



Quick Relief Medicines For Asthma

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DRAFT

Produced by:
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Health Resources Commission

The State of Oregon’s Health Resources Commission is a volunteer commission appointed by the Governor. The Health Resources Commission provides a public forum for discussion and development of consensus regarding significant emerging issues related to medical technology. Created by statute in 1991, it consists of four physicians experienced in health research and the evaluation of medical technologies and clinical outcomes; one representative of hospitals; one insurance industry representative; one business representative; one representative of labor organizations; one consumer representative and two pharmacists. All Health Resources Commissioners are selected with conflict of interest guidelines in mind. Any minor conflict of interest is disclosed.

The Commission is charged with conducting medical assessment of selected technologies, including prescription drugs. The commission may use advisory committees or subcommittees, the members to be appointed by the chairperson of the commission subject to approval by a majority of the commission. The appointees have the appropriate expertise to develop a medical technology assessment. Subcommittee meetings and deliberations are public, where public testimony is encouraged. Subcommittee recommendations are presented to the Health Resources Commission in a public forum. The Commission gives strong consideration to the recommendations of the advisory subcommittee meetings and public testimony in developing its final reports.

Overview

The 2001 session of the Oregon Legislature passed Senate Bill 819, authorizing the creation of a Practitioner-managed Prescription Drug Plan (PMPDP). The statute specifically directs the Health Resources Commission (HRC) to advise the Oregon Medical Assistance (OMAP) Department of Human Services (DHS) on this Plan.

In 2007 the Oregon Health Resources Commission (HRC) appointed a pharmaceutical subcommittee to perform evidence-based reviews of pharmaceutical agents. Members of the subcommittee for this review consisted of three Physicians, a Nurse Practitioner, and two pharmacists. All meetings were held in public with appropriate notice provided. The HRC director worked with the Center for Evidence-based Policy (Center) and the Oregon Health and Science University’s (OHSU) Evidence-based Practice Center (EPC) to develop and finalize key questions for this drug class review, specifying patient populations, medications to be studied and outcome measures for analysis, considering both effectiveness and safety. Evidence was specifically sought for subgroups of patients based on race, ethnicity and age, demographics, other medications and co-morbidities. Using standardized methods, the EPC reviewed systematic databases, the medical literature and dossiers submitted by pharmaceutical manufacturers. Inclusion and exclusion criteria were applied to titles and abstracts, and each study was assessed for quality according to predetermined criteria.

The EPC’s report, “*Quick Relief Medications for Asthma*”, October 2008, was circulated to subcommittee members and posted on the web. The subcommittee met to review the document and this report is the consensus result of those meetings. Time was allotted for public comment, questions and testimony.

This report does not recite or characterize all the evidence that was discussed by the OHSU EPC, the Subcommittee or the HRC. This report is not a substitute for any of the information provided during the subcommittee process, and readers are encouraged to review the source materials. This report is prepared to facilitate the HRC in providing recommendations to the Department of Human Services. The HRC, working together with the EPC, the Center for Evidence Based Policy, DMAP, and the Oregon State University College of Pharmacy, will monitor medical evidence for new developments in this drug class. Approximately twice per year new pharmaceuticals will be reviewed and if appropriate, a recommendation for inclusion in the PMPDP will be made. For pharmaceuticals on the plan, significant new evidence will be assessed and Food and Drug Administration changes in indications and safety recommendations will be evaluated. This report will be updated if indicated. Substantive changes will be brought to the attention of the Health Resources Commission, who may choose to approve the report, or reconvene a subcommittee.

The full OHSU Evidence-based Practice Center's draft report, "*Quick Relief Medications For Asthma*" is available via the Office for Oregon Health Policy & Research, Practitioner-Managed Prescription Drug Plan website:

www.oregon.gov/DAS/OHPPR/ORRX/HRC/evidence_based_reports.shtml

Information regarding the Oregon Health Resources Commission and its subcommittee policy and process can be found on the Office for Oregon Health Policy & Research website:

<http://www.oregon.gov/DAS/OHPPR/HRC/index.shtml>

You may request more information including copies of the draft report from:

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Information dossiers submitted by pharmaceutical manufacturers are available upon request from the OHSU Center for Evidence-based Policy by contacting:

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There will be a charge for copying and handling in providing documents from both the Office of Oregon Health Policy & Research and the Center for Evidence Based Policy.

Critical Policy

Senate Bill 819

– “The Department of Human Services shall adopt a Practitioner-managed Prescription Drug Plan for the Oregon Health Plan. The purpose of the plan is to ensure that enrollees of the Oregon Health Plan receive the most effective prescription drug available at the best possible price.”

Health Resources Commission

– “Clinical outcomes are the most important indicators of comparative effectiveness”

– “If evidence is insufficient to answer a question, neither a positive nor a negative association can be assumed.”

Clinical Overview

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 Survey³ 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 beta2-agonists.^{1, 2} Medications for quick relief of bronchoconstriction and acute symptoms include short-acting beta2-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, FEV1). 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 beta2-agonist 15 minutes prior to exercise.⁴ Additional, daily therapy may be required for management of underlying chronic asthma.

