD 2.5)	-0.74, *P*=0.001	
	Symptoms	AE (Asthma) at 4 weeks	Albuterol 1.25 mg	68	NR	68	5 (7.4%)	NR	
			Albuterol 2.5 mg	74	NR	74	6 (8.1%)	NR	

Author Year	Outcome category	Outcome at time point	Intervention	Baseline N	Baseline Mean (SD) or Number (%)	Follow-up N	Follow-up Mean (SD) or Number (%)	Change from baseline, Mean (SD), *P* value	Comments
			Levalbuterol 0.63 mg	72	NR	72	5 (6.9%)	NR	
			Levalbuterol 1.25 mg	73	NR	73	4 (5.5%)	NR	
		AE (Asthma) increase at 4 weeks	Albuterol 1.25 mg	68	NR	68	2 (2.9%)	NR	
			Albuterol 2.5 mg	74	NR	74	2 (2.7%)	NR	
			Levalbuterol 0.63 mg	72	NR	72	1 (1.4%)	NR	
			Levalbuterol 1.25 mg	73	NR	73	3 (4.1%)	NR	
Children									
Berger 2006	Rescue medication use	Days/week over 28-day follow-up	Levalbuterol MDI 90 µg QID	76	NR	76	NR	-0.72± 0.17	
			Albuterol MDI 180 µg QID	39	NR	39	NR	-0.62 ±0.24	
			Placebo MDI QID	35	NR	35	NR	0.35 ±0.24	
		No. of nebulizer treatments/day	Levalbuterol MDI 90 µg QID	76	NR	76	NR	-0.15 ±0.05	*P* value compared with placebo, levalbuterol <0.01
			Albuterol MDI 180 µg QID	39	NR	39	NR	-0.05 ±0.07	
			Placebo MDI QID	35	NR	35	NR	0.14 ±0.07	
	Quality of Life	During 28-day follow-up	Levalbuterol MDI 90 µg QID	76	NR	NR	NR	NR	No clinically meaningful differences between the active placebo groups for the Pediatric Quality of Life, Child Health Questionnaire and patient and provider evaluations
			Albuterol MDI 180 µg QID	39	NR	NR	NR	NR	
			Placebo MDI QID	35	NR	NR	NR	NR	
Carl 2003	Healthcare utilization	Hospital admissions (number)	Albuterol 2.5 mg	269	NR	269	122 (45.4%)	NR	Mean difference between Albuterol and levalbuterol, 9% (*P*=0.02)
			Levalbuterol 1.25 mg	278	NR	278	101 (36.3%)	NR	
		Length of stay in ED at discharge	Albuterol 2.5 mg	269	NR	269	2.2 h (0.8)	NR	Albuterol compared with levalbuterol, *P*=0.25
			Levalbuterol 1.25 mg	278	NR	278	2.3 H (0.9)	NR	
		NNT with	Albuterol 2.5	NR	NR	NR	NR	NR	NNT=10.6;

Author Year	Outcome category	Outcome at time point	Intervention	Baseline N	Baseline Mean (SD) or Number (%)	Follow-up N	Follow-up Mean (SD) or Number (%)	Change from baseline, Mean (SD), *P* value	Comments
		Levalbuterol to prevent 1 admission (number) at discharge)	mg						95% CI, 5.8 to 71.4, *P*<0.05
			Levalbuterol 1.25 mg	NR	NR	NR	NR	NR	
		Risk of admission with > 3 aerosols 12 h	Albuterol 2.5 mg	NR	NR	NR	NR	NR	Albuterol compared with levalbuterol, Relative risk =1.25, 95% CI 1.01 to 1.51, *P*=0.04
			Levalbuterol 1.25 mg	NR	NR	NR	NR	NR	
	Symptoms	Respiratory rate (bpm) at ED discharge	Albuterol 2.5 mg	269	NR	269	35.6 (12.6)	NR	Albuterol compared with levalbuterol, *P*=0.26
			Levalbuterol 1.25 mg	278	NR	278	37.0 (10.4)	NR	
Hardasmalani 2005	Healthcare utilization	Need for extra treatments (number) during ED visit	Albuterol 2.5 mg/3mL TID	34	NR	34	7 (21%)	NR	Albuterol compared with levalbuterol, *P*=NS
			Levalbuterol 1.25 mg/3mL TID	36	NR	36	5 (14%)	NR	
		Need for hospitalization (No.) during study	Albuterol 2.5 mg/3mL TID	34	NR	34	2 (6%)	NR	Albuterol compared with levalbuterol, *P*=NS
			Levalbuterol 1.25 mg/3mL TID	36	NR	36	3 (8%)	NR	
Milgrom 2001	Symptoms	Asthma, control days (day) at day 14-21	Albuterol 1.25 mg	67	NR	NR	0	NR	Day 0: Significantly more patients immediately responded to levalbuterol 0.31 mg (62.9%) than to albuterol 1.25 mg (41.8%), *P*=0.012. NSD among treatment groups for overall asthma symptom score or symptom-free days
			Albuterol 2.5 mg	66	NR	NR	NR		
			Levalbuterol 0.31 mg	70	NR	NR	1.6 (NR)		
			Levalbuterol 0.63 mg	70	NR	NR	0.25 (NR)		
Qureshi 2005	Healthcare utilization	% patients hospitalized after ED visit (number)	Albuterol 2.5-5 mg	64	NR	64	8 (13%)	NR	Albuterol compared with levalbuterol, *P*=NS
			Levalbuterol 1.25-2.5 mg	65	NR	65	7 (11%)	NR	
		Length of care	Albuterol	64	NR	64	125	NR	Albuterol

Author Year	Outcome category	Outcome at time point	Intervention	Baseline N	Baseline Mean (SD) or Number (%)	Follow-up N	Follow-up Mean (SD) or Number (%)	Change from baseline, Mean (SD), *P* value	Comments
		median min (interquartile range)	2.5-5 mg				(95,167)		compared with levalbuterol, *P*=NS
			Levalbuterol 1.25-2.5 mg	65	NR	65	121 (90,160)	NR	
	Rescue medication	Median number of nebulizer treatments: median number (interquartile range)	Albuterol 2.5-5 mg	64	NR	64	3 (3,5)	NR	Albuterol compared with levalbuterol, *P*=NS
			Levalbuterol 1.25-2.5 mg	65	NR	65	3 (3,4)	NR	
	Symptoms	Asthma score, % change from baseline after 5th treatment	Albuterol 2.5-5 mg	64	10	17	NR	20%	Albuterol compared with levalbuterol, *P*=NS
			Levalbuterol 1.25-2.5 mg	65	10	16	NR	22%	
		Median change (interquartile range in respiratory rate, median change (number/min) after 5th treatment	Albuterol 2.5-5 mg	64	NR	64	NR	-4 (-6,-2)	Albuterol compared with levalbuterol, *P*=NS
			Levalbuterol 1.25-2.5 mg	65	NR	65	NR	-5 (-12,-1)	
Skoner 2005	Quality of life	Pediatric Asthma Caregiver's Quality of Life Questionnaire (at 3 weeks	Albuterol 1.25-2.5 mg TID	52	NR	NR	NR	0.33 (1.20)	Overall score at 3 weeks exceeded 0.5 minimally important difference in levalbuterol groups but not albuterol or placebo groups; *P*=NS among groups; for patients <33 lbs, change in questionnaire score was greater for levalbuterol (both doses) than albuterol
			Levalbuterol 0.31 mg TID	58	NR	NR	NR	0.61 (1.10), NR	
			Levalbuterol 0.63 mg TID	51	NR	NR	NR	0.74 (0.96), NR	
	Symptoms	Pediatric Asthma Questionnaire – mean change in score at week 1	Albuterol 1.25-2.5 mg TID	52	NR	NR	NR	-1.5 (NR), NR	Mean changes interpolated from graph. NSD among groups. Authors conducted subgroup analyses for
			Levalbuterol 0.31 mg TID	58	NR	NR	NR	1.5 (NR), NR	
			Levalbuterol 0.63 mg TID	51	NR	NR	NR	-2.2 (NR), NR	

Author Year	Outcome category	Outcome at time point	Intervention	Baseline N	Baseline Mean (SD) or Number (%)	Follow-up N	Follow-up Mean (SD) or Number (%)	Change from baseline, Mean (SD), *P* value	Comments
									patients <33 lbs and ≥ 33 lb. For patients > 33 lb, levalbuterol had significantly better questionnaire score at weeks 1 and 2.
		Pediatric Asthma Questionnaire – mean change at week 2	Albuterol 1.25-2.5 mg TID	52	NR	NR	NR	-2.0 (NR), NR	Comparison of PACQLQ score. See comment above.
			Levalbuterol 0.31 mg TID	58	NR	NR	NR	-2.9 (NR), NR	
			Levalbuterol 0.63 mg TID	51	NR	NR	NR	-2.4 (NR), NR	
		Pediatric Asthma Questionnaire mean change (number) at week 3	Albuterol 1.25-2.5 mg TID	52	NR	NR	NR	-2.9 (4.1), NR	
			Levalbuterol 0.31 mg TID	58	NR	NR	NR	-3.5 (3.1)	
			Levalbuterol 0.63 mg TID	51	NR	NR	NR	-3.3 (4.3) *P*=NS for all groups at week 3	

Abbreviations: MDI, metered dose inhaler; NNT, number needed to treat; NR, not reported; TID, three times a day; QID, four times a day.
[a] Study population ≥ 12 years of age.

Table 7. Albuterol compared with pirbuterol: Demographic and study characteristics of included efficacy and effectiveness studies

Author Year	Study duration	Intervention	N	Mean age in years (SD)	% Female	Other medications permitted during the study	Quality	Funder
Adult asthma								
Beumer 1980 Beumer 1979	Single dose	Albuterol 200 µg MDI Pirbuterol 200 µg MDI Pirbuterol 400 µg MDI Pirbuterol 600 µg MDI	12	57.6	0%	Oral salbutamol (9 patients), antihistamine (3), oxtriphylline (92), salbutamol aerosol (1), fenoterol tablets (1), bronchodilators (unspecified)	Poor	Not reported
Pediatric asthma								
Volkl 1991	Single dose	Albuterol 0.1 mg MDI Pirbuterol 0.2 mg BAI	17	9.8 (1.5)	47%	No inhalational drug apart from the test preparations was allowed. Patients' other therapies were unchanged during the study.	Fair	Not reported

Abbreviations: MDI, metered dose inhaler.

Table 8. Albuterol compared with fenoterol: Demographic and study characteristics of included studies (studies with effectiveness outcomes only)

Author Year	Study duration	Intervention	N	Mean age in years (SD)	% Female	Other medication permitted during the study	Quality	Funding
Adult asthma								
Hanley 1979	2 puffs overnight	Albuterol 100 µg MDI Fenoterol 200 µg MDI	19	NR	NR	NR	Poor	W.B. Pharmaceuticals supplied the fenoterol and placebo aerosols

Abbreviations: MDI, metered dose inhaler; NR, not reported.

Table 9. Albuterol compared with fenoterol: Effectiveness outcomes of included studies

Author Year	Outcome Category	Outcome (Unit) at time point	Intervention	Baseline		Follow-up	
				N	Mean (SD) or No (%)	N	Mean (DS) or No (%)
Adult asthma							
Hanley 1979	Symptoms	Preference on waking, based on patient assessment (number) at NR	Albuterol 100 µg Fenoterol 200 µg No preference	28 (cross-over)	NR	19	2 (11%) 7 (37%) 10 (53%)

Abbreviations: NR, not reported.

