

Drug Class Review on Beta₂-Agonists

Final Report

November 2006

**The Agency for Healthcare Research and
Quality has not yet seen or approved this report**

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.

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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 that is often reversible, either spontaneously or with treatment. Airway inflammation also causes an increase in bronchial hyper-responsiveness to a variety of stimuli, resulting in increased susceptibility to bronchospasm. In addition to bronchospasm and inflammation, airway remodeling can also occur in some patients, leading to more severe and persistent disease. Airway reversibility may be incomplete in some patients.^{1,2}

Asthma is diagnosed when: 1) there are episodic symptoms of airflow obstruction; 2) airflow obstruction is at least partially reversible; and 3) alternative diagnoses are excluded. Most frequently asthma begins in childhood and in these children is often associated with atopy. Asthma can, however, develop at any time in life and can be related to allergens or can be non-allergic (or intrinsic).²

It is estimated that 10.5% (30.2 million) of the US population have been diagnosed with asthma in their lifetime, according to the 2004 National Health Interview Survey.³ This includes 9.9% (21.3 million) adults 18 years and over, and 12.2% (8.9 million) children under age 18 years. An estimated 4.1% of Americans (11.7 million people) had a recent asthma attack. Among children under age 18 years, 5.4% (4.0 million) had at least one asthma attack in the past 12 months; the corresponding figure among adults 18 years and over is 3.6% (7.7 million). Asthma prevalence increased from 1980 to 1996 at which time new asthma prevalence measures were adopted. These measures suggest that the prevalence has remained relatively stable from 1997 to 2004.³

There are two general classes of asthma medications: medications for long-term control and medications for the acute relief of airflow obstruction and symptoms.² Persons with persistent asthma require both short- and long-term medications. Long-term control medications include corticosteroids, cromolyn sodium and nedocromil, methylxanthines, leukotriene modifiers, and long-acting beta₂-agonists (LABAs).² Medications for quick relief of bronchoconstriction and acute symptoms include short-acting beta₂-agonists (SABAs) and anticholinergics.

Exercise-Induced Asthma (EIA)

EIA is a condition characterized by symptoms of coughing, wheezing, shortness of breath, and chest tightness during or after exercise.⁴ EIA is associated with airway obstruction after exercise, as indicated by a decrease in forced expiratory volume in one second (FEV₁). Exercise-induced bronchospasm (EIB) refers to the condition where exercise precipitates airway obstruction, but the person has normal lung function at rest.⁴ The term EIA is sometimes used to refer to persons who have exacerbation of their chronic asthma during exercise. We use the term EIA to encompass both this latter condition as well as EIB.

The mechanisms underlying EIA are not well understood. The hyperosmolarity theory proposes that water loss from the airway induces hypertonicity of the airway cells, leading to release of inflammatory mediators and subsequent bronchoconstriction.⁴ Another theory suggests that hyperventilation leads to cooling of the airway cells, and after exercise the rewarming process leads to dilatation of the bronchiolar vessels and fluid exudation, mediator release, and bronchoconstriction.

EIA can affect recreational athletes as well as elite athletes. Prevalence is reported as 17% in winter Olympic athletes,⁴ 35% among competitive athletes in cold weather sports,⁴ and 9% among school children.⁴

The goals of treatment are avoidance of the specific athletic activities which precipitate bronchospasm, adequate warm-up periods, as well as pharmacologic therapy. The latter usually consists of an inhaled SABA 15 minutes prior to exercise.⁴ Additional, daily therapy may be required for management of underlying chronic asthma.

Chronic Obstructive Pulmonary Disease (COPD)

COPD is a slowly progressive disease of the airways that is characterized by a gradual loss of lung function. The term COPD includes emphysema, chronic bronchitis, chronic obstructive bronchitis, and a combination of these conditions.⁵ Cigarette smoking is linked causally to COPD in more than 80% of cases.⁶

COPD should be considered among persons who have chronic cough, sputum production, dyspnea, or a history of exposure to risk factors for the disease (most notably smoking). The diagnosis requires spirometry; post-bronchodilator FEV₁/forced vital capacity (FVC) <0.7 and an FEV₁ <80% of predicted, combined with symptoms and exposure to risk factors, confirms the diagnosis (in mild COPD the FEV₁ is >80% of predicted).⁷

In the U.S., an estimated 12.1 million adults were diagnosed with COPD in 2001.³ Many persons may be undiagnosed as they have minimal or no symptoms, so the number of affected persons is likely much higher.³ COPD is the fourth leading cause of death in the USA and Europe⁷ and the death rate from COPD is increasing, particularly among women.³ For U.S. women, the rate rose from 20.1 to 56.7 deaths per 100,000 women from 1980 to 2000; during the same period the death rate rose from 73.0 to 82.6 deaths per 100,000 men⁵ COPD death rates are also consistently higher among whites than blacks.⁵ These figures underestimate the true disease burden of COPD, as it is an important contributor to other causes of morbidity and mortality, including ischemic heart disease and pneumonia.⁶

The goals of treatment are to reduce or alleviate symptoms, increase exercise capacity, reduce the number and severity of exacerbations, and improve health and function. Currently no treatment has been shown to modify the rate of decline in lung function⁷ except for smoking cessation.⁶ Since airflow obstruction is present in all persons with COPD, bronchodilators (beta-agonists, anticholinergic drugs, and methylxanthines) are a key part of therapy.

Inhaled beta₂-agonists

Beta₂-agonists act primarily 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.⁶

The long-acting inhaled beta₂-agonists (LABAs) have a duration of at least 12 hours after a single dose, and are used for the long-term control of symptoms, particularly nocturnal symptoms.¹ The LABAs are not appropriate for the treatment of acute exacerbations.¹ Rather, LABAs are indicated concomitantly with inhaled corticosteroids for long-term control and prevention of symptoms in moderate and severe persistent asthma² and for the prevention of exercise-induced bronchospasm (EIB).¹

Foradil® Aerolizer® (formoterol) is the only single-agent containing formoterol fumarate currently approved and available for use in the U.S.; Turbuhaler®, Turbohaler®, Oxis®, and Oxeze® are marketed outside of the U.S. Salmeterol is marketed in the U.S. as Serevent Diskus®. Neither drug is available in the U.S. as an MDI formulation.

The SABAs 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 EIB. The SABAs are not recommended for regularly scheduled, daily use.¹

The U.S. Food and Drug Administration announced on March 31, 2005, that albuterol metered-dose inhalers using chlorofluorocarbon (CFC) propellants must no longer be produced, marketed, or sold in the U.S. after December 31, 2008, as they deplete stratospheric ozone.¹ Numerous clinical studies have demonstrated that albuterol (hydrofluoroalkane 134a (HFA) formulations have comparable safety and efficacy to CFC albuterol formulations.⁸⁻¹⁰

Table 1. Pharmacokinetics, indications and dosing of included drugs¹¹

Drug Trade Name(s)	How supplied	Half-life and other relevant pharmacokinetic features	FDA labeled indications	Dosing (inhaled doses)	Dose adjustments for special populations
<i>Long-acting beta-agonists</i>					
Salmeterol Serevent Diskus®	Inhalation powder: 50 mcg/actuation	Absorption: Time to peak concentration, 5-10 min (also 45 min due to absorption of swallowed portion of dose) Elimination half-life: 5.5 hrs	Asthma COPD Exercise-induced asthma, prophylaxis	Asthma: 1 inhalation (50 mcg) twice daily, 12 hr apart COPD: 1 inhalation (50 mcg) twice daily, 12 hr apart	Pediatric patients: Asthma: age 4-12 yr, 1 inhalation (50 mcg) twice daily, 12 hr apart Exercise-induced asthma; Prophylaxis: 1 inhalation (50 mcg) 30 minutes before exercise

Drug Trade Name(s)	How supplied	Half-life and other relevant pharmacokinetic features	FDA labeled indications	Dosing (inhaled doses)	Dose adjustments for special populations
				Exercise-induced asthma; Prophylaxis: 1 inhalation (50 mcg) 30 minutes prior to exercise	
Formoterol <i>Foradil Aerolizer®</i> (other formulations not available in the United States include: Oxeze®, Oxis®, Turbohaler®)	Inhalation capsule: 0.012 MG	Absorption: Time to peak concentration, 5 min Elimination half-life: 10 hrs (mean)	Asthma COPD Exercise-induced asthma, prophylaxis	Asthma: 12 mcg (1 capsule) every 12 hr via Aerolizer(TM) inhaler; MAX 24 mcg/day COPD: 12 mcg (1 capsule) every 12 hr via Aerolizer™ inhaler Exercise-induced asthma; Prophylaxis: 12 mcg (1 capsule) at least 15 min before exercise as needed via Aerolizer™ inhaler	Pediatric patients: Asthma: maintenance: 5 yr and older, same as adult dosing (12 mcg (1 capsule) every 12 hr via Aerolizer™ inhaler) Exercise-induced asthma; Prophylaxis: age 5 yr and older, same as adult dosing (12 mcg (1 capsule) every 12 hr via Aerolizer™ inhaler)
<i>Short-acting beta-agonists</i>					
Albuterol <i>Ventolin HFA®, Proventil®</i> (also available generically)	Inhalation Aerosol Powder: 0.09 MG/Actuation Kit: 0.09 MG/Actuation	Absorption: Time to peak concentration, 3 to 4 h Elimination half-life: 3-6.5 hrs	Asthma; Treatment and Prophylaxis Exercise-induced asthma; Prophylaxis	Asthma; Treatment and Prophylaxis: 2 inhalations every 4-6 h or 1 inhalation every 4 h Exercise-induced asthma; Prophylaxis: 2 inhalations 15 min before exercise	Pediatric patients: Asthma; Treatment and Prophylaxis: 4 y and older, 2 inhalations every 4-6 h or 1 inhalation every 4 h Exercise-induced asthma; Prophylaxis: 4 y and older, 2 inhalations 15 min before exercise
Fenoterol (not available in the US)	Inhaled: 0.5 to 5 MG/dose	Absorption: Time to peak concentration, 2-3 hrs Elimination half-life: 7 hrs (parent)	Asthma Exercise-induced asthma; Prophylaxis	Inhaled: 1 to 2 actuations (200 mcg) 2 to 4 times daily	Pediatric patients: actuation (200 mcg) initially, with a dose repeated in 5 minutes when necessary.

Drug Trade Name(s)	How supplied	Half-life and other relevant pharmacokinetic features	FDA labeled indications	Dosing (inhaled doses)	Dose adjustments for special populations
		compound)			
Levalbuterol <i>Xopenex®</i> <i>Xopenex HFA®</i>	Inhalation Solution: 0.31 mg/3 ml, 0.63 mg/3 ml, 1.25 mg/3 ml, 1.25 mg/0.5 ml Inhalation Aerosol: 15mg (200 actuations of 45mcg)	Absorption: Time to peak concentration, 12 mins Elimination half-life: 4 hrs (+/- 1.05 hrs)	Bronchospasm (pts >6yrs w/ reversible obstructive airway disease)	Bronchospasm: 1.25 mg inhalation solution 3 times/day (every 6-8 hr) 2 inhalations up to 2x/day inhalation aerosol	Pediatric patients: 6-11 yr, 0.31 mg inhalation solution 3 times/day initially, MAX 0.63 mg 3 times/day Inhalation aerosol not indicated for children <4yrs
Metaproterenol <i>Alupent®</i> (also available generically)	Inhalation Aerosol Liquid: 0.65 MG/Actuation Inhalation Aerosol Powder: 0.65 MG/Actuation Inhalation Solution: 0.4 %, 0.6 %, 5 %	Absorption: Bioavailability, approximately 3%	Asthma - Bronchospasm	Asthma - Bronchospasm: 2-3 puffs every 3-4 hr; MAX 12 puffs/day (aerosol); 0.3 mL (5%) in 2.5 mL NS every 4-6 hr or more often as needed (nebulized)	Pediatric patients: Asthma - Bronchospasm: 12 yr and older, 1-3 puffs every 3-4 hr, MAX 12 puffs/day (aerosol); 6-12 yr, 0.1-0.2 mL (5%) in 3 mL NS every 4-6 hr or more often if needed; 12 yr and older, 0.2-0.3 mL (5%) in 2.5 mL NS every 4-6 hr or more often if needed (nebulized)
Pirbuterol <i>Exirel®</i> , <i>Maxair®</i>	Inhalation Aerosol Powder: 0.2 MG/Actuation	Elimination half-life: about 2 hrs	Asthma	Asthma: 1-2 puffs every 4-6 hr, up to 12 puffs/day	Not FDA-approved in children under 12 yr
Terbutaline (not available in inhaled form in the US)	MDI: vary between 25-microliter to 100-microliter/250-microgram dose, delivered at pressures from 350kPa to 500kPa	Time to peak concentration: 0.5-1 hr Elimination half-life: 11-26 hrs	Asthma - Bronchospasm Other bronchopulmonary disorders in which bronchospasm or reversible airways obstruction is a complicating factor.	Bronchospasm: 2 puffs (400 mcg) every 4-6 hr	Not approved in children less than 12 years of age 12 years and older, 2 puffs (400 mcg) every 4-6 hr

Scope and Key Questions

The purpose of this review is to compare the benefits and harms of different pharmacologic treatments for beta₂-agonists. 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 were reviewed and revised by representatives of organizations participating in the Drug Effectiveness Review Project (DERP).

The participating organizations of DERP are responsible for ensuring that the scope of the review reflects the populations, drugs, and outcome measures of interest to both clinicians and patients. The participating organizations approved the following key questions to guide this review:

Key Questions

Efficacy and effectiveness

1. When used in adults with asthma or chronic obstructive pulmonary disease (COPD), are there differences in efficacy or effectiveness among long-acting, inhaled beta₂-agonists, when used in the outpatient setting?
2. When used in adults with asthma or COPD, are there differences in efficacy or effectiveness among the following short-acting inhaled beta₂-agonists when used in the outpatient setting: albuterol, fenoterol, levalbuterol, pirbuterol, metaproterenol and terbutaline?
3. When used in children with asthma, are there differences in efficacy or effectiveness among long-acting, inhaled beta₂-agonists, when used in the outpatient setting?
4. When used in children with asthma, are there differences in efficacy or effectiveness among the following short-acting inhaled beta₂-agonists when used in the outpatient setting: albuterol, fenoterol, levalbuterol, pirbuterol, metaproterenol and terbutaline?

Safety

5. When used in adults with asthma or COPD, are there differences in safety or rates of adverse events among long-acting, inhaled beta₂-agonists, when used in the outpatient setting?
6. When used in adults with asthma or COPD, are there differences in safety or rates of adverse events among the following short-acting inhaled beta₂-agonists when used in the outpatient setting: albuterol, fenoterol, levalbuterol, pirbuterol, metaproterenol and terbutaline?
7. When used in children with asthma, are there differences in safety or rates of adverse events among long-acting, inhaled beta₂-agonists, when used in the outpatient setting?
8. When used in children with asthma, are there differences in safety or rates of adverse events among the following short-acting inhaled beta₂-agonists, when used in the outpatient setting: albuterol, fenoterol, levalbuterol, pirbuterol, metaproterenol and terbutaline?

Subpopulations

9. Are there subgroups of patients based on demographic characteristics (age, racial groups, gender), other medications (drug-drug interactions), comorbidities (drug-disease interactions), or pregnancy for which one long-acting, inhaled beta₂-agonist is more efficacious, effective, or associated with fewer adverse events than another inhaled beta₂-agonist?
10. Are there subgroups of patients based on demographic characteristics (age, racial groups, gender), other medications (drug-drug interactions), comorbidities (drug-disease interactions), or pregnancy for which one of the following short-acting, inhaled beta₂-

agonists is more efficacious, effective, or associated with fewer adverse events: albuterol, levalbuterol, pirbuterol, and metaproterenol?

METHODS

Literature Search

To identify relevant citations, two 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). 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, Thompson Scientific).

Articles deemed potentially relevant after review of titles and abstracts were then 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

The pharmacotherapeutic agents reviewed were a selection of drugs currently available in the United States and of interest to the Drug Effectiveness Review Stakeholders (Table 2). In addition, we were asked to review two drugs available only in Canada: terbutaline (Bricanyl™) and fenoterol (Berotec™).

We included all formulations of the included drugs reviewed in the literature, including formulations not currently available in the U.S. (for example, salmeterol as a MDI).

Participants in included studies were adults or children with asthma or exercise-induced asthma, and adults with COPD. Studies were excluded which examined mixed populations where outcomes were not presented for subgroups of interest to us.

We examined studies that present one or more of the primary outcomes of interest to this review: effectiveness outcomes and outcomes related to safety and harms. For both effectiveness as well as 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. These 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 (RCTs) and controlled clinical trials which made direct comparison between the drugs of interest to us (i.e., 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, and case series with a sample size ≥ 10 , in addition to RCTs and controlled clinical trials. Clinical trials are often 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 time period, utilize higher quality methodological techniques for assessing adverse events, or examine larger sample sizes.

Table 2. Inclusion and exclusion criteria

Inclusion Criteria

Populations

- Adult or pediatric outpatients with asthma
 - Chronic (maintenance) therapy
 - Acute (rescue) therapy
- Adults and pediatric outpatients with exercise-induced asthma
- Adult outpatients with COPD

Interventions

Long-acting

- Salmeterol xinofoate = Serevent Discus
- Formoterol fumarate = Foradil, Oxeze, others

Short-acting

- Albuterol = ventolin, ventolin HFA, proventil, albuterol HFA, salbutamol, salbumol, racemic albuterol, albuterol sulfate = proventil HFA, salbutamol sulphate
- Fenoterol = Berotec (only available in Canada)
- Levalbuterol HCL= Xopenex = (R) albuterol
- Metaproterenol = alupent = orciprenaline
- Pirbuterol acetate= maxair autoinhaler
- Terbutaline= Bricanyl (only available in Canada)

Method of delivery

- All approved methods of delivery for inhalation will be considered for each of these drugs: metered-dose inhaler (aerosol), discus, solution (nebulizer), products using HFA, CFC

Effectiveness outcomes

- Symptoms (e.g., cough, wheezing, shortness of breath)
- Quality of life, including functional capacity, ability to participate in work, school, or sports
- Health care utilization: emergency department or urgent medical care visits, hospitalizations
- Mortality
- Change in concurrent medication use (inhaled steroids, oral steroids, antibiotics) and use of rescue medications

Safety outcomes

- Overall adverse effects
- Withdrawals due to adverse effects
- Serious adverse events
- Specific adverse events or withdrawals due to specific adverse events

Study designs

- Sample size ≥ 10 participants
- For efficacy and effectiveness: randomized controlled trials and systematic reviews
- For safety: any study design, including randomized controlled trials, controlled clinical trials, and observational studies

Comparisons

- Studies examining H2H comparison (data from indirect comparisons were not examined)

Exclusion criteria

Populations or conditions

- Acute bronchitis
- Bronchiectasis
- Children < 2 years with recurrent or persistent wheezing
- Cystic fibrosis
- High-altitude pulmonary edema
- Studies where bronchospasm was induced by methacholine, histamine, cold

Data Abstraction

We abstracted relevant descriptive and outcomes data into a relational database developed for this review. We recorded results achieved with an intention-to-treat analytic approach, 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. This was because of the potential for bias due to differential withdrawal prior to crossover, the possibility of a “carryover effect” (from the first treatment) in studies without 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 U.S. Preventive Services Task Force and the National Health Service Centre for Reviews and Dissemination. For each included trial, we assessed the following criteria: methods used for randomization; allocation concealment; blinding of participants, investigators, and assessors of outcomes; the similarity of comparison groups at baseline; adequate reporting of attrition, crossover, adherence, and contamination; post-allocation exclusions, and the use of intention-to-treat analysis.

We assessed observational and other study designs with adverse event data based on non-biased selection of patients, loss to follow-up, non-biased 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 of poor quality are presented in the in-text tables and the evidence tables, 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 which fulfilled inclusion criteria were rated for quality using pre-defined criteria (see Appendix B): a clear statement of the questions and inclusion criteria; adequacy of the search strategy; quality assessment of individual trials; the adequacy of information provided; and appropriateness of the methods of synthesis.

Data Analysis and Synthesis

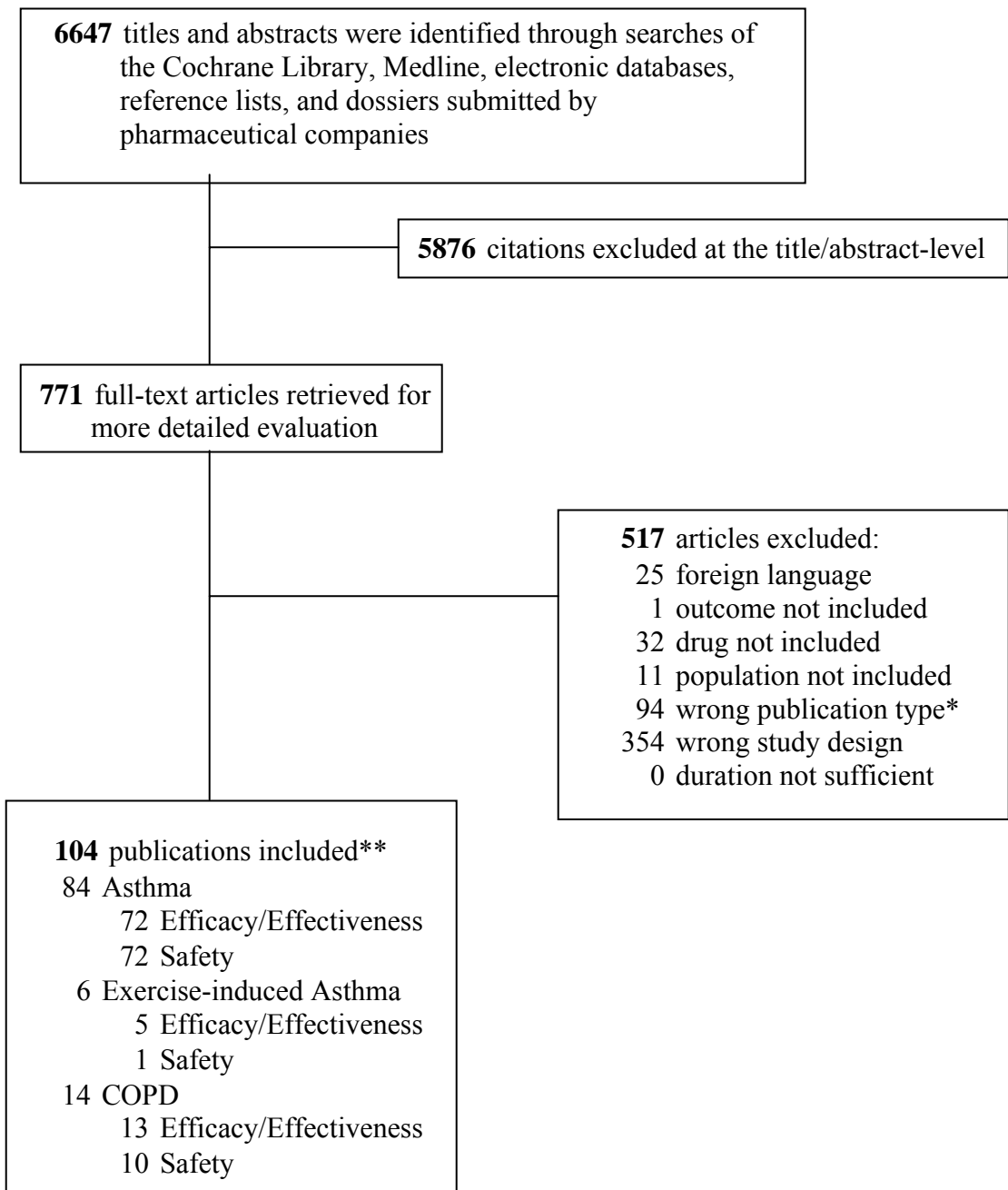
We compared LABA to LABA and SABA to SABA, as these two types of inhaled beta₂-agonists are indicated in different situations which are not generally considered interchangeable.¹ The LABA are indicated for maintenance treatment in persistent asthma and for chronic use in some patients with COPD, whereas the SABA are used for rescue (acute symptomatic) treatment and are not generally recommended for regularly scheduled daily use.¹

Important descriptive information about the population, setting, and intervention, as well as quality assessment are presented in tabular format. Data were synthesized and are presented in a narrative fashion as there was too much clinical and methodologic diversity to pool the data in a meta-analysis.

RESULTS

Database searches identified 6,629 citations. Following application of inclusion/exclusion criteria, 104 studies were included in this review (Figure 1). Included studies for each between-drug comparison are depicted in Table 3. We identified one or more studies for all comparisons of interest except for levalbuterol: available studies only compared it to albuterol and not to any other drugs. The quality assessment of nine studies was rated as poor for measures of effectiveness.¹²⁻²¹

Figure 1. Literature search results



Numbers represent number of publications
 * Wrong publication type (letter with insufficient information, editorial, non-systematic review, case report, case series < 10 patients)
 **All remaining studies used as background

Table 3. Beta₂-agonist comparison table

	Salmeterol	Fenoterol*	Levalbuterol	Metaproterenol	Pirbuterol	Terbutaline*
Formoterol	21 (25) ^{16, 19, 22-44}					
Albuterol		24 (24) ^{20, 45-67}	14 (15) ^{17, 68-81}	5 (6) ⁸²⁻⁸⁷	3 (4) ^{13, 14, 87, 88}	23 (22) ^{12, 15, 18, 21, 56, 59, 66, 87, 89-102}
Fenoterol*				1 (1) ¹⁰³		12 (11) ^{56, 59, 66, 104-111}
Levalbuterol						
Metaproterenol					3 (3) ^{87, 112, 113}	3 (3) ^{87, 114, 115}
Pirbuterol						1 (1) ⁸⁷
*Canada only; Studies (Publications)						

Systematic reviews

No systematic reviews were identified which provided head-to-head data on the comparisons of interest to this review. In the Cochrane Database of Systematic Reviews, there are a number of reviews related to inhaled beta₂-agonists. None of these reviews fulfilled our inclusion criteria; the most common reason was their focus on placebo-controlled trials only (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.

