

Drug Class Review

Quick-relief Medications for Asthma

Final Report Update 1
Executive Summary

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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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.

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).

Asthma medications fall into 2 general classes: medications for long-term control and medications for quick relief of airflow obstruction and symptoms. Persons with persistent asthma require long term controller and quick relief medications. This report focuses on medications for the quick relief of bronchoconstriction and acute symptoms, including short acting beta₂-agonists and anticholinergic agents.

Beta₂-agonists act mainly to relax airway smooth muscle by stimulating beta₂-receptors, which in turn increase cyclic AMP and produce functional antagonism to bronchoconstriction. The short-acting beta₂-agonists relax airway smooth muscle, increase airflow within 30 minutes, 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 beta₂-agonists are not recommended for regularly scheduled, daily use.

Anticholinergic (antimuscarinic) agents such as ipratropium bromide 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 beta₂-agonists, but its effects last up to 6 hours.

Exercise-induced asthma

Exercise-induced asthma is characterized by coughing, wheezing, shortness of breath, and chest tightness during or after exercise. 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, FEV₁). In exercise-induced bronchospasm exercise precipitates airway obstruction, but lung function is normal at rest. 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.

Scope and Key Questions

The purpose of this review is to compare the benefits and harms of short-acting beta₂-agonists and ipratropium bromide used for quick relief of asthma symptoms.

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

To identify relevant citations, 2 independent reviewers identified potentially relevant titles and abstracts from the Cochrane Central Register of Controlled Trials (Issue 2, 2008), Cochrane Database of Systematic Reviews, DARE, and MEDLINE (1966 to June 2, 2008). 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. In addition, we were asked to review 2 drugs available only in Canada: terbutaline (Bricanyl™) and fenoterol (Berotec™).

We abstracted relevant descriptive and outcomes data into a relational database developed for this review. We assessed the internal validity (quality) of controlled clinical trials using predefined criteria that are based on those used by the United States Preventive Services Task Force and the National Health Service Centre for Reviews and Dissemination. These criteria were then used to categorize studies into good-, fair-, and poor-quality studies. 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.

Inclusion and exclusion criteria: Update 1

Included populations

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

Included interventions

1. Inhaled short-acting beta₂-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

Included comparisons

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

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 room

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

RESULTS

For the original report we identified 95 papers on children or adult asthma; 61 of those had relevant data on effectiveness and safety or withdrawal data (the remainder had efficacy data only). For Update 1 we identified 10 new studies in addition to 2 systematic reviews which were used as the basis for the review of ipratropium bromide.

Systematic reviews

The original report identified no systematic reviews of head-to-head comparisons of interest. We used 2 recent systematic reviews as the basis for our review of ipratropium bromide for Update 1. Both of these reviews focused on chronic asthma; 1 review examined anticholinergic agent use for more than 1 week in children more than 2 years of age; the other review was of adults with anticholinergic use for more than 24 hours. The results of these reviews are summarized in the relevant section for each drug comparison.

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?

Adults

Albuterol compared with levalbuterol

One randomized controlled trial compared the regular use albuterol and levalbuterol, both given three times daily via nebulizer to patients with moderate to severe asthma. Less rescue medication was required at 4-week follow up compared to baseline in all active treatment groups, but was statistically significant (at $\alpha = 0.05$) only with 1.25 mg levalbuterol ($P < 0.001$). Other effectiveness data were not reported in this study.

Two studies compared levalbuterol to albuterol in the emergency department for acute asthma exacerbations. A pilot, controlled clinical trial found a decreased need for additional treatment with levalbuterol compared with comparable albuterol dosages, but hospital admission rates were similar. A study found no significant difference overall between groups in rates of admission or relapse or time in the emergency department. For patients not using corticosteroids, levalbuterol decreased admission rates compared with albuterol ($P = 0.03$). A third randomized controlled trial was of poor quality.

Albuterol compared with albuterol plus ipratropium bromide

In a Cochrane review of 8 trials with regular usage of these two treatment regimes, there was no significant difference in symptom score or rates of adverse events between treatments. In 1 additional randomized controlled trial of this comparison, use in the emergency department produced no significant difference in the rate of hospital admissions.