Table 10. Albuterol compared with terbutaline: Demographic and study characteristics of included studies (studies with effectiveness outcomes only)

Author Year	Study duration	Intervention	N	Mean age in years (SD)	% Female	Other medications permitted during the study	Quality	Funding
Adults								
Anani 1989	3 weeks	Albuterol 400 µg QID Terbutaline 500 µg QID turbohaler	30	35	76.7	Patients used their usual bronchodilator pressurized aerosol as rescue therapy and the number of doses used each day was recorded. Other asthma medication was continued unchanged	Poor	NR
Gioulekas 1996	3 weeks	Albuterol 0.4 mg TID Terbutaline 0.5 mg TID turbohaler	32	34	34.4	Additional doses of trial medication only	Poor	NR
Lindsay 1994[a]	4 weeks	Albuterol 0.1 mg BID MDI Terbutaline 0.5 mg BID turbohaler	46	34.5	45.7	No other $beta_2$-agonists or nebulized therapy were allowed. Treatment with oral or other inhaled bronchodilators, including anticholinergics and theophylline, was allowed provided that doses remained constant throughout the study.	Poor	Author N.L. Russell associated with Astra Pharmaceuticals Pty. Ltd., Australia
Vilsvik 1993	2 weeks	Albuterol 0.1 mg MDI Terbutaline 0.5 mg turbohaler	159	49	39.6	Oral bronchodilators and steroids, local as well as systemic, were allowed provided the dose was unchanged in the 4 weeks before inclusion and was maintained during the whole study period	Fair	NR

Author Year	Study duration	Intervention	N	Mean age in years (SD)	% Female	Other medications permitted during the study	Quality	Funding
						The patients' usual beta$_2$-agonists were used as rescue medications		
Children								
Chandra 2004	Single dose	Albuterol 100 µg Terbutaline 250 ug	60	9.5	21.7	NR	Good	NR
Hung 2001	Single dose	Albuterol 0.125 mg/kg Nebulizer Terbutaline 0.125 mg/kg nebulizer	30	8018	43.3	NR	Fair	NR
Oldaeus 1995	2 weeks	Albuterol 0.4 mg TID Terbutaline 0.5mg TID turbohaler	20	3.5	70.0	Six children were on regular treatment with sodium cromoglycate and 3 children used inhaled steroids throughout the study. These medications were kept constant 1 month before inclusion and throughout the study.	Fair	Author Elisabeth Stahl affiliated with Astra Draco AB, Clinical Research & Development
Towns 1983	Single dose	Albuterol 200 µg rotahaler	25	9	48.0	Children were asked to cease their regular bronchodilator therapy at least 6 hours before testing. All other medications (sodium cromoglycate, beclomethasone 1 diproprionate, and orally administered corticosteroids) were allowed.	Fair	Astra Pharmaceuticals; Glaxo Australia
Pedersen 1985	Single dose	Albuterol 0.2 mg rotahaler Terbutaline	24	9.6	33.3	On a regular basis 9 children were treated with beclomethasone	Fair	NR

Author Year	Study duration	Intervention	N	Mean age in years (SD)	% Female	Other medications permitted during the study	Quality	Funding
		0.25 mg tube spacer				and 11 with disodium cromoglycate. In addition, all subjects regularly inhaled beta-2 agonists. No children used a beta-2 agonist for 1 h before exercise on the days of the study.		

Abbreviations: BID, twice a day; MDI, metered dose inhaler; NR, not reported; TID, three times a day.
[a] Study population ≥ 12 years of age.

Table 11. Albuterol compared with terbutaline: Effectiveness outcomes of included studies

Author Year	Outcome category	Outcome (unit) at time point	Intervention	Baseline N	Baseline Mean (SD) or No (%)	Follow-up N	Follow-up Mean (SD) or No (%)	Comments
Adult asthma								
Anani 1989	Symptoms	Preference, effect (number) at NR	NR	NR	NR	NR	NR	Albuterol vs. terbutaline, *P*>0.05
Gioulekas 1996	Rescue medication	Number of rescue treatments required	Albuterol 0.4 mg TID	32 (cross-over)	NR	25	8 (32%)	Albuterol vs. terbutaline, *P*>0.05
			Terbutaline 0.5 mg TID				9 (36%)	
	Symptoms							
		Preference, effect	Albuterol 0.4mg TID				8 (32%)	
			No preference				4 (16%)	
			Terbutaline 0.5mg TID				13 (52%)	
		Preference, overall						
			Albuterol 0.4 mg TID				4 (16%)	
			No preference				10 (40$)	
			Terbutaline 0.5 mg TID				11(56%)	
		Preference, side effects at up to 3 weeks.	Albuterol 0.4 mg TID				1 (4%)	
			No preference				14 (56%)	
			Terbutaline 0.5 mg TID				10 (10%)	
								Albuterol vs. terbutaline, *P*>0.05
		Symptom scores from diary recording daytime	Albuterol 0.4 mg TID				0.55 (NR)	
			Terbutaline 0.5mg				0.4 (NR)	
								Albuterol vs. terbutaline, *P*>0.05
		Symptom scores from diary recording nighttime	Albuterol 0.4 mg TID				0.65 (NR)	
			Terbutaline 0.5 mg TID				0.52 (NR)	
Lindsay 1994[a]	Rescue medication	Number of doses taken over 24 hr	Albuterol 0.1 mg BID	45 (cross-over)	NR	45	5.8 (2.3)	Data reported over the last 14 days of each treatment
			Terbutaline 0.5 mg BID		NR		3.2 (1.6)	
		Number of asthma exacerbations	Albuterol 0.1 mg BID		NR		2 (4%)	
			Terbutaline 0.5 mg BID		NR		1 (2%)	
		Breathlessness on exertion, symptom score	Albuterol 0.1 mg BID		0.6 (0.67)		0.6 (2.68)	Albuterol vs. terbutaline, mean difference: -0.03 (SD 0.34), 95% CI -0.1 to 0.1, *P*=0.09
			Terbutaline 0.5 mg BID		0.6 (0.67)		0.6 (0.67)	
		Preference	Albuterol 0.1 mg BID		NR		18 (39%)	
			No preference		NR		8(17%)	
			Terbutaline 0.5 mg BID		NR		20 (44%)	
		Total symptom score at 4	Albuterol 0.1 mg BID		2.0 (2.01)		2.0 (2.01)	Albuterol vs. terbutaline, mean

Author Year	Outcome category	Outcome (unit) at time point	Intervention	Baseline N	Baseline Mean (SD) or No (%)	Follow-up N	Follow-up Mean (SD) or No (%)	Comments
		weeks	Terbutaline 0.5 mg BID		1.8 (2.01)		1.8 (2.01)	difference: -0.2 (1.34), CI -0.6 to 0.2, *P*=0.3
		Wheeze, symptom score at 4 weeks	Albuterol 0.1 mg BID Terbutaline 0.5 mg BID		0.5 (0.67) 0.4 (0.67)		0.5 (0.67) 0.5 (0.67)	Albuterol vs. terbutaline, mean difference: -0.50 (0.0), CI -0.2 to 0.1, *P*=0.4
Vilsvik 1993	Symptoms	Asthma, Symptom score evening mean	Albuterol 0.1 mg, 2 doses	158 (cross-over)	NR	158	0.57 (NR)	No rescue medication was used in either period. Albuterol vs. terbutaline, mean difference 0.07 (0.39), *P*<0.001.
		Asthma, symptom score morning, mean	Terbutaline 0.5 mg Albuterol 0.2 mg Terbutaline 0.5 mg				0.50 (NR) 0.77 (NR) 0.67 (NR)	
		Preference						
			Albuterol 0.1 mg, 2 doses No preference Terbutaline 0.5 mg				39 (24.5%) 33 (20.7%) 87 (54.7%)	39% favor of terbutaline. No rescue medication was used in either period; albuterol vs. terbutaline, *P*<0.001
Pediatric asthma								
Chandra 2004	Symptoms	Composite Asthma Score, median (number) at 30 min	Albuterol 100 µg Terbutaline 250 µg	29 31	1 (NR) 2 (NR)	29 31	1 (NR) 1 (NR)	Albuterol vs. terbutaline, *P*=0.75
		Respiratory rate (rpm) at 30 min	Albuterol 100 µg Terbutaline 250 µg	29 31	26 (NR) 26 (NR)	29 31	26 (NR) 26 (NR)	Albuterol vs. terbutaline, *P*=0.72
		Wheeze score: 0 at 30 min	Albuterol 100 µg Terbutaline 250 µg	29 31	14 (48%) 15(48%)	29 31	21 (72%) 24 (77%)	Albuterol vs. terbutaline, *P*=0.66
		Wheeze score: 1at 30 min	Albuterol 100 µg Terbutaline 250 µg	29 31	15 (52%) 16 (52%)	29 31	8 (28%) 7 (23%)	
Hung 2001	Symptoms	Respiratory rate (rpm) at 30 min	Albuterol 0.125 mg/kg	15	35.34 (3.50)	30	27.41 (2.85)	Mean difference *P*<0.01
			Terbutaline 0.125 mg/kg	15	30.20 (5.12)		26.1 (3.25)	Mean difference: *P*<0.01
Oldaeus 1995	Rescue medication	Extra inhalations, day (number)	Albuterol 0.4 mg TID Terbutaline 0.5 mg TID	20 (cross-over)	NR	20	0.11 (.29) 0.13 (0.21)	
		Extra inhalations, night (number)	Albuterol 0.4 mg TID Terbutaline 0.5 mg TID				0.10 (0.20) 0.13 (0.31)	

Author Year	Outcome category	Outcome (unit) at time point	Intervention	Baseline N	Baseline Mean (SD) or No (%)	Follow-up N	Follow-up Mean (SD) or No (%)	Comments
	Symptoms	Asthma, symptom score day (score)	Albuterol 0.4 mg TID Terbutaline 0.5 mg TID				0.11 (0.29) 0.38 (0.46)	
		Asthma, symptom score night (score)	Albuterol 0.4 mg TID Terbutaline 05 mg TID				0.47 (0.6) 0.46 (0.58)	
Towns 1983	Symptoms	Preference (number)	Albuterol 200 µg No preference Terbutaline 500 µg	25 (cross-over)	NR	25	18 (72%) 2 (8%) 5 (20%)	
		Symptom score (score)	Albuterol 200 µg Terbutaline 500 µg				NR NR	Albuterol vs. terbutaline, *P*> 0.05 Mean difference: *P*<0.05
Pediatric exercise-induced bronchospasm								
Pedersen 1985	Rescue medication	Aminophylline required after treatment (number of patients)	Albuterol 0.2 mg Terbutaline 0.25 mg	24 (cross-over)	NR NR	24	5 (21%) 2 (8%)	FEV_1, 5 mins and 10 mins after the first treatment: albuterol <terbutaline, *P*<0.05 Breath holding periods varied from 5 to 10 s (mean 8.7 s), no significant difference

Abbreviations: BID, twice a day; NR, not reported; TID, three times a day.
[a] Study population ≥ 12 years of age

Table 12. Fenoterol compared with terbutaline: Demographic and study characteristics of studies with effectiveness outcomes

Author Year	Study duration	Intervention	Total N	Mean age in years (SD)	% Female	Other medications permitted during the study	Quality	Funding
Adult asthma								
Anderson 1979	Single dose	Fenoterol 0.4 mg Terbutaline 0.5 mg	17	52	35.3	All bronchodilator drugs were discontinued at least 10 h before the trial and during the whole of the trial period but patients taking corticosteroids and sodium cromoglycate continued to do so	Fair	NR
Trembath 1979	4 weeks	Fenoterol MDI Terbutaline MDI	23	44.7 (15.0)	56.5	Beclomethasone aerosol, sodium cromoglycate, theophylline derivatives	Fair	W.B. Pharmaceuticals

Abbreviations: MDI, metered dose inhaler; NR, not reported.

Table 13. Fenoterol compared with terbutaline: Effectiveness outcomes

Author Year	Outcome Category	Outcome (unit) at time point	Intervention	Baseline Total N	Baseline Mean (SD) or No (%)	Follow-up Total N	Follow-up Mean (SD) or No (%)	Comments
Adult asthma								
Anderson 1979	Symptoms	Breathing scores, a little better (number)	Fenoterol 0.4 mg	17	NR	17	5 (29%)	Breathing scores subjectively reported by patients
			Terbutaline 0.5 mg		NR		6 (35%)	
		Breathing scores, much better (number)	Fenoterol 0.4 mg		NR		2 (12%)	
			Terbutaline 0.5 mg		NR		2 (12%)	
		Breathing score, no change (number)	Fenoterol 0.4 mg		NR		3 (18%)	
			Terbutaline 0.5 mg		NR		7 (41%)	
		Breathing scores, very much better (number)	Fenoterol 0.4 mg		NR		2 (12%)	
			Terbutaline 0.5 mg		NR		1 (6%)	
		Breathing scores, worse (number	Fenoterol 0.4 mg		NR		0 (0%)	
			Terbutaline 0.5 mg		NR		1 (6%)	
Trembath 1979	Symptoms	Preference (number)	Fenoterol	23	NR	15	6 (40%)	
			No preference		NR		2 (23.3%)	
			Terbutaline		NR		7 (46.7%)	

Abbreviations: NR, not reported.