Efficacy and effectiveness

Key Question 1. When used in adults with asthma or chronic obstructive pulmonary disease (COPD), are there differences in efficacy or effectiveness among long-acting, inhaled beta₂-agonists, when used in the outpatient setting?

Key Question 2. When used in adults with asthma or COPD, are there differences in efficacy or effectiveness among the following short-acting inhaled beta₂-agonists when used in the outpatient setting: albuterol, fenoterol, levalbuterol, pirbuterol, metaproterenol and terbutaline?

Key Question 3. When used in children with asthma, are there differences in efficacy or effectiveness among long-acting, inhaled beta₂-agonists, when used in the outpatient setting?

Key Question 4. When used in children with asthma, are there differences in efficacy or effectiveness among the following short-acting inhaled beta₂-agonists when used in the outpatient setting: albuterol, fenoterol, levalbuterol, pirbuterol, metaproterenol and terbutaline?

Salmeterol vs formoterol

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

Adults with asthma

Studies with either effectiveness or safety data encompassed a total of 1676 participants in 10 studies; mean age 49.5 years and half of the study participants were female (Table 4 and Evidence Table 3). Note that various formulations are presented, but only 'Foradil® Aerolizer® (formoterol) and Serevent Discus® (salmeterol) are available in the U.S.

Data were not frequently provided on effectiveness outcomes. Of the four fair-quality studies with effectiveness data,^{35, 41, 116, 117} three of these compared dry power delivery systems (formoterol Tubohaler® or Aerolizer® with salmeterol Accuhaler® or Serevent Diskhaler®). The fourth study compared formoterol and salmeterol delivered via MDI (neither of which are currently available in the U.S.).⁴¹

No differences were found between formoterol and salmeterol (both delivered via dry powder systems) for the outcomes of symptoms (three studies^{22, 23, 35, 44}), use of rescue medications (three studies^{22, 23, 35, 44}), healthcare utilization (two studies^{22, 23, 44}), and quality of life (one study³⁹) in the fair-quality studies examining these outcomes. Campbell and colleagues²² noted more symptom-free days and reduced severity of daytime asthma symptoms at 4 weeks with formoterol Turbohaler compared to salmeterol Accuhaler, but these differences were not sustained at 8-week follow-up.

Formoterol via Turbohaler was preferred over salmeterol MDI (the latter is no longer available in the U.S.); there was no difference in patient preference between formoterol via Turbohaler and salmeterol via Accuhaler.²² Formoterol via MDI was preferred by more patients than salmeterol via MDI in a second study.⁴¹ Both of these studies were sponsored by the makers of formoterol.

Children with asthma

One open-label trial presented effectiveness data^{31, 32} among three studies which addressed this population using dry powder delivery systems. Children aged 6 to 17 years (n=156) used formoterol 9ug (a dosage not currently available in the U.S.) or salmeterol 50ug bid, added to current inhaled steroid use. More patients using formoterol discontinued the study after randomization (21 with formoterol [5 due to deterioration in asthma, 4 due to AEs]; 12 with salmeterol [4 due to deterioration in asthma, 1 due to AEs]). Compliance was similar in the two groups. Both drugs decreased the as-needed use of SABAs, with a greater decline with formoterol by week 12 (inhalations/24h; p=0.043). Multiple other comparisons were made: there was no significant difference between groups for frequency of poorly controlled days (p=0.107), frequency of mild exacerbations (p=0.051), percentage of patients experiencing a severe exacerbation by week 12 (p>0.05), and school attendance. Formoterol was favored for clinician-assessed asthma severity score at night (p=0.049) and patient-assessed asthma severity score during the daytime (p=0.052).^{31, 32}

Adults or children with EIA

Only one study was identified which examined EIA. Richter and colleagues³⁸ examined acute protection against exercise-induced bronchoconstriction in 25 adults. Exercise challenges were performed on 12 separate days and up to 60 minutes after inhalation of a single dose of one of formoterol (12 ug Turbohaler), salmeterol (50 ug Diskus) and terbutaline (500 ug Turbohaler) or placebo. Maximum fall in FEV₁ did not differ significantly among the treatments. The onset of bronchodilation, however, was slower after salmeterol compared to both other treatments (p<0.05). Bronchodilation, expressed as % increase of FEV₁ compared to baseline, was evaluated between inhalation of study drug and start of exercise. Formoterol provided greater bronchodilation than salmeterol at 5 (p<0.01), 30 (p<0.05), and 60 minutes (p<0.01) after inhalation.

COPD

Seven small studies examined these drugs among persons with COPD, with a total of 145 participants.^{24-29, 34} The mean age was 62.2 years and the majority of subjects were male. Two studies that examined symptoms found no difference between the two drugs. Kottakis and colleagues³⁴ found no significant difference between formoterol 12ug (dry powder via Aerolizer®) and salmeterol 50ug (via Aerolizer®) at 1 and 4-hour follow-up for breathing effort and breathing discomfort. In a single-dose study²⁹ there were no differences in dyspnea symptoms 30 minutes after treatment with salmeterol 50ug or formoterol 12 ug, both via MDI. There were no other head-to-head data available on effectiveness outcomes among persons with COPD.

Table 4. Salmeterol vs Formoterol: Demographic and Study Characteristics of Included Studies

Author, Year	Study duration	Intervention	n	Mean age in years (SD)	% Female	Other medications permitted during the study	Quality	Funding
Adult Asthma								
1. Campbell, 1999; Campbell, 2000	8 weeks	Formoterol 12ug BID dry powder administered via Turbohaler	460	40.2	NR	NR	Fair	Astra Pharmaceuticals U.K. Ltd.
		Salmeterol 50ug BID aerosol administered via pMDI						
		Salmeterol 50ug BID dry powder administered via Accuhaler						
2. Condemini, 2001	24 weeks	Formoterol 12ug BID dry powder administered via Aerolizer	528	NR		Rescue medication as needed	Poor	Novartis Pharmaceutical Corporation, East Hanover, New Jersey.
		Salmeterol 50ug BID dry powder administered via Diskus						
3. Eryonucu, 2005	Single dose	Formoterol 12ug inhaled drug without a spacer	39	35.0(7)	54.0	NR	NA	NR
		Salmeterol 50ug inhaled drug without a spacer						
4. Grembiale, 2005	Single dose	Formoterol 12ug MDI	10	53.2(17)	30	Patients taking either inhaled or oral corticosteroids or inhaled cromoglycates were allowed to continue these therapies at a constant dose throughout the study (the treatments noted were budesonide 400, 1600, 800ug/d and fluticasone	Fair	NR
		Salmeterol 50ug MDI						

Author, Year	Study duration	Intervention	n	Mean age in years (SD)	% Female	Other medications permitted during the study	Quality	Funding
5. Grove, 1996	Single dose	Formoterol 12ug MDI		37(11.7)	50	Fenoterol cumulative dose of 3200ug. At the time of the study, 10 patients were using inhaled corticosteroids in doses of 400-2400ug/d, together with inhaled short-acting bronchodilators on an as required basis; four patients were taking oral corticosteroids	Poor	NR
		Salmeterol 25ug MDI						
6. Nightingale, 2002	4 weeks	Formoterol 12ug BID dry powder inhaler	42	45.4(13.61)	69.05	All patients continued to receive maintenance medication throughout the trial to prevent bias between groups	Fair	Novartis Pharmaceuticals
		Salmeterol 50ug BID dry powder diskhaler						
7. Palmqvist, 1997	Single dose	Formoterol 12ug dry powder administered via Turbohaler	28	45.6	60.71	All patients treated with short-acting beta-2-agonists as required and all, except two, were treated with inhaled glucocorticoids (beclamethasone dipropionate and budosonise, ranging from 200-1600ug/d). Slow release theophylline and or slow release beta-2-agonists	Fair	Astra Draco, Herman Krefting's Foundation for Asthma and Allergy Research
		Formoterol 24ug dry powder administered via Diskus						
		Formoterol 6ug dry powder administered via Turbohaler						
		Salmeterol 50ug dry powder administered via Diskus						

Author, Year	Study duration	Intervention	n	Mean age in years (SD)	% Female	Other medications permitted during the study	Quality	Funding
8. Schermer, 2004	12-17 day	Formoterol 12ug BID MDI	35	52.7(12.5)	57.14	All subjects used inhaled corticosteroids before as well as during the trial. Budesonide was used by 14(40%), beclomethasone by 12(34%), and fluticasone by 9(26%) subjects.	Fair	Novartis Pharma BV (Arnhem, The
		Salmeterol 50ug BID MDI						
9. van Noord, 1996	Single dose	Formoterol 24ug aerosol administered via MDI	30	54(8)	26.67	The following drugs were permitted if taken in a stable dose: nedocromil sodium, cromolyn sodium, inhaled or oral steroids and antihistamines. Smoking and drinks containing caffeine	Fair	NR
		Salmeterol 50ug aerosol administered via MDI						
10. Vervloet, 1998; Rutten-van Molken, 1998	24 weeks	Formoterol 12ug BID dry powder administered via Aerolizer	482	48(15)	54.15	Inhaled corticosteroids (constant dose)	Fair	Novartis Pharmaceuticals
		Salmeterol 50ug BID dry powder administered via Diskhaler						
Summary:	Single dose: 5 Other: 5		1676 range: 10-482	43.5 range: 24.0-54.0	49.5 range: 26.7-69.0		Good: 0 Fair: 7 Poor: 2 NA: 1	Industry: 6 Public: 0 NR: 4
Adult COPD								
11. Cazzola, 1994	Single dose, over 8 non-consecutive days	Formoterol 24ug MDI with holding chamber	16	64.3	0	Subjects had not taken any inhaled bronchodilators for at least 48 h before the investigation started.	Fair	NR
		Salmeterol 50ug MDI with holding chamber						

Author, Year	Study duration	Intervention	n	Mean age in years (SD)	% Female	Other medications permitted during the study	Quality	Funding
12. Cazzola, 1995 (efficacy only)	Single dose	Formoterol 12ug MDI with holding chamber	12	62.6		Subjects had not taken any inhaled bronchodilator drug for at least 12 h, or oral bronchodilators for at least 24 h before the investigation	Fair	NR
		Formoterol 24ug MDI with holding chamber						
		Formoterol 36ug MDI with holding chamber						
		Salmeterol 25ug MDI with holding chamber						
		Salmeterol 50ug MDI with holding chamber						
		Salmeterol 75ug MDI with holding chamber						
13. Cazzola, 1998a	Single dose	Formoterol 24ug MDI and holding chamber	16	NR	NR	No oral bronchodilators were permitted for 1 week before and during the study, whereas inhaled SABA and inhaled long acting bronchodilator agents were not permitted for at least 12 h and 24 h prior to each test	Fair	NR
		Salmeterol 50ug MDI and holding chamber						

Author, Year	Study duration	Intervention	n	Mean age in years (SD)	% Female	Other medications permitted during the study	Quality	Funding
14. Cazzola, 1998b	Single dose	Formoterol 12ug MDI Formoterol 24ug MDI Salmeterol 50ug MDI	12	60.2	25	No oral bronchodilators were permitted for 1 week before and during the study, whereas inhaled short-acting bronchodilator drugs and inhaled long-acting bronchodilator agents were not permitted for at least 12 h and 24 h prior to each test, respectively.	Fair	NR
15. Celik, 1999	Single dose	Formoterol 12ug MDI Salmeterol 50ug MDI	22	57.3(5.4)	9.09	During the whole study period, no concomitant medication was given except inhaler corticosteroids which were allowed if the patient was under maintenance corticosteroid therapy	Fair	NR
16. Di Marco, 2003	Single dose	Formoterol 12ug MDI with holding chamber (Fluspacer) Salmeterol 50ug MDI with holding chamber (Fluspacer)	20	65(2)	30	NR	Fair	NR

Author, Year	Study duration	Intervention	n	Mean age in years (SD)	% Female	Other medications permitted during the study	Quality	Funding
17. Kottakis, 2002	Single dose for 5 days	Formoterol 12ug dry powder via Aerolizer Formoterol 24ug dry powder via Aerolizer Salmeterol 100ug dry powder via Diskus Salmeterol 50ug dry powder via Diskus	47	63.5(8.6)	19.15	Patients were expected to avoid using bronchodilators during the 4h test periods at visits 2 to 6 and during the washout periods before these visits. Treatment with inhaled or nasal corticosteroids and stable doses of oral modified-release theophylline	Fair	Novartis Pharma AG (Basel, Switzerland)
Summary:	Single dose: 7 Other: 1		145 range: 12-47	62.2 range: 57.3- 65.0	13.8 range: 0.0-30.0		Good: 0 Fair: 7 Poor: 0	Industry: 1 Public: 0 NR: 6
Adult Exercise-induced								
18. Richter, 2002	Single dose	Formoterol 12ug Turbohaler Salmeterol 50ug Diskus	25	33(6.1)	40	Antihistamines, anticholinergics, inhaled cromoglycates and prednisolone were not permitted at all. Eleven patients were treated with inhaled corticosteroids	Fair	Astra GmbH (Wedel, Germany)
Summary:	Single dose: 1 Other: 0		25 range: NA	33 range: NA	40 range: NA		Good: 0 Fair: 1 Poor: 0	Industry: 1 Public: 0 NR: 0
Pediatrics Asthma								
19. Everden, 2002; Everden, 2004	12 weeks	Formoterol 12ug (9ug delivered dose) BID, Oxis Turbohaler Salmeterol 50ug BID Accuhaler	145	11.7	44.83	All patients were on inhaled corticosteroids and continued these through the study.	Fair-poor	Astra Zeneca, UK

Author, Year	Study duration	Intervention	n	Mean age in years (SD)	% Female	Other medications permitted during the study	Quality	Funding
20. Pohunek, 2004	Single dose	Formoterol 18ug (=24ug dose) Turbohaler	68	11.9	NR	Inhaled and nasal corticosteroids and disodium cromoglycate at a constant rate	Fair	Astra Zeneca
		Formoterol 36ug (=48 ug dose) Turbohaler						
		Formoterol 4.5ug (=6 ug dose) Turbohaler						
		Formoterol 9ug (=12 ug dose) Turbohaler						
		Salmeterol 50ug Diskhaler						
21. Verini, 1998 (efficacy only)	Single dose, 5 days	Formoterol 24ug MDI with 750ml chamber	27	9.1(2.7)	33.33	All children were treated with ketotifen and salbutamol when necessary. Exclusion criteria included the use of oral long-acting beta-2-agonists, theophylline, sodium cromoglycate, antihistamines or corticosteroids; relevant bronchial obstruction reversed	Fair	NR
		Salmeterol 50ug MDI with 750ml chamber						
Summary:	Single dose: 2 Other: 1		250 range: 27-155	10.4 range: 9.7-11.7	35.0 range: 33.3-36.7		Good: 0 Fair: 3 Poor: 0	Industry: 2 Public: 0 NR: 1

Table 5. Salmeterol vs Formoterol: Effectiveness Outcomes of Included Studies

Author Year	Outcome Category	Outcome (unit) at timepoint	Intervention	Baseline:		Follow-Up:		Change from Baseline, Mean(SD), p-value	Comments
				n	Mean(SD) or No(%)	n	Mean(SD) or No(%)		
Adult Asthma									
Campbell, 1999; Campbell, 2000	Healthcare utilization	Patients with hospital admits or visits to A&E (%) at 8 wks	Formoterol 12ug	230	NR	230	1 (4%)	NR	
			Salmeterol 50ug Accuhaler	119	NR	119	1 (7%)	NR	Form vs Sal, p=0.02
	Symptoms	% of days symptom-free and use no bronchodilator (%) at over 8 wks	Salmeterol 50ug pMDI	111	NR	111	2 (15%)	NR	Form vs Sal, p=0.21
			Formoterol 12ug	230	NR	228	32.8 (2.3)	NR	The differences between treatments were not statistically significant NR
			Salmeterol 50ug Accuhaler	119	NR	118	24.1 (2.6)	NR	
			Salmeterol 50ug pMDI	111	NR	108	28.0 (3.2)	NR	
		Daytime asthma symptoms (score) at 4 wks	Formoterol 12ug	230	NR	NR	NR	-0.54 (NR), NR	Formoterol vs salmeterol accuhaler p=0.014; NSD between Formoterol and salmeterol MDI or between the 2 salmeterol groups NR
			Salmeterol 50ug Accuhaler	119	NR	NR	NR	-0.35 (NR), NR	Form vs Sal, =0.014
			Salmeterol 50ug pMDI	111	NR	NR	NR	NR	
			Nights/week of undisturbed sleep at 8wks (number) at over 8 wks	NR	NR	NR	NR	NR	All groups increased by 1-1.5 nights/week; NSD between groups NR
	No. of patients with worsening of asthma (number) at over 8 wks	Formoterol 12ug	230	NR	230	26 (11%)	NR	NR	
		Salmeterol 50ug Accuhaler	119	NR	119	14 (12%)	NR		
		Salmeterol 50ug pMDI	111	NR	111	13 (12%)	NR		

Author Year	Outcome Category	Outcome (unit) at timepoint	Intervention	Baseline:		Follow-Up:		Change from Baseline, Mean(SD), p-value	Comments
				n	Mean(SD) or No(%)	n	Mean(SD) or No(%)		
Condemni, 2001	Rescue medication	Actuation rescue med /wk within 30min of RX drug (number) at over 4 wks	Formoterol 12ug	256	0 (0)	256	1.4 (NR)	NR	There were no statistically significant differences between treatments in terms of nighttime or daytime symptom
			Salmeterol 50ug	260	0 (NR)	260	2.1 (NR)	NR	
	Use of rescue medication, daytime (number/wk) at over 4 wks	Formoterol 12ug	NR	NR	NR	NR	5.6 (NR), NR	Form vs Sal, p<0.03	
		Salmeterol 50ug	NR	NR	NR	NR	7.7 (NR), NR		
		Formoterol 12ug	NR	NR	NR	NR	2.8 (NR), NR	Form vs Sal, p<0.03	
		Salmeterol 50ug	NR	NR	NR	NR	4.2 (NR), NR		
	Symptoms	Asthma (number) at over 4 wks	Formoterol 12ug	262	NR	262	53 (20.2%)	NR	
			Salmeterol 50ug	266	NR	266	49 (18.4%)	NR	
Episode-free days (days) at over 4 wks		Formoterol 12ug	256	NR	256	9.5 (9.0)	NR	Form vs Sal, p<0.04	
		Salmeterol 50ug	260	NR	260	7.8 (8.7)	NR		
Nightingale, 2002	Rescue medication	No. of rescue inhaler use (puffs/day) at 4	Formoterol 12ug	42	6.1 (4.54)	35	4.1 (5.32)	NR	There were no significant treatment effects.
			Salmeterol 50ug	42	6.1 (4.54)	35	3.6 (4.73)	NR	
	Symptoms	Daytime symptom score at over 2 wks	Formoterol 12ug	42	1.2 (0.65)	35	0.9 (0.59)	NR	Form vs Sal, p=0.05
			Salmeterol 50ug	42	1.2 (0.65)	33	0.8 (0.57)	NR	
		Nighttime symptom score at over 2 wks	Formoterol 12ug	42	0.9 (0.65)	35	0.6 (0.59)	NR	Form vs Sal, p=0.20
			Salmeterol 50ug	42	0.9 (0.65)	33	0.4 (0.57)	NR	
Schermer, 2004	Symptoms	Treatment preference (number) at NR	Formoterol 12ug	34	NR	32	17 (50%)	NR	The distribution of subjects over these preference categories was statistically significant, p<0.001 NR
			No preference	34	NR	32	6 (18%)	NR	
			Salmeterol 50ug	34	NR	32	10 (29%)	NR	

Author Year	Outcome Category	Outcome (unit) at timepoint	Intervention	Baseline:		Follow-Up:		Change from Baseline, Mean(SD), p-value	Comments
				n	Mean(SD) or No(%)	n	Mean(SD) or No(%)		
Vervloet, 1998; Rutten-van Molken, 1998	Healthcare utilization	ER visits per patient (number) at over 6m	Formoterol 12ug	241	NR	241	0.027 (0.2)	NR	Form vs Sal 25ug, p=0.188
			Salmeterol 50ug	241	NR	241	0.095 (0.78)	NR	
		Health professional contacts per patient (number) at over 6m	Formoterol 12ug	241	NR	241	0.49 (1.33)	NR	Form vs Sal 25ug, p=0.996
			Salmeterol 50ug	241	NR	241	0.59 (1.91)	NR	
		Inpatients hospital days per patient (day) at over 6m	Formoterol 12ug	241	NR	241	0.58 (5.38)	NR	
			Salmeterol 50ug	241	NR	241	0.43 (3.5)	NR	
	QOL	% of patients with QOL improved (%) at 6	Formoterol 12ug	241	NR	241	154 (64%)	NR	Quality of Life was measured using St. George Respiratory Questionnaire NR
			Salmeterol 50ug	241	NR	241	149 (62%)	NR	
		Days of absence from paid work/patient (day) at 6 m	Formoterol 12ug	241	NR	241	3.19 (16.0)	NR	Form vs Sal 50ug, p=0.144
			Salmeterol 50ug	241	NR	241	2.60 (16.1)	NR	
		Days unable to perform usual activities (day) at 6 m	Formoterol 12ug	241	NR	241	4.09 (24.32)	NR	Form vs Sal 50ug, p=0.439
			Salmeterol 50ug	241	NR	241	6.3 (21.59)	NR	
	Rescue medication	No. of rescue medication, daytime (number) at 1 mo.	Formoterol 12ug	241	2.2 (NR)	NR	0.9 (NR)	NR	No data reported. Values estimated from graph. NR
			Salmeterol 50ug	241	1.9 (NR)	NR	0.9 (NR)	NR	
		No. of rescue medication, daytime (number) at 6 mos.	Formoterol 12ug	241	2.2 (NR)	NR	0.5 (NR)	NR	
			Salmeterol 50ug	241	1.9 (NR)	NR	0.65 (NR)	NR	
		No. of rescue medication, nighttime (number) at 1 mo.	Formoterol 12ug	241	1.2 (NR)	NR	0.6 (NR)	NR	
			Salmeterol 50ug	241	1.1 (NR)	NR	0.5 (NR)	NR	
No. of rescue medication, nighttime (number) at 6 mos.	Formoterol 12ug	241	1.2 (NR)	NR	0.35 (NR)	NR			
	Salmeterol 50ug	241	1.1 (NR)	NR	0.45 (NR)	NR			

Author Year	Outcome Category	Outcome (unit) at timepoint	Intervention	Baseline:		Follow-Up:		Change from Baseline, Mean(SD), p-value	Comments
				n	Mean(SD) or No(%)	n	Mean(SD) or No(%)		
Vervloet, 1998; Rutten van Molken, 1998	Symptoms	Asthma, exacerbation (number) at NR	Formoterol 12ug	241	NR	241	4 (1.7%)	NR	4 (1.7%) NR
			Salmeterol 50ug	241	NR	241	4 (1.7%)		
	Symptoms	Asthma, exacerbations (number) at NR	Formoterol 12ug	241	NR	241	41 (17%)	NR	
			Salmeterol 50ug	241	NR	241	54 (22%)	NR	
			Episode free days (day) at 6 m	Formoterol 12ug	241	NR	241	97 (64)	NR
				Salmeterol 50ug	241	NR	241	95 (62)	NR
			Respiratory symptom score at daytime at 1 mo.	Formoterol 12ug	241	0.9 (NR)	NR	0.6 (NR)	NR
				Salmeterol 50ug	241	0.8 (NR)	NR	0.5 (NR)	NR
			Respiratory symptom score at daytime at 6 mo.	Formoterol 12ug	241	0.6 (NR)	NR	0.4 (NR)	NR
				Salmeterol 50ug	241	0.5 (NR)	NR	0.4 (NR)	NR
Respiratory symptom score at nighttime (score) at 1 mo.	Formoterol 12ug	241	0.6 (NR)	NR	0.3 (NR)	NR			
	Salmeterol 50ug	241	0.5 (NR)	NR	0.3 (NR)	NR			
Respiratory symptom score at nighttime, month 6	Formoterol 12ug	NR	NR	NR	NR	NR			
	Salmeterol 50ug	NR	NR	NR	NR	NR			
Adult COPD									
Cazzola, 1994	Symptoms	Onset of action (hours) at up to 12 hrs	Formoterol 50ug	16	NR	16	3min 56 s (%)	NR	Form 24ug vs Sal 50ug, mean diff 6min 12sec, p<0.05
			Salmeterol 50ug	16	NR	16	10min 8 sec (%)	NR	
Di Marco, 2003	Symptoms	Dyspnea symptoms (VAS 0- 20, (+)=improved (number) at 30 min	Formoterol 12ug		NR		NR	NR	Form vs Sal, p>0.05
			Salmeterol 50ug		NR		NR	NR	