Ipratropium bromide compared with ipratropium bromide plus albuterol

In one small, fair-to-poor quality randomized controlled trial where these drugs were used on a regular basis as metered dose inhalers, the mean time to loss of control was shorter in the albuterol/ipratropium group than with ipratropium alone ($P = 0.03$).

Levalbuterol compared with albuterol plus ipratropium bromide

No effectiveness data were identified.

Albuterol compared with pirbuterol

No effectiveness data were identified.

Comparisons of interest in Canada: Adults

Terbutaline compared with albuterol

Symptom scores did not differ between the two treatment groups in 1 fair-quality study. Three other poor-quality studies were also identified.

Fenoterol compared with terbutaline

One randomized controlled trial found no significant difference in symptoms scores and a second trial found no difference in patient preferences between the two drugs.

Fenoterol compared with albuterol

No effectiveness data were identified (1 poor-quality randomized controlled trial).

Terbutaline compared with pirbuterol

No effectiveness data were identified.

Fenoterol compared with ipratropium bromide

No effectiveness data were identified.

Children

Albuterol compared with levalbuterol

Three randomized controlled trials examined regular use of these two drugs. The first study demonstrated no significant difference in symptoms, quality of life, or the use of rescue medications at 21 days. There were, however, fewer days of adequately controlled asthma with levalbuterol 0.63 mg and albuterol 1.25 mg than with levalbuterol 0.31 mg on days 14-21 ($P<0.04$). The second study of children age 2-5 years showed improvement in all groups with no significant difference in symptom control between groups. The third study showed no significant difference in use of rescue medication between albuterol metered dose inhaler and levalbuterol metered dose inhaler administered four times daily for 28 days.

Three other randomized controlled trials examined the treatment of children with acute asthma exacerbations in the emergency department. There was no significant difference in symptoms (2 studies), need for additional treatments (3 studies), or length of stay in emergency department (2 studies). 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 plus ipratropium bromide

In the one relevant study where children were treated in the emergency department, there were no significant differences in length of stay in the emergency department or hospital, or in the number of nebulization treatments. Fewer levalbuterol patients, however, required adjunct medications ($P=0.02$).

Albuterol compared with albuterol plus ipratropium bromide

In a Cochrane review, 1 randomized controlled trial was identified and showed no significant difference in symptoms scores between groups with regular usage via metered dose inhaler. We identified two additional fair-quality randomized controlled trials of this comparison, both involving the treatment of acute asthma. One of these trials showed no significant difference in hospital admissions or rescue medication use; the second trial noted no significant difference in symptoms 30 minutes after treatment.

Ipratropium bromide compared with ipratropium bromide plus albuterol

No effectiveness data were identified.

Albuterol compared with pirbuterol

No effectiveness data were identified.

Comparisons of interest in Canada: Children

Terbutaline compared with albuterol

There was no significant difference in symptoms between the two drugs in three randomized controlled trials.

Fenoterol compared with ipratropium bromide

In a Cochrane review, 1 randomized controlled trial was identified which demonstrated no significant difference in symptom scores after one week of regular usage. We did not identify any additional studies of this comparison.

Fenoterol compared with fenoterol plus ipratropium bromide

In a Cochrane review, 1 randomized controlled trial was identified but did not have sufficient data to draw conclusions about comparative effectiveness.

Fenoterol compared with terbutaline

No effectiveness data were identified.

Terbutaline compared with pirbuterol

No effectiveness data were identified.

Fenoterol compared with albuterol

No effectiveness data were identified.

Exercise-induced asthma: Adults and children

Data were very sparse on exercise-induced asthma. In a comparison of terbutaline and albuterol 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 (no between-group statistics).

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?

Adverse events related to sympathomimetic side effects are expected with these medications. In addition, there was a broad range of gastrointestinal, musculoskeletal, and other miscellaneous adverse events. There were generally no clinically significant differences in the rates and severity of adverse events between the various drugs examined (at comparable dosages) in this review.

Adults

Albuterol compared with levalbuterol

There were no significant differences in withdrawal rates between study groups (3 studies). Heart rate increased with both drugs (3 studies). In 1 study providing between-group statistics, there

was a greater increase in heart rate with albuterol. There were no significant difference in blood pressure (1 study), palpitations (1 study), tachycardia (1 study), increased blood glucose (1 study), or dizziness/nervousness/anxiety/tremor (6 studies). Potassium decreased acutely in all 5 studies examining this outcome, with no significant difference between drugs for comparable dosages.