Table 14. Withdrawal rates for included studies[a]

Population	Author Year	Study duration	Intervention	N	Total withdrawals (%)	Withdrawals due to adverse events (%)
Albuterol compared with fenoterol						
Adult asthma	Newhouse 1996	Multidose, 1 day	Albuterol 100 µg Fenoterol 200 µg	129 128	0 0.8	0 0
Albuterol compared with levalbuterol						
Adult asthma	Hamilos 2007	QID for 6 months to 1 year	Levalbuterol 90 µg Albuterol 180 µg	495 250	65.5 56.8	9.3 10.0
	Nowak 2004	3 doses/h in ED	Albuterol 2.5 mg Albuterol 5.0 mg Levalbuterol 0.63 mg Levalbuterol 1.25 mg Levalbuterol 2.5 mg Levalbuterol 3.75 mg Levalbuterol 5.0 mg	14 13 12 14 12 14 12	0 0 0 0 0 0 0	0 0 0 0 0 0 0
	Nowak 2006	4 doses in first hour, then 1 dose every 40 min for 3 doses, then as needed for 24 h	Levalbuterol 1.25 mg Albuterol 2.5 mg	315 312	0 0.32	0 0
	Nelson 1998 Pleskow 2004[b]	4 weeks	Albuterol 1.25 mg Albuterol 2.5 mg Levalbuterol 0.63 mg Levalbuterol 1.25 mg	68 74 72 73	NR NR NR NR (Reported only for total randomized population: 9.4%)	2.9 5.4 4.2 11.0
Pediatric Asthma	Berger 2006	28 days	Levalbuterol HFA 90 µg (2 actuations (45 µg each) Albuterol 180ug (2 asctuations, 90ug each)	76 39	Reported only for treatment groups combined: 10.7%	1.3 2.6
	Hardasmalani, 2005	3 treatments, 1 hr	Albuterol 2.5 mg/3mL Levalbuterol 1.25 mg/3mL	34 36	NR NR	NR NR
	Milgrom 2001	3 weeks	Albuterol 1.25 mg Albuterol 2.5 mg Levalbuterol 0.31	67 66 70	2.9 9.1 8.6	NR NR NR

Population	Author Year	Study duration	Intervention	N	Total withdrawals (%)	Withdrawals due to adverse events (%)
			mg Levalbuterol 0.63 mg	70	1.4	NR
	Skoner 2005	3 weeks	Albuterol 1.25-2.5 mg Levalbuterol 0.31 mg Levalbuterol 0.63 mg	52 58 51	3.8 6.9 11.8	5.8 8.6 15.7
Albuterol compared with terbutaline						
Adult asthma	Anani 1989	3 weeks	Albuterol 400 µg QID Terbutaline 500 µg QID	30 (cross-over)	13.3 6.7	3.3 3.3
	Gioulekas 1996	3 weeks	Albuterol 0.4 mg TID Terbutaline 0.5 mg TID	32 (cross-over)	15.6 6.2	0 6.2
	Lindsay 1994[b]	4 weeks	Albuterol 0.1 mg BID Terbutaline 0.5 mg BID	47 (cross-over)	0 5.0%	0 0
	Vilsvik 1993	2 weeks	Albuterol 0.1 mg Terbutaline 0.5 mg	170 (cross-over)	Reported for total group only: 6.5%	0 0
	Webb 1982	1 week	Albuterol 200 µg Terbutaline 500 µg	16 (cross-over)	0 0	0 0
Pediatrics Asthma	Oldaeus 1995	2 weeks	Albuterol 0.4 mg TID Terbutaline 0.5 mg TID	20 (cross-over)	0 0	0 0
Fenoterol compared with terbutaline						
Adult asthma	Gray 1982	3 days	Up to 8 puffs each: Fenoterol 100 ug/dose Terbutaline 250 ug/dose	12 (cross-over)	0	0
Levalbuterol compared with albuterol plus ipratropium bromide						
Pediatric asthma	Ralston 2005	1 treatment	Racemic albuterol ≤ 3 nebulized treatments 1 mL (5.0 mg) plus ipratropium bromide 1.25 mL (0.25 mg) followed by ≤ 3 racemic albuterol treatments as needed	76	10.5	0
			Levalbuterol ≤ 6 nebulized	78	7.7	0

Population	Author Year	Study duration	Intervention	N	Total withdrawals (%)	Withdrawals due to adverse events (%)
			treatments 3.0 mL (1.25 mg)			
Albuterol compared with albuterol plus ipratropium bromide						
Pediatric asthma	Chakraborti 2006	4 actuations of salbutamol plus 4 actuations of either ipratropium bromide or placebo over 30 min	Salbutamol 100 µg plus ipratropium bromide 20 µg Salbutamol 100 µg	Total N=60; treatment group n NR	NR	NR
	Sharma 2004	4h	3 doses for each group: Salbutamol 0.3 ml/kg/dose Salbutamol 0.3 ml/kg/dose + IB 250ug/dose	 25 25	 0 0	 0 0
	Watansomsiri 2006	6 doses in 2 hrs, then additional doses of salbutamol as needed	Salbutamol 1.2 mg for children weighing <10 kg; 2.5 mg for >10 kg plus ipratropium bromide 250 µg for all weights Salbutamol 1.2 mg for <10 kg; 2.5 mg for >10 kg	38 33	Reported only for treatment groups combined: 4.1%	0
Adult asthma	Salo 2006	2 hrs	Albuterol 7.5 mg/h plus ipratropium bromide 1.0 mg/h Albuterol 7.5 mg/h	33 30	2/33 (6.1%) 1/30 (3.3%)	1/33 (3.0%) 1/30 (3.0%)
Ipratropium bromide compared with albuterol plus ipratropium bromide						
Adult asthma	Wraight 2004	Phase 1: 4 puffs TID for 2 weeks. Phase 2: study duration until deterioration in asthma control	Salbutamol 100 µg plus ipratropium bromide 20 µg Ipratropium bromide 20 µg	18 18	16.6 16.6	Reported only for treatment groups combined: 22

Abbreviations: BID, twice a day; ED, emergency department; IB, ipratropium bromide; TID, three times a day; QID, four times a day.
[a] Studies were included only if they reported withdrawal rates. Single-dose studies were excluded.
[b] Study population ≥ 12 years of age.

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Appendix A. Search strategies

Original Search

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <1st Quarter 2006>
Search Strategy:
---
1 Salmeterol.mp. (1116)
2 Serevent.mp. (21)
3 Formoterol.mp. (743)
4 Foradil.mp. (65)
5 Oxeze.mp. (0)
6 Albuterol.mp. (2365)
7 Fenoterol.mp. (783)
8 Berotec.mp. (57)
9 Levalbuterol.mp. (30)
10 Xopenex.mp. (3)
11 Orciprenaline.mp. (339)
12 Metaproterenol.mp. (163)
13 alupent.mp. (28)
14 Pirbuterol.mp. (63)
15 maxair.mp. (9)
16 Terbutaline.mp. (1099)
17 Bricanyl.mp. (89)
18 proventil.mp. (26)
19 ventolin.mp. (91)
20 salbutamol.mp. {mp=title, original title, abstract, mesh headings, heading words, keyword} (2462)
21 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 (6373)
22 (asthma$ or copd or chronic obstructive pulmonary disease$ or chronic obstructive lung disease$).mp. {mp=title, original title, abstract, mesh headings, heading words, keyword} (18092)
23 21 and 22 (4800)

Database: EBM Reviews - Cochrane Database of Systematic Reviews <1st Quarter 2006>
Search Strategy:
---
1 Salmeterol.mp. (36)
2 Serevent.mp. (5)
3 Formoterol.mp. (28)
4 Foradil.mp. (1)
5 Oxeze.mp. (0)
6 Albuterol.mp. (77)
7 Fenoterol.mp. (40)
8 Berotec.mp. (0)

9 Levalbuterol.mp. (1)
10 Xopenex.mp. (0)
11 Orciprenaline.mp. (17)
12 Metaproterenol.mp. (26)
13 alupent.mp. (3)
14 Pirbuterol.mp. (12)
15 maxair.mp. (2)
16 Terbutaline.mp. (74)
17 Bricanyl.mp. (10)
18 proventil.mp. (3)
19 alupent.mp. (3)
20 salbutamol.mp. {mp=title, abstract, full text, keywords, caption text} (116)
21 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 (153)
22 (asthma$ or copd or chronic obstructive pulmonary disease$ or chronic obstructive lung disease$).mp. {mp=title, abstract, full text, keywords, caption text} (463)
23 21 and 22 (118)

Non-clinical
Database: Ovid MEDLINE(R) <1966 to February Week 3 2006>
Search Strategy:
---
1 Salmeterol.mp. (1247)
2 Serevent.mp. (30)
3 Formoterol.mp. (717)
4 Foradil.mp. (35)
5 Oxeze.mp. (0)
6 Albuterol.mp. (6808)
7 Fenoterol.mp. (1866)
8 Berotec.mp. (101)
9 Levalbuterol.mp. (60)
10 Xopenex.mp. (4)
11 Orciprenaline.mp. (1582)
12 Metaproterenol.mp. (390)
13 alupent.mp. (128)
14 Pirbuterol.mp. (130)
15 maxair.mp. (4)
16 Terbutaline.mp. (3253)
17 Bricanyl.mp. (91)
18 proventil.mp. (29)
19 ventolin.mp. (124)
20 salbutamol.mp. {mp=title, original title, abstract, name of substance word, subject heading word} (4854)
21 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 (14125)
22 exp Asthma/dt {Drug Therapy} (22196)

23 exp Pulmonary Disease, Chronic Obstructive/dt {Drug Therapy} (1728)
24 22 or 23 (23552)
25 21 and 24 (4632)
26 limit 25 to (guideline or meta analysis or randomized controlled trial) (1715)
27 Adrenergic beta-Agonists/ (12737)
28 24 and 27 (2462)
29 limit 28 to (guideline or meta analysis or randomized controlled trial) (545)
30 26 or 29 (1823)
31 limit 30 to english language (1687)
32 limit 31 to humans (1687)
33 25 not 30 (2917)
34 limit 33 to (humans and english language) (2258)

Clinical
Database: Ovid MEDLINE(R) <1966 to February Week 3 2006>
Search Strategy:
---
1 Salmeterol.mp. (1247)
2 Serevent.mp. (30)
3 Formoterol.mp. (717)
4 Foradil.mp. (35)
5 Oxeze.mp. (0)
6 Albuterol.mp. (6808)
7 Fenoterol.mp. (1866)
8 Berotec.mp. (101)
9 Levalbuterol.mp. (60)
10 Xopenex.mp. (4)
11 Orciprenaline.mp. (1582)
12 Metaproterenol.mp. (390)
13 alupent.mp. (128)
14 Pirbuterol.mp. (130)
15 maxair.mp. (4)
16 Terbutaline.mp. (3253)
17 Bricanyl.mp. (91)
18 proventil.mp. (29)
19 alupent.mp. (128)
20 salbutamol.mp. {mp=title, original title, abstract, name of substance word, subject heading word} (4854)
21 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 (14115)
22 exp Asthma/dt {Drug Therapy} (22196)
23 exp Pulmonary Disease, Chronic Obstructive/dt {Drug Therapy} (1728)
24 22 or 23 (23552)
25 21 and 24 (4630)
26 limit 25 to (guideline or meta analysis or randomized controlled trial) (1715)
27 Adrenergic beta-Agonists/ (12737)