Author Year	Outcome Category	Outcome (unit) at timepoint	Intervention	Baseline:		Follow-Up:		Change from Baseline, Mean(SD), p-value	Comments
				n	Mean(SD) or No(%)	n	Mean(SD) or No(%)		
Kottakis, 2002	Symptoms	Degree of breathing discomfort (VAS) (mm) at 1hr		NR	NR	NR	NR	NR	Form vs Sal, mean diff -5.201 CI: -10.72,0.32, p=0.646
		Degree of breathing discomfort (VAS) (mm) at 4 hrs		NR	NR	NR	NR	NR	Form vs Sal, mean diff. -4.404 CI: -10.44,1.63, p=0.1519
	Effort to breathe (VAS) (mm) at 1 hr	Formoterol 12ug	47	NR	44	NR	-1.4 (1.3), NR	Between group mean difference was the end point difference. FEV ₁ data NR, shown only in graphs	
			Formoterol 24ug	47	NR	45	NR		-1.4 (1.4), NR
		Salmeterol 100ug	47	NR	46	NR	-1.0 (1.3), NR		
		Salmeterol 50ug	47	NR	45	NR	-1.1 (1.3), NR		
		Effort to breathe (VAS) (mm) at 4 hrs	Formoterol 12ug	47	NR	44	NR		-0.8 (1.2), NR
			Formoterol 24ug	47	NR	45	NR		-0.8 (1.4), NR
Salmeterol 100ug	47	NR	46	NR	-0.8 (1.4), NR	p=0.0853			
Salmeterol 50ug	47	NR	45	NR	-0.6 (1.0), NR	Form 24ug vs Sal 50ug, mean diff., -3.827, CI: -9.67, 2.02 p=0.1984			
Pediatrics Asthma									
Everden, 2002; Everden, 2004	Compliance	% taking >=75% of doses of study medication (%) at over 12 weeks	Formoterol 12ug (9ug delivered dose) BID	79	NR	79	90(NR)	NR	Form vs Sal, mean diff 2%
			Salmeterol 50ug BID	76	NR	76	88(NR)	NR	
	Healthcare utilization	Unscheduled GP visits (number per person) at 12 weeks	Formoterol 12ug (9ug delivered dose) BID	73	NR	73	0.05 (0.23)	NR	
			Salmeterol 50ug BID	72	NR	72	0.01 (0.12)	NR	
	QOL	Change in HRQL: Activity; Parent-reported (number) at 12 wks	Formoterol 12ug (9ug delivered dose) BID	NR	NR	NR	NR	0.52 (NR), NR	Values based on estimates from graph NR. Form vs Sal, mean diff 0.31, p<0.05
			Salmeterol 50ug	NR	NR	NR	NR	0.21 (NR), NR	
		Change in HRQL: Activity; Pt.-reported (number) at 12 wks	Formoterol 12ug (9ug delivered dose) BID	NR	NR	NR	NR	1.07 (NR), NR	Form vs Sal, mean diff. 0.35
			Salmeterol 50ug BID	NR	NR	NR	NR	0.72 (NR), NR	
		Change in HRQL: Emotion; Parent-reported (number) at 12 wks	Formoterol 12ug (9ug delivered dose) BID	NR	NR	NR	NR	0.53 (NR), NR	Form vs Sal, mean diff. 0.11
			Salmeterol 50ug BID	NR	NR	NR	NR	0.42 (NR), NR	
	Change in HRQL: Emotion; Pt.-reported (number) at 12 wks	Formoterol 12ug (9ug delivered dose) BID	NR	NR	NR	NR	0.86 (NR), NR	Form vs Sal, mean diff. 0.31	
		Salmeterol 50ug BID	NR	NR	NR	NR	0.55 (NR), NR		
Change in HRQL: Overall; Parent-reported (number) at 12 wks	Formoterol 12ug (9ug delivered dose) BID	NR	NR	NR	NR	0.52 (NR), NR	Form vs Sal, mean diff. 0.15		
	Salmeterol 50ug BID	NR	NR	NR	NR	0.52 (NR), NR			

Author Year	Outcome Category	Outcome (unit) at timepoint	Intervention	Baseline:		Follow-Up:		Change from Baseline, Mean(SD), p-value	Comments	
				n	Mean(SD) or No(%)	n	Mean(SD) or No(%)			
Everden, 2002; Everden, 2004			Salmeterol 50ug BIDNR	NR	NR	NR	NR	0.37 (NR), NR		
		Change in HRQL: Overall; Pt.-reported (number) at 12 wks	Formoterol 12ug (9ug delivered dose) BID	NR	NR	NR	NR	0.92 (NR), <0.01	Form vs Sal, mean diff. 0.38 p>0.05	
			Salmeterol 50ug BID	NR	NR	NR	NR	0.54 (NR), <0.01		
		Change in HRQL: Symptoms; Pt.-reported (number) at 12 wks	Formoterol 12ug (9ug delivered dose) BID	NR	NR	NR	NR	1.03 (NR), NR	Form vs Sal, mean diff. 0.36	
			Salmeterol 50ug BID	NR	NR	NR	NR	0.67 (NR), NR		
		Limited activity days because of asthma (days/wk) at 12 wks	Formoterol 12ug (9ug delivered dose) BID	79	NR	79	NR	-0.92 (2.03), p<0.001	Form vs Sal, mean diff. -0.26,; CI: -0.90, 0.38, p=0.622	
			Salmeterol 50ug BID	76	NR	76	NR	-0.66 (1.91), p<0.001		
		Parents unable to attend work or activities (days) at 12 weeks	Formoterol 12ug (9ug delivered dose) BID	79	NR	79	NR	NR	Form vs Sal, p=0.071	
			Salmeterol 50ug BID	76	NR	76	NR	NR		
		Patient unable to join activities (days) at 12 weeks	Formoterol 12ug (9ug delivered dose) BID	79	NR	79	NR	NR	Form vs Sal. P=0.178	
			Salmeterol 50ug BID	76	NR	76	NR	NR		
		Rescue medication	Able to stop using SABA at week 12 (%) at 12 weeks	Formoterol 12ug (9ug delivered dose) BID	79	NR	79	NR	NR	Form vs Sal, mean diff. 18%, CI: 1%, 35%, p=0.04
				Salmeterol 50ug BID	76	NR	76	NR	NR	
			Change in PRN B2 agonist use (inhalations/24 hrs) at 12 weeks	Formoterol 12ug (9ug delivered dose) BID	79	NR	79	NR	-2.45 (2.29), <0.001	Form vs Sal, mean diff, -0.70, CI: -1.37,-0.03, p=0.043
				Salmeterol 50ug BID	76	NR	76	NR	-2.05 (2.50), <0.001	
			Change in PRN B2 agonist use, daytime (inhalations/day) at 12 weeks	Formoterol 12ug (9ug delivered dose) BID	79	NR	79	NR	-1.85 (1.90), <0.001	Form vs Sal, mean diff. -0.46 CI: -0.97, 0.05, p=0.081
				Salmeterol 50ug BID	76	NR	76	NR	-1.72 (2.02), <0.001	
			Change in PRN B2 agonist use, nighttime (inhalations/night) at 12 weeks	Formoterol 12ug (9ug delivered dose) BID	76	NR	76	NR	-0.56 (0.83), <0.001	Form vs Sal, mean diff, -0.17 CI: -0.42, 0.09, p=0.251
				Salmeterol 50ug BID	76	NR	76	NR	-0.39 (0.69), <0.001	
			Short-acting B2-agonist usage, inhalations (number) at 12 weeks	Formoterol 12ug (9ug delivered dose) BID	73	NR	73	109 (145)	NR	
			Salmeterol 50ug BID	72	NR	72	164 (178)	NR		

Author Year	Outcome Category	Outcome (unit) at timepoint	Intervention	Baseline:		Follow-Up:		Change from Baseline, Mean(SD), p-value	Comments
				n	Mean(SD) or No(%)	n	Mean(SD) or No(%)		
Everden, 2002; Everden, 2004		Use of severe exacerbation meds (eg steroids) (number) at 12 weeks	Formoterol 12ug (9ug delivered dose) BID	73	NR	73	0.03 (0.16)	NR	
			Salmeterol 50ug BID	72	NR	72	0 (0)	NR	
	Symptoms	Asthma, mild exacerbations (day) at 12	Formoterol 12ug (9ug delivered dose) BID	79	NR	79	7.8 (NR)	NR	Form vs Sal, p=0.051
			Salmeterol 50ug BID	79	NR	79	12.2 (NR)	NR	
		Clinician asthma severity score (0-3), day at 12 wks	Formoterol 12ug (9ug delivered dose) BID	79	NR	79	NR	-0.74 (0.88), <0.001	Form vs Sal, mean diff. -0.12 CI: -0.40, 0.15, p=0.324
			Salmeterol 50ug BID	76	NR	76	NR	-0.61 (0.82), <0.001	
		Clinician asthma severity score (0-3), night at 12 wks	Formoterol 12ug (9ug delivered dose) BID	79	NR	79	NR	-0.75 (0.94), <0.001	Form vs Sal, mean diff. -0.27 CI: -0.52, 0.05, p=0.049
			Salmeterol 50ug BID	76	NR	76	NR	-0.51 (0.85), <0.001	
		Patient asthma severity score (0-3), day (score) at 12 wks	Formoterol 12ug (9ug delivered dose) BID	79	NR	79	NR	-7.0 (0.62), <0.001	Form vs Sal, mean diff. -0.17 CI: -0.36, 0.02, p=0.052
			Salmeterol 50ug BID	76	NR	76	NR	-0.53 (0.57), <0.001	
		Patient asthma severity score (0-3), night (score) at 12 wks	Formoterol 12ug (9ug delivered dose) BID	79	NR	79	NR	-0.5 (0.59), <0.001	Form vs Sal, mean diff. -0.02 CI: -0.22, 0.17, p=0.687
			Salmeterol 50ug BID	76	NR	76	NR	-0.47 (0.62), <0.001	
		Poorly controlled days (days) at 12 weeks	Formoterol 12ug (9ug delivered dose) BID	79	NR	79	12.4 (NR)	NR	Form vs Sal, p=0.107
			Salmeterol 50ug BID	76	NR	76	17.0 (NR)	NR	
		Severe asthma exacerbation of asthma (%) at 12 weeks	Formoterol 12ug (9ug delivered dose) BID	79	NR	80	(17%)	NR	
			Salmeterol 50ug BID	76	NR	76	(17%)	NR	

Albuterol vs levalbuterol

Demographic and study characteristics are summarized in Table 6 and effectiveness outcomes in Table 7.

Adult asthma

Nelson and colleagues⁷⁶ and Pleskow et al.⁷⁸ examined 362 patients 12 years of age and older with moderate to severe asthma. Each participant was given a nebulizer three times daily of either levalbuterol (0.63 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 treatment groups and 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 controlled clinical trial⁷⁷ ($n = 91$) examined adults presenting to the emergency department with asthma. Treatment consisted of three doses of albuterol (2.5 and 5.0 mg) or levalbuterol (0.63 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 three doses than after treatment with albuterol. However, hospitalization rates were similar between the two drugs for matched dosages. (Rates for levalbuterol were: 0.63 mg, 0%; 1.25 mg, 7%; 2.5 mg, 8%; 3.75 mg, 29%; and 5.0 mg, 8%. Rates for albuterol were: 2.5 mg, 7%; 5.0mg, 0%). No statistical comparisons were presented for these outcomes.

An HFA 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. We did not identify any published data on the comparative effectiveness or safety of this preparation with respect to albuterol.

Pediatric asthma

Symptoms and rescue medication use were not different between drugs in the four pediatric studies that compared albuterol and levalbuterol.^{73, 75, 79, 81} Two of these studies took place in the ER. Qureshi and colleagues⁷⁹ examined children aged 2 to 14 years ($n = 129$) presenting to a pediatric emergency department with a moderate to severe acute asthma exacerbation (asthma score > 8 out of a possible score of 15). These children were given three nebulized treatments of either albuterol 2.5 to 5.0 mg (depending on weight) or levalbuterol 1.25 to 2.5 mg at 20-minute intervals, with subsequent treatments given at 30- and 60-minute intervals based on clinical assessment and pulmonary function testing. There were no significant differences between groups after the first, third, and fifth nebulizer treatment 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 colleagues⁷³ (n=70) randomized patients aged 5 to 21 presenting to the emergency department to levalbuterol 1.25 mg or albuterol 2.5 mg via nebulization, along with ipratropium bromide 250 ug in children <30 kg and 500 ug 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, and the need for extra treatments.

Two studies examined regular daily use of levalbuterol and albuterol. Milgrom and colleagues⁷⁵ examined 338 children aged 4 to 11 years with at least mild asthma for ≥ 60 days prior to screening and randomized them to receive 21 days of three-times-a-day of either levalbuterol 0.31 mg, levalbuterol 0.63 mg, albuterol 1.25 mg, or 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, symptom-free days, quality of life, or rescue medication use. Asthma control days were not difference 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 colleagues⁸¹ randomized asthmatic children age 2 to 5 years to albuterol (1.25 mg or 2.5 mg, depending on weight) or levalbuterol (0.31 mg or 0.63 mg, independent of weight), each given three 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 (PACQLQ) improved more for the levalbuterol groups, although between-group differences were not significant. In a subgroup analysis of patients less than 33 pounds, overall PACQLQ score was significantly improved after levalbuterol 0.63 mg than albuterol ($p = 0.016$). This study was of fair quality: although it reported using intention-to-treat analyses for efficacy/effectiveness measures, the number of subjects actually analyzed was unclear. Study completion rate was 83.4%.

Healthcare utilization outcomes varied among the three studies that examined these outcomes.^{68, 73, 79} These all took place in the emergency department, and were similarly-designed RCTs, with blinding of the patient and treating physician.

Qureshi and colleagues⁷⁹ (see details above) reported a per-protocol analysis of 129, primarily African-American, children. Ten patients were excluded from analysis, including six 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 ER, 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 their study was underpowered to detect a possible difference in rates between groups.

Similar results were reported by Hardasmalani and colleagues,⁷³ 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 to 3 of 36 children (4.3%) in the levalbuterol group (between-group, $p=0.528$).

In contrast to the two 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.⁶⁸ This study ($n=547$) of predominantly African-American males with moderate to severe chronic asthma, randomized children aged 1 to 18 years upon presentation to the emergency room, to three treatments via nebulizer at 20-minute intervals of either 1.25 mg levalbuterol or 2.5 mg of albuterol. 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 colleagues⁶⁸ noted a hospital admission rate of 122/269 (45%) with albuterol and 101/278 (36%) after levalbuterol (between-group, $p=0.02$). The use of albuterol in the 24 hours prior to the emergency department visit correlated with hospital admission rate ($p=0.002$). After controlling for recent use of albuterol (>3 aerosols in the last 24 hours), levalbuterol was still associated with a lower admission rate 43% vs 53% with albuterol (RR, 1.25, 95% CI, 1.01-1.51). 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

There were no studies comparing albuterol and levalbuterol in persons with EIA.

COPD

The single study comparing these two drugs⁷⁰ did not provide data on effectiveness outcomes.

Table 6. Albuterol vs Levalbuterol: Demographic and Study Characteristics of Included Studies

Author, Year	Study duration	Intervention	n	Mean age in years (SD)	% Female	Other medications permitted during the study	Quality	Funding
Adult Asthma								
1. Cockcroft, 1997	Single dose	Albuterol 2.5mg Nebulizer	12	23.58(1.98)	50	Inhaled steroids at stable dose (only 1 patient used)	Fair	Sepracor Inc,
		Levalbuterol 1.25mg						
2. Gumbhir-Shah, 1999	4 cumulative doses	Albuterol 2.5mg QID Solution administered via Nebulizer	13	28.7(7.0)	46	Stable doses of other medications were allowed.	Fair	NR; affiliation of 1 author Sepracor Inc.
		Levalbuterol 1.25mg QID Solution administered via Nebulizer						
3. Handley, 2000	Single dose	Albuterol 2.5mg MDI	20	36	75	Patients were allowed to take anti-inflammatory medications for their asthma, provided they had been initiated at least 3 months before the study and if they were taken during the study at stable doses. Patients were required to withhold racemic salmeterol.	Fair	Sepracor Inc.
		Levalbuterol 0.31mg solution administered via Nebulizer						
		Levalbuterol 0.63mg solution administered via Nebulizer						
		Levalbuterol 1.25mg solution administered via Nebulizer						
4. Lotvall J 2001	Multidose, single days	Albuterol 12.5 to 3200 ug solution administered via Nebulizer	20	50	40	Regular maintenance treatments (eg inhaled steroid)	Fair	Glaxo Wellcome R&D Ltd.
		Levalbuterol 6.25 to 1600 ug solution administered via Nebulizer						

Author, Year	Study duration	Intervention	n	Mean age in years (SD)	% Female	Other medications permitted during the study	Quality	Funding
5. Nowak, 2004	3 doses	Albuterol 2.5mg 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, for cohort	Sepracor, In.
		Albuterol 5.0mg Nebulizer Levalbuterol 0.63mg Levalbuterol 1.25mg Levalbuterol 2.5mg Nebulizer Levalbuterol 3.75mg Levalbuterol 5.0mg Nebulizer						
6. Ramsay, 1999	Single dose	Albuterol 200ug Nebulizer	22	39.4	72.73	Eighteen of the subjects were taking corticosteroids by inhalation regularly and were maintained on the same dose throughout the study.	Fair	Sepracor Inc.
		Levalbuterol 100ug Nebulizer						
7. Nelson, 1998; Pleskow, 2004	4 weeks	Albuterol 1.25mg TID	362	36.5(15)	60	Patients were allowed to take other medications for asthma or allergic rhinitis, including inhaled and intranasal corticosteroids, sodium cromoglycate, and nedocromil sodium if withheld for a sufficient period of time before study visits.	Fair	Sepracor Inc.
		Albuterol 2.5mg TID Nebulizer						
		Levalbuterol 0.63mg TID Nebulizer						
		Levalbuterol 1.25mg TID Nebulizer						
Summary:	Single dose: 3 Other: 3		540 range: 12-362	35.3 range: 23.6-- 50.0	55.6 range: 40.0-75.0		Good: 0 Fair: 6 Poor: 0 NA: 1	Industry: 5 Public: 0 NR: 1

Author, Year	Study duration	Intervention	n	Mean age in years (SD)	% Female	Other medications permitted during the study	Quality	Funding
Adult COPD								
8. Datta, 2003	Single dose	Albuterol 2.5mg Solution administered via nebulizer	30	69(15)	16.67	Maintenance bronchodilator medications were withheld prior to each test drug administration according to the following schedule: theophylline, 48 h; salmeterol, 24 h; ipratropium, 8 h, and albuterol, 6h	Fair	NR
		Levalbuterol 1.25mg Solution administered via nebulizer						
Summary:	Single dose: 1 Other: 0		30 range: NA	69 range: NA	16.67 range: NA		Good: 0 Fair: 1 Poor: 0	Industry: 0 Public: 0 NR: 1
Pediatrics Asthma								
9. Carl, 2003	Single dose	Albuterol 2.5mg solution administered via Nebulizer	547	7.1	33	Use of oral steroids in the past 24 h during study	Good	NR
		Levalbuterol 1.25mg solution administered via Nebulizer						
10. Gawchik, 1999	Single dose	Albuterol 1.25mg solution administered via Nebulizer	43	8.3(2.3)	48.84	Subjects were able to continue to use their routine asthma medications during the study, but specific washout periods were established before study visits. Albuterol was withheld for 8 hours or more before testing on study	Poor	NR
		Albuterol 2.5mg solution administered via Nebulizer						
		Levalbuterol 0.16mg solution administered via Nebulizer						
		Levalbuterol 0.31mg solution administered via Nebulizer						
		Levalbuterol 0.63mg solution administered via Nebulizer						
		Levalbuterol 1.25mg solution Nebulizer						

Author, Year	Study duration	Intervention	n	Mean age in years (SD)	% Female	Other medications permitted during the study	Quality	Funding
11. Hardasmalani, 2005	3 treatments, 1 hr	Albuterol 2.5mg/3mL TID Nebulizer	70	12.3	40	Ipratropium (250 ug in children <30kg and 500 ug ?30 kg) given with study drug via nebulizer; oral steroids 2mg/kg given after 2nd treatment	Fair	NR
		Levalbuterol 1.25mg/3m TIDL Nebulizer						
12. Milgrom, 2001	3 weeks	Albuterol 1.25mg Nebulizer	338	8.5(1.9)	41.72	Stable doses of inhaled corticosteroids initiated ≥60 days before randomization were permitted	Fair	Sepracor Inc.
		Albuterol 2.5mg Nebulizer						
		Levalbuterol 0.31mg						
		Levalbuterol 0.63mg						
13. Qureshi, 2005	Single dose	Albuterol 2.5-5mg Nebulizer	129	5.8	34.11	Ipratropium bromide therapy delayed until after the third nebulized study treatment. Prednisone or equivalent corticosteroid given to all children with second albuterol treatment.	Fair	Sepracor Inc.
		Levalbuterol 1.25-2.5mg Nebulizer						

Author, Year	Study duration	Intervention	n	Mean age in years (SD)	% Female	Other medications permitted during the study	Quality	Funding
14. Skoner, 2005	3 weeks	Albuterol 1.25mg-2.5mg TID Nebulizer Levalbuterol 0.31mg TID Nebulizer Levalbuterol 0.63mg TID Nebulizer Placebo Nebulizer	211	3.4(1.1)	69.24	Pts receiving matching blinded medications (lev 1.25mg for the lev groups & alb 2.5mg for the alb groups. Non-beta-2-agonist asthma med including ipratropium bromide and inhaled corticosteroids.	Fair	Sepracor Inc.
Summary:	Single dose: 3 Other: 3		1338 range: 43-547	7.0 range: 3.4-12.3--	39.2 range: 33-69.24		Good: 1 Fair: 4 Poor: 1	Industry: 3 Public: 0 NR: 3
*Study population ≥ 12 years of age								

Table 7. Albuterol vs Levalbuterol: Effectiveness Outcomes of Included Studies

Author Year	Outcome Category	Outcome (unit) at timepoint	Intervention	Baseline:		Follow-Up:		Change from Baseline, Mean(SD), p-value	Comments
				n	Mean(SD) or No(%)	n	Mean(SD) or No(%)		
Adult Asthma									
Nowak, 2004	Healthcare utilization	Patients discharged after three doses (number) at NR	Albuterol 2.5mg	14	NR	14	7 (50%)	NR	Not an RCT
			Albuterol 5.0mg	13	NR	13	8 (62%)	NR	
			Levalbuterol 0.63mg	12	NR	12	11 (92%)	NR	
			Levalbuterol 1.25mg	14	NR	14	12 (86%)	NR	
			Levalbuterol 2.5mg	12	NR	12	8 (67%)	NR	
			Levalbuterol 3.75mg	14	NR	14	5 (36%)	NR	
		Patients hospitalized (number) at NR	Levalbuterol 5.0mg	12	NR	12	10 (83%)	NR	
			Albuterol 2.5mg	14	NR	14	1 (7%)	NR	
			Albuterol 5.0mg	13	NR	13	0 (0%)	NR	
			Levalbuterol 0.63mg	12	NR	12	0 (0%)	NR	
			Levalbuterol 1.25mg	14	NR	14	1 (7%)	NR	
			Levalbuterol 2.5mg	12	NR	12	1 (8%)	NR	
		Patients requiring additional therapy poststudy (number) at NR	Levalbuterol 3.75mg	14	NR	14	4 (29%)	NR	
			Levalbuterol 5.0mg	12	NR	12	1 (8%)	NR	
			Albuterol 2.5mg	14	NR	14	6 (43%)	NR	
			Albuterol 5.0mg	13	NR	13	4 (31%)	NR	
			Levalbuterol 0.63mg	12	NR	12	1 (8%)	NR	
			Levalbuterol 1.25mg	14	NR	14	1 (7%)	NR	
			Levalbuterol 2.5mg	12	NR	12	3 (25%)	NR	
			Levalbuterol 3.75mg	14	NR	14	5 (36%)	NR	
			Levalbuterol 5.0mg	12	NR	12	1 (8%)	NR	