Albuterol compared with albuterol plus ipratropium bromide

In the relevant Cochrane review, all 7 included studies had similar withdrawal rates between the 2 treatment groups. We identified no other data on adverse events for this comparison.

Albuterol compared with pirbuterol

There were no comparative adverse event data.

Levalbuterol compared with albuterol plus ipratropium bromide

There were no comparative adverse event data.

Ipratropium bromide compared with albuterol plus ipratropium bromide

There were no comparative adverse event data.

Comparisons of interest in Canada: Adults

Fenoterol compared with albuterol

In adults, blood pressure decreased 1 to 6 mm Hg after both drugs (7 studies), while heart rate response varied (-5 to +15 beats/minute) (9 studies). The decrease in potassium was not significantly different between treatment groups (2 studies).

In a case control examining the predictors for severe life threatening asthma in a tertiary care hospital in South Africa, 30 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 for the use of inhaled fenoterol (200 µg metered dose inhaler) compared with the use of albuterol was 6.8 (95% CI 2.2 to 16.2; $P=0.0004$).

Terbutaline compared with albuterol

In adults, effects on blood pressure were similar between treatment groups (1 study). Heart rate increased 5 to 15 beats/minute ($P<0.05$) (3 studies). Headache was rare with both drugs (2 studies).

Terbutaline compared with fenoterol

There were no comparative adverse event data in either children or adults.

Terbutaline compared with pirbuterol

There were no comparative adverse event data in either children or adults.

Children

Albuterol compared with levalbuterol

Withdrawal rates varied in the 2 studies reporting these data. An increase in heart rate was noted in 3 studies, with no significant differences between comparable dosing groups. There were no

data on blood pressure. There was no significant difference between drugs for adverse effects of tremor (1 study), light-headedness (1 study), dizziness (1 study), or nervousness (1 study). Blood glucose increased and potassium decreased with both drugs, with no significant differences between the two treatments for comparable dosages.

Albuterol compared with pirbuterol

There were no comparative adverse event data.

Levalbuterol compared with albuterol plus ipratropium bromide

In the emergency department heart rate increased more with albuterol 5.0 mg plus ipratropium bromide 0.25 mg than with levalbuterol 1.25 mg. Rates of tremor, nervousness, nausea, and headache were not significantly different between groups.

Albuterol compared with albuterol plus ipratropium bromide

In two studies in the emergency department and one with regular use for 1 week, there were no significant differences in adverse events between treatment groups.

Ipratropium bromide compared with albuterol plus ipratropium bromide

There were no comparative adverse event data.

Comparisons of interest in Canada: Children

Fenoterol compared with albuterol

There was minimal reporting of adverse events in these studies. Tremor was noted to be more marked with salbutamol than with terbutaline or with fenoterol (1 study). Heart rate increased more with salbutamol and fenoterol than with terbutaline ($P < 0.05$).

Terbutaline compared with albuterol

In children, potassium decreased approximately 0.5 meq/L with both drugs 30 minutes after treatment (1 study). Palpitations were noted in a small number of children (1 study).

Terbutaline compared with fenoterol

There were no comparative adverse event data.

Terbutaline compared with pirbuterol

There were no comparative adverse event data.

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. 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, 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 and no study stratified results based on race. Two studies compared albuterol with levalbuterol in predominantly African American pediatric patients with asthma and 2 studies examined minority adult patients. One of the studies in children showed a decreased rate of hospitalization with levalbuterol compared with albuterol; the other showed no significant difference. In adults, 1 randomized controlled trial showed no significant difference in hospitalization rates; the second trial in adults did not examine effectiveness outcomes. In the only other study with a predominantly minority population, albuterol was compared with albuterol plus ipratropium bromide for adults with acute asthma in the emergency room, and subgroups based on age or disease severity revealed no significant difference between groups (specific outcomes referred to are unclear).

Comorbidities

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

CONCLUSIONS

Table 1. 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	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.
	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	
	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).