28 24 and 27 (2462)
29 limit 28 to (guideline or meta analysis or randomized controlled trial) (545)
30 26 or 29 (1823)
31 limit 30 to english language (1687)
32 limit 31 to humans (1687)
33 from 32 keep 1-1687 (1687)

Update Search

Update of SABA in original report: trials in asthma
Database: EBM Reviews - Cochrane Central Register of Controlled Trials <1st Quarter 2008>
Search Strategy:
---
1 Salmeterol.mp. (1324)
2 Serevent.mp. (23)
3 Formoterol.mp. (866)
4 Foradil.mp. (65)
5 Oxeze.mp. (0)
6 Albuterol.mp. (2574)
7 Fenoterol.mp. (794)
8 Berotec.mp. (61)
9 Levalbuterol.mp. (47)
10 Xopenex.mp. (2)
11 Orciprenaline.mp. (337)
12 Metaproterenol.mp. (163)
13 alupent.mp. (28)
14 Pirbuterol.mp. (61)
15 maxair.mp. (8)
16 Terbutaline.mp. (1125)
17 Bricanyl.mp. (90)
18 proventil.mp. (25)
19 ventolin.mp. (96)
20 salbutamol.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (2565)
21 2 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 (5732)
22 (asthma$ or ((exercis$ or exert$) adj5 bronchospas$)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (16253)
23 21 and 22 (3776)
24 limit 23 to yr="1898 - 1985" (957)
25 limit 23 to yr="1986 - 1993" (890)
26 limit 23 to yr="1994 - 1999" (928)
27 limit 23 to yr="2000 - 2007" (1001)

28 from 27 keep 1-1001 (1001)

Searches were restricted from 2006 to June 2008 at the Endnote level

Database: Ovid MEDLINE(R) <1996 to April Week 2 2008>
Search Strategy:
---
1 Serevent.mp. (24)
2 Foradil.mp. (38)
3 Oxeze.mp. (0)
4 Albuterol.mp. (3685)
5 Fenoterol.mp. (385)
6 Berotec.mp. (20)
7 Levalbuterol.mp. (85)
8 Xopenex.mp. (6)
9 Orciprenaline.mp. (112)
10 Metaproterenol.mp. (59)
11 alupent.mp. (2)
12 Pirbuterol.mp. (19)
13 maxair.mp. (2)
14 Terbutaline.mp. (947)
15 Bricanyl.mp. (20)
16 proventil.mp. (17)
17 ventolin.mp. (79)
18 salbutamol.mp. [mp=title, original title, abstract, name of substance word, subject heading word] (2076)
19 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 (5501)
20 exp Asthma/dt [Drug Therapy] (11071)
21 19 and 20 (1878)
22 (2006$ or "2007" or 2008$).ed. (831103)
23 21 and 22 (234)
24 from 23 keep 1-234 (234)

Database: EBM Reviews - Cochrane Database of Systematic Reviews <1st Quarter 2008>
Search Strategy:
---
1 Salmeterol.mp. (35)
2 Serevent.mp. (10)
3 Formoterol.mp. (33)
4 Foradil.mp. (3)
5 Oxeze.mp. (0)
6 Albuterol.mp. (48)
7 Fenoterol.mp. (31)
8 Berotec.mp. (0)

9 Levalbuterol.mp. (1)
10 Xopenex.mp. (0)
11 Orciprenaline.mp. (14)
12 Metaproterenol.mp. (15)
13 alupent.mp. (2)
14 Pirbuterol.mp. (12)
15 maxair.mp. (1)
16 Terbutaline.mp. (45)
17 Bricanyl.mp. (8)
18 proventil.mp. (2)
19 ventolin.mp. (12)
20 salbutamol.mp. [mp=title, abstract, full text, keywords, caption text] (83)
21 2 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 (106)
22 (asthma$ or ((exercis$ or exert$) adj5 bronchospas$)).mp. [mp=title, abstract, full text, keywords, caption text] (376)
23 21 and 22 (76)
24 from 23 keep 1-76 (76)

Searches were restricted from 2006 to June 2008 at the Endnote level

Ipratropium Bromide Searches

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <1st Quarter 2008>
Search Strategy:
---
1 ipratropium.mp. (1137)
2 (cholinerg$ adj3 (antagon$ or block$)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (435)
3 1 or 2 (1508)
4 (asthma$ or ((exercis$ or exert$) adj5 bronchospas$)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (16253)
5 3 and 4 (577)
6 from 5 keep 1-577 (577)

Searches were restricted from 2006 to June 2008 at the Endnote level

Ipratropium bromide: systematic reviews

Database: Ovid MEDLINE(R) <1996 to April Week 2 2008>
Search Strategy:
---
1 ipratropium.mp. [mp=title, original title, abstract, name of substance word, subject heading word] (754)
2 exp Asthma/dt [Drug Therapy] (11071)

3 1 and 2 (199)
4 limit 3 to (guideline or meta analysis or randomized controlled trial) (73)
5 exp Cholinergic Antagonists/ (17108)
6 2 and 5 (241)
7 limit 6 to (guideline or meta analysis or randomized controlled trial) (66)

Ipratropium bromide, EIB: trials from 1950 to current
Database: Ovid MEDLINE(R) <1950 to May Week 3 2008>
Search Strategy:
---

1 asthma, exercise induced/
2 ipratropium. Mp
3 1 and 2
4 cholinergics.mp.
5 1 and 4
6 Limit 3 to English
7 Limit 6 to human
8 From 7 keep 1-38

Appendix B. Quality assessment methods for drug class reviews for the Drug Effectiveness Review Project

This appendix outlines the methods used by the Oregon Evidence-based Practice Center, based at Oregon Health & Science University, and any subcontracting Evidence-based Practice Centers in producing drug class reviews for the Drug Effectiveness Review Project.

The procedure outlined in this appendix ensures that the reviews created by using these methods are scientifically defensible, reproducible, and well documented. These methods were adapted from the Procedure Manual developed by the Methods Work Group of the United States Preventive Services Task Force (version 1.9, September 2001), with additional material from the National Health Service Centre for Reviews and Dissemination report *Undertaking Systematic Reviews of Research on Effectiveness: CRD's Guidance for Carrying Out or Commissioning Reviews* (2nd edition, 2001) and "The Database of Abstracts of Reviews of Effects (DARE)" in *Effectiveness Matters*, vol. 6, issue 2, December 2002, published by the Centre for Reviews and Dissemination.

All included studies and systematic reviews are assessed for quality and assigned a rating of "good," "fair," or "poor". Studies that have a fatal flaw in 1 or more criteria are rated poor quality. Studies that meet all criteria are rated good quality. The remainder are rated fair quality. As the "fair-quality" category is broad, studies with this rating vary in their strengths and weaknesses: The results of some fair quality studies are *likely* to be valid, while others are only *probably* valid. A poor-quality trial is not valid: Its results are at least as likely to reflect flaws in the study design as a true difference between the compared drugs.

Controlled Trials

Assessment of Internal Validity

1. Was the assignment to treatment groups really random?
    - Adequate approaches to sequence generation:
        - Computer-generated random numbers
        - Random numbers tables
    - Inferior approaches to sequence generation:
        - Use of alternation, case record number, date of birth, or day of week
    - Not reported

2. Was the treatment allocation concealed?
    - Adequate approaches to concealment of randomization:
        - Centralized or pharmacy-controlled randomization
        - Serially-numbered identical containers
        - On-site computer based system with a randomization sequence that is not readable until allocation
        - Other approaches sequence to clinicians and patients
    - Inferior approaches to concealment of randomization:
        - Use of alternation, case record number, date of birth, or day of week
        - Open random numbers lists

Serially numbered envelopes (even sealed opaque envelopes can be subject to manipulation)

Not reported

3. Were the groups similar at baseline in terms of prognostic factors?

4. Were the eligibility criteria specified?

5. Were outcome assessors blinded to the treatment allocation?

6. Was the care provider blinded?

7. Was the patient kept unaware of the treatment received?

8. Did the article include an intention-to-treat analysis or provide the data needed to calculate it (that is, number assigned to each group, number of subjects who finished in each group, and their results)?

9. Did the study maintain comparable groups?

10. Did the article report attrition, crossovers, adherence, and contamination?

11. Is there important differential loss to follow-up or overall high loss to follow-up? (Give numbers in each group.)

Assessment of External Validity (Generalizability)

1. How similar is the population to the population to whom the intervention would be applied?

2. How many patients were recruited?

3. What were the exclusion criteria for recruitment? (Give numbers excluded at each step)

4. What was the funding source and role of funder in the study?

5. Did the control group receive the standard of care?

6. What was the length of follow-up? (Give numbers at each stage of attrition.)

For Studies Reporting Complications/Adverse Events

Assessment of Internal Validity

1. Was the selection of patients for inclusion non-biased; that is, was any group of patients systematically excluded?

2. Is there important differential loss to follow-up or overall high loss to follow-up? (Give numbers in each group.)

3. Were the investigated events specified and defined?

4. Was there a clear description of the techniques used to identify the events?

5. Was there unbiased and accurate ascertainment of events (independent ascertainers, validation of ascertainment technique)?

6. Were potential confounding variables and risk factors identified and examined using acceptable statistical techniques?

7. Was the duration of follow-up reasonable for investigated events? (Did it meet the stated threshold?)

Assessment of External Validity

1. Was the description of the population adequate?

2. How similar is the population to the population to whom the intervention would be applied?

3. How many patients were recruited?

4. What were the exclusion criteria for recruitment? (Give numbers excluded at each step.)

5. What was the funding source and role of funder in the study?

Systematic Reviews

1. Are a clear review question and inclusion and exclusion criteria reported for the primary studies?

A good-quality review should focus on a well defined question or set of questions, which ideally refer to the inclusion/exclusion criteria by which decisions are made on whether to include or exclude primary studies. The criteria should reflect 4 components: study design, indications (patient populations), interventions (drugs), and outcomes of interest. In addition, details should be reported about the process of decision-making; that is, how many reviewers

were involved, whether the studies were examined independently, and how disagreements between reviewers were resolved.

2. Is there evidence of a substantial effort to search for all relevant research?

The answer to this question usually is yes if details of electronic database searches and other identification strategies are given. Ideally, search terms and date and language restrictions should be presented. In addition, descriptions of hand-searching, attempts to identify unpublished material, and any contact with authors, industry, or research institutes should be provided. The appropriateness of the database(s) searched by the authors should also be considered. For example, if only MEDLINE was searched for a review on health education, then it is unlikely that all relevant studies were located.

3. Is the validity of included studies adequately assessed?

A systematic assessment of the quality of primary studies should include an explanation of the criteria used (for example, what method of randomization was used, whether outcome assessment was blinded, and whether analysis was on an intention-to-treat basis). Authors may use either a published checklist or scale or one that they designed specifically for their review. Again, the process relating to the assessment should be explained (that is, how many reviewers were involved, whether the assessment was independent, and how discrepancies between reviewers were resolved).

4. Is sufficient detail of the individual studies presented?

The review should demonstrate that the included studies are suited to answering the question posed and that a judgement on the appropriateness of the authors' conclusions can be made. If a paper includes a table giving information on the design and results of the individual studies or includes a narrative description of the studies within the text, this criterion is usually fulfilled. If relevant, the tables or text should include information on study design, sample size in each study group, and patient characteristics. They also should include a description of interventions, settings, outcome measures, follow-up, drop-out rate (withdrawals), effectiveness results, and adverse events.

5. Are the primary studies summarized appropriately?

The authors should attempt to synthesize the results from individual studies. In all cases, there should be a narrative summary of results, which may or may not be accompanied by a quantitative summary (meta-analysis).

For reviews that use a meta-analysis, heterogeneity between studies should be assessed using statistical techniques. If heterogeneity is present, the possible reasons (including chance) should be investigated. In addition, the individual evaluations should be weighted in some way (for example, according to sample size or by inverse of the variance) so that studies that are thought to provide the most reliable data have greater impact on the summary statistic.