Author Year	Outcome Category	Outcome (unit) at timepoint	Intervention	Baseline:		Follow-Up:		Change from Baseline, Mean(SD), p-value	Comments	
				n	Mean(SD) or No(%)	n	Mean(SD) or No(%)			
Nelson, 1998; Pleskow, 2004*	Rescue medication	% of patients using any rescue medication (number) at 4 weeks	Albuterol 1.25mg	68	NR	68	66 (97.1%)	NR (NR), >0.05	FEV ₁ : Levalbuterol 0.63 and albuterol 2.5 mg had similar peak improvements and duration of action at weeks 0,2,4 FEV ₁ : comparing combined lev treatments and combined alb treatments, lev increased more in FEV ₁	
			Albuterol 2.5mg	74	NR	74	72 (97.3%)	NR (NR), 0.056		
			Levalbuterol 0.63mg	72	NR	72	69 (95.8%)	NR (NR), >0.05		
		Levalbuterol 1.25mg	73	NR	73	70 (95.9%)	NR			
		No. of puffs of rescue medication puffs per day (puffs/day) at NR	Albuterol 1.25mg	68	3.59 (NR)	68	3.6 (3.0)	0.01 (NR), 0.99		Albuterol vs placebo, p=0.12
			Albuterol 2.5mg	74	4.3 (NR)	74	3.8 (2.9)	-0.5 (NR), 0.056		Albuterol vs placebo, p=0.42
			Levalbuterol 0.63mg	72	3.75 (NR)	72	3.5 (3.2)	-0.25 (NR), 0.372		Lev vs placebo, p=0.006
	Symptoms	Asthma (number) at 4 weeks	Albuterol 1.25mg	68	NR	68	5 (7.4%)	NR	Lev vs placebo, p<0.0001	
			Albuterol 2.5mg	74	NR	74	6 (8.1%)	NR		
			Levalbuterol 0.63mg	72	NR	72	5 (6.9%)	NR		
		Asthma, increase (number) at 4 weeks	Levalbuterol 1.25mg	73	NR	73	4 (5.5%)	NR		
			Albuterol 1.25mg	68	NR	68	2 (2.9%)	NR		
			Albuterol 2.5mg	74	NR	74	2 (2.7%)	NR		
			Levalbuterol 0.63mg	72	NR	72	1 (1.4%)	NR		
Placebo TID	Levalbuterol 1.25mg	73	NR	73	3 (4.1%)	NR				
	Placebo TID	75	NR	75	2 (2.7%)	NR				

Author Year	Outcome Category	Outcome (unit) at timepoint	Intervention	Baseline:		Follow-Up:		Change from Baseline, Mean(SD), p-value	Comments	
				n	Mean(SD) or No(%)	n	Mean(SD) or No(%)			
Pediatrics Asthma										
Carl, 2003	Healthcare utilization	Hospital admissions (number) at 2h	Albuterol 2.5mg	269	NR	269	122 (45.4%)	NR	Alb vs Lev, mean diff: 9%, p=0.02	
			Levalbuterol 1.25mg	278	NR	278	101 (36.3%)	NR		
		Length of stay in ER (hrs) at discharge	Albuterol 2.5mg	269	NR	269	2.2 (0.8)	NR		Alb vs Lev, p=0.25
			Levalbuterol 1.25mg	278	NR	278	2.3 (0.9)	NR		
		NNT with levalbuterol to prevent 1 admission (number) at discharge	Albuterol 2.5mg	NR	NR	NR	NR	NR		Alb vs Lev, NNT=10.6, : CI: 5.8-71.4, p<0.05
			Levalbuterol 1.25mg	NR	NR	NR	NR	NR		
	Risk of admission, with >3 aerosols 12hrs prior (number) at NR	Albuterol 2.5mg	NR	NR	NR	NR	NR	Alb vs Lev, RR=1.25 CI: 1.01, 1.51, p=0.04		
		Levalbuterol 1.25mg	NR	NR	NR	NR	NR			
	Symptoms	Respiratory rate (bpm) at ER discharge	Albuterol 2.5mg	269	NR	269	35.6 (12.6)	NR	Albuterol vs Levalbuterol, p=0.26	
			Levalbuterol 1.25mg	278	NR	278	37.0 (10.4)	NR		
Hardasmalani, 2005	Healthcare utilization	Need for extra treatments (number) at During ER visit	Albuterol 2.5mg/3mL TID	34	NR	34	7 (21%)	NR	Albuterol vs Levalbuterol, p>0.05	
			Levalbuterol 1.25mg/3m TIDL	36	NR	36	5 (14%)	NR		
	Need for hospitalization (number) at during study	Albuterol 2.5mg/3mL TID	34	NR	34	2 (6%)	NR	Albuterol vs Levalbuterol, p>0.05		
		Levalbuterol 1.25mg/3m TIDL	36	NR	36	3 (8%)	NR			
Milgrom, 2001	Symptoms	Asthma, control days (day) at Day 14-21	Albuterol 1.25mg	67	NR	NR	0 (NR)	NR	Day 0, there wre significant more patients responding to levalbuterol 0.31mg (62.9%) than to albuterol 1.25mg (41.8%), p=0.012 immediately after treatment. NSD among treatment groups for overall asthma symptom assessment score and, symptom-free days Alb vs Lev, p<0.04 Lev 0.31 vs Lev 0.63, p<0.04	
			Albuterol 2.5mg	66	NR	NR	NR	NR		
			Levalbuterol 0.31mg	70	NR	NR	1.6 (NR)	NR		
			Levalbuterol 0.63mg	70	NR	NR	0.25 (NR)	NR		

Author Year	Outcome Category	Outcome (unit) at timepoint	Intervention	Baseline:		Follow-Up:		Change from Baseline, Mean(SD), p-value	Comments
				n	Mean(SD) or No(%)	n	Mean(SD) or No(%)		
Qureshi, 2005	Healthcare utilization	% of patients hospitalized after ER visit (number) at NR	Albuterol 2.5-5mg	64	NR	64	13 (NA%)	NR	Alb vs Lev, p>0.05
			Levalbuterol 1.25-2.5mg	65	NR	65	11 (NA%)	NR	
		Length of care (median) (min) at NR	Albuterol 2.5-5mg	64	NR	64	125 (NR)	NR	Alb vs Lev, p>0.05
			Levalbuterol 1.25-2.5mg	65	NR	65	121 (NR)	NR	
	Rescue medication	No. of nebulizations, median (number) at NR	Albuterol	64	NR	64	3 (NR)	NR	Alb vs Lev, p>0.05
			Levalbuterol	65	NR	65	3 (NR)	NR	
	Symptoms	Asthma score, % change from baseline (%) at after 5th RX	Albuterol 2.5-5mg	17	NR	17	NR	20%,NR	Alb vs Lev, mean diff=0, p>0.05
			Levalbuterol 1.25-2.5mg	16	NR	16	NR	22%,NR	
		Respiratory rate, median change (number/min) at 5th nebulization	Albuterol	64	NR	64	NR	-4 (NR), NR	Alb vs Lev, p>0.05
			Levalbuterol	65	NR	65	NR	-5 (NR), NR	
Skoner, 2005	QOL	Pediatric Asthma Caregiver's QOL Questionnaire (number) at 3 wks	Albuterol 1.25mg-2.5mg TID	NR	NR	NR	NR	0.33 (1.20), NR	Authors report minimum clinically significant improvement in both lev groups, but not albuterol or placebo; NSD among groups; for pts <33lbs, change in PACQLQ was greater for lev 0.31 and 0.63 than albuterol
			Levalbuterol 0.31mg TID	NR	NR	NR	NR	0.61 (1.10), NR	
			Levalbuterol 0.63mg TID	NR	NR	NR	NR	0.74 (0.96), NR	
			Placebo	NR	NR	NR	NR	0.19 (1.04), NR	

Author Year	Outcome Category	Outcome (unit) at timepoint	Intervention	Baseline:		Follow-Up:		Change from Baseline, Mean(SD), p-value	Comments	
				n	Mean(SD) or No(%)	n	Mean(SD) or No(%)			
Skoners, 2005	Symptoms	Pediatric Asthma Questionnaire - mean change (number) at week 1	Albuterol 1.25mg-2.5mg TID	NR	NR	NR	NR	-1.5 (NR), NR	Mean change values interpolated from graph. NSd among groups Authors conducted some subgroup analysis based on pts <33 and > or = 33 lbs. The only time significance was reached was in comparison PACQLQ score for pts >33lbs in favor of levalbuterol:	
			Levalbuterol 0.31mg TID	NR	NR	NR	NR	-2.2 (NR), NR		
			Levalbuterol 0.63mg TID	NR	NR	NR	NR	-1.5 (NR), NR		
		Pediatric Asthma Questionnaire - mean change (number) at week 2	Albuterol 1.25mg-2.5mg TID	NR	NR	NR	NR	-2.0 (NR), NR		Mean change values interpolatd from graph. NSD among groups Authors conducted some subgroup analysis based on pts <33 and > or = 33 lbs. The only time significance was reached was in comparison PACQLQ score for pts >33lbs in favor of levalbuterol:
			Levalbuterol 0.31mg TID	NR	NR	NR	NR	-2.9 (NR), NR		
			Levalbuterol 0.63mg TID	NR	NR	NR	NR	-2.4 (NR), NR		
	Pediatric Asthma Questionnaire - mean change (number) at week 3	Albuterol 1.25mg-2.5mg TID	NR	NR	NR	NR	-2.9 (4.1), NR	Mean change values and SD values presented in text (other timepoints interpolated from graph). NSD among groups Authors conducted some subgroup analysis based on pts <33 and > or = 33 lbs. The only time significance was reached was in comparison		
		Levalbuterol 0.31mg TID	NR	NR	NR	NR	-3.5 (3.1), NR			
		Levalbuterol 0.63mg TID	NR	NR	NR	NR	-3.3 (4.3), NR			

*Study population ≥ 12 years of age

Albuterol vs metaproterenol

Demographic and study characteristics are summarized in Table 8. There were no effectiveness data for any of these five fair-quality studies.^{82-84, 86, 87}

In an exercise-challenge study of adolescents with exercise-induced bronchospasm,⁸³ albuterol and metaproterenol were equally efficacious in blocking exercise-induced bronchospasm initially. The duration of action of albuterol was significantly longer than for metaproterenol ($p < 0.05$).

Table 8. Albuterol versus Metaproterenol: Demographic and Study Characteristics of Included Studies

Author, Year	Study duration	Intervention	n	Mean age in years (SD)	% Female	Other medications permitted during the study	Quality	Funding
Adult Asthma								
1. Choo-Kang, 1969	Single dose	Albuterol 200ug MDI	24	56.3	70.83	Previous users of prednisolone allowed to continue - doses 5-20 mg	Fair	NR
		Metaproterenol 1500ug MDI						
Summary:	Single dose: 1 Other: 0		24 range: NA	56.3 range: NA	70.83 range: NA--		Good: 0 Fair: 1 Poor: 0	Industry: 0 Public: 0 NR: 1
Adult COPD								
2. Berezuk, 1983	Single dose	Albuterol 180ug MDI	11	59.5	0	Theophylline allowed, however participants were requested to take AM dose at least 2hrs prior to test session	Fair	Univ of Arizona
		Metaproterenol 1300ug MDI						
3. Peacock, 1992	4 weeks	Albuterol 0.18mg MDI	22	69	31.82	inhaled corticosteroid: n=10; oral theophylline n=14	Fair	NR
		Metaproterenol 1.3mg MDI						
		Pirbuterol 0.4mg MDI						
		Terbutaline 0.4mg MDI						
Summary:	Single dose: 1 Other: 1		33 range: 11-22	65.8 range: 59.5-69	21.2 range: 0-31.82--		Good: 0 Fair: 2 Poor: 0	Industry: 0 Public: 1 NR: 1
Pediatrics Asthma								
4. Milner, 1971	Single dose	Albuterol Nebulizer	12	11.8	50	The parent was asked not to give the child any bronchodilator or isoprenaline on the day of the test but steroids were not	Fair	Asth. Res. Council
		Metaproterenol Nebulizer						
Summary:	Single dose: 1 Other: 0		12 range: NA	11.8 range: NA	50 range: NA		Good: 0 Fair: 1 Poor: 0	Industry: 0 Public: 1 NR: 0

Author, Year	Study duration	Intervention	n	Mean age in years (SD)	% Female	Other medications permitted during the study	Quality	Funding
Pediatrics Exercise-induced								
5. Berkowitz, 1986	Single dose	Albuterol MDI	18	14.5	61.11	All medications including all theophylline medication, were withheld for at least eight hours prior to each test day,	Fair	NR
		Metaproterenol MDI						
Summary:	Single dose: 1 Other: 0		18 range: NA	14.5 range: NA	61.11 range: NA		Good: 0 Fair: 1 Poor: 0	Industry: 0 Public: 0 NR: 1

Albuterol vs pirbuterol

Demographic and study characteristics are summarized in Table 9.

Of the three studies (in four publications) which provided direct comparative data on these drugs,^{13, 14, 87, 88} two were of poor quality,^{13, 14} and one was of fair quality.⁸⁷ None of these studies provided data on effectiveness outcomes.

Table 9. Albuterol vs Pirbuterol: Demographic and Study Characteristics of Included Studies

Author, Year	Study duration	Intervention	n	Mean age in years (SD)	% Female	Other medications permitted during the study	Quality	Funding
Adult Asthma								
1. Beumer, 1980; Beumer 1979	Single dose	Albuterol 200ug MDI	12	57.6	0	Medication other than the test aerosol taken during the course of the study was as follows: oral salbutamol (9 patients), anihistamine (3), oxtriphylline 92), salbutamol aerosol (1), fenoterol tablets (1); some patients received bronchodilator therapy	Poor	NR
		Pirbuterol 200ug MDI Pirbuterol 400ug MDI Pirbuterol 600ug MDI						
Summary:	Single dose: 1 Other: 0		12 range: NA	57.6 range: NA	0 range: NA--		Good: 0 Fair: 0 Poor: 1	Industry: 0 Public: 0 NR: 1
Adult COPD								
2. Peacock, 1992	4 weeks	Albuterol 0.18mg MDI	22	69	31.82	inhaled corticosteroid: n=10; oral theophylline n=14	Fair	NR
		Metaproterenol 1.3mg MDI Pirbuterol 0.4mg MDI Terbutaline 0.4mg MDI						
Summary:	Single dose: 0 Other: 1		22 range: NA	69 range: NA	31.82 range: NA--		Good: 0 Fair: 1 Poor: 0	Industry: 0 Public: 0 NR: 1
Pediatrics Asthma								
3. Volkl, 1991	Single dose	Albuterol 0.1mg MDI	17	9.8(1.5)	47.06	Concomitant therapy of the patients (except antiasthmatic therapy) was not changes prior to or during the study. No inhalational drug apart from the test preparations were allowed during the study.	Fair	NR
		Pirbuterol 0.2mg BAI						
Summary:	Single dose: 1 Other: 0		17 range: NA	9.8 range: NA	47.06 range: NA--		Good: 0 Fair: 1 Poor: 0	Industry: 0 Public: 0 NR: 1

Metaproterenol vs pirbuterol

Demographic and study characteristics are summarized in Table 10.

There were no data on effectiveness outcomes in two identified studies of COPD^{87, 112} and in one study of asthma in adults.¹¹³

Table 10. Metaproterenol versus Pirbuterol: Demographic and Study Characteristics of Included Studies

Author, Year	Study duration	Intervention	n	Mean age in years (SD)	% Female	Other medications permitted during the study	Quality	Funding
Adult Asthma								
1. Tinkelman, 1990	12 weeks	Metaproterenol	133	45	56.39	maintenance oral steroids (n=22 in metaproterenol group, 19 in pibuterol group); oral xanthines (n=54 in metaproterenol group, 60 in pirbuterol)	Fair	Riker Labs, Inc.
		Pirbuterol						
Summary:	Single dose: 0 Other: 1		133 range: NA	45 range: NA	56.39 range: NA		Good: 0 Fair: 1 Poor: 0	Industry: 1 Public: 0 NR: 0
Adult COPD								
2. Chodosh, 1989	Single dose	Metaproterenol MDI	26	57	50	During the study, subjects were prohibited from receiving other beta-2 sympathomimetic bronchodilators or other investigational drugs.	Fair	3M Riker
		Pirbuterol 0.2mg MDI						
		Pirbuterol 0.4mg MDI						
3. Peacock, 1992	4 weeks	Albuterol 0.18mg MDI	22	69	31.82	inhaled corticosteroid: n=10; oral theophylline n=14	Fair	NR
		Metaproterenol 1.3mg MDI						
		Pirbuterol 0.4mg MDI						
		Terbutaline 0.4mg MDI						
Summary:	Single dose: 1 Other: 1		48 range: 22-26	32.5 range: 57-69	14.6 range: 31.82-50		Good: 0 Fair: 2 Poor: 0	Industry: 1 Public: 0 NR: 1

Albuterol vs fenoterol

Demographic and study characteristics are summarized in Table 11 and effectiveness outcomes in Table 12.

Only one of the 24 head-to-head studies identified comparing these two drugs reported outcomes other than efficacy data. Manicatide and colleagues⁵⁶ reported drug preference (all delivered by pressurized aerosol) by patients with COPD, with 30% of subjects preferring salbutamol, 25% terbutaline, 33% preferred fenoterol, and 11% were undecided. There was no clarification as to how patient preference was measured. No between-group statistics were provided and no health or utilization outcomes were reported.

Table 11. Albuterol vs Fenoterol: Demographic and Study Characteristics of Included Studies

Author, Year	Study duration	Intervention	n	Mean age in years (SD)	% Female	Other medications permitted during the study	Quality	Funding
Adult Asthma								
1. Garrett, 1996	3.5y retrospective study	Albuterol MDI or nebulizer Fenoterol MDI or nebulizer	655	NR	64.0	Inhaled beta agonists, ipratropium, oral beta agonists, theophylline, sodium cromoglycate, inhaled corticosteroids, and oral corticosteroids.	NA	Asthma Found. Of New Zealand; Boehringer Ingelheim Ltd.
2. Hanley, 1979	2 puffs overnight	Albuterol 100ug MDI Fenoterol 200ug MDI	19	NR	NR	NR	Poor	W.B. Pharmaceuticals supplied the fenoterol and placebo aerosols.
3. Hockley, 1983	Single dose	Albuterol 5mg Nebulizer Fenoterol 5mg Nebulizer	10	50	60	All patients were in a chronic steady state and had not taken B-agonist therapy for 12 hr before the study. All were on routine salbutamol inhalers, 6 on beclomethasone and 5 were receiving oral corticosteroids	Poor	W.B. Pharmaceuticals
4. Huhti, 1978	Single dose	Albuterol 0.1mg MDI Fenoterol 0.2mg MDI	12	46	66.67	Patients were asked not to use any bronchodilator drugs for 10 hours before the tests; however, if the patient was receiving therapy with corticosteroids, this was continued in the usual dosage.	Fair	NR
5. Konig, 1985	Single dose	Albuterol 180ug MDI Fenoterol 320ug MDI	24	28.7	16.67	Subjects refrained from using B-adrenergic drugs and caffeine-containing beverages for ten hours before each day's testing, but were allowed to continue their maintenance asthma medications, provided their dosages were held constant	Fair	Boehringer Ingelheim Ltd.

Author, Year	Study duration	Intervention	n	Mean age in years (SD)	% Female	Other medications permitted during the study	Quality	Funding
6. Lipworth, 1995	Single dose	Albuterol 200ug	18	40(14)	33.33	Fifteen patients were taking inhaled corticosteroids and all were taking inhaled B2-agonists. Three were taking regular inhaled B2-agonists, with the remainder using on demand B2-agonists with a total daily dose of less than 400 ug salbutamol or 1000 ug	Fair	Boehringer Ingelheim (UK) Ltd
		Albuterol 4,000ug (cumulative dosage)						
		Fenoterol 200ug Fenoterol 4,000ug (cumulative dosage)						
7. Maesen, 1984	Single dose	Albuterol 0.4mg Rotahaler	20	40.4	40	All bronchospasmodic therapy was stopped at least 12 h before the study. All caffeine-containing drinks were forbidden, but corticosteroids were allowed, provided they were given in constant low dosage	Fair	Author P.J.G. Cornelissen affiliated with Boehringer Ingelheim BVV, Alkmaar, The Netherlands
		Fenoterol 0.2mg Powder inhaler						
8. Newhouse, 1994	Single dose	Albuterol 2500ug Nebulizer	12	52.2(12.12)	75	Before each test day, subjects refrained from taking inhaled bronchodilators or short-acting theophyllines for at least 8 h, oral B-agonist bronchodilators for 24 h, or long-acting theophylline preparations for 48 h.	Fair	Boehringer Ingelheim Canada Ltd.
		Fenoterol 2500ug Nebulizer	12	52.2(12.12)	75			
9. Newhouse, 1996	Multidose, 1 day	Albuterol 100ug MDI	257	29.4	54.09	NR	Good	Boehringer Ingelheim (Canada) Ltd.
		Fenoterol 200ug MDI						

Author, Year	Study duration	Intervention	n	Mean age in years (SD)	% Female	Other medications permitted during the study	Quality	Funding
10. Spitzer, 1992	7.3y retrospective study.	Albuterol MDI Fenoterol MDI	12,301	NR	NR	NR	NA	Boehringer Ingelheim (Canada) Ltd.
11. Windom, 1990	Single dose	Albuterol 400ug MDI Fenoterol 400ug MDI	12	27	41.67	All subjects were receiving an inhaled B-agonist in addition to [. . .] inhaled corticosteroid in eight subjects and in combination with an oral theophylline and inhaled sodium cromoglycate in one	Fair	Medical Research Council of New Zealand; the Asthma Foundation of New Zealand.
12. Wong, 1990	Single dose	Albuterol 100ug MDI Fenoterol 200ug MDI Terbutaline 250ug MDI	10	NR	20	Regular medication consisted of inhaled treatment only, including no more than 4 puffs of an inhaled B2-agonist per day, and regular inhaled corticosteroids in five subjects (400 - 500 ug beclomethasone dipropionate	Fair	NR
Summary:	Single dose: 6 Other: 6		13350 range: 10-12301	39.2 range: 27.0-52.2	47.1 range: 16.7-75.0		Good: 1 Fair: 7 Poor: 2 NA: 2	Industry: 9 Public: 0 NR: 2
Adult COPD								
13. Manicatide, 1978	Single dose	Albuterol 400ug Fenoterol 400ug Terbutaline 500ug	63	56.5	25.4	Administration of any bronchodilating substance was stopped 15 hrs before the beginning of the study	Fair	Ventolin, Bricanyl and Berotec were supplied by Allen & Hanburys Ltd., A.B. Draco and C.H. Boehringer Ingelheim,
14. McIntosh, 1983	8 weeks	Albuterol 400ugl Fenoterol 400ug Terbutaline 500ug	20	62.0	15.0	Unusual drugs continued for 1st mo of study before switching to. fenoterol	NA	WB Pharmaceuticals

Author, Year	Study duration	Intervention	n	Mean age in years (SD)	% Female	Other medications permitted during the study	Quality	Funding
15. Tandon, 1980	Single dose	Albuterol 100ug MDI Fenoterol 160ug MDI	15	52.5	6.67	NR	Fair	NR
16. Yang, 1996	Single dose	Albuterol 2mg Nebulizer Fenoterol 2mg Nebulizer	13	66	15.38	Maintenance medications included oral long-acting theophylline inhaled anticholinergic agents and inhaled B2-adrenergic agonists on demand. None of our patients required treatment with inhaled B2-adrenergic agonists of more than 200 mg fenoterol or salbuterol	Fair-Poor	NR
17. Tang, 1984	Single dose	Albuterol 100ug MDI Fenoterol 100ug MDI	24	59.6	20.83	NR	Fair	W.B. Pharmaceuticals
Summary:	Single dose: 4 Other: 1		135 range: 13-63	59.3 range: 52.5-66	16.7 range: 25.4--		Good: 0 Fair: 3 Fair/Poor: 1 NA: 1	Industry: 3 Public: 0 NR: 2
Adult Exercise-induced								
18. Sturani, 1983	Single dose	Albuterol 0.2mg 2 puffs MDI Fenoterol 0.4mg 2 puffs MDI	12	23	41.67	All short-acting bronchodilators had been excluded for at least 12 hours and all long-acting bronchodilators, antihistamines and sodium cromoglycate	Fair	NR
Summary:	Single dose: 1 Other: 0		12 range: NA	23 range: NA	41.67 range: NA--		Good: 0 Fair: 1 Poor: 0	Industry: 0 Public: 0 NR: 1
Pediatrics Asthma								
19. Asher, 1985	Single dose	Albuterol 0.2mg Rotahaler Fenoterol 0.2mg Inhalator	25	6.6	40	regular drug therapy . . . Also included sodium cromoglycate Spincaps (12 subjects), beclomethasone dipropionate Rotacaps (seven subjects) and theophylline tablets (seven subjects); B2-sympathomimetics were withheld for at least 12 h before each study day	Fair	Boehringer Ingelheim (NZ) Limited

Author, Year	Study duration	Intervention	n	Mean age in years (SD)	% Female	Other medications permitted during the study	Quality	Funding
20. Blackhall, 1976	Single dose	Albuterol 2mg Nebulizer	30	9.8(0.4)	50	disodium cromoglycate; steroids (not specified)	Fair	NR
		Fenoterol 2mg Nebulizer						
21. Dawson, 1985	Single dose	Albuterol 400ug Inhalator	40	8.9	45	NR	Good	NR
		Albuterol 400ug Rotahaler						
		Fenoterol 200ug Rotahaler						
		Fenoterol 400ug Inhalator						
22. Graff-Lonnevig, 1976	Single dose	Albuterol 200ug MDI	16	10.4	6.25	One of the patients was on continuous steroid therapy in aerosol form (Becotide®). All symptomatic treatment, including steroid therapy for one of the children, was suspended at least 12 h	Fair	NR
		Fenoterol 100ug MDI						
23. Holt, 1983	3 weeks	Albuterol 0.075mg/kg Nebulizer	11	11.7	27.27	NR	Fair	NR
		Fenoterol 0.2mg powder inhaler						
24. Scalabrin, 1996	Single dose	Albuterol 5mg Nebulizer	21	10.41	42.86		Fair	NR
		Fenoterol 0.083mg/kg Nebulizer						
		Terbutaline 0.1mg/kg						
Summary:	Single dose: 5 Other: 1		143 range: 11-40	9.6 range: 6.6-11.7	35.2 range: 6.3-50--		Good: 1 Fair: 5 Poor: 0	Industry: 1 Public: 0 NR: 5

Table 12. Albuterol vs Fenoterol: Effectiveness Outcomes of Included Studies

Author Year	Outcome Category	Outcome (unit) at timepoint	Intervention	Baseline:		Follow-Up:	
				n	Mean(SD) or No(%)	n	Mean(SD) or No(%)
Adult Asthma							
Hanley, 1979	Symptoms	Preference on waking, based on patient assessment (number) at NR	Albuterol 100ug	24	NR	19	2 (11%)
			Fenoterol 200ug	24	NR	19	7 (37%)
			No preference	24	NR	19	10 (53%)
Adult COPD							
Manicatide,	Symptoms	Preference (number) at NR	Albuterol 400ug	63	NR	63	19 (30.2%)
			Fenoterol 400ug	63	NR	63	21 (33.3%)
			No preference	63	NR	63	7 (11.1%)
			Terbutaline 500ug	63	NR	63	16 (25.4%)

Albuterol vs terbutaline

Demographic and study characteristics are summarized in Table 13 and effectiveness outcomes in Table 14.