Inhaled beta2-agonists

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.² Beta2-agonists may also have anti-inflammatory properties, as suggested by in vitro experiments.⁵

The short-acting beta2-agonists relax airway smooth muscle and increase airflow within 30 minutes¹ 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.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 beta2-agonists, but its effects last up to 6 hours.⁹ In a 2000 Cochrane review Plotnick and colleagues¹⁰ 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 beta2-agonists improves lung function and avoids hospital admission in some patients.

Quality of the Evidence

For quality of evidence the EPC and subcommittee took into account the number of studies, the total number of patients in each study, the length of the study period and the endpoints of the studies. Statistical significance was an important consideration. The subcommittee utilized the EPC's ratings of "good, fair or poor" for grading the body of evidence. Overall quality ratings for an individual study were based on the internal and external validity of the trial.

Internal validity of each trial was based on:

- 1) Methods used for randomization
- 2) Allocation concealment and blinding
- 3) Similarity of compared groups at baseline and maintenance of comparable groups
- 4) Adequate reporting of dropouts, attrition, and crossover
- 5) Loss to follow-up
- 6) Use of intention-to-treat analysis

External validity of trials was assessed based on:

- 1) Adequate description of the study population
- 2) Similarity of patients to other populations to whom the intervention would be applied
- 3) Control group receiving comparable treatment
- 4) Funding source that might affect publication bias.

Weighing the Evidence

A particular randomized trial might receive two different ratings: one for efficacy and another for adverse events. The overall strength of evidence for a particular key question reflects the quality, consistency, and power of the body of evidence relevant to that question.

Scope and Key Questions

To identify relevant citations, 2 independent reviewers identified potentially relevant titles and abstracts from the Cochrane Central Register of Controlled Trials (Issue 1, 2006 to June 2, 2008), Cochrane Database of Systematic Reviews, DARE, and MEDLINE (1966 to June 2, 2008).

Table 1. Pharmacokinetics, indications and dosing of included drugs¹¹

Drug: Trade name(s)	How supplied	Pharmacokinetic features	FDA labeled indications	Dosing (inhaled doses)	Dose adjustments for special populations	Black Box Warning?
<i>Short-acting beta-agonists</i>						
Albuterol <i>Ventolin HFA®</i> , <i>Proventil HFA®</i> <i>ProAir HIFA®</i>	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	
Levalbuterol: <i>Xopenex®</i> <i>Xopenex HFA®</i>	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: <i>Exirel®, Maxair®</i>	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	
<i>Anticholinergic drugs</i>						
Ipratropium bromide: <i>Atrovent HFA®</i>	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	
<i>Combination drugs</i>						
Ipratropium bromide and albuterol sulfate: <i>Combivent®</i>	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	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	

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

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.

The following key questions were used 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?**

Conclusions

Limitations of the evidence:

1. There were very few studies that met inclusion criteria for medications other than albuterol or levalbuterol.
2. Many studies utilized non-equivalent dosing schedules.

Conclusions:

1. Evidence suggests that there is no clinically significant difference between levalbuterol and albuterol for adults and children for effectiveness/ efficacy or adverse events.
2. There were three studies of children presenting to the Emergency Room which showed conflicting results. One of these studies, a good quality (n=547) study found a statistically significant reduction in admissions for patients treated with levalbuterol vs. albuterol (36% vs 45% P= 0.02)
3. There is insufficient evidence to determine a difference for subgroups for any included medication.

Supporting Evidence:

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

Adult asthma

Nelson and colleagues⁵⁴ and Pleskow and others⁵⁶ 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 colleagues⁵⁵ (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 colleagues¹⁰² 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 colleagues⁶⁰ 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.

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 colleagues⁵⁷ 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 FEV1.

Hardasmalani and colleagues⁵¹ ($N=70$) 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 colleagues⁵³ 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 colleagues⁵⁹ 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 colleagues⁶¹ 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 colleagues⁵⁷ 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 colleagues⁴⁶ 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 colleagues⁸⁸ 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 colleagues¹² was used as the basis for this drug comparison. This review examined the effectiveness of anticholinergic agents compared with placebo and compared with beta2-agonists, or as adjuncts to beta2-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 beta2-agonist combination therapy with beta2-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 beta2-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 colleagues⁸⁴ 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 colleagues⁹ 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 beta2-agonist monotherapy.

For this review we evaluated 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 colleagues⁸⁷ 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 waking 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 FEV1 (% 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 colleagues¹² 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

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.

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

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 weeks⁵⁴) among the 4 studies reporting this

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 Palpitations¹⁰⁶ and tachycardia⁵⁴ 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 colleagues¹⁰² 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 beta2-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).

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 study⁵⁹ (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 colleagues⁵³ 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 ($P<0.043$) in children. Among children age 2 to 5 years, Skoner and colleagues⁵⁹ 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 colleagues⁵⁹ 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

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 colleagues⁸⁸ 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 colleagues¹² reported fewer withdrawals with beta2-agonist monotherapy than with beta2-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 children⁹ 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 India⁸⁵ 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 colleagues⁸⁷ 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.

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 FEV1 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 trial⁸⁴ 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.