Appendix C. Cochrane systematic reviews related to beta$_2$-agonists

Author, year Title (abbreviated)	Objective	Number of trials	Conclusions
Camargo C 2003 Continuous versus intermittent beta-agonists for acute asthma	To determine the efficacy (for example, reductions in admission, improvement in pulmonary functions) and risks (for example, adverse events, effects on vital signs) of continuous versus intermittent inhaled beta-agonists for the treatment of patients with acute asthma managed in the emergency department.	8	Current evidence supports the use of continuous beta-agonists in patients with severe acute asthma who present to the emergency department to increase their pulmonary function and reduce hospitalization. Moreover, continuous beta-agonist treatment appears to be safe and well tolerated in patients who receive it.
Chroinin M, 2004 Addition of inhaled long-acting beta$_2$-agonists to inhaled steroids	To compare the efficacy of initiating anti-inflammatory therapy using either the combination of inhaled corticosteroids plus long-acting beta$_2$-agonists or inhaled corticosteroids alone in steroid-naive children and adults with persistent asthma.	18	In steroid-naive patients with mild to moderate airway obstruction, the initiation of inhaled corticosteroids in combination with long-acting beta$_2$-agonists does not significantly reduce the rate of exacerbations over that achieved with inhaled corticosteroids alone; it does improve lung function and symptom-free days but does not reduce rescue beta$_2$-agonist use as compared to inhaled steroids alone. Both options appear safe. There is insufficient evidence to recommend use of combination therapy rather than inhaled corticosteroids alone as a first-line treatment.
Chroinin M, 2005 Long-acting beta$_2$-agonists versus placebo in addition to inhaled corticosteroids	To quantify in asthmatic patients the safety and efficacy of the addition of long-acting beta$_2$-agonists to inhaled corticosteroids on the incidence of asthma exacerbations, pulmonary function, and other measures of asthma control.	49	In patients who are symptomatic on low to high doses of inhaled corticosteroids, the addition of a long-acting beta$_2$-agonist reduces the rate of exacerbations requiring systemic steroids and improves lung function, symptoms, and use of rescue short-acting beta$_2$-agonists. The similar number of serious adverse events and withdrawal rates in both groups provides some indirect evidence of the safety of long-acting beta$_2$-agonists as add-on therapy to inhaled corticosteroids.
Gibson P, 2005 Long-acting beta$_2$-agonists as an inhaled corticosteroid-sparing agent	To determine the efficacy of adding long-acting beta$_2$-agonists to maintenance inhaled corticosteroid therapy in reducing the requirement for inhaled corticosteroids while maintaining control of chronic asthma.	10	In adults with asthma who use moderate to high maintenance doses of inhaled corticosteroids, the addition of long-acting beta$_2$-agonists has an inhaled corticosteroid-sparing effect. The addition of long-acting beta$_2$-agonists permits more participants on minimum maintenance inhaled corticosteroids to reduce inhaled corticosteroid. The precise magnitude of the inhaled corticosteroid dose reduction requires further study.
Greenstone I, 2005 Combination of inhaled long-acting beta$_2$-agonists and inhaled steroids	To determine, in asthmatic patients, the effect of the combination of long-acting beta$_2$-agonists and inhaled corticosteroids compared with a higher dose of inhaled corticosteroids on the incidence of asthma exacerbations, on	30	In adults with asthma there was no significant difference between the combination of long-acting beta$_2$-agonists and inhaled corticosteroids and a higher dose of inhaled corticosteroids for the prevention of exacerbations requiring systemic corticosteroids. Overall, the combination therapy led to greater

Author, year Title (abbreviated)	Objective	Number of trials	Conclusions
	pulmonary function, and on other measures of asthma control, and to look for characteristics associated with greater benefit for either treatment option.		improvement in lung function, symptoms, and use of rescue beta$_2$-agonists, (although most of the results are from trials of up to 24 weeks duration). There were fewer withdrawals due to poor asthma control in this group than in groups using a higher dose of inhaled corticosteroids. Apart from an increased rate of tremor, the 2 options appear safe, although adverse effects associated with long-term inhaled corticosteroid treatment were seldom monitored.
Plotnick L, 2000 Combined inhaled anticholinergics and beta$_2$-agonists	To estimate the therapeutic and adverse effects attributable to the addition of inhaled anticholinergics to beta$_2$ agonists in acute pediatric asthma.	13	A single dose of an anticholinergic agent is not effective for the treatment of mild and moderate exacerbations and is insufficient for the treatment of severe exacerbations. Adding multiple doses of anticholinergics to beta$_2$-agonists appears safe, improves lung function, and would avoid hospital admission in 1 of 12 such treated patients. Although multiple doses should be preferred to single doses of anticholinergics, the available evidence supports only their use in school-aged children with severe asthma exacerbation. There is no conclusive evidence for using multiple doses of anticholinergics in children with mild or moderate exacerbations.
Ram F, 2002 Pressurized metered dose inhalers (pMDI) versus all other hand-held inhaler devices	To determine the clinical effectiveness of pMDI compared with any other available handheld inhaler device for the delivery of short-acting beta-2 agonist bronchodilators in non-acute asthma in children and adults.	84	In patients with stable asthma, short-acting beta-2 bronchodilators in standard chlorofluorocarbon-pMDIs are as effective as any other devices. The effect of hydrofluoroalkane-pMDI on requirement for oral corticosteroid courses to treat acute exacerbations should be confirmed. Effectiveness studies that use an intention-to-treat analysis are required.
Ram F, 2005 Long-acting beta$_2$-agonists versus leukotriene receptor antonists (LTRA) as add-on therapy	We compare the efficacy and safety profile of adding either daily long-acting beta$_2$-agonists or LTRA in asthmatic patients with asthma who remained symptomatic on inhaled corticosteroids.	8	In asthmatic adults inadequately controlled on low doses of inhaled steroids, the addition of long-acting beta$_2$-agonists is superior to LTRA for preventing exacerbations requiring systemic steroids and for improving lung function, symptoms, and use of rescue beta$_2$-agonists.
Shah L, 2003 Long-acting beta$_2$-agonists versus theophylline	To assess the comparative efficacy, safety, and side effects of long-acting beta$_2$-agonists and theophylline in the maintenance treatment of adults and adolescents with asthma.	12	Long-acting beta$_2$-agonists are at least as effective as theophylline in reducing asthma symptoms including night waking and in improving lung function. Fewer adverse events occurred in participants using long-acting beta$_2$-agonists (salmeterol and formoterol) than theophylline.
Walters E, 2002 Regular treatment with long-acting beta agonists versus short-	To determine the benefit or detriment of treatment with regular short- or long-acting inhaled beta-agonists in chronic asthma.	31	Long-acting inhaled beta-agonists have advantages across a wide range of physiological and clinical outcomes for regular treatment.

Author, year Title (abbreviated)	Objective	Number of trials	Conclusions
acting agents			
Walters E, 2003 Inhaled short-acting beta$_2$-agonsts in chronic asthma	To assess the effects of using short-acting inhaled beta$_2$-agonsts regularly or only on demand in asthmatic adults and children on indices of asthma control.	49	In general these results support current guidelines, although it has given reassuring evidence against concerns over regular use of inhaled short-acting beta$_2$-agonsts.
Walters E, 2003 Long-acting beta$_2$-agonists for stable chronic asthma	To determine the benefit or detriment on the primary outcome of asthma control of regular use of long acting inhaled beta$_2$-agonists compared with placebo.	85	Long acting beta$_2$-agonists are effective in the control of chronic asthma, and evidence supports their use in addition to inhaled corticosteroids, as emphasized in current guidelines. Further research is needed on their use in children under 12 and in patients with mild asthma who are not taking inhaled corticosteroids.

Appendix D. Excluded studies

Reasons for exclusion:

1 = Foreign language
2 = Outcome not included
3 = Drug not included
4 = Population not included
5 = Wrong publication type[a]
6 = Wrong study design[b]

[a] Wrong publication type (letter with insufficient information, editorial, non-systematic review, case report, case series < 10 patients)
[b] Wrong study design (placebo-controlled trial, active-controlled trial, sample size < 10 patients, focus on delivery method, dosing range study, LABA vs. SABA)

Citation	Exclusion Code
A levalbuterol metered-dose inhaler (Xopenex HFA) for asthma. *Medical Letter on Drugs & Therapeutics.* 2006 Mar 13 2006;48(1230):21-22.	5
Aggarwal P, Pande JN, Guleria JS. Bronchodilators in acute bronchial asthma : a comparative study. *Indian J Chest Dis Allied Sci.* 1986;28(1):21-27.	3
Agostini, M., G. Barlocco, et al. (1983). "Protective effect of fenoterol spray, ipratropium bromide plus fenoterol spray, and oral clenbuterol, on exercise induced asthma in children. Double blind controlled and randomized clinical trial." *European Journal of Respiratory Diseases*	6
Ahlstrom H, Svenonius E, Svensson M. Treatment of asthma in pre-school children with inhalation of terbutaline in Turbuhaler compared with Nebuhaler. *Allergy.* 1989;44(7):515-518.	6-DELIVERY
Albertini M, Pin I, Toussaint S, Fragneaud C. Efficacy of salmeterol versus alternative treatments in non-controlled asthmatic children. *European Respiratory Society.* 1999.	5
Alvarez GG, Schulzer M, Jung D, Fitzgerald JM. A systematic review of risk factors associated with near-fatal and fatal asthma. *Can Respir J.* Jul-Aug 2005;12(5):265-270.	5
Ameredes BT. Adverse effects of short-acting beta-agonists: potential impact when anti-inflammatory therapy is inadequate: comment. *Respirology.* Nov 2004;9(4):570-571.	5
American Lung Association Asthma Clinical Research, C., S. P.Peters, et al. (2007). "Randomized comparison of strategies for reducing treatment in mild persistent asthma." *The New England Journal of Medicine* 356(20): 2027-39.	3
Andersen LH, Haghfelt T. Regional lung function in asthmatics in remission, before and after fenoterol. *B Eur Physiopath Res.* 1980;16(2):215-228.	6-DESIGN
Anderson H, Ayres J, Sturdy P, et al. Bronchodilator treatment and deaths from asthma: case-control study. *BMJ.* 2005;330:117-124.	6
Anderson SD, Rozea PJ, Dolton R, Lindsay DA. Inhaled and oral bronchodilator therapy in exercise induced asthma. *Aust N Z J Med.* 1975;5(6):544-550.	6