The use of rescue medications was similar in two studies that examined this outcome.^{18, 21} Lindsay and colleagues²¹ examined 46 subjects over the age of 7 years, and the mean number of doses of beta₂-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 ug (no between-group comparisons). In an adult asthma population, Gioulekas et al.¹⁸ did not find a significant difference in rescue medication usage.

Symptom scores were not different between albuterol and terbutaline in adults with asthma in two studies.^{18, 21} 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 compared to albuterol 0.1 mg two puffs twice daily, in a third RCT of 159 adults with asthma.¹⁰⁰ No rescue medications were used during this study.

In pediatric asthma, there was no significant difference between the two drugs for symptoms^{90, 97, 99} and respiratory rate decreased after both treatments.⁹⁷

Among persons with COPD, only one head-to-head study compared these two drugs and reported outcomes other than efficacy data. Manicattide and colleagues⁵⁶ reported patient preference, with 30% of subjects preferring salbutamol, 25% terbutaline, 33% preferred fenoterol, and 11% were undecided. No between-group statistics were provided and no health or utilization outcomes were reported.

In EIA in a pediatric population, the only effectiveness outcome reported was the need for aminophylline treatment, with 21% of patients receiving albuterol 0.2 mg needing treatment and 8% of those treated with terbutaline 0.25 mg requiring aminophylline⁹⁸ (no between-group statistics).

Table 13. Albuterol vs Terbutaline: Demographic and Study Characteristics of Included Studies

Author, Year	Study duration	Intervention	n	Mean age in years (SD)	% Female	Other medications permitted during the study	Quality	Funding
Adult Asthma								
1. Anani, 1989	3 weeks	Albuterol 400ug QID	30	35	76.67	Patients were allowed to use 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
		Terbutaline 500ug QID Turbohaler						
2. Choo-Kang, 1973	Single dose	Albuterol 200ug MDI	13	49.3	NR	All but one patient was being treated with long-term daily or intermittent prednisolone.	Poor	Astra Chemicals Ltd., England
		Terbutaline 500ug MDI						
3. Eryonucu, 2001	Single dose	Albuterol 200ug MDI	20	37.0(6.0)	NR	NR	NA	NR
		Terbutaline 500ug MDI						
4. Gioulekas, 1996	3 weeks	Albuterol 0.4mg TID	32	34	34.38	Only additional doses of trial medication allowed.	Poor	NR
		Terbutaline 0.5mg TID Turbohaler						
5. Malinen, 2000	Single dose	Albuterol 100ug Easyhaler	29	48	55.17	Other allergy or asthma medication excluding inhaled corticosteroids were stopped for eight hours before laboratory measurements.	Good	Orion Pharma, Finland
		Terbutaline 250ug Turbohaler						

Author, Year	Study duration	Intervention	n	Mean age in years (SD)	% Female	Other medications permitted during the study	Quality	Funding
6. Vilsvik, 1993	2 weeks	Albuterol 0.1mg MDI	159	49	39.62	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. The patients' usual B2-agonists were to be used as rescue medications.	Fair	NR
		Terbutaline 0.5mg Turbohaler						
7. Wong, 1990	Single dose	Albuterol 100ug MDI	10	NR	20	Regular medication consisted of inhaled treatment only, including no more than 4 puffs of an inhaled B2-agonist per day, and regular inhaled corticosteroids in five subjects (400 - 500 ug beclomethasone dipropionate)	Fair	NR
		Fenoterol 200ug MDI						
		Terbutaline 250ug MDI						
8. Capecchi, 1978*	Single dose	Albuterol 0.2mg	14	50.2	42.86	Subjects were instructed to avoid any treatment which might influence results during the 12 hours preceding the beginning of each test.	Fair	NR
		Terbutaline 0.5mg						
9. Lindsay, 1994*	4 weeks	Albuterol 0.1mg BID MDI	46	34.5	45.65	No other β 2-agonist or nebulized therapy were allowed. Treatment with oral or other inhaled bronchodilators, including anticholinergics and theophylline, was allowed provided that their doses remained constant throughout the study.	Poor	Author N.L. Russell associated with Astra Pharmaceuticals Pty. Ltd., Australia
		Terbutaline 0.5mg BID Turbohaler						

Author, Year	Study duration	Intervention	n	Mean age in years (SD)	% Female	Other medications permitted during the study	Quality	Funding
10. Munzenberger, 1989*	2 weeks	Albuterol 400ug MDI Terbutaline 360ug MDI	20	17.8	35	Patients were instructed to continue the use of other asthma medications. To minimize their impact, the study patient's drug regimens were not altered throughout the entire study.	Fair	NR
11. Vilsvik, 1991*	Single dose	Albuterol 0.1mg MDI Terbutaline 0.5mg Turbohaler	21	30.6	NR	None of the patients used oral beta ₂ -agonists or theophylline and only one patient used oral steroids. They were able to manage without inhaled beta ₂ -agonists for at least six hours before exercise challenge. Inhaled B2-agonist was withdrawn.	Poor	Author Stig Holthe affiliated with Astra Farmasoytiske A/S
12. Webb, 1982*	1 weeks	Albuterol 200ug Terbutaline 500ug	16	NR		Each patient was studied over 8 weeks and during this period was given a turbutaline aerosol and asked to use this only in an attack of asthma. Patients were asked not to use their aerosols for at least 4 hours before recording PEF.	Fair	Astra Laboratories
Summary:	Single dose: 6 Other: 6		410 range: 10-159	38.5 range: 17.8-- 50.2	44.9 range: 20.0-76.7		Good: 1 Fair: 5 Poor: 5 NA: 1	Industry: 5 Public: 0 NR: 7
Adult COPD								
13. Manicattide, 1978	Single dose	Albuterol 400ug Fenoterol 400ug Terbutaline 500ug	63	56.5	25.4	Administration of any bronchodilating substance was stopped 15 hrs before the beginning of the study	Fair	Ventolin, Bricanyl and Berotec were supplied by Allen & Hanburys Ltd., A.B. Draco and C.H. Boehringer Ingelheim

Author, Year	Study duration	Intervention	n	Mean age in years (SD)	% Female	Other medications permitted during the study	Quality	Funding
14. McIntosh, 1983	8 weeks	Albuterol 400ugl Fenoterol 400ug Terbutaline 500ug	20	62.0	15.0	Unusual drugs continued for 1st mo of study before switching to fenoterol	NA	WB Pharmaceuticals
15. Peacock, 1992	4 weeks	Albuterol 0.18mg MDI Metaproterenol 1.3mg MDI Pirbuterol 0.4mg MDI Terbutaline 0.4mg MDI	22	69	31.82	Inhaled corticosteroid: n=10; oral theophylline n=14	Fair	NR
Summary:	Single dose: 1 Other: 2		105 range: 20-63	62.5 range: 56.5-- 69.0	24.1 range: 15.0-31.8		Good: 0 Fair: 2 Poor: 0 NA: 1	Industry: 2 Public: 0 NR: 1
Pediatrics Asthma								
16. Chandra, 2004	Single dose	Albuterol 100ug Terbutaline 250ug	60	9.5	21.67	NR	Good	NR
17. Francis, 1983	Single dose	Albuterol 400ug Rotahaler Terbutaline 500ug Tube	10	12	30	Bronchodilator therapy was withheld for at least eight days	Fair	NR
18. Hung, 2001	Single dose	Albuterol 0.125mg/kg Nebulizer Terbutaline 0.125mg/kg Nebulizer	30	8.18	43.33	NR	Fair	NR
19. Oldaeus, 1995	2 weeks	Albuterol 0.4mg TID Terbutaline 0.5mg TID Turbohaler	20	3.5	70	Six children were on regular treatment with disodium cromoglycate and three children used inhaled steroids throughout the study. The medication was kept constant 1 month before inclusion and throughout the study.	Fair	Author Elisabeth Stahl affiliated with Astra Draco AB, Clinical Research & Development

Author, Year	Study duration	Intervention	n	Mean age in years (SD)	% Female	Other medications permitted during the study	Quality	Funding
20. Scalabrin, 1996	Single dose	Albuterol 5mg Nebulizer Fenoterol 0.083mg/kg Nebulizer Terbutaline 0.1mg/kg	21	10.41	42.86	NR	Fair	NR
21. Towns, 1983	Single dose	Albuterol 200ug Rotahaler Terbutaline 500ug Misthaler	25	9	48	While the children were asked to cease their regular broncholiator therapy at least six hours before testing, all other medications (sodium cromoglycate, beclomethasone diprionate, and orally administered corticosteroids) were allowed	Fair	Astra Pharmaceuticals; Glaxo Australia.
Summary:	Single dose: 5 Other: 1		166 range: 10-60	8.8 range: 3.5-12.0	42.6 range: 21.7-70.0		Good: 1 Fair: 5 Poor: 0 NA: 0	Industry: 2 Public: 0 NR: 4
Pediatrics Exercise-induced								
22. Lopes dos Santos, 1991	Single dose	Albuterol 0.4mg Rotahaler Terbutaline 0.5mg Turbohaler	19	10	26.32	Inhaled B ₂ -agonists were withdrawn 6 h prior to the investigational events. No patients were taking oral B ₂ -agonists or theophyllines.	Fair	NR
23. Pedersen, 1985	Single dose	Albuterol 0.2mg Rotahaler Terbutaline 0.25mg Tube spacer	24	9.6	33.33	On a regular basis nine children were treated with beclomethasone and 11 with disodium cromoglycate. In addition, all subjects regularly inhaled beta ₂ -agonists. No children had taken a beta ₂ -agonist for 1 h before exercise on the days of the study	Fair	NR

Author, Year	Study duration	Intervention	n	Mean age in years (SD)	% Female	Other medications permitted during the study	Quality	Funding
Summary:								
	Single dose: 2 Other: 0		43 range: 19-24	9.7 range: 9.6-10.0-	30.23 range: 26.32- 33.33		Good: 0 Fair: 2 Poor: 0 NA: 0	Industry: 0 Public: 0 NR: 2
*Study Population ≥ 12 years of age								

Table 14. Albuterol vs Terbutaline: Effectiveness Outcomes of Included Studies

Author Year	Outcome Category	Outcome (unit) at timepoint	Intervention	Baseline:		Follow-Up:		Comments
				n	Mean(SD) or No(%)	n	Mean(SD) or No(%)	
Adult Asthma								
Anani, 1989	Symptoms	Preference, effect (number) at NR	NR	NR	NR	NR	NR	Albuterol vs Terbutaline, p-value >0.05
Gioulekas, 1996	Rescue medication	No. of rescue treatment required (number) at NR	Albuterol 0.4mg TID	32	NR	25	8 (32%)	Albuterol vs Terbutaline, p-value > 0.05
			Terbutaline 0.5mg TID	32	NR	25	9 (36%)	
	Symptoms	Preference, effect (number) at NR	Albuterol 0.4mg TID	32	NR	25	8 (32%)	
			No preference	32	NR	25	4 (16%)	
		Preference, overall (number) at NR	Terbutaline 0.5mg TID	32	NR	25	13 (52%)	
			Albuterol 0.4mg TID	32	NR	25	4 (16%)	
		Preference, side effect (number) at up to 3 wks.	No preference	32	NR	25	10 (40%)	
			Terbutaline 0.5mg TID	32	NR	25	11 (56%)	
			Albuterol 0.4mg TID	32	NR	25	1 (4%)	
			No preference	32	NR	25	14 (56%)	
Symptom scores from diary recording, daytime (score) at NR	Albuterol 0.4mg TID	32	NR	25	0.55 (NR)	Albuterol vs Terbutaline, p-value >0.05		
	Terbutaline 0.5mg TID	32	NR	25	0.4 (NR)			
Symptom scores from diary recording, nighttime (score) at NR	Albuterol 0.4mg TID	32	NR	25	0.65 (NR)	Albuterol vs Terbutaline, p-value > 0.05		
	Terbutaline 0.5mg TID	32	NR	25	0.52 (NR)			
Vilsvik, 1993	Symptoms	Asthma, symptom score evening mean (number) at NR	Albuterol 0.1mgX2	158	NR	158	0.57 (NR)	No rescue medication was used in either period; albuterol vs terbutaline, mean diff. 0.07(0.39), p < 0.001
			Terbutaline 0.5mg	158	NR	158	0.50 (NR)	
	Asthma, symptom score morning mean (number) at NR	Albuterol 0.2mg	156	NR	156	0.77 (NR)		
		Terbutaline 0.5mg	156	NR	156	0.67 (NR)		
	Preference (number) at NR	Albuterol 0.1mgX2	159	NR	159	39 (24.5%)	39% in favor of Terbutaline No rescue medication was used in either period; albuterol vs terbutaline, p < 0.001	
		No preference	159	NR	159	33 (20.7%)		
		Terbutaline 0.5mg	159	NR	159	87 (54.7%)		

Author Year	Outcome Category	Outcome (unit) at timepoint	Intervention	Baseline:		Follow-Up:		Comments
				n	Mean(SD) or No(%)	n	Mean(SD) or No(%)	
Lindsay, 1994*	Rescue medication	No. of doses taken over 24hrs (number) at	Albuterol 0.1mg BID	45	NR	45	5.8 (2.3)	Data reported over the last 14 days of each treatment.
			Terbutaline 0.5mg BID	45	NR	45	3.2 (1.6)	
	Asthma, exacerbations (number) at NR	Albuterol 0.1mg BID	45	NR	45	2 (4%)		
		Terbutaline 0.5mg BID	45	NR	45	1 (2%)		
	Breathlessness on exertion, symptom score (number) at 4 wks	Albuterol 0.1mg BID	45	0.6 (0.67)	45	0.6 (2.68)	Albuterol vs Terbutaline, mean diff.: -0.03(0.34), CI: -0.1, 0.1, p = 0.09	
		Terbutaline 0.5mg BID	45	0.6 (0.67)	45	0.6 (0.67)		
	Preference (number) at NR	Albuterol 0.1mg BID	46	NR	46	18 (39%)		
		No preference	46	NR	46	8 (17%)		
		Terbutaline 0.5mg BID	46	NR	46	20 (44%)		
	Total symptom score (number) at 4 wks	Albuterol 0.1mg BID	45	2.0 (2.01)	45	2.0 (2.01)	Albuterol vs Terbutaline, mean diff.: -0.2(1.34), CI: -0.6, 0.2, p = 0.3	
Terbutaline 0.5mg BID		45	1.8 (2.01)	45	1.8 (2.01)			
Wheeze, symptom score (number) at 4 wks	Albuterol 0.1mg BID	45	0.5 (0.67)	45	0.5 (0.67)	Albuterol vs Terbutaline, mean diff.: -0.05(0.0), CI: -0.2,0.1, p = 0.4		
	Terbutaline 0.5mg BID	45	0.4 (0.67)	45	0.5 (0.67)			
Adult COPD								
Manicatide, 1978	Symptoms		Albuterol 400ug	63	NR	63	19 (30.2%)	
			Fenoterol 400ug	63	NR	63	21 (33.3%)	
			No preference	63	NR	63	7 (11.1%)	
			Terbutaline 500ug	63	NR	63	16 (25.4%)	
Pediatrics Asthma								
Chandra, 2004	Symptoms	Composite Asthma Score (CAS), median (number) at 30 min	Albuterol 100ug	29	1 (NR)	29	1 (NR)	Albuterol vs Terbutaline, p = 0.75
			Terbutaline 250ug	31	2 (NR)	31	1 (NR)	
	Respiratory rate (rpm) at 30 min	Albuterol 100ug	29	26 (NR)	29	26 (NR)	Albuterol vs Terbutaline, p=0.72	
		Terbutaline 250ug	31	26 (NR)	31	26 (NR)		
	Wheeze score: 0 (number) at 30 min	Albuterol 100ug	29	14 (48%)	29	21 (72%)	Albuterol vs Terbutaline, p=0.66	
		Terbutaline 250ug	31	15 (48%)	31	24 (77%)		
Wheeze score: 1 (number) at 30 min	Albuterol 100ug	29	15 (52%)	29	8 (28%)			
	Terbutaline 250ug	31	16 (52%)	31	7 (23%)			
Hung, 2001	Symptoms	Respiratory rate (rpm) at 30 min	Albuterol 0.125mg/kg	30	35.34 (3.50)	30	27.41 (2.85)	Mean difference: p <0.01 Mean difference: <0.01
			Terbutaline 0.125mg/kg	30	30.20 (5.12)	30	26.1 (3.25)	

Author Year	Outcome Category	Outcome (unit) at timepoint	Intervention	Baseline:		Follow-Up:		Comments
				n	Mean(SD) or No(%)	n	Mean(SD) or No(%)	
Oldaeus, 1995	Rescue medication	Extra inhalations, day (number) at NR	Albuterol 0.4mg TID	20	NR	20	0.11 (.29)	
			Terbutaline 0.5mg TID	20	NR	20	0.13 (0.21)	
		Extra inhalations, night (number) at NR	Albuterol 0.4mg TID	20	NR	20	0.10 (0.20)	
			Terbutaline 0.5mg TID	20	NR	20	0.13 (0.31)	
	Symptoms	Asthma, symptom score day (score) at NR	Albuterol 0.4mg TID	20	NR	20	0.11 (0.29)	
			Terbutaline 0.5mg TID	20	NR	20	0.38 (0.46)	
		Asthma, symptom score night (score) at NR	Albuterol 0.4mg TID	20	NR	20	0.47 (0.6)	
			Terbutaline 0.5mg TID	20	NR	20	0.46 (0.58)	
		Preference (number) at NR	Albuterol 0.4mg TID	20	NR	20	12 (60%)	
			Neither	20	NR	20	1 (5%)	
Townes, 1983	Symptoms	Preference (number) at NA	Albuterol 200ug	25	NR	25	18 (72%)	
			No preference	25	NR	25	2 (8%)	
			Terbutaline 500ug	25	NR	25	5 (20%)	
			Terbutaline 0.5mg TID	20	NR	20	5 (25%)	
	Symptom score (score) at NA		Albuterol 200ug	25	NR	25	NR	
			Terbutaline 500ug	25	NR	25	NR	
							Albuterol vs Terbutaline, p > 0.05	
							Mean difference: p < 0.05	
Pediatrics Exercise-induced								
Pedersen,	Rescue medication	Aminophylline required after treatment (number) at NR	Albuterol 0.2mg	24	NR	24	5 (21%)	FEV ₁ , 5 mins and 10 mins after the first treatment: - albuterol < terbutaline, p<0.05 Breathholding periods; - varied from 5 to 10 sec (mean 8.7 sec), no significant
			Terbutaline 0.25mg	24	NR	24	2 (8%)	
*Study population ≥ 12 years of age								

Metaproterenol vs fenoterol

Demographic and study characteristics are summarized in Table 15. No effectiveness outcomes were reported.

Table 15. Metaproterenol versus Fenoterol: Demographic and Study Characteristics of Included Studies

Author, Year	Study duration	Intervention	n	Mean age in years (SD)	% Female	Other medications permitted during the study	Quality	Funding
Adult Asthma								
1. Burgess, 1990	Single dose	Fenoterol MDI	12	NR	58.33	Subjects were instructed to withhold their inhaled beta-agonist for a minimum of 6 h prior to each study day. All other medication was kept constant during the study	Fair	NR
		Metaproterenol MDI						
Summary:	Single dose: 1 Other: 0		12 range: NA	NR range: NA	58.33 range: NA--		Good: 0 Fair: 1 Poor: 0	Industry: 0 Public: 0 NR: 1

Metaproterenol vs terbutaline

Demographic and study characteristics are summarized in Table 16. No effectiveness outcomes were reported.

Table 16. Metaproterenol versus Terbutaline: Demographic and Study Characteristics of Included Studies

Author, Year	Study duration	Intervention	n	Mean age in years (SD)	% Female	Other medications permitted during the study	Quality	Funding
Adult Asthma								
1. Chester, 1978	Single dose	Metaproterenol 1300ug	16	36	31.25	Patients used no bronchodilator durg for 12h before testing on each of the days.	Fair	NR
		Terbutaline 500ug						
2. Roth, 1977	1 day	Metaproterenol 650ugx3	21	45	61.9	Isoproterenol aerosol up to three hours before study	NA	NR
		Terbutaline 125ugx3						
Summary:	Single dose: 1 Other: 1		37 range: 16-21	40.5 range: 36-45	46.6 range: 31.3-61.9--		Good: 0 Fair: 1 Poor: 0	Industry: 0 Public: 0 NR: 2
Adult COPD								
3. Peacock, 1992	4 weeks	Albuterol 0.18mg MDI	22	69	31.82	inhaled corticosteroid: n=10; oral theophylline n=14	Fair	NR
		Metaproterenol 1.3mg MDI						
		Pirbuterol 0.4mg MDI						
		Terbutaline 0.4mg MDI						
Summary:	Single dose: 0 Other: 1		22 range: NA	69 range: NA	31.82 range: NA--		Good: 0 Fair: 1 Poor: 0	Industry: 0 Public: 0 NR: 1

Fenoterol vs terbutaline

Demographic and study characteristics are summarized in Table 17. Effectiveness outcomes are summarized in Table 18.

Among adults with asthma, Anderson and colleagues¹⁰⁴ found no significant difference in symptom scores between fenoterol 0.4 mg and terbutaline 0.5 mg. There was no difference in patient preference between the two drugs in another study.¹¹¹

Only one study examined patients with COPD and found that 33% of participants preferred fenoterol and 25% terbutaline.⁵⁶

Table 17. Fenoterol vs Terbutaline: Demographic and Study Characteristics of Included Studies

Author, Year	Study duration	Intervention	n	Mean age in years (SD)	% Female	Other medications permitted during the study	Quality	Funding
Adult Asthma								
1. Anderson, 1979	Single dose	Fenoterol 0.4mg	17	52	35.29	All bronchodilator drugs were discontinued at least 10h before the trial and during the whole of the trial period but patients taking corticosteroids and sodium cromoglycate continued to do so.	Fair	NR
		Terbutaline 0.5mg						
2. Gray, 1982	3 day	Fenoterol 100ug MDI	12	33	58.33	Before each study day the patients were asked to discontinue their usual inhaled beta-agonist for the preceding 12h and oral aminophylline for the precedign 36h. Patients on oral or inhaled steroids or inhaled disodium cromoglycate were allowed to continue	Fair	Astra Pharmaceuticals; WB Pharmaceuticals
		Terbutaline 250ug MDI						
3. Lawford, 1987	2 days	Fenoterol 200ug Nebuhaler	18	56	NR	Inhaled or oral corticosteroids	Fair	NR
		Terbutaline 250ug Nebuhaler						
4. Carmicheal, 1980	NR	Fenoterol 0.5mg Nebulizer Fenoterol 1mg Nebulizer Fenoterol 2mg Nebulizer Terbutaline 10mg Nebulizer Terbutaline 2.5mg Nebulizer Terbutaine 5mg Nebulizer	12	51.8	33.3	NR	NA	Astra Chemicals Ltd; W.B. Pharmaceuticals
5. Trembath, 1979	4 weeks	Fenoterol MDI	23	44.7(15.0)	56.52	beclomethasone aerosol, sodium cromoglycate, theophylline derivatives.	Fair	W.B. Pharmaceuticals
		Terbutaline MDI						

Author, Year	Study duration	Intervention	n	Mean age in years (SD)	% Female	Other medications permitted during the study	Quality	Funding
6. Wong, 1990	Single dose	Albuterol 100ug MDI Fenoterol 200ug MDI Terbutaline 250ug MDI	10	NR	20	Regular medication consisted of inhaled treatment only, including no more than 4 puffs of an inhaled B2-agonist per day, and regular inhaled corticosteroids in five subjects (400 - 500 ug beclomethasone dipropionate)	Fair	NR
Summary:	Single dose: 2 Other: 3 NR: 1		92 range: 10-23	47.5 range: 33-56-	40.7 range: 20.0-58.3		Good: 0 Fair: 5 Poor: 0 NA: 1	Industry: 3 Public: 0 NR: 3
Adult COPD								
7. Manicatide, 1978	Single dose	Albuterol 400ug Fenoterol 400ug Terbutaline 500ug	63	56.5	25.4	Administration of any bronchodilating substance was stopped 15 hrs before the beginning of the study	Fair	Ventolin, Bricanyl and Berotec were supplied by Allen & Hanburys Ltd., A.B. Draco and C.H. Boehringer Ingelheim,
8. McIntosh, 1983	8 weeks	Albuterol 400ugl Fenoterol 400ug Terbutaline 500ug	20	62.0	15.0	Unusual drugs continued for 1st mo of study before switching to fenoterol	NA	WB Pharmaceuticals
Summary:	Single dose: 1 Other: 1		83 range: 20-63	59.3 range: 56.5- 62.0	20.2 range: 15.0-25.4		Good: 0 Fair: 1 Poor: 0 NA: 1	Industry: 2 Public: 0 NR: 0
Adult Exercised-induced								
9. Tammivaara, 1976	NR	Fenoterol Terbutaline	11	35.5	NR	NR	NA	NR
Summary:	Single dose: 0 Other: 0 NR: 1		1 range: NA	35.5 range: NA-	NR range: NA		Good: 0 Fair: 0 Poor: 0	Industry: 0 Public: 0 NR: 1

Author, Year	Study duration	Intervention	n	Mean age in years (SD)	% Female	Other medications permitted during the study	Quality	Funding
							NA: 1	
Pediatrics Asthma								
10. Ribeiro, 1990	Single dose, 2 weeks	Fenoterol 0.2mg TID Turbohaler	36	9	30.56	Children/parents were instructed not to use any inhaled bronchodilator other than trial medication during the study. Doses of inhaled or oral corticosteroids, disodium cromoglycate and oral broncodilators were to be kept constant during the study.	Fair	AB Draco
		Terbutaline 0.5mg TID Diskhaler(?)						
11. Scalabrin, 1996	Single dose	Albuterol 5mg Nebulizer	21	10.41	42.86	NR	Fair	NR
		Fenoterol 0.083mg/kg Nebulizer						
		Terbutaline 0.1mg/kg						
12. Lin, 2002	Single dose	Fenoterol 1.25mg Nebulizer	108	8.1	44.4	NR	NAr	NR
		Terbutaline 5.0mg Nebulizer						
Summary:	Single dose: 3 Other: 0		165 range: 21-108	9.2 range: 8.1-10.4	39.3 range: 30.6-44.4		Good: 0 Fair: 2 Poor: 0 NA: 1	Industry: 1 Public: 0 NR: 2

Table 18. Fenoterol vs Terbutaline: Effectiveness Outcomes of Included Studies

Author Year	Outcome Category	Outcome (unit) at timepoint	Intervention	Baseline:		Follow-Up:		Comments
				n	Mean(SD) or No(%)	n	Mean(SD) or No(%)	
Adult Asthma								
Anderson, 1979	Symptoms	Breathing scores, a little better (number)	Fenoterol 0.4mg	17	NR	17	5 (29%)	Breathing scores subjectively reported by patients
			Terbutaline 0.5mg	17	NR	17	6 (35%)	
		Breathing scores, much better (number)	Fenoterol 0.4mg	17	NR	17	2 (12%)	
			Terbutaline 0.5mg	17	NR	17	2 (12%)	
		Breathing scores, no change (number)	Fenoterol 0.4mg	17	NR	17	3 (18%)	
			Terbutaline 0.5mg	17	NR	17	7 (41%)	
		Breathing scores, very much better (number)	Fenoterol 0.4mg	17	NR	17	2 (12%)	
			Terbutaline 0.5mg	17	NR	17	1 (6%)	
Breathing scores, worse (number)	Fenoterol 0.4mg	17	NR	17	0 (0%)			
	Terbutaline 0.5mg	17	NR	17	1 (6%)			
Trembath, 1979	Symptoms	Preference (number)	Fenoterol	23	NR	15	6 (40%)	
			No preference	23	NR	15	2 (13.3%)	
			Terbutaline	23	NR	15	7 (46.7%)	
			Terbutaline	23	NR	15	7 (46.7%)	
Adult COPD								
Manicatide, 1978	Symptoms	Preference (number)	Albuterol 400ug	63	NR	63	19 (30.2%)	
			Fenoterol 400ug	63	NR	63	21 (33.3%)	
			No preference	63	NR	63	7 (11.1%)	
			Terbutaline 500ug	63	NR	63	16 (25.4%)	

Pirbuterol vs terbutaline

Demographic and study characteristics are summarized in Table 19. No effectiveness outcomes were reported.

Table 19. Pirbuterol vs Terbutaline: Demographic and Study Characteristics of Included Studies

Author, Year	Study duration	Intervention	n	Mean age in years (SD)	% Female	Other medications permitted during the study	Quality	Funding
Adult COPD								
1. Peacock, 1992	4 weeks	Albuterol 0.18mg MDI Metaproterenol 1.3mg MDI Pirbuterol 0.4mg MDI Terbutaline 0.4mg MDI	22	69	31.82	inhaled corticosteroid: n=10; oral theophylline n=14	Fair	NR
Summary:	Single dose: 0 Other: 1		22 range: NA	69 range: NA	31.82 range: NA		Good: 0 Fair: 1 Poor: 0	Industry: 0 Public: 0 NR: 1

Safety

Key Question 5. When used in adults with asthma or COPD, are there differences in safety or rates of adverse events among long-acting, inhaled beta₂-agonists, when used in the outpatient setting?

Key Question 6. When used in adults with asthma or COPD, are there differences in safety or rates of adverse events among the following short-acting inhaled beta₂-agonists when used in the outpatient setting: albuterol, fenoterol, levalbuterol, pirbuterol, metaproterenol and terbutaline?

Key Question 7. When used in children with asthma, are there differences in safety or rates of adverse events among long-acting, inhaled beta₂-agonists, when used in the outpatient setting?

Key Question 8. When used in children with asthma, are there differences in safety or rates of adverse events among the following short-acting inhaled beta₂-agonists, when used in the outpatient setting: albuterol, fenoterol, levalbuterol, pirbuterol, metaproterenol and terbutaline?

Overview of adverse events

Withdrawal rates are presented in Table 20 and specific adverse events for each drug comparison are shown in Appendix E. Adverse events primarily related to sympathomimetic side effects are expected with these medications and are discussed below. There were also a broad range of gastrointestinal, musculoskeletal, and other miscellaneous adverse events which are noted in Appendix E. There were no apparent differences between the various drugs being compared in this review.

Salmeterol vs formoterol

Adults

Rates of total withdrawals and withdrawals due to adverse events from studies were similar between these two drugs and rates of total withdrawals ranged from 0 to 12.5% (Table 20).

There were no data on the comparative effect of these two drugs on blood pressure. Neither salmeterol (single dose 50 ug) or formoterol (single dose 24 ug) had significantly different effects on maximum heart rate response to salbutamol 1 to 2 hours after treatment in a fair-quality study²⁴ and a poor-quality study.¹⁹ Cazzola and colleagues²⁵ reported a “statistically significant” increase in heart rate with a single dose of formoterol 24ug (not available in the U.S.) compared to formoterol 12ug and salmeterol 50 ug between 2 and 9 hours post inhalation (p<0.05) in COPD patients with preexisting cardiac arrhythmias. There was no significant difference in the increase in heart rate between single-dose formoterol 12 ug and salmeterol 50 ug (p<0.05).

One participant noted palpitations with formoterol 12ug,²⁸ and in a COPD population 4 of 241 patients noted palpitations with formoterol 12 ug twice daily over 6 months; no palpitations were noted in the salmeterol group.⁴⁴ In a 12-hour study, 5 of 28 patients noted some subjective symptoms (either tachycardia, palpitation, or tremor) with formoterol 24ug and no patient noted adverse events after salmeterol.³⁶ Cazzola and colleagues²⁵ reported similar numbers (p>0.05) of ventricular premature beats over 24 hours after formoterol (12ug) and salmeterol (50ug).

Potassium decreased over a 9-hour follow-up period with a maximum decrease of 1.12 mmol/L after formoterol 24ug, 0.45 mmol/L after salmeterol 50 ug and 0.49 mmol/L after formoterol 12ug.²⁵ There were no significant changes in potassium 1 hour after treatment in a poor-quality study examining this outcome.¹⁹ There were no data on the comparative effect of these drugs on blood glucose.

The reporting of headache ranged from 0 to 5% of study participants, with no differences reported between study drugs.^{16, 28, 32, 37, 44} Tremor was reported in a small percent of participants taking both formoterol or salbutamol, with no apparent difference between the two drugs (between-group statistics not reported).^{19, 28, 37, 44}

Children

In the single study reporting withdrawals, 26.6% of participants taking formoterol 12ug (delivered dose 9 ug, not available in the U.S.) bid and 15.8% of those taking salmeterol 50ug bid withdrew over the 12-week study.³¹ Withdrawals were due to deteriorating asthma control (6.3% formoterol; 5.3% salmeterol) and to adverse events (5.1% formoterol; 1.2% salmeterol). One serious adverse event was reported in each treatment group but neither was thought related to the treatment (testicular torsion and diabetes mellitus).

Palpitations were not reported in any participants in a pediatric study.³⁷ Tremor was reported in 1 of 68 patients taking formoterol 36mg and none with lower dosages or with salmeterol 50ug.³⁷ Headaches were reported in 22.4% of children taking salmeterol 50ug bid and 17.5% in those taking formoterol 12ug bid over 12 weeks with no significant difference between groups.^{31, 32}

Albuterol vs levalbuterol

Adults

Total withdrawal rates ranged from 0 to 11.0% (the latter rate with levalbuterol 1.25 mg in adult asthmatic patients over 4 weeks⁷⁶) among the four studies reporting these data.^{71, 76, 77, 118} Withdrawal rates were similar between the two drugs with neither drug consistently reporting higher rates. These studies reported several dosages for each drug and no relationship between dose and withdrawal rates was noted.

The available data indicate that heart rate increases 5 to 15 beats per minute 20 minutes after treatment with both albuterol or levalbuterol, but returns to baseline by 3 hours in adults.^{69, 79, 118} Between-group statistical comparisons were rarely reported; in one study of adults with asthma who were treated three 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 versus 2.4; data estimated from graph) ($p < 0.05$).⁷⁶

In the only study examining blood pressure, there were no significant changes in either group.⁶⁹ Palpitations¹¹⁸ and tachycardia⁷⁶ were reported in a similar percent of patients with both drugs.

Light-headedness, dizziness, nervousness, anxiety, restlessness were reported in a number of studies with similar rates for both albuterol 1.25 to 2.5 mg and levalbuterol 0.63 to 1.25 mg.^{69, 76, 79} 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 three studies with comparable rates between treatment drugs.^{70, 76, 118}

Blood glucose increased 3 hours after 4 doses of albuterol 2.5 mg and levalbuterol 1.25 mg with no significant difference between the two drugs ($p = 0.70$).⁷¹ 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 three times daily dosing.⁷⁶ 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.⁷⁷

In an adult asthma population, potassium was noted to decrease 3 hours after 4 doses of albuterol 2.5 mg and levalbuterol 1.25 mg with no significant difference between the two drugs ($p = 0.17$).⁷¹ Two other studies also recorded a decrease in potassium 1-10 hours after both levalbuterol and albuterol, with no significant difference between the two drugs.^{71, 77, 79}

Children

Study withdrawal rates in pediatric studies were inconsistent in the two studies that reported these data.^{75, 81} The overall rate of adverse events was generally similar for each treatment group: placebo 52%, levalbuterol 0.31 mg 53.4%, levalbuterol 0.63mg 60.8% and albuterol 1.25 mg 53.8%.⁸¹

Heart rate increased 5 to 15 beats per minute 20 minutes after treatment with both albuterol or levalbuterol, but returned to baseline by 3 hours.^{17, 75, 81} There was no significant difference between groups in the degree of increased heart rate between treatment groups.^{17, 68} Skoner and colleagues⁸¹ noted a greater increase in heart rate ($p < 0.04$) with levalbuterol 0.63 mg three times daily (4.1 peats per minute) and albuterol 1.25 mg (2.6 beats per minute), both compared to levalbuterol 0.31 mg.

Light-headedness, tremor and headache were reported with similar rates for up to five doses of albuterol 2.5 mg and levalbuterol 1.25 mg.⁷⁹ Tremulousness was reported in 37% and 33% of pediatric patients using levalbuterol and racemic albuterol, respectively⁷⁹ with no significant difference between groups.

Milgrom and colleagues⁷⁵ 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 three times a day ($p=0.043$) in children. Among children age 2 to 5 years, Skoner and colleagues⁸¹ 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,¹⁷ 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 1.25 mg levalbuterol). Increases were also seen after racemic albuterol 1.25 and 2.5 mg (16 and 20 mg/dL, respectively).

A decrease in serum potassium was noted 1-10 hours after both levalbuterol and albuterol, with no significant difference between the two drugs.⁷⁹ In a study of albuterol and levalbuterol given three 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 two drugs at day 21.⁷⁵ Skoner and colleagues⁸¹ 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 (-0.5 meq/L).¹⁷

Albuterol vs metaproterenol

No data on withdrawals were provided in the included studies.

A single study⁸⁶ examined the comparative effect of these drugs on blood pressure and noted that systolic blood pressure was increased in both drugs, with no significant difference between the drugs in peak pressure or area under the curve. Albuterol had shorter time to peak systolic pressure ($p>0.05$). Heart rate also increased with both drugs, with the peak rate greater with albuterol ($p=0.05$), but no significant difference in area under the curve (beats/min). There were no comparative data on cardiovascular, metabolic, or neurologic adverse events.

Albuterol vs pirbuterol

No comparative data on withdrawals or cardiovascular, metabolic, or neurologic adverse events were provided in the included studies. One comparative study in a pediatric population reported no 'cardiac side effects' in 17 patients.⁸⁸

Metaproterenol vs pirbuterol

Rates of withdrawals were similarly low in both treatment groups in the only available study.¹¹³

There were no comparative data on blood pressure or heart rate on these drugs. A single study in an adult population noted that ‘tachycardia’ was reported in 2 patients taking metaproterenol (n= 67) and 2 taking pirbuterol (n= 66).¹¹³ Headache, dizziness, tremors, nausea occurred in $\leq 6\%$ of participants with no significant differences between treatment groups. Nervousness was reported in about 20% of patients taking pirbuterol and 10% taking metaproterenol, but this difference was also not significant ($p>0.05$).

Albuterol vs fenoterol

The only trial reporting withdrawals was a study of acute asthma treatment of adults in the emergency department.⁵⁷ Here the only ‘withdrawal’ was one death from asthma among 128 study participants receiving fenoterol. The other studies comparing albuterol and fenoterol were cohort^{48, 119} or case control^{60, 62} studies and rate data were not provided.

Blood pressure in adult patients decreased from 1 to 6 mm Hg for both drugs 1-2 hours following treatments. Between-group comparisons were not reported, but the 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. Both drugs produced a change within studies, with greater increases occurring in the pediatric age groups. Palpitations were occasionally reported with both drugs,^{50, 66} with no difference between groups.

A minor decrease in potassium was reported in two studies,^{65, 66} with a greater decline with higher dosage (26 puffs of terbutaline 250 ug [decrease in potassium 0.52 mmol/l], fenoterol 200 ug [0.76 mmol/l], or albuterol 100ug [0.46 mmol/l]).⁶⁶

Data were not available on the comparative effect of these drugs on blood glucose or gastrointestinal AEs. Headache was noted in a small study (n=10) with 2 patients with terbutaline 250ug, 3 patients with albuterol 100 ug, and 5 patients with fenoterol 200 ug.⁶⁶

Albuterol vs terbutaline

Total withdrawals ranged from 0 to 15.6% and withdrawals due to adverse events from 0 to 6.3% in the six studies reporting these data. Rates were similar between the two study drugs. The high rate of total withdrawals occurred in an adult asthmatic population using albuterol 0.4 mg three times daily over 3 weeks; none of the withdrawals in this study were felt due to adverse events.¹⁸

Effects on systolic blood pressure (SBP) and diastolic blood pressure (DBP) were similar between the two drugs in the only study reporting these data.⁸⁹ Heart rates generally increased 5

to 10 beats per minutes from 15 minutes to 2 hours after treatment, with similar changes after both drugs. Palpitations were noted in a small number of patients with both drugs.^{12, 66, 90, 96}

Potassium decreased 0.48 meq/l after terbutaline 0.125 mg/kg and 0.85 meq/L after albuterol 0.125 mg/kg at 30 minutes post-treatment (within-group p-value <0.05 for both groups; no between-group p-values reported).⁹³ Similar changes in potassium were noted after both terbutaline and albuterol 26 puffs each.⁶⁶

Headache was reported in 20-30% of patients taking either terbutaline or albuterol in two small studies.^{66, 96}

Metaproterenol vs fenoterol

No data on withdrawals were provided in the included studies. The sparse available data on adverse events are found in Appendix E.

Metaproterenol vs terbutaline

The single study reporting withdrawals was a 3-hour study in adult asthma and no withdrawals were noted.¹¹⁵

Fenoterol vs terbutaline

There were limited data on withdrawal rates, with only four studies reporting these data.^{106, 109, 111, 119} In a study of pediatric asthma patients, 2 of 38 participants using terbutaline withdrew due to deteriorating asthma, and none in the fenoterol group.¹⁰⁹ In the other study of COPD sample sizes were too small to draw conclusions (1 of 2 patients taking fenoterol dropped out).¹¹⁹ The other studies reporting these data were also had very small sample sizes.^{106, 111} The sparse available data on adverse events are found in Appendix E.

Pirbuterol vs terbutaline

No data on withdrawals were provided in the included studies. The available data on adverse events are found in Appendix E.

Table 20. Withdrawals from Included Studies*

Population	Author, year	Study duration	Intervention	n	Total withdrawals (%)	Total withdrawals due AEs (%)	
Albuterol vs Fenoterol							
Adult Asthma	Newhouse, 1996	Multidose, 1 day	Albuterol 100ug	257	0	0	
			Fenoterol 200ug	257	0.78	0	
Albuterol vs Levalbuterol							
Adult Asthma	Gumbhir-Shah, 1999	4 cumulative doses	Albuterol 2.5mg QID	13	0	0	
			Levalbuterol 1.25mg QID	13	0	0	
	Lotvall J 2001	Multidose, single days	Albuterol 12.5 to 3200 ug	20	0	0	
			Levalbuterol 6.25 to 1600 ug	20	0	0	
	Nowak, 2004	3 doses in ER per hr	Albuterol 2.5mg	91	0	0	
			Albuterol 5.0mg	91	0	0	
			Levalbuterol 0.63mg	91	0	0	
			Levalbuterol 1.25mg	91	0	0	
			Levalbuterol 2.5mg	91	0	0	
			Levalbuterol 3.75mg	91	0	0	
	Nelson, 1998; Pleskow, 2004*	4 weeks	Levalbuterol 5.0mg	91	0	0	
			Albuterol 1.25mg TID	362	2.9	2.9	
			Albuterol 2.5mg TID	362	5.4	5.4	
			Levalbuterol 0.63mg TID	362	4.1	4.2	
Levalbuterol 1.25mg TID			362	10.9	10.9		
Albuterol 2.5mg/3mL TID			70	0	0		
Pediatrics Asthma	Hardasmalani,	3 treatments, 1 hr	Levalbuterol 1.25mg/3m TIDL	70	0	0	
			Albuterol 1.25mg	338	2.9	0	
	Milgrom, 2001	3 weeks	Albuterol 2.5mg	338	9.1	0	
			Levalbuterol 0.31mg	338	8.6	0	
			Levalbuterol 0.63mg	338	1.4	0	
	Skoner, 2005	3 weeks	Albuterol 1.25mg-2.5mg TID	211	5.8	3.8	
			Levalbuterol 0.31mg TID	211	8.6	6.9	
			Levalbuterol 0.63mg TID	211	15.7	11.8	
	Albuterol vs Terbutaline						
	Adult Asthma	Anani, 1989	3 weeks	Albuterol 400ug QID	30	13.3	3.3
Terbutaline 500ug QID				30	6.7	3.3	
Gioulekas, 1996		3 weeks	Albuterol 0.4mg TID	32	15.6	0	
			Terbutaline 0.5mg TID	32	6.2	6.2	
Vilsvik, 1993		2 weeks	Albuterol 0.1mg	159	6.9	1.9	
			Terbutaline 0.5mg	159	6.9	1.3	
Lindsay, 1994**		4 weeks	Albuterol 0.1mg BID	46	2.2	0	
			Terbutaline 0.5mg BID	46	2.2	0	
Webb, 1982		1 weeks	Albuterol 200ug	16	0	0	

Population	Author, year	Study duration	Intervention	n	Total withdrawals (%)	Total withdrawals due AEs (%)
Pediatrics Asthma	Oldaeus, 1995	2 weeks	Terbutaline 500ug	16	0	0
			Albuterol 0.4mg TID	20	0	0
			Terbutaline 0.5mg TID	20	0	0
Fenoterol vs Terbutaline						
Adult Asthma	Gray, 1982	3 day	Fenoterol 100ug	12	0	0
			Terbutaline 250ug	12	0	0
Formoterol vs Salmeterol						
Adult Asthma	Conдеми, 2001	24 weeks	Formoterol 12ug BID	528	13.4	5.7
			Salmeterol 50ug BID	528	11.3	3.4
	Nightingale, 2002	4 weeks	Formoterol 12ug BID	42	11.9	11.9
			Salmeterol 50ug BID	42	7.1	7.1
	Vervloet, 1998; Rutten-van Molken, 1998	24 weeks	Formoterol 12ug BID	482	9.9	4.9
			Salmeterol 50ug BID	482	12.4	5.4
Pediatrics Asthma	Everden, 2002; Everden, 2004	12 weeks	Formoterol 12ug (9ug delivered dose)	145	26.6	5.1
			Salmeterol 50ug BID	145	15.8	1.3
Metaproterenol vs Pirbuterol						
Adult Asthma	Tinkelman, 1990	12 weeks	Metaproterenol	133	1.5	1.5
			Pirbuterol	133	1.5	1.5
Metaproterenol vs Terbutaline						
Adult Asthma	Roth, 1977	3 puffs, 3 hrs	Metaproterenol 650ug	21	0	0
			Terbutaline 125ug	21	0	0
*Note: Studies are included only if they reported data on withdrawal rates. Single-dose studies were excluded.						
**Study population ≥ 12 years of age						

Subpopulations

Key Question 9. Are there subgroups of patients based on demographic characteristics (age, racial groups, gender), other medications (drug-drug interactions), comorbidities (drug-disease interactions), or pregnancy for which one long-acting, inhaled beta₂-agonists is more efficacious, effective, or associated with fewer adverse events than another inhaled beta₂-agonist?

Key Question 10. Are there subgroups of patients based on demographic characteristics (age, racial groups, gender), other medications (drug-drug interactions), comorbidities (drug-disease interactions), or pregnancy for which one of the following short-acting, inhaled beta₂-agonists is more efficacious, effective, or associated with fewer adverse events: albuterol, levalbuterol, pirbuterol, metaproterenol, terbutaline, or fenoterol?

Age and sex

No study specifically examined an older (>65 years of age) population. In several studies of COPD the mean population age was ≥ 65 years: formoterol vs salmeterol,²⁹ albuterol vs fenoterol,⁶⁷ albuterol vs levalbuterol,⁷⁰ and metaproterenol vs terbutaline.⁸⁷ The age range was up to 80 years in two studies comparing formoterol to salmeterol.^{27, 34}

Consistent with the epidemiology of COPD, male participants dominated these trials and in a number of these, more than 80% of participants were male.^{13, 14, 26-28, 34, 63, 70, 82, 119}

Several trials examined predominantly male asthmatics.^{49, 53, 66}

No study examined a predominantly female population either as part of the main study or as a subgroup, for either asthma or COPD.

Albuterol vs levalbuterol

Datta and colleagues⁷⁰ examined levalbuterol versus albuterol in a COPD population which was 83% male with a mean age of 69 years. No significant differences were noted between treatment groups for improvements in FEV₁ and increase in pulse rate. There were no differences between treatment groups and in treatment groups compared to placebo group in oxygen saturation or hand tremor.

Salmeterol vs formoterol

Cazzola and colleagues²⁷ examined the time course of salmeterol and formoterol in 16 male patients with moderate to severe COPD and mean age 64.3 years (range 50-80 years) and found no significant differences between these drugs for mean time of onset; time to mean peak response was faster with formoterol. Heart rate and blood pressure did not change significantly during the study.

In another small study of older males²⁶ salmeterol was equally as effective, but longer acting, than formoterol. Celik and colleagues²⁸ also noted comparable bronchodilation and side effects between the drugs in a predominantly male COPD population.

Formoterol was again noted to have faster onset of action by Kottakis and colleagues³⁴ with a greater improvement in during the first hour, but the two drugs produced similar improvements in effort to breathe, breathing discomfort and change in effort to breathe by both 1 and 4 hours post treatment. This population of mean age 63.5 years (range 42 to 80 years) was 81% male.

Di Marco and colleagues²⁹ compared drug effects over 120 minutes in 20 COPD patients of mean age 65 years (range not reported). Formoterol increased inspiratory capacity (% predicted) more than salmeterol. There was no significant difference between these drugs for FEV₁, however. Adverse events were not reported in this study.

Albuterol vs metaproterenol

Four inhaled beta₂-agonists were compared⁸⁷ in 18 COPD patients of mean age 69 years (range 59-79 years): albuterol 0.18 mg, metaproterenol 1.30 mg, pirbuterol 0.4 mg, and terbutaline 0.4 mg. After single doses of the drugs, FEV₁ was not different among the four agents. Patients then took the agent that provided the greatest and least response for 4-week periods; the responses to the two agents were not significantly different.