Citation	Exclusion Code
Angelici E, Delfino M, Carlone S, Serra P, Fineberg NS, Farber MO. Tolerance to inhaled fenoterol. *Am Rev Respir Dis.* Jun 1984;129(6):1014-1016.	6-DESIGN
Ankerst J, Lotvall J, Cassidy S, Byrne N. Comparison of the bronchodilating effects of formoterol and albuterol delivered by hydrofluoroalkane pressurized metered-dose inhaler. *Treat Respir Med.* 2005;4(2):123-127.	6-LONG VS. SHORT
Appleton S, Pilotto L, Smith B, Muhammad J. Anticholinergic bronchodilators versus beta$_2$-adrenoceptor agonists for stable chronic obstructive pulmonary disease. *Cochrane Db Syst Rev.* 2006;1.	5
Appleton S, Poole P, Smith B, Cates C, Veale A, Bara A. Long-acting beta$_2$-agonists for chronic obstructive pulmonary disease patients with poorly reversible airflow limitation. *Cochrane Db Syst Rev.* 2006;1.	6
Appleton, S., T. Jones, et al. (2008). "Ipratropium bromide versus short acting beta-2 agonists for stable chronic obstructive pulmonary disease." *Cochrane Database of Systematic Reviews.*	4
Aquilina R, Bergero F, Noceti P, et al. Protective effect of Duovent versus salbutamol in long-term treatment. *Respiration.* 1986;50(SUPPL. 2):240-244.	6
Ariano R, Giacca S. Variations of individual susceptibility to beta-adrenergic and anticholinergic bronchodilator drugs. *Minerva Pneumologie.* 1981;20(3):141-147.	1
Arledge TE, Liddle R, Stahl E, Rossing TH. Salmeterol does not cause tolerance during long-term asthma therapy. *J Allergy Clin Immun.* 1996;98(6 Pt 1):1116-1119.	6-LONG VS. SHORT
Aronson N, Lefevre F, Piper M, et al. Management of chronic asthma. *Evid Rep Technol Assess.* Sep 2001(44):1-10.	6-DESIGN
Arvidsson P, Larsson S, Lofdahl CG. Objective and subjective bronchodilation over 12 hours after inhaled formoterol: individual responses. *J Asthma.* 1993;30(6):459-465.	6-LONG VS. SHORT
Arvidsson P, Larsson S, Lofdahl CG, Melander B, Svedmyr N, Wahlander L. Inhaled formoterol during one year in asthma: a comparison with salbutamol. *Eur Respir J.* 1991;4(10):1168-1173.	6-LONG VS. SHORT
Arvidsson P, Larsson S, Lofdahl CG, Melander B, Wahlander L, Svedmyr N. Formoterol, a new long-acting bronchodilator for inhalation. *Eur Respir J.* 1989;2(4):325-330.	6-LONG VS. SHORT
AstraZeneca (2006). "A comparison of the control of asthma inflammation provided by Symbicort turbuhaler 160/4.5 mcg/inhalation bid plus as-needed versus symbicort turbuhaler 320/9 µg/inhalation bid plus pulmicort turbuhaler 400µg/dose bid plus terbutaline turbuhaler 0.4mg/inhalation as-needed." ClinicalTrials.gov	6
Aubier M, Pieters WR, Schlosser NJ, Steinmetz KO. Salmeterol/fluticasone propionate (50/500 microg) in combination in a Diskus inhaler (Seretide) is effective and safe in the treatment of steroid-dependent asthma. *Respir Med.* 1999;93(12):876-884.	3
Auerbach D, Hill C, Baughman R, et al. Routine nebulized ipratropium and albuterol together are better than either alone in COPD. *Chest.* 1997;112(6):1514-1521.	6
Avila-Castanon L, Casas-Becerra B, Del Rio-Navarro BE, Velazquez-Armenta Y, Sienra-Monge JJ. Formoterol vs. albuterol administered via Turbuhaler system in the emergency treatment of acute asthma in children. *Allergol Immunopathol.* 2004;32(1):18-20.	6-LONG VS. SHORT

Citation	Exclusion Code
Ayers ML, Mejia R, Ward J, Lentine T, Mahler DA. Effectiveness of salmeterol versus ipratropium bromide on exertional dyspnoea in COPD. *Eur Respir J.* 2001;17(6):1132-1137.	6
Bach-Mortensen N. Experience with the inhalation of Berotec powder in the treatment of asthma in children. *Eur J Respir Dis.* 1983;130:25-27.	6
Backlund L, Fagerberg E. Ventilatory capacity after bronchodilatation with a new beta-sympathomimetic substance. *Scand J Respir Dis.* 1968;49(4):284-290.	6-DESIGN
Bacon CJ. Nebulised salbutamol in treatment of acute asthma in children. *Lancet.* Jan 21 1978;1(8056):158.	5
Bannister OM. The effectiveness of nebulised salbutamol in the management of acute asthma in children. *Physiotherapy.* May 1980;66(5):144-146.	6
Barnabe R, Rossi M, Rottoli P. Fenoterol inhalation powder in long-term therapy of bronchial asthma. *Eur J Respir Dis.* 1983;128((Pt 2)):533-535.	6-DESIGN
Barnes N. Bronchodilation subsensitivity to salbutamol after salmeterol. *Lancet.* Oct 7 1995;346(8980):968; author reply 968-969.	5
Barnes, P. J. (2006). "Treatment with (R)-albuterol has no advantage over racemic albuterol." *American Journal of Respiratory & Critical Care Medicine* 174(9): 969-72; discussion 972-4.	5
Barr RG, Rowe BH. Short acting $beta_2$-agonists for exercise induced asthma. *Cochrane Db Syst Rev.* 2006;1.	5
Bass BH, Disney ME, Morrison-Smith J. Effect of salbutamol on respiratory function in children with asthma. *Lancet.* Aug 23 1969;2(7617):438.	5
Beach JR, Young CL, Harkawat R, et al. Effect on airway responsiveness of six weeks treatment with salmeterol. *Pulm Pharmacol.* 1993;6(2):155-157.	6-LONG VS. SHORT
Becker AB, Simons FE. Formoterol, a new long-acting selective beta 2-adrenergic receptor agonist: double-blind comparison with salbutamol and placebo in children with asthma. *J Allergy Clin Immun.* 1989;84(6 Pt 1):891-895.	6-LONG VS. SHORT
Becker AB, Simons FE. Formoterol, a new long-acting selective beta 2-agonist, decreases airway responsiveness in children with asthma. *Lung.* 1990;168(Suppl):99-102.	6-LONG VS. SHORT
Behling B, Matthys H. Comparison of efficacy and safety of formoterol with terbutaline in children with mild to moderate asthma. *European Respiratory Society.* 1999.	5
Bell R, Sahay JN, Barber PV, Chatterjee SS, Cox G. A therapeutic comparison of ipratropium bromide and salbutamol in asthmatic patients. *Curr Med Res Opin.* 1982;8(4):242-246.	6
Bellamy D, Penketh A. A cumulative dose comparison between salbutamol and fenoterol metered dose aerosols in asthmatic patients. *Postgrad Med J.* 1987;63(740):459-461.	6-SAMPLE SIZE
Benhamou D, Cuvelier A, Muir JF, et al. Rapid onset of bronchodilation in COPD: a placebo-controlled study comparing formoterol (Foradil Aerolizer) with salbutamol (Ventodisk). *Respir Med.* 2001;95(10):817-821.	6-LONG VS. SHORT
Bennett JA, Smyth ET, Pavord ID, Wilding PJ, Tattersfield AE. Systemic effects of salbutamol and salmeterol in patients with asthma. *Thorax.* 1994;49(8):771-774.	6-LONG VS. SHORT

Citation	Exclusion Code
Bennis J, Svedmyr N. A controlled comparison of salbutamol and terbutaline inhaled by IPPV in asthmatic patients: a dose-response study. *Scand J Respir Dis.* 1977;101:113-117.	6-SAMPLE SIZE
Bensch G, Lapidus RJ, Levine BE, et al. A randomized, 12-week, double-blind, placebo-controlled study comparing formoterol dry powder inhaler with albuterol metered-dose inhaler. *Ann Allergy Asthma Immunol.* 2001;86(1):19-27.	6-LONG VS. SHORT
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Drug Class Review

Quick-relief Medications for Asthma

Final Report Update 1
Evidence Tables

October 2008

The purpose of this report is to make available information regarding the comparative effectiveness and safety profiles of different drugs within pharmaceutical classes. Reports are not usage guidelines, nor should they be read as an endorsement of, or recommendation for, any particular drug, use or approach. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.

Update 1
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TABLE OF CONTENTS

Evidence Table 1. Included studies

Berger, 2006 **Quality rating:** Poor

Design:

Study design RCT DB **Run-in:** 1-week SB **Setting:** Clinic
Country: USA

Sample: # Screened / Eligible / Enrolled
NR / 173/ 150

Withdrawn / Lost to follow-up / Analyzed
16/ NR/134

Inclusion criteria: Children aged 4-11 years; stable asthma for at least 6 months before screening; FEV between 45% and 80% predicted with ≥ 12% reversibility to 2.5 mg of nebulized racemic albuterol at screening

Exclusion criteria: Participation in an investigational study within 30 days of screening; known sensitivity to study medications or components; hospitalization for asthma within 60 days prior to screening; clinically significant upper or lower respiratory tract infection within 2 weeks of screening; clinically significant ECG abnormalities

Comments

Intervention:

Duration: 28 days

Drug name	Dosage	N	Mean age (years)	Gender
Levalbuterol HFA MDI	90µg (2 puffs, 45µg/puff) qid	76	8.3	49% male
Placebo HFA MDI		35	8.1	22% male
Racemic albuterol HFA MDI	180µg (2 puffs, 90µg/puff) qid	39	8.6	23% male

Outcomes:

Effectiveness Outcomes:

Symptoms: NR

Change in treatment regimen for the exacerbation:

	Levalbuterol	Racemic Albuterol	Placebo
LS mean change ± SD in rescue medication usage (days/week)	0.72 ± 0.17*	0.62 ± 0.24*	0.35 ± 0.24
LS mean number ± SD of nebules/day	-0.15± 0.05	-0.05± 0.07	0.14 ± 0.07
Mean ± SD number of asthma control days/week	5.45 ± 1.58	5.76 ± 1.23	4.98 ± 1.88

*P <0.001 levalbuterol vs. placebo; P <0.01 racemic albuterol vs. placebo

Healthcare utilization:

Quality of life

No clinically meaningful differences between the active treatments and placebo for the : Pediatric Asthma QOL Questionnaire, the Child Health Questionnaire, or the patient and physician overall evaluations (data not reported)

Mortality: NR

Other Effectiveness Outcomes and Comments:

Adverse Events and Comments:

	Levalbuterol n (%)	Racemic Albuterol n(%)	Placebo n (%)
Any adverse event	33(43.4)	22(56.4)	18(51.4)
Discontinued due to AEs	1(1.3)	1(2.6)	3(8.6)
Potentially related AEs	6(7.9)	6(15.4)	5(14.3)
β- mediated AEs	1(1.3)	1(2.6)	1(2.9)
Respiratory AEs	21(27.6)	16(41.0)	12(34.2)
Asthma AEs	8(10.5)	5(12.8)	5(14.3)

Evidence Table 1. Included studies

Chakraborti, 2006 **Quality rating :** Fair

Design:

Study design RCT DB **Run-in:** NR **Setting:** Hospital clinic
Country: India

Sample: # Screened / Eligible / Enrolled
NR / NR/ 60

Withdrawn / Lost to follow-up / Analyzed
NR/ NR/ 60

Inclusion criteria: Children between 5-15 years of age; mild to moderate acute exacerbation of asthma who were able to perform spirometry

Exclusion criteria: Severe acute exacerbation; coexisting cardiac or renal disease; known intolerance to salbutamol or ipratropium bromide; glaucoma, urinary retention and children who had used oral bronchodilator in the last 12 hours or inhaled bronchodilator in the last 6 hours

Comments Patients could be enrolled twice in study if events were more than one month apart

Intervention:

Duration: 30 minutes

Drug name	Dosage	N	Mean age	Gender
Salbutamol with ipratroprium bromide*	100 µg /actuation of salbutamol; 20µg ipratropium	30	106 months	63% males
Salbutamol*	100 µg /actuation	30	118 months	57% males

*All patients were administered 4 actuations of salbutamol through similar looking MDI and spacer. Then 4 actuations of either ipratropium or placebo were administered

Outcomes:

Effectiveness Outcomes:

Symptoms

Comparison of salbutamol with ipratropium bromide and salbutalmol after treatment

	Salbutamol with ipratropium	Salbutamol	p-value
Heart rate/min	119.43±17.09	115.3±18.70	0.38
Respiratory rate/min	27.9±4.67	28.97±5.84	0.44
Wheeze score	1.07±0.83	1.2±0.71	0.51
Accessory muscle score	0.17±0.46	0.43±0.82	0.24

Change in treatment regimen for the exacerbation: NR
Healthcare utilization: NR
Mortality: NR

Other Effectiveness Outcomes and Comments:

Adverse Events and Comments:

NR

Evidence Table 1. Included studies

Hamilos, 2007 **Quality rating:** Poor

Design:

Study design RCT Open **Run-in:** 1-week SB **Setting:** NR **Country:** USA

Sample:

# Screened / Eligible / Enrolled	# Withdrawn / Lost to follow-up / Analyzed
NR / 932 / 746	330/ 40 /746

Inclusion criteria:

≥ 12 years; had stable asthma for at least 6 months; an FEV_1 of 50% or higher and 80% or lower of predicted, 12% or higher of reversibility of airflow obstruction within 13 to 30 minutes after administration of 180µg of racemic albuterol MDI; used a β_2 - adrenergic agonist, antiasthma anit-inflammatory medication, or over-the-counter asthma medication for at least 6 months before screening