Metaproterenol was equivalent to albuterol for pulmonary function outcomes and side effects were also similar in a single small study.⁸²

Albuterol vs pirbuterol vs metaproterenol

Peacock and colleagues⁸⁷ examined these comparisons as noted above (albuterol vs metaproterenol comparison).

In a poor-quality study of 12 males,^{13, 14} no differences were found in lung function 4 hours after the use of pirbuterol 400 ug and salbutamol 200 ug and there were no side effects or changes of clinical relevance impulse rate, blood pressure, ECG or laboratory test results.

Comparisons relevant to Canada

Albuterol vs fenoterol

Yang and colleagues⁶⁷ examined 13 (11 male) COPD patients' response to exercise and found no significant difference in cardiopulmonary response between nebulized fenoterol or

salbutamol (2 mg) 30 minutes given prior to exercise. They did note that plasma potassium was significantly lower after exercise after fenoterol compared to the saline control and salbutamol.

Among predominantly male patients with COPD, Tandon⁶³ found no differences in bronchodilator efficacy between these drugs, but heart rates increased significantly more with fenoterol than salbutamol after 7 to 13 puffs.

Among 24 adults with asthma⁵³ (mean age 29 years, 83% male), median duration of 15% bronchodilation was 6 hours for fenoterol (320 ug) and 3.5 hours for albuterol (180ug) (p<0.01) with no significant changes in heart rate, blood pressure and ECG changes in either treatment group. Mild adverse symptoms were noted in 11 of 24 patients on fenoterol; none were noted with albuterol.

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 reports.⁴⁹

Metaproterenol vs terbutaline

Peacock and colleagues⁸⁷ examined these comparisons as noted above (albuterol vs metaproterenol comparison).

Fenoterol vs terbutaline vs albuterol

In a small, cross-over study⁶⁶ of eight men and two women, fenoterol, salbutamol and terbutaline all produced similar bronchodilation. However, the increase in heart rate, QTc interval and tremor and fall in plasma potassium were greater after fenoterol than after salbutamol or terbutaline.

Race

For the most part, race or ethnicity data were not provided in studies. No studies were exclusively of African-American or other minority populations; two studies compared albuterol vs levalbuterol in predominantly African-American, pediatric asthma patients,^{68, 79} and one study examined asthmatic adults.⁷⁷

Albuterol vs levalbuterol

In an RCT in the emergency department,⁶⁸ a primarily African American population of children (86% Black) age 1 to 8 years (n=482) received either 2.5 mg of albuterol or 1.25 mg levalbuterol via nebulizer every 10 minutes to a maximum of six 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 was not different in the two groups ($p=0.63$) and no significant adverse events occurred in either group.

In a similar RCT in the emergency department,⁷⁹ 129 children aged 2 to 14 years (83% African American), there were no significant differences between treatment group for the primary outcome of clinical asthma score and the FEV₁ after 1, 3 and 5 treatments. There were also no differences in the number of treatments, length of emergency room 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 two groups.

Comorbidities

Only one included study specifically examined comorbidities.²⁴ Many COPD trials indicated the presence of comorbidities, but data were not presented that permitted subgroup analyses of specific conditions.

Among 12 COPD patients with preexisting cardiac arrhythmias, Cazzola and colleagues²⁴ noted a greater increase in heart rate with formoterol 24ug (10 beats per minute 4 hours after treatment) compared to salmeterol 50 ug (5.5 beats per minute) post inhalation of a single dose. They also observed more supraventricular or ventricular premature beats after formoterol 24ug, although between-group statistics were not presented.

CONCLUSIONS

Table 21. Summary of the evidence by Key Question

Key Question	Quality of Evidence (No. effectiveness or AE studies and quality)	Conclusions
1. When used in adults with asthma or chronic obstructive pulmonary disease (COPD), are there differences in efficacy or effectiveness among long-acting, inhaled beta ₂ -agonists, when used in the outpatient setting?	Salmeterol vs formoterol: 7 fair, 1 poor	Salmeterol vs formoterol: Among asthma patients, NSD between these drugs (delivered via dry powder devices) for symptoms (3 studies), use of rescue medications (3), healthcare utilization (2) and quality of life (1). Among COPD patients, 2 studies found NSD between drugs for respiratory symptoms (1 MDI, 1 dry powder devices); no other effectiveness outcomes were examined. In EIA in adults, 1 single-dose study (dry powder delivery) found NSD in FEV ₁ after exercise; formoterol had faster onset of action and greater % increase in FEV ₁ prior to exercise.
2. When used in adults with asthma or COPD, are there differences in efficacy or effectiveness among the following short-acting inhaled beta ₂ -agonists when used in the outpatient setting: albuterol, fenoterol, levalbuterol, pirbuterol, metaproterenol and terbutaline?	Albuterol vs levalbuterol: 2 fair Albuterol vs metaproterenol: 0 Albuterol vs pirbuterol: 0 Metaproterenol vs pirbuterol: 0 Comparisons of interest to Canada: Fenoterol vs albuterol: 1 fair, 1 poor Terbutaline vs albuterol: 2 fair, 3 poor Fenoterol vs metaproterenol: 0 Terbutaline vs fenoterol: 3 fair Terbutaline vs metaproterenol: 0 Terbutaline vs pirbuterol: 0	Albuterol vs levalbuterol: Among adults with asthma, 1 RCT found less rescue medication use with levalbuterol (no between-group statistics) with no apparent difference in symptoms. A controlled clinical trial in the ER found a decrease in need for additional treatment with levalbuterol compared to comparable albuterol dosages, but hospital admission rates were similar. No data in COPD or EIA. Albuterol vs metaproterenol: No effectiveness data. Albuterol vs pirbuterol: No effectiveness data. Metaproterenol vs pirbuterol: No effectiveness data. Comparisons of interest to Canada: Fenoterol vs albuterol: No effectiveness data. Terbutaline vs albuterol: In adult asthma patients, there was NSD in rescue medication use (3 studies). In COPD, there were no effectiveness data. Fenoterol vs metaproterenol: No effectiveness data. Terbutaline vs fenoterol: NSD symptoms scores (1 study) Terbutaline vs metaproterenol: No effectiveness data. Terbutaline vs pirbuterol: No effectiveness data.
3. When used in children with asthma, are there differences in efficacy or effectiveness among long-acting, inhaled beta ₂ -agonists, when used in the outpatient setting?	Salmeterol vs formoterol: 1 fair	Salmeterol vs formoterol: 1 study comparing dry powder formulations showed similar symptom outcomes between groups; parent-assessed QOL (activity), SABA use, and some specific symptoms scores improved more for formoterol.

Key Question	Quality of Evidence (No. effectiveness or AE studies and quality)	Conclusions
4. When used in children with asthma, are there differences in efficacy or effectiveness among the following short-acting inhaled beta ₂ -agonists when used in the outpatient setting: albuterol, fenoterol, levalbuterol, pirbuterol, metaproterenol and terbutaline?	<p>Albuterol vs levalbuterol: 1 good, 4 fair</p> <p>Albuterol vs metaproterenol: 1 fair</p> <p>Albuterol vs pirbuterol: 1 fair</p> <p>Metaproterenol vs pirbuterol: 0</p> <p>Comparisons of interest to Canada:</p> <p>Fenoterol vs albuterol: 1 good, 5 fair</p> <p>Terbutaline vs albuterol: 1 good, 3 fair</p> <p>Fenoterol vs metaproterenol: 0</p> <p>Terbutaline vs fenoterol: 3 fair</p> <p>Terbutaline vs metaproterenol: 0</p> <p>Terbutaline vs pirbuterol: 0</p>	<p>Albuterol vs levalbuterol: Daily regular use (2 studies): NSD between drugs for symptoms and use of rescue medications with 21-day use; fewer asthma control days with levalbuterol 0.63 and albuterol 1.25 compared to levalbuterol 0.31 day 14-21 (p<0.04); NSD uncontrolled days in 2nd study</p> <p>Emergency room treatment (3 studies); NSD symptoms (2 studies), need for additional treatments (3), ER length of stay (2); Hospital admissions: NSD in two studies; third study found fewer admissions with levalbuterol 1.25 mg 3 doses vs albuterol 2.5 mg 3 doses, (P=0.02). This latter study was larger and was powered to detect a difference in this outcome. This result needs to be replicated in other settings.</p> <p>Albuterol vs metaproterenol: EIA: Equally efficacious in blocking bronchospasm initially; duration of action of albuterol was greater than for metaproterenol</p> <p>Albuterol vs pirbuterol: No effectiveness data.</p> <p>Metaproterenol vs pirbuterol: No effectiveness data.</p> <p>Comparisons of interest to Canada:</p> <p>Fenoterol vs albuterol: No effectiveness data.</p> <p>Terbutaline vs albuterol: In pediatric asthma, there was NSD in symptoms (3 studies).</p> <p>Fenoterol vs metaproterenol: No effectiveness data.</p> <p>Fenoterol vs terbutaline: No effectiveness data.</p> <p>Terbutaline vs metaproterenol: No effectiveness data.</p> <p>Terbutaline vs pirbuterol: No effectiveness data.</p>
5. When used in adults with asthma or COPD, are there differences in safety or rates of adverse events among long-acting, inhaled beta ₂ -agonists, when used in the outpatient setting?	<p>Salmeterol vs formoterol: 4 fair, 2 poor</p>	<p>Salmeterol vs formoterol: Withdrawal rates (total and AE-related) were similar. NSD heart rate at 2h (formoterol 24ug and salmeterol 50ug) (1 study) and up to 24 hours (formoterol 12ug and salmeterol 50ug) (1 study). Palpitations and ventricular premature beats more common with formoterol (2 studies; 1 with formoterol 12ug bid and 1 with single dose 24ug [an unapproved dose]); NSD at approved doses (1 study). Decrease potassium more in formoterol (1 study). NSD tremor (3) and headache (4).</p>
6. When used in adults with asthma or COPD, are there differences in safety or rates of adverse events among the following short-acting inhaled beta ₂ -agonists when used in the outpatient setting: albuterol,	<p>Albuterol vs levalbuterol: 2 fair</p> <p>Albuterol vs metaproterenol: 0</p> <p>Albuterol vs</p>	<p>Albuterol vs levalbuterol: NSD withdrawal rates (3 studies). Heart rate increases with both drugs (3); increase more with albuterol (1). NSD BP (1), palpitations (1), tachycardia (1), increased blood glucose (1), dizziness/nervousness/anxiety/tremor (5). Decreased potassium: NSD between drugs (4); potassium decreased more with albuterol 2.5mg tid</p>

Key Question	Quality of Evidence (No. effectiveness or AE studies and quality)	Conclusions
fenoterol, levalbuterol, pirbuterol, metaproterenol and terbutaline?	pirbuterol: 0 Metaproterenol vs pirbuterol: 0 Comparisons of interest to Canada: Fenoterol vs albuterol: 1 poor Terbutaline vs albuterol: 3 fair, 2 poor Fenoterol vs metaproterenol: 0 Terbutaline vs fenoterol: 2 fair, 1 poor Terbutaline vs metaproterenol: 0 Terbutaline vs pirbuterol: 0	than levalbuterol 0.63 mg tid (p<0.05) (1). Albuterol vs metaproterenol: NSD BP, HR (1 study); no other AE data. Albuterol vs pirbuterol: No comparative AE data. Metaproterenol vs pirbuterol: NSD withdrawals, headache, dizziness, tremors, nausea, nervousness (1 study) Comparisons of interest to Canada: Fenoterol vs albuterol: Blood pressure decreased 1-6 (7 studies) mm Hg after both drugs and heart rate response varied (-5 to +15 BBM) after treatment (9). Decrease in K ⁺ with NSD between groups (2). Terbutaline vs albuterol: Similar effects on BP (1 study). Heart rate increased 5-15 BBM with NSD (4). K ⁺ decreased approximately 0.5 meq/L in both drugs (1). Headache rare in both drugs (2). Fenoterol vs metaproterenol: Sparse data on comparative safety. Terbutaline vs fenoterol: Sparse data on comparative safety. Terbutaline vs metaproterenol: Sparse data on comparative safety. Terbutaline vs pirbuterol: Sparse data on comparative safety.
7. When used in children with asthma, are there differences in safety or rates of adverse events among long-acting, inhaled beta ₂ -agonists, when used in the outpatient setting?	Salmeterol vs formoterol: 1 poor	Salmeterol vs formoterol: Withdrawals greater with formoterol (1 study). NSD between groups for: headaches (1), tremor (1), palpitations (1), respiratory infections (1). No data on potassium.
8. When used in children with asthma, are there differences in safety or rates of adverse events among the following short-acting inhaled beta ₂ -agonists, when used in the outpatient setting: albuterol, fenoterol, levalbuterol, pirbuterol, metaproterenol and terbutaline?	Albuterol vs levalbuterol: 1 good, 3 fair Albuterol vs metaproterenol: 0 Albuterol vs pirbuterol: 0 Metaproterenol vs pirbuterol: 0 Comparisons of interest to Canada: Fenoterol vs albuterol: 0 Terbutaline vs albuterol: 1 good, 3 fair Fenoterol vs metaproterenol: 0 Terbutaline vs	Albuterol vs levalbuterol: Withdrawal rates variable (2 studies); NSD increase heart (3 studies); no data on BP; NSD tremor (1), light-headedness (1), dizziness (1), nervousness (1). Blood glucose increased with both drugs, more with albuterol (1). NSD decrease K ⁺ (1); lower K ⁺ with albuterol (1 study at day 0, NSD day 21; 2 nd study provided no data). Albuterol vs metaproterenol: No data on comparative effectiveness Albuterol vs pirbuterol: No data on comparative effectiveness Metaproterenol vs pirbuterol: No data on comparative effectiveness Comparisons of interest to Canada: (results pending) Fenoterol vs albuterol: No data on withdrawals. Increase heart rate 2-25 BBM in both drugs with NSD (3). No BP data. No data on K ⁺ , blood glucose,

Key Question	Quality of Evidence (No. effectiveness or AE studies and quality)	Conclusions
	fenoterol: 0 Terbutaline vs metaproterenol: 0 Terbutaline vs pirbuterol: 0	neurologic AEs. Terbutaline vs albuterol: Heart rate response variable with no pattern or difference between drugs (3). No BP data. K+ decreased approximately 0.5 meq/L in both drugs (1). No neurological comparative data. Fenoterol vs metaproterenol: Sparse data on comparative safety. Terbutaline vs fenoterol; Sparse data on comparative safety. Terbutaline vs metaproterenol: Sparse data on comparative safety. Terbutaline vs pirbuterol: Sparse data on comparative safety.
9. Are there subgroups of patients based on demographic characteristics (age, racial groups, gender), other medications (drug-drug interactions), comorbidities (drug-disease interactions), or pregnancy for which one long-acting, inhaled beta ₂ -agonists is more efficacious, effective, or associated with fewer adverse events than another inhaled beta ₂ -agonst?	Salmeterol vs formoterol: 5 fair	Salmeterol vs formoterol: Older, male COPD patients: Efficacy (5 studies), effectiveness (1), withdrawals (1) and AEs (5) were similar between the two drugs. No data on race or comorbidities.
10. Are there subgroups of patients based on demographic characteristics (age, racial groups, gender), other medications (drug-drug interactions), comorbidities (drug-disease interactions), or pregnancy for which one of the following short-acting, inhaled beta ₂ -agonsts is more efficacious, effective, or associated with fewer adverse events: albuterol, levalbuterol, pirbuterol, and metaproterenol?	Albuterol vs levalbuterol: 1 fair Albuterol vs metaproterenol: 1 fair, 1 poor Albuterol vs pirbuterol; 1 fair Metaproterenol vs pirbuterol: 1 fair Comparisons of interest to Canada: No data on subgroups identified.	Albuterol vs levalbuterol: Older, predominantly male COPD population: NSD in efficacy, heart rate, tremor; no effectiveness data in this study. No data on race or comorbidities. Albuterol vs metaproterenol: In older COPD patients, NSD efficacy between drugs (2 studies). Albuterol vs pirbuterol: In older COPD patients, NSD efficacy between drugs (1 fair). Metaproterenol vs pirbuterol: In older COPD patients, NSD efficacy between drugs (1). Comparisons of interest to Canada: No data on subgroups identified.

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99. Towns, S. J., et al. Bronchodilator effects of salbutamol powder administered via Rotahaler and of terbutaline aerosol administered via Misthaler. A comparison study in children with asthma. *Med J Aust.* 1983; 1(13): 633-636.
100. Vilsvik, J., et al. Comparison between Bricanyl Turbuhaler and Ventolin metered dose inhaler in the treatment of exercise-induced asthma in adults. *Ann Allergy.* 1991; 67(3): 315-318.
101. Vilsvik, J. S., et al. Comparison of the acceptability of the Ventolin metered-dose inhaler and the Bricanyl Turbuhaler. *Ann Allergy.* 1993; 70(4): 300-304.
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105. Carmichael, J., et al. Comparison of fenoterol and terbutaline administered by intermittent positive pressure breathing. *Brit J Dis Chest.* 1980; 74(3): 268-272.
106. Gray, B. J., et al. A comparative double-blind study of the bronchodilator effects and side effects of inhaled fenoterol and terbutaline administered in equipotent doses. *Brit J Dis Chest.* 1982; 76(4): 341-350.

107. Lawford, P., et al. Fenoterol is as effective as terbutaline in the pear-shaped spacer. *Practitioner*. 231(1429): 642.
108. Lin, Y. Z., et al. A comparison of terbutaline and fenoterol unit dose vials in treating children with acute asthmatic attacks. *Acta Paediatr Taiwan*. 2002; 43(4): 187-192.
109. Ribeiro, L. B., et al. Comparison of Bricanyl Turbuhaler and Berotec dry powder inhaler. *Allergy*. 1990; 45(5): 382-385.
110. Tammivaara, R. The efficacy of terbutaline and fenoterol aerosols on adult exercise-induced asthma. *Scand J Respir Dis*. 1979; 103(212-213).
111. Trembath, P. W., et al. Comparison of four weeks' treatment with fenoterol and terbutaline aerosols in adult asthmatics. A double-blind crossover study. *J Allergy Clin Immun*. 1979; 63(6): 395-400.
112. Chodosh, S., et al. Comparative effects of pirbuterol acetate, metaproterenol, and placebo aerosols on pulmonary function and incidence of cardiac ectopy. *J Asthma*. 1989; 26(5): 309-315.
113. Tinkelman, D. G., et al. Comparison of safety and efficacy of inhaled pirbuterol with metaproterenol. *Ann Allergy*. 1990; 64(2 Pt 2): 202-206.
114. Chester, E. H., et al. Bronchodilating effect of terbutaline aerosol. *Clin Pharmacol Ther*. 1978; 23(6): 630-634.
115. Roth, M. J., et al. A comparative study of the aerosolized bronchodilators, isoproterenol, metaproterenol and terbutaline in asthma. *Ann Allergy*. 1977; 38(1): 16-21.
116. Campbell, S. For COPD a combination of ipratropium bromide and albuterol sulfate is more effective than albuterol base. *Arch Intern Med*. 1999; 159(2): 156-160.
117. Vervloet, D., et al. Comparative trial of Maxair Autohaler versus Ventodisks in poorly coordinated asthma patients. *Rev Fr Allergol*. 1994; 34(2): 185-190.
118. Lotvall, J. Pharmacological similarities and differences between beta₂-agonists. *Respir Med*. 2001; 95 Suppl B(S7-11).
119. McIntosh, D. A trial of fenoterol for nocturnal bronchospasm. *Practitioner*. 1983; 227(1385): 1757-1764.

Appendix A. Search Strategies

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)

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

The purpose of this document is to outline the methods used by the Oregon Evidence-based Practice Center (EPC), based at Oregon Health & Science University, and any subcontracting EPCs, in producing drug class reviews for the Drug Effectiveness Review Project.

The methods outlined in this document ensure that the products created in this process are methodologically sound, scientifically defensible, reproducible, and well documented. This document has been 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 NHS Centre for Reviews and Dissemination (CRD) report on *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 CRD.

All studies or systematic reviews that are included are assessed for quality, and assigned a rating of “good”, “fair” or “poor”. Studies that have a fatal flaw in one or more criteria are rated poor quality; studies which 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—the results are at least as likely to reflect flaws in the study design as the true difference between the compared drugs.

For Controlled Trials:

Assessment of Internal Validity

1. Was the assignment to the 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 numbers, birth dates or week days

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 numbers, birth dates or week days

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 (i.e., 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 EffectsAssessment of Internal Validity

1. Was the selection of patients for inclusion non-biased (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 events investigated specified and defined?
4. Was there a clear description of the techniques used to identify the events?
5. Was there non-biased 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. Did the duration of follow-up correlate to reasonable timing for investigated events? (Does 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. Is there a clear review question and inclusion/exclusion criteria reported relating to the primary studies?

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

i.e., 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?

This is usually the case if details of electronic database searches and other identification strategies are given. Ideally, details of the search terms used, date and language restrictions should be presented. In addition, descriptions of hand-searching, attempts to identify unpublished material, and any contact with authors, industry, and research institutes should be provided. The appropriateness of the database(s) searched by the authors should also be considered, e.g. if MEDLINE is searched for a review looking at health education, then it is unlikely that all relevant studies will have been 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 (e.g., method of randomization, whether outcome assessment was blinded, whether analysis was on an intention-to-treat basis). Authors may use either a published checklist or scale, or one that they have designed specifically for their review. Again, the process relating to the assessment should be explained (i.e. how many reviewers 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 studies included are suitable to answer 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, patient characteristics, 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 (e.g., according to sample size, or inverse of the variance) so that studies that are considered to provide the most reliable data have greater impact on the summary statistic.

Appendix C. Cochrane Systematic Reviews Related to Beta₂-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 (e.g., reductions in admission, improvement in pulmonary functions) and risks (e.g., 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 CBA in patients with severe acute asthma who present to the emergency department to increase their pulmonary functions and reduce hospitalization. Moreover, CBA 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 the combination of inhaled corticosteroids and long-acting beta ₂ -agonists (ICS+LABA) as compared to inhaled corticosteroids alone (ICS alone) in steroid-naïve children and adults with persistent asthma.	18	In steroid-naïve 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 at present to recommend use of combination therapy rather than ICS 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 β 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 β ₂ -agonist reduces the rate of exacerbations requiring systemic steroids, improves lung function, symptoms and use of rescue short-acting β 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 β 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 LABA to maintenance ICS therapy in reducing the requirement for ICS while maintaining control of chronic asthma.	10	In adults with asthma, using moderate to high maintenance doses of ICS, the addition of LABA has an ICS-sparing effect. The addition of LABA permits more participants on minimum maintenance ICS to reduce ICS. The precise magnitude of the ICS 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 β ₂ agonists and inhaled corticosteroids compared to a higher dose of inhaled corticosteroids on the incidence of	30	In adult asthmatics, there was no significant difference between the combination of LABA and ICS and a higher dose of ICS for the prevention of exacerbations requiring systemic corticosteroids. Overall, the combination therapy led to greater

Author, year Title (abbreviated)	Objective	Number of trials	Conclusions
	asthma exacerbations, on 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 β_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 when using a higher dose of inhaled corticosteroids. Apart from an increased rate of tremor, the two options appear safe although adverse effects associated with long-term ICS treatment were seldom monitored.
Plotnick L, 2000 Combined inhaled anticholinergics and beta ₂ -agonists	The aims of this study were 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 only supports 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 Pressurised metered dose inhalers 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 CFC-pMDI's are as effective as any other devices. The effect of HFA-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 anti-leukotrienes as add-on therapy	We compare the efficacy and safety profile of adding either daily LABA or LTRA in asthmatic patients with asthma who remained symptomatic on ICS.	8	In asthmatic adults inadequately controlled on low doses of inhaled steroids, the addition of LABA is superior to LTRA for preventing exacerbations requiring systemic steroids, and for improving lung function, symptoms, and use of rescue β_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 improving lung function. Fewer adverse events occurred in participants using long-acting beta-2 agonists (salmeterol and formoterol) as compared to theophylline.
Walters E, 2002 Regular treatment	To determine the benefit or detriment of treatment with regular short- or long acting inhaled beta-	31	Long acting inhaled beta-agonists have advantages across a wide range of physiological and clinical outcomes for

Author, year Title (abbreviated)	Objective	Number of trials	Conclusions
with long acting beta agonists versus daily regular treatment	agonists in chronic asthma.		regular treatment.
Walters E, 2003 Inhaled short acting beta ₂ -agonists use in chronic asthma	To assess the effects of using short-acting inhaled beta-2 agonists 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 agonists.
Walters E, 2003 Long-acting beta ₂ -agonists for stable chronic asthma	This review aimed to determine the benefit or detriment on the primary outcome of asthma control with the 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 the 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 mild asthmatics not taking ICS.