Exclusion criteria: History of life-threatening asthma within 3 months of screening or if they were hospitalized for acute asthma within 45 days of screening; greater than 10-pack-year history of cigarette smoking within 6 months of screening

Comments * The study protocols were amended to reduce the study period to 6 mos for newly-enrolled patients. 7% of patients were from prior phase 3 trials with no reason given

Intervention:

Duration: 6 months to 1 year

Drug name	Dosage	N	Mean age	Gender
Levalbuterol	MDI 90ug qid	496	38	35.3% male
Racemic albuterol	MDI 180ug qid	250	39	33.2% male

Outcomes:

Effectiveness Outcomes:

Symptoms: NR

Healthcare utilization: NR

Asthma Quality of Life Questionnaire (AQLQ)

Both groups improved to a similar extent on the adult AQLQ.
Pediatric AQLQ was greater for levalbuterol than racemic albuterol:
levalbuterol 0.96±0.92; racemic albuterol -0.02+1.18

	Levalbuterol	Racemic Albuterol
Compliance Rate (12 months; %)	95.70%	96.10%
Rescue Medication Use	72.60%	68.90%

Mortality: 0

Other Effectiveness Outcomes and Comments:

Adverse Events and Comments:

	No. (%) of patients	
	Levalbuterol	**Racemic albuterol**
Adverse events		
Body as a whole	180 (36.3)	104 (41.6)
Abdominal pain	18 (3.6)	17 (6.8)
Unintentional injury	37 (7.5)	26 (10.4)
Flu syndrome	19 (3.8)	17 (6.8)
Headache	67 (13.5)	38 (15.2)
Pain	48 (9.7)	33 (13.2)
Respiratory system	272 (54.8)	141 (56.4)
Asthma	91 (18.3)	49 (19.6)
Bronchitis	36 (7.3)	18 (7.2)
Cough increased	40 (8.1)	24 (9.6)
Pharyngitis	49 (9.9)	25 (10.0)

Rhinitis	48 (9.7)	39 (15.6)	
Sinusitis	56 (11.3)	31 (12.4)	
Viral infection	150 (30.2)	71 (28.4)	
Overall frequency of Aes (%)	72	76.8	(p = 0.12)
At least 1 adverse event	357 (72.0)	192(76.8)	
Serious adverse events[1]	18 (3.6)	13 (5.2)	
Asthma adverse events			
Overall	91(18.3)	49(19.6)	
No. of single events	70(14.1)	33(13.2)	
Duration > 24 hours	83(16.7)	43(17.2)	
Asthma attack[2]			
Overall	81(16.3)	46(18.4)	
No. of single events	61(12.3)	34(13.6)	
Duration > 24 hours	74(14.9)	41(16.4)	
Expanded - definition asthma adverse events[3]			
Overall	131(26.4)	83(33.2)	
No. of single events	71(14.3)	48(19.2)	
Duration > 24 hours	123(24.8)	77(30.8)	

[1] Serious adverse events included any event that was fatal or life threatening, was permanently disabling, required hospitalization, was a congential anomaly, or required intervention to prevent permanent damage

[2]Defined as an asthma adverse event that required hospitalization, emergency department visit, treatment with oral burst or parentera cortocosteroids, or an unscheduled clinic visit

[3] Defined as adverse events of asthma, combined with adverse events of bronchitis, cough increase, dysponea, or lung disorder

Evidence Table 1. Included studies

Nowak, 2006 **Quality rating:** Fair

Design:

Study design RCT DB **Run-in:** NR **Setting:** Hospital ED/clinic
Country: USA

Sample: # Screened / Eligible / Enrolled: NR /NR/627
Withdrawn / Lost to follow-up / Analyzed: 1/0/626

Inclusion criteria: ≥ 18 years; presented to ED/clinic with acute exacerbation of asthma; an FEV_1 value of 20-55% predicted; at least a 6-month history of physician diagnosed asthma; an oxygen saturation of at least 90% with no more than 6L/min supplemental oxygen; non-pregnant; no other known (non-asthma) cause of wheezing or shortness of breath

Exclusion criteria: Respiratory distress of sufficient severity to preclude enroolment in the trial were excluded to avoid delayed treatment; patients administered therapy other than oxygen after ED/clinic arrival; history of severe asthma within previous 12 months; undergone treatemnt of acute asthma within 2 weeks; or hospitalization within 1 month of presentation; ≥ 10-pack year smoking history

Comments

Intervention:

Duration:

Drug name	Dosage	N	Mean age	Gender
Levalbuterol	1.25 mg	315	37.2	62.2% female
Racemic albuterol	2.5 mg	312	37	61.2% female Note: all patients received 40 mg of prednisone

Both treatment drugs were administered every 20 minutes in the first hour, then every 40 minutes for 3 additional doses, then as necessary for up to 24 hours. All patients received 40 mg prednisone Po.

Outcomes:

Effectiveness Outcomes:

Symptoms: NR
Change in treatment regimen for the exacerbation: NR

Healthcare utilization:	Levalbuterol		Racemic albuterol		
Time to discharge (min)	76		78.5		p= .74
Admission rate (%)	7	(95% CI 4.2-9.8)	9.3	(95%CI 6.1-12.6)	p= .28
Relapse rate (% at 30 days)	5.5		5		p= NR
Blood glucose	NSD		NSD		
Potassium	NSD		NSD		

Mortality: NR

Other Effectiveness Outcomes and Comments:

Adverse Events and Comments:

	Levalbuterol(%)	Racemic albuterol (%)
Overall	9.80	10.90
Headache	1.00	3.20
Nervousness	3.20	2.20
Tremor	2.20	2.20
Tachycardia	1.9	2.9
Asthma event	4.8	3.5

Evidence Table 1. Included studies

Ralston, 2005 **Quality rating:** Fair

Design:

Study design RCT DB **Run-in:** NA **Setting:** Hospital **Country:** USA

Sample: # Screened / Eligible / Enrolled: 833 / 306/ 154; # Withdrawn / Lost to follow-up / Analyzed: 14/ 0/ 140

Inclusion criteria: Patients 6-18 years; history of asthma of any severity; demonstrated ability to use a peak flow meter and with a PEF of <80% on presentation to ED

Exclusion criteria: Known sensitivity to study meds; previous study enrollment; impending or actual respiratory arrest or treatment or treatment with Levalbuterol or Ipratropium bromide within the 6 h of study enrollment

Comments

Intervention:

Duration: 1 treatment

	Dosage	N	Mean age (years)	Gender
Drug name				
Racemic albuterol and ipratropium bromide	Up to 3 nebulized treatments 1mL (5.0 mg) RAC mixed with 1.25 mL (0.25 mg) IB followed as needed by RAC dosing	76	11.5	50 % male
Levalbuterol	Up to 6 nebulized treatments 3.0 mL (1.25mg) LEV	78	11.7	58% male

Outcomes:

	Racemic albuterol and Ipratropium bromide n (%)	Levabuterol n(%)
Effectiveness Outcomes:		
New symptoms no. (%)		
Tremor	20(29)	17(24)
Nervousness	13(19)	8(11)
Nausea or vomiting	6(9)	2(3)
Palpitations	9(13)	5(7)
Headache	9(13)	6(8)
Any symptoms	33(49)	29(40)
HR_{final} beats/min mean (SE)	126 (3.0)	114(2.7)
HR_{max} beats/min mean (SE)	130 (3.4)	119(3.1)
Increase $HR_{initial\ to\ final}$		
Beats/ min mean (SE)	26(2.8)	10(3.0)
% Median (Q_1, Q_3)	20(13,43)	8(-1,23)
Increase $HR_{initial\ to\ max}$		
Beats/ min mean (SE)	29 (3.1)	16(3.0)
% Median (Q_1, Q_3)	26(14, 48)	9 (2, 27)
HR_{max} above normal range for age # (%)	47(73)	35(51)

Symptoms: NR

Change in treatment regimen for the exacerbation: NR

Healthcare utilization:

	Racemic albuterol and Ipratropium bromide	Levabuterol	p Value
ED length of stay (LOS) min median (Q_1, Q_3)	94(70, 133)	80 (60, 122)	0.13
72 hr return for asthma	0(0)	1(1)	1
Number of adjunctive meds in ED # (%)	9(13)	21(29)	0.022

Oral steroids in ED # (%)	59(87)	50(70)	0.014
i.v. steroids in ED # (%)	0(0)	1(1)	1

Admission rate: admission rate : 1.4% for study population; 2 study patients admitted 1 (RAC/IB) to PICU and 1(LEV) to ED

Mortality: NR

Other Effectiveness Outcomes and Comments:

Adverse Events and Comments:

No serious AEs reported

Evidence Table 1. Included studies

Salo, 2006 **Quality rating:** Good

Design:

Study design RCT DB **Run-in:** NR **Setting:** Hospital ED
Country: USA

Sample:

# Screened / Eligible / Enrolled	# Withdrawn / Lost to follow-up / Analyzed
375 / 166/63	1/ NR/ 62

Inclusion criteria: >18 years; PEFR<70% predicted; prior history of asthma; wheezing; or wheezing for the first time and meeting ATS definition of asthma including patients who had a history of asthma diagnosed by a physician or who had episodes of wheezing that improved with β-2 agonist inhalers

Exclusion criteria: Refusal to give informed consent; use of ipratroprium bromide in the past 48 hours; previous enrollment in this study; greater than 20 pack year history of smoking ; symptomatic angina pectoris; known symptomatic atherosclerotic heart disease;; patients who can perform a PEFR; pregnant women; HR >150 beats per minute, BP> 180/100 mm Hg; cystic fibrosis; tuberculosis or pulmonary malignancies; any infection controlled with antibiotics; pneumonia; active in any study at enrollment or 4 weeks prior; taking any oral steroids; known allergies to study medications; current alcohol or drug use

Comments

Intervention:

Duration: 120 minutes

Drug name	Dosage	N	Median age	Gender
Albuterol and ipratropium bromide*	7.5 mg/h and 1.0 mg/h	33	33	
Albuterol*	A: 7.5 mg/h	30	38	

* Both treatments given continously over 120 minutes

Outcomes:

Effectiveness Outcomes:

Symptoms: NR
Change in treatment regimen for the exacerbation: NR
Healthcare utilization:

Admission rates

Albuterol and ipratropium bromide	8/32 (25%)	OR: 1.66 (95% CI, 0.48 - 5.8) p = 0.621
	5/30 (16.7%)	

Mortality: NR

Other Effectiveness Outcomes and Comments:

Adverse Events and Comments:

Shortness of breath

Albuterol and ipratropium bromide	1 (3%)
Albuterol	1 (3%)

Mild congestive heart failure

Albuterol	1 (3%)

Evidence Table 1. Included studies

Sharma, 2004 **Quality rating:** Poor

Design:

Study design RCT NB **Run-in:** NR **Setting:** Hospital ED **Country:** India

Sample: # Screened / Eligible / Enrolled: NR/ NR/ 50; # Withdrawn / Lost to follow-up / Analyzed: NR/ NR /50

Inclusion criteria: 6-14 years; reported to ED with acute exacerbation of bronchial asthma

Exclusion criteria: Life threatening or severe attack characterized by cyanosis, silent chest or poor air entry maked by dyspnoea so that a child was unable to speak 3-4 words; PEFR <30% for height; received bronchodilator 6 hours prior to admission; history of previous admission to ICU

Comments Listed refernce did not provide specific wheeze or dypnea score

Intervention:

Duration: 240 minutes

Drug name	Dosage	N	Mean age	Gender
Salbutamol (via nebulizer)	150ug/kg/dose every 20 minutes for 3 doses; maximum 5.0mg dose	25	10.3	NR
Combined salbutamol and ipratropium bromide (via nebulizer)	250 µgm /dose for 3 doses every 20 minutes	25	10.6	NR

Outcomes:

Effectiveness Outcomes:

		Wheeze Score*	*p-value*	Dysponea Score*	*p-value*
Symptoms	Salbutamol (via nebulizer)	0.52±0.1	<0.05	0.60±0.24	<0.05
	Combined salbutamol and ipratropium bromide (via nebulizer)	0.2±0.08	<0.05	0.20±0.08	<0.05

* 240 minutes

Change in treatment regimen for the exacerbation: NR
Healthcare utilization: Hospitalization rate: salbutamol 4/25 (16%) ; salbutamol and ipratropium bromide 1/25 (4%)
Mortality: NR

Other Effectiveness Outcomes and Comments:

Adverse Events and Comments:

	No. of patients (%)	
	Salbutamol	**Salbutamol and Ipratroipium Bromide**
Tremors	8(32%)	4(16%)
Vomiting	3(12%)	1(4%)
Cough	0	6(24%)
Transient eye irritation	0	2(8%)

Evidence Table 1. Included studies

van der Merwe L, 2006 **Quality rating:**

Design:

Study design: Case-control **Run-in:** N/A **Setting:** Hospital and respiratory clinic
Country: South Africa

Sample: Severe life threatening asthma (SLTA): 30
Control: 60

Inclusion criteria: 13-45 years
SLTA: meet admission criteria for SLTA

Exclusion criteria: < 13 years; > 45 years
Control: history of an asthma related admission to an ICU

Comments: The SLTA group were drawn from patients admitted to the emergency room while the control group was drawn from an outpatient respiratory clinic

Population: **Mean age (SE):** SLTA 31 (1.7); Control 30.8(1.1)
Gender (% female): SLTA 83.3; Control 60

Intervention:

Duration:

Drug name	Dosage	N	Mean age	Gender
Various drugs (includes fenoterol 200 ug MDI)	NR			

Outcomes:

Adverse Events and Comments:

Mortality:
SLTA: 13% (4/30)
Control: NR

Treatment with asthma medications in study patients
β agonists (%) - Inhaled fenoterol*
Cases: 68 (17/25)
Control: 28.8 (17/59)
OR 6(95% CI 2.2 TO 16.2)
p = 0.0004
* Subjects not on fenterol were on salbutamol except for one patient in the SLTA group who was suing inhaled anticholinergic medication

Evidence Table 1. Included studies

Watanasomsiri, 2006 **Quality rating:** Fair

Design:

Study design: RCT DB **Run-in:** NR **Setting:** Hospital
Country: Thailand

Sample:

# Screened / Eligible / Enrolled	# Withdrawn / Lost to follow-up / Analyzed
NR / NR/ 74	3/ 0 / 71

Inclusion criteria: A clinical diagnosis of asthma. Patients < 5 years had to have ≥ 3 episodes of wheezing before the presenting illness and a history of physician diagnosed wheezing.

Exclusion criteria: Patients excluded if they presented with a first-time wheezing episode and if they had 1 or more of the following conditions: coexistent cardiac, renal, or other chronic pulmonary diseases; bronchopulmonary dysplasia;intolerance to salbutamol or ipratroprium bromide; glaucoma; or urinary retention. Patients who had used ipratroprium bromide within 24 hours, used oral corticosteroids within 3 days, and required immediate resuscitation or airway intervention were also excluded from the study

Comments

Population:

Intervention:

Duration: Every 20 minutes for 120 minutes and additional doses of salbutamol every 30 minutes PRN

Drug name:	Dosage	N	Mean age	Gender
Salbutamol mixed with 250 µ of ipratropium bromide (Treatment)	NR	38	7.4 years	NR
Salbutamol mixed with isotonic NaCL solution (Control)	NR	33	6.6 years	NR

Comments: The dose of salbutamol was 1.2 mg for body weight < 10 kg and 2.5 mg for body weight > 10 kg.
All patients received 0.5 mg/kg of an oral steroid with the second dose of nebulized solution

Outcomes:

Effectiveness Outcomes:

Symptoms: Authors reported no statistically significant differences in percent change in clinical scores (Accessory muscle score; Wheeze score; Dyspnea score) were found. Subgroup analysis by age and severity showed no statistically significant differences between the 2 groups at any time point. No baseline or follow-up data reported for clinical scores.

Change in treatment regimen for the exacerbation: NR

Healthcare utilization (%): Treatment 5 (2/38); Control 9 (3/33) were hospitalized

Mortality: NR

Other Effectiveness Outcomes and Comments:

Adverse Events and Comments:

Headache (%)
Treatment: 3 (1/38)
Control: 0
Nausea (%)
Treatment: 3 (1/38)
Control: 3(1/33)

Evidence Table 1. Included studies

Wraight, 2004 **Quality rating:** Fair-poor

Design:

Study design RCT NR Parallel **Run-in:** 2 weeks **Setting:** **Country:** New Zealand

Sample: # Screened / Eligible / Enrolled 47 / 40/ 40 # Withdrawn / Lost to follow-up / Analyzed 9/ NR / 31

Inclusion criteria: 18-70 years, taking a minimum of 200 µ/day of inhaled beclomethasone or equivalent; methacoline PD < 8 µmol; and non-smokers or ex-smokers (< 5 pack-years).

Exclusion criteria: History of life-threatening asthma; a requirement for oral prednisone within the previous 3 months; inability to withdraw short or long-acting beta agonists; and any other significant medical conditions.

Comments The 2-week run-in period withdrew all beta-agonist treatment from patients and substituted ipratropium bromide as the sole reliever medication.

Intervention:

Duration: Phase 1: 2 weeks; Phase 2: continued until a deterioration in asthma control (LOC) occurred after inhaled corticosteroid therapy (ICS) withdrawal.

Drug name	Dosage	N	Mean age	Gender
Salbutamol/ Ipratropium	100 µg/20 µg, 4 puffs tid	18	41.2	39 % male 61 % female
Ipratropium	20 µg, 4 puffs tid	18	39.8	56% male 44% female

Outcomes:

Effectiveness Outcomes:

Symptoms: Mean time to loss of asthma control (days): Salbutamol/Ipratropium 8.9 (14.5 to 13.3); Ipratropium 16.8 (12.2 to 21.4) p = .03
Change in treatment regimen for the exacerbation:
Healthcare utilization: NR
Mortality: NR

Other Effectiveness Outcomes and Comments:

Adverse Events and Comments:

Unstable asthma	1 (2.5%)
Required β-agonist	1(2.5%)
Inadequate rise in eNO	5(12.5%)

Evidence Table 2. Quality assessment of controlled trials for quick relief medications for asthma

Internal validity

Author Date Country	Was the assignment to the treatment groups really random?	Was the treatment allocation concealed?	Were the groups similar at baseline in terms of prognostic factors?	Were the eligibility criteria specified?	Were outcome assessors blinded to the treatment allocation	Was the care provider blinded?	Was the patient kept unaware of the treatment received	Did the article include an ITT analysis, or provide the data needed to calculate it?	Did the study maintain comparable groups?
Berger, W 2006 USA	Unclear, methods NR	Unclear, methods NR	Yes	Yes	Unclear; reported as DB	Unclear; reported as DB	Yes	Yes (5/150 patients excluded)	Yes
Chakraborti, A 2006 India	Yes	Yes (3rd party administration of MDIs)	Yes (salbutaomol group 12m older, p=0.04)	Yes	Yes	Yes	Yes	Unclear; attriton NR	Unclear
Hamilos, D 2007 USA	Unclear, methods NR	Unclear, methods NR	Yes	Yes	No	No	No	Unclear	Unclear
Nowak, R 2006 USA	Unclear, methods NR	Unclear, methods NR	Yes	Yes	Unclear; reported as DB	Unclear; reported as DB	Unclear	Yes (Table 2 accounts for 626/627 subjects)	Yes
Ralston, M 2005 USA	Yes (random number table)	Yes (central randomization)	Yes	Yes	Yes	Yes	Yes	No (completers only analyzed, 90.9% of total)	Yes
Salo, D 2006 USA	Yes (random number table)	Yes (central randomization)	Yes	Yes	Unclear; reported as DB	Yes (treatments were identical)	Yes (treatments were identical)	Yes; 62/63 randomized were analyzed	Yes
Sharma, A 2004 India	Unclear, methods NR	Unclear, methods NR	Yes	Yes	No, open label	No, open label	No, open label	Unclear; appears that all subjects were analyzed; no correction of multiple comparisons	Yes
Watanasomsiri, A 2006 Thailand	Unclear, methods NR	Yes (central randomization and dispensing by 3rd party)	No, are statistical differences in SaO2 and time of onset of attack between groups; SaO2 differered by 1.3%	Yes	Yes	Yes	Yes	No, 71/74 were analyzed	Yes
Wraight 2004 New Zealand	Unclear, methods NR	Unclear, methods NR	Yes, groups were statistically the same but FEV1 was greater in the IB group; post hoc analysis with matching on FEB1 was therefore performed.	Yes	Unclear; no mention blinding	Unclear; no mention blinding	Unclear; no mention blinding	No; appears that only completers were analyzed (31/40)	Unclear; FEV1 differed at baseline (P>0.05)

Evidence Table 2. Quality assessment of controlled trials for quick relief medications for asthma

				External validity					
Author Date Country	**Did the article report attrition, crossovers, adherence, and contamination?**	**Was there important differential loss to follow-up or overall high loss to follow-up?(give numbers in each group)**	**Quality**	**How similar is the population to the population to whom the intervention would be applied?**	**How many patients were recruited?**	**What were the exclusion criteria for recruitment? (Give numbers excluded at each step)**	**What was the funding source and role of funder in the study?**	**Did the control group receive the standard of care?**	**What was the length of follow-up? (Give numbers at each stage of attrition)**
Berger, W 2006 USA	Yes No No No	No	Fair	Unclear; 150/173 patients randomized	Unclear; NR for run-in period; 173 started run-in	NR	Sepracor Inc; role NR; 2 coauthors are from Sepracor	No, qid regular dosing of albuterol is not usual care	28 days
Chakraborti, A 2006 India	No No No No	Unclear	Fair	Unclear; recruitment NR	NR	Severe asthma; comorbid conditions	NR	Yes (albuterol)	Outcomes measured "after treatment" but time interval NR
Hamilos, D 2007 USA	Yes No Yes No	High loss to F/U (44% (similar rates between groups); authors amended protocol from 12 to 6-m F/U and defined completion with respect to 6 months; no rationale for change given	Poor	Unclear 746/932 enrolled	932/ accessi ble popuolation NR	Recent, severe asthma attack	Sepracore Inc.; role NR; 4 coauthors from Sepracor		52 weeks
Nowak, R 2006 USA	No No No No	Unclear; appear to have only lost 1 patient (table 2) but did use LOCF for FEV1 data	Fair	Unclear; total accessible population NR	Unclear; 627 entered study	Severe respiratory distress	Sepracor Inc; role NR	Yes	24 hours
Ralston, M 2005 USA	Yes No No No	No	Fair	Unclear; only 154/833 elegible patients were recruited	154	impending respiratory arrest, treatmen with levalbuterol or IB in last 6h	NR: site of study was Naval Medical Center, Portsmouth, Virginia	Yes	Length of ER visit
Salo, D 2006 USA	Yes Yes No No	No	Good	Unclear; 66/375 were enrolled	66	92/375 potential patients were 'missed' for inclusion; exclusion criteria: use of IB in last 48h and others	Funder NR; B&B Technologies supplied the Hope Nebulizers for the study	Yes (continuous albuterol)	Length of ER visit
Sharma, A 2004 India	Unclear No No No	Unclear	Poor	Unclear	MR	Exclusion criteria NR	NR	Yes (albuterol)	240 minute (ER visit)
Watanasomsiri, A 2006 Thailand	Yes No No No	No	Fair	Unclear; recruitment NR	NR	First-time wheezers, other comorbidities, etc	NR	Yes (albuterol)	Length of ER visit
Wraight 2004 New Zealand	Yes No Yes No	No; 5 patients withdrawn as failed to demonstrate a significant increase in airway inflammation after withdrawal of steroids	Fair-poor	Unclear (recruitment NR)	47 were screened	Severe asthma, recent oral steroids		No, both groups received regular SABA and steroids were withdrawn from both groups	Phase 1 was 2 weeks; phase 2 until loss of control; longest time to loss of control NR