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*
- 6 = Wrong study design**

* Wrong publication type (letter with insufficient information, editorial, non-systematic review, case report, case series < 10 patients)

** 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. <i>Medical Letter on Drugs & Therapeutics</i> . 2006 Mar 13 2006;48(1230):21-22.	5
Aggarwal P, Pande JN, Guleria JS. Bronchodilators in acute bronchial asthma : a comparative study. <i>Indian J Chest Dis Allied Sci</i> . 1986;28(1):21-27.	3
Ahlstrom H, Svenonius E, Svensson M. Treatment of asthma in pre-school children with inhalation of terbutaline in Turbuhaler compared with Nebuhaler. <i>Allergy</i> . 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. <i>European Respiratory Society</i> . 1999.	5
Alvarez GG, Schulzer M, Jung D, Fitzgerald JM. A systematic review of risk factors associated with near-fatal and fatal asthma. <i>Can Respir J</i> . 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. <i>Respirology</i> . Nov 2004;9(4):570-571.	5
Andersen LH, Haghfelt T. Regional lung function in asthmatics in remission, before and after fenoterol. <i>B Eur Physiopath Res</i> . 1980;16(2):215-228.	6-DESIGN
Anderson H, Ayres J, Sturdy P, et al. Bronchodilator treatment and deaths from asthma: case-control study. <i>BMJ</i> . 2005;330:117-124.	6
Anderson SD, Rozea PJ, Dolton R, Lindsay DA. Inhaled and oral bronchodilator therapy in exercise induced asthma. <i>Aust N Z J Med</i> . 1975;5(6):544-550.	6
Angelici E, Delfino M, Carlone S, Serra P, Fineberg NS, Farber MO. Tolerance to inhaled fenoterol. <i>Am Rev Respir Dis</i> . Jun 1984;129(6):1014-1016.	6-DESIGN

Citation	Exclusion Code
Ankerst J, Lotvall J, Cassidy S, Byrne N. Comparison of the bronchodilating effects of formoterol and albuterol delivered by hydrofluoroalkane pressurized metered-dose inhaler. <i>Treat Respir Med.</i> 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. <i>Cochrane Db Syst Rev.</i> 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. <i>Cochrane Db Syst Rev.</i> 2006;1.	6
Aquilina R, Bergero F, Noceti P, et al. Protective effect of Duovent versus salbutamol in long-term treatment. <i>Respiration.</i> 1986;50(SUPPL. 2):240-244.	6
Ariano R, Giacca S. Variations of individual susceptibility to beta-adrenergic and anticholinergic bronchodilator drugs. <i>Minerva Pneumologie.</i> 1981;20(3):141-147.	1
Arledge TE, Liddle R, Stahl E, Rossing TH. Salmeterol does not cause tolerance during long-term asthma therapy. <i>J Allergy Clin Immun.</i> 1996;98(6 Pt 1):1116-1119.	6-LONG VS SHORT
Aronson N, Lefevre F, Piper M, et al. Management of chronic asthma. <i>Evid Rep Technol Assess.</i> 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. <i>J Asthma.</i> 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. <i>Eur Respir J.</i> 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. <i>Eur Respir J.</i> 1989;2(4):325-330.	6-LONG VS SHORT
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. <i>Respir Med.</i> 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. <i>Chest.</i> 1997;112(6):1514-1521.	6
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Appendix E. Adverse Events for Included Studies

Population	Author, Year	Outcome (unit) at time point	Intervention	n	Baseline, Mean(SD) or No(%)	Follow-Up, Mean(SD) or No(%)	Change from Baseline, Mean (SD), p-value	Comments
<u>Formoterol vs Salmeterol</u>								
Adverse Events: Other								
	Condemi, 2001	Viral infection (number) at up to 6 mos.	Formoterol 12ug	528	NR	50 (19.1%)	NR	
			Salmeterol 50ug	528	NR	52 (19.5%)	NR	
	Vervloet, 1998; Rutten-van Molken, 1998	Adverse events assessed by the investigator (number) at up to 6	Formoterol 12ug	482	NR	32 (13%)	NR	
			Salmeterol 50ug	482	NR	21 (9%)	NR	
Adverse Events: Rate								
	Condemi, 2001	No. with at least 1 adverse events (number) at up to 6 mos.	Formoterol 12ug	528	NR	202 (77.1%)	NR	
			Salmeterol 50ug	528	NR	201 (75.6%)	NR	

Population	Author, Year	Outcome (unit) at time point	Intervention	n	Baseline, Mean(SD) or No(%)	Follow-Up, Mean(SD) or No(%)	Change from Baseline, Mean (SD), p-value	Comments
Formoterol vs Salmeterol								
Adverse Events: Rate								
Adult Asthma	Nightingale, 2002	Total adverse events (number) at	Formoterol 12ug	42	NR	17 (48.6%)	NR	1 pt w/ serious AE, a transient ischemic attack while taking formoterol
			Salmeterol 50ug	42	NR	13 (39.4%)	NR	
	Vervloet, 1998; Rutten-van Molken, 1998	Overall adverse events (number) at up to 6 mos.	Formoterol 12ug	482	NR	190 (79%)	NR	
			Salmeterol 50ug	482	NR	193 (80%)	NR	
Pediatric Asthma	Everden, 2002; Everden, 2004	Adverse events reported (number) at up to 12 wks.	Formoterol 12ug (9ug delivered dose) BID	145	NR	44 (55%)	NR	
			Salmeterol 50ug BID	145	NR	45 (59%)	NR	
Cardiovascular: Heart Rate								
Adult Asthma	Grove, 1996	Heart rate (bpm) at 1 hr	Formoterol 12ug	10	76 (6.32)	72 (6.32)	NR	
			Salmeterol 25ug	10	71 (6.32)	70 (6.32)	NR	
Adult COPD	Cazzola, 1998a	Heart rate, after cumulative doses of albuterol (bpm) at 2 hrs	Formoterol 24ug	16	80.0 (NR)	81.3 (NR)	1.3 (NR), NR	
			Salmeterol 50ug	16	77.9 (NR)	82.3 (NR)	4.4 (NR), NR	
Cardiovascular: Palpitations								
Adult Asthma	Vervloet, 1998; Rutten-van Molken, 1998	Palpitations (number) at up to 6	Formoterol 12ug	482	NR	4 (1.7%)	NR	
			Salmeterol 50ug	482	NR	0 (0%)	NR	
Adult COPD	Celik, 1999	Palpitations (number) at up to 12	Formoterol 12ug	22	NR	1 (5%)	NR	For pharmacological predictable AEs NSD between groups.
			Salmeterol 50ug	22	NR	0 (0%)	NR	
Pediatric Asthma	Pohunek, 2004		Formoterol 18ug	68	NR	0 (0%)	NR	Reported AEs mild to moderate. Most common being respiratory disorders (rhinitis & respiratory infection). NSD.
			Formoterol 36ug	68	NR	0 (0%)	NR	
			Formoterol 4.5ug	68	NR	0 (0%)	NR	
			Formoterol 9ug	68	NR	0 (0%)	NR	
			Salmeterol 50ug	68	NR	0 (0%)	NR	
Cardiovascular: Tachycardia								
Adult Asthma	Palmqvist, 1997	Tachycardia, palpitation and tremor (number) at NR	Formoterol 12ug	28	NR	1 (4%)	NR	Headache in 6 to 7 pts after treatment.
			Formoterol 24ug	28	NR	5 (18%)	NR	

Population	Author, Year	Outcome (unit) at time point	Intervention	n	Baseline, Mean(SD) or No(%)	Follow-Up, Mean(SD) or No(%)	Change from Baseline, Mean (SD), p-value	Comments
Formoterol vs Salmeterol								
Cardiovascular: Tachycardia								
Adult Asthma	Palmqvist, 1997	Tachycardia, palpitation and tremor (number) at NR	Formoterol 6ug	28	NR	1 (4%)	NR	
			Salmeterol 50ug	28	NR	0 (0%)	NR	
Cardiovascular: Ventricular Arrhythmias								
Adult COPD	Cazzola, 1998b	Ventricular PBs, isolated, no. of patients (number) at NR	Formoterol 12ug	12	NR	6 (58%)	NR	NSD in increase in HR between Form 12ug & sal 50ug, both >placebo, p<0.05
			Formoterol 24ug	12	NR	7 (25%)	NR	
		Ventricular PBs, mean (beats/24 hrs) at over 24 hrs	Salmeterol 50ug QD	12	NR	5 (42%)	5 (NR), NR	
			Formoterol 12ug	12	NR	2.6 (2.9)	NR	
		Ventricular PBs, multiform, no. of patients (number) at Holter monitoring for 24 hours during treatment	Formoterol 24ug	12	NR	3.2 (4.7)	NR	
			Salmeterol 50ug QD	12	NR	2.2 (3.5)	NR	
		Ventricular PBs, no. of patients after treatment (number) at NR	Formoterol 12ug	12	NR	2 (17%)	NR	
			Formoterol 24ug	12	NR	3 (25%)	NR	
		Ventricular PBs, no. of patients after treatment (number) at NR	Salmeterol 50ug QD	12	NR	0 (0%)	NR	
			Formoterol 12ug	12	NR	12 (100%)	NR	
		Ventricular PBs, paired, no. of patients (number) at NR	Formoterol 24ug	12	NR	12 (100%)	NR	
			Salmeterol 50ug QD	12	NR	11 (92%)	NR	
		Ventricular PBs, several, no. of pts in any hour (number) at NR	Formoterol 12ug	12	NR	0 (0%)	NR	
			Formoterol 24ug	12	NR	1 (8%)	NR	
		Ventricular PBs, several, no. of pts in any hour (number) at NR	Salmeterol 50ug QD	12	NR	0 (0%)	NR	
			Formoterol 12ug	12	NR	4 (33%)	NR	
		Ventricular PBs, several, no. of pts in any hour (number) at NR	Formoterol 24ug	12	NR	4 (33%)	NR	
			Salmeterol 50ug QD	12	NR	3 (25%)	NR	

Population	Author, Year	Outcome (unit) at time point	Intervention	n	Baseline, Mean(SD) or No(%)	Follow-Up, Mean(SD) or No(%)	Change from Baseline, Mean (SD), p-value	Comments
Formoterol vs Salmeterol								
Metabolic: Potassium								
Adult Asthma	Grove, 1996	K+ (mmol/L) at 1 hr	Formoterol 12ug	10	4.02 (0.19)	3.97 (0.19)	NR	
			Salmeterol 25ug	10	3.86 (0.16)	3.93 (0.19)	NR	
Adult COPD	Cazzola, 1998b	K+, maximum decrease in plasma level (mmol/L) at 9 hours	Formoterol 12ug	12	NR	NR	-0.49 (NR), NR	Reduced K+ at 2h
			Formoterol 24ug	12	NR	NR	-1.12 (NR), NR	Reduced K+ at 9h vs placebo
			Salmeterol 50ug QD	12	NR	NR	-0.45 (NR), NR	Reduced K+ at 6h
Musculoskeletal								
Adult Asthma	Condemi, 2001	Back pain (number) at up to 6	Formoterol 12ug	528	NR	4 (1.5%)	NR	
			Salmeterol 50ug	528	NR	19 (7.1%)	NR	
Neurologic: Headache								
		Headache (number) at up to 6 mos.	Formoterol 12ug	528	NR	18 (6.9%)	NR	
			Salmeterol 50ug	528	NR	13 (4.9%)	NR	
	Vervloet, 1998; Rutten-van Molken, 1998		Formoterol 12ug	482	NR	7 (2.9%)	NR	
			Salmeterol 50ug	482	NR	11 (4.6%)	NR	
Adult COPD	Celik, 1999	Headache (number) at up to 12	Formoterol 12ug	22	NR	0 (0%)	NR	
			Salmeterol 50ug	22	NR	1 (5%)	NR	
Pediatric Asthma	Everden, 2002; Everden, 2004	Headache (number) at up to 12	Formoterol 12ug (9ug delivered dose) BID	145	NR	14 (17.5%)	NR	
			Salmeterol 50ug BID	145	NR	17 (22.4%)	NR	
	Pohunek, 2004	Headache (number) at up to 12	Formoterol 18ug	68	NR	0 (0%)	NR	
			Formoterol 36ug	68	NR	0 (0%)	NR	
			Formoterol 4.5ug	68	NR	0 (0%)	NR	
			Formoterol 9ug	68	NR	0 (0%)	NR	
			Salmeterol 50ug	68	NR	0 (0%)	NR	
Neurologic: Other								
Adult Asthma	Campbell, 1999; Campbell, 2000	Central and peripheral nervous (number) at up to 8 wks.	Formoterol 12ug	460	NR	44 (10%)	NR	
			Salmeterol 50ug Accuhaler	460	NR	19 (9%)	NR	

Population	Author, Year	Outcome (unit) at time point	Intervention	n	Baseline, Mean(SD) or No(%)	Follow-Up, Mean(SD) or No(%)	Change from Baseline, Mean (SD), p-value	Comments
<u>Formoterol vs Salmeterol</u>								
Neurologic: Other								
Adult Asthma	Campbell, 1999; Campbell, 2000	Central and peripheral nervous (number) at up to 8 wks.	Salmeterol 50ug pMDI	460	NR	17 (8%)	NR	
		Pain (number) at up to 8 wks.	Formoterol 12ug	460	NR	71 (17%)	NR	
		Salmeterol 50ug Accuhaler	460	NR	21 (10%)	NR		
		Salmeterol 50ug pMDI	460	NR	28 (13%)	NR		
Neurologic: Tremor								
Adult COPD	Grove, 1996	Tremor (log unit) at 1 hr	Formoterol 12ug	10	2.25 (0.51)	2.27 (0.32)	NR	
			Salmeterol 25ug	10	2.31 (0.47)	2.09 (0.28)	NR	
	Vervloet, 1998; Rutten-van Molken, 1998	Tremor (number) at up to 6 mos.	Formoterol 12ug	482	NR	5 (2%)	NR	
			Salmeterol 50ug	482	NR	2 (0.8%)	NR	
Adult COPD	Celik, 1999	Tremor (number) at up to 12 hrs.	Formoterol 12ug	22	NR	2 (9%)	NR	
			Salmeterol 50ug	22	NR	1 (5%)	NR	
Pediatric Asthma	Pohunek, 2004		Formoterol 18ug	68	NR	0 (0%)	NR	
			Formoterol 36ug	68	NR	1 (1.5%)	NR	
			Formoterol 4.5ug	68	NR	0 (0%)	NR	
			Formoterol 9ug	68	NR	0 (0%)	NR	
			Salmeterol 50ug	68	NR	0 (0%)	NR	
Respiratory: Cough								
Adult Asthma	Condemi, 2001	Cough (number) at up to 6 mos.	Formoterol 12ug	528	NR	11 (4.2%)	NR	
			Salmeterol 50ug	528	NR	15 (5.6%)	NR	
Respiratory: Other								
	Campbell, 1999; Campbell, 2000	Respiratory system disorders, total (number) at up to 8 wks.	Formoterol 12ug	460	NR	167 (40%)	NR	
			Salmeterol 50ug Accuhaler	460	NR	94 (43%)	NR	
			Salmeterol 50ug pMDI	460	NR	89 (43%)	NR	
	Condemi, 2001	Bronchitis (number) at up to 6 mos.	Formoterol 12ug	528	NR	19 (7.3%)	NR	
Salmeterol 50ug			528	NR	23 (8.6%)	NR		

Population	Author, Year	Outcome (unit) at time point	Intervention	n	Baseline, Mean(SD) or No(%)	Follow-Up, Mean(SD) or No(%)	Change from Baseline, Mean (SD), p-value	Comments
<u>Formoterol vs Salmeterol</u>								
<u>Respiratory: Other</u>								
Adult Asthma	Condemi, 2001	Pharyngitis (number) at up to 6	Formoterol 12ug	528	NR	7 (2.7%)	NR	
			Salmeterol 50ug	528	NR	15 (5.6%)	NR	
		Rhinitis (number) at up to 6 mos.	Formoterol 12ug	528	NR	17 (6.5%)	NR	
			Salmeterol 50ug	528	NR	11 (4.1%)	NR	
		Sinusitis (number) at up to 6 mos.	Formoterol 12ug	528	NR	37 (14.1%)	NR	
			Salmeterol 50ug	528	NR	40 (15%)	NR	
Pediatric Asthma	Everden, 2002; Everden, 2004	Upper respiratory tract infection (number) at up to 6 mos.	Formoterol 12ug	528	NR	68 (26%)	NR	
			Salmeterol 50ug	528	NR	51 (19.2%)	NR	
		Drug discontinuation due to asthma deterioration (number) at	Formoterol 12ug (9ug delivered dose) BID	145	NR	5 (6.4%)	NR (NR),	
			Salmeterol 50ug BID	145	NR	4 (3.3%)	NR (NR),	
		Upper respiratory tract infection (number) at up to 12 wks.	Formoterol 12ug (9ug delivered dose) BID	145	NR	7 (8.8%)	NR	
			Salmeterol 50ug BID	145	NR	9(11.8%)	NR	

Population	Author, Year	Outcome (unit) at time point	Intervention	n	Baseline, Mean(SD) or No(%)	Follow-Up, Mean(SD) or No(%)	Change from Baseline, Mean (SD), p-value	Comments
Albuterol vs Levalbuterol								
Adverse Events: Other								
Mixed Asthma	Nelson, 1998; Pleskow, 2004	Serious adverse events (number) at up to 4 wks	Albuterol 1.25mg	362	NR	1 (1.5%)	NR	Medications well tolerate, 22.9% pts reported AEs potentially related to drug. NSD across groups (p=0.18).
			Albuterol 2.5mg	362	NR	1 (1.4%)	NR	
			Levalbuterol 0.63mg	362	NR	3 (4.2%)	NR	
			Levalbuterol 1.25mg	362	NR	1 (1.4%)	NR	
Pediatric Asthma	Qureshi, 2005	Other adverse events (number) at up to 1 hr.	Albuterol	129	NR	1 (2%)	NR	
			Levalbuterol	129	NR	1 (2%)	NR	
Adverse Events: Rate								
Adult Asthma	Gumbhir-Shah, 1999	Total adverse events (number) at 1 day	Albuterol 2.5mg QID	13	NR	12 (92.3%)	NR	Freq. and severity of AEs w/ R or RS-alb were comparable (p-value NR)
			Levalbuterol 1.25mg QID	13	NR	11 (84.6%)	NR	
	Lotvall, 2001	Total adverse events (number) at 1 day	Albuterol 12.5 to 3200 ug	20	NR	30 (NR)	NR	
			Levalbuterol 6.25 to 1600 ug	20	NR	24 (NR)	NR	
		Total B-2-mediated events (number) at 1 day	Albuterol 12.5 to 3200 ug	20	NR	20 (100%)	NR	
			Levalbuterol 6.25 to 1600 ug	20	NR	17 (85%)	NR	
Mixed Asthma	Nelson, 1998; Pleskow, 2004	No. of patients with any adverse events (number) at 4 wks	Albuterol 1.25mg	362	NR	14 (20.6%)	NR	NSD across groups, most common were asthma related, nervousness, tremor, headache, & tachycardia
			Albuterol 2.5mg	362	NR	20 (27.0%)	NR	
			Levalbuterol 0.63mg	362	NR	12 (16.7%)	NR	

Population	Author, Year	Outcome (unit) at time point	Intervention	n	Baseline, Mean(SD) or No(%)	Follow-Up, Mean(SD) or No(%)	Change from Baseline, Mean (SD), p-value	Comments
<u>Albuterol vs Levalbuterol</u>								
Adverse Events: Rate								
Mixed Asthma	Nelson, 1998; Pleskow, 2004	No. of patients with any adverse events (number) at 4 wks	Levalbuterol 1.25mg	362	NR	23 (31.5%)	NR	
Pediatric Asthma	Gawchik, 1999	No. of patients reporting adverse events (number) at up to 48 hrs.	Albuterol 1.25mg	43	NR	NR	NR	Therapy well tolerated, mild to moderate AEs, 22 pts reported 49 AEs, NSD
			Albuterol 2.5mg	43	NR	NR	NR	
			Levalbuterol 0.16mg	43	NR	5 (12%)	NR	
			Levalbuterol 0.31mg	43	NR	1 (2%)	NR	
			Levalbuterol 0.63mg	43	NR	5 (12%)	NR	
			Levalbuterol 1.25mg	43	NR	2 (5%)	NR	
	Milgrom, 2001	Overall (number) at NR	Albuterol 1.25mg	338	NR	NR	NR	AEs included fever, headache, asthma
			Albuterol 2.5mg	338	NR	NR	NR	pharyngitis and rhinitis
			Levalbuterol 0.31mg	338	NR	NR	NR	
			Levalbuterol 0.63mg	338	NR	NR	NR	
	Skoner, 2005	% of pts experiencing any AE (number) at study duration	Albuterol 1.25mg-2.5mg TID	211	NR	NR	NR	All pts had decrease in K+ & glucose 30-60min after last dose on day21
			Levalbuterol 0.31mg TID	211	NR	NR	NR	
			Levalbuterol 0.63mg TID	211	NR	NR	NR	
			Placebo	211	NR	NR	NR	
Cardiovascular: Blood Pressure								
Adult Asthma	Cockcroft, 1997	DBP (mmHg) at 20 min	Albuterol 2.5mg	12	68 (5.89)	67 (10.05)	NR	NSD for any drug
			Levalbuterol 1.25mg	12	70 (9.01)	66 (11.09)	NR	
		DBP (mmHg) at 3 hrs	Albuterol 2.5mg	12	68 (5.89)	67 (10.05)	NR	
			Levalbuterol 1.25mg	12	70 (9.01)	66 (11.09)	NR	
		SBP (mmHg) at 20 min	Albuterol 2.5mg	12	110 (6.93)	115 (7.27)	NR	
			Levalbuterol 1.25mg	12	108 (9.35)	110 (9.35)	NR	
		SBP (mmHg) at 3 hrs	Albuterol 2.5mg	12	110 (6.93)	107 (6.24)	NR	
			Levalbuterol 1.25mg	12	108	109 (3.96)	NR	

Population	Author, Year	Outcome (unit) at time point	Intervention	n	Baseline, Mean(SD) or No(%)	Follow-Up, Mean(SD) or No(%)	Change from Baseline, Mean (SD), p-value	Comments
<u>Albuterol vs Levalbuterol</u>								
Cardiovascular: Heart Rate								
Adult Asthma	Cockcroft, 1997	Heart rate (bpm) at 20 min	Albuterol 2.5mg	12	72.6 (9.7)	84.0 (11.09)	NR	PR increase for racemic salb & R-salb @ 20min (p<0.0001); NSD for other drugs at 20 & 180ming
			Levalbuterol 1.25mg	12	71.3 (9.35)	84.1 (8.66)	NR	
		Heart rate (bpm) at 3 hrs	Albuterol 2.5mg	12	72.6 (9.7)	76.6 (NR)	NR	
			Levalbuterol 1.25mg	12	71.3 (9.35)	75.4 (9.7)	NR	
	Gumbhir-Shah, 1999	Heart rate, AUC 0-10h (number) at 2-10 hrs	Albuterol 10mg	13	NR	12.6 (24.5)	NR	Average change in HR is similar for both
			Levalbuterol 1.25mg QID	13	NR	18.3 (22.6)	NR	
	Lotvall, 2001	Heart rate, change from baseline in highest dosage (bpm) at 1 day	Albuterol 12.5 to 3200 ug	20	NR	NR	14.0 (NR), NR	
			Levalbuterol 6.25 to 1600 ug	20	NR	NR	12.4 (NR), NR	
	Nowak, 2004	Heart rate, maximum change (bpm) at 60 min	Albuterol 2.5mg	91	NR	NR	15 (NR), NR	
			Levalbuterol 1.25mg	91	NR	NR	17 (NR), NR	
Levalbuterol 5.0mg			91	NR	NR	35 (NR), NR		
Adult COPD	Datta, 2003	Heart rate (bpm) at 1 hr	Albuterol	30	NR	NR	2.5 (NR), NR	NSD between griyos
			Levalbuterol	30	NR	NR	3.7 (NR), NR	
		Heart rate (bpm) at 30 min	Albuterol 2.5mg	30	NR	NR	5.5 (NR), NR	
			Levalbuterol 1.25mg	30	NR	NR	5.6 (NR), NR	
		Heart rate (bpm) at 6 hrs	Albuterol	30	NR	NR	1 (NR), NR	
			Levalbuterol	30	NR	NR	2 (NR), NR	
Mixed Asthma	Nelson, 1998; Pleskow, 2004	Heart rate increase (BPM) at Day 28, 15min after dose	Albuterol 2.5mg TID	362	NR	NR	2.3 (NR),	HR: lev 0.63mg & alb 1.25mg had similar increase (3.6-4.9 bpm)
			Levalbuterol 0.63mg TID	362	NR	NR	4.9 (NR),	
Pediatric Asthma	Carl, 2003	Heart rate (bpm) at 20 min - 2 hrs	Albuterol 2.5mg	547	NR	129.7 (25.5)	NR	
			Levalbuterol 1.25mg	547	NR	130.1 (23.3)	NR	
	Gawchik, 1999	Heart rate, mean change (bpm) at 8 hrs	Albuterol 1.25mg	43	NR	NR	10.6 (NR), NR	
			Albuterol 2.5mg	43	NR	NR	10.2 (NR), NR	

Population	Author, Year	Outcome (unit) at time point	Intervention	n	Baseline, Mean(SD) or No(%)	Follow-Up, Mean(SD) or No(%)	Change from Baseline, Mean (SD), p-value	Comments
<u>Albuterol vs Levalbuterol</u>								
Cardiovascular: Heart Rate								
Pediatric Asthma	Gawchik, 1999	Heart rate, mean change (bpm) at 8 hrs	Levalbuterol 0.16mg	43	NR	NR	0.4 (NR), NR	
			Levalbuterol 0.31mg	43	NR	NR	6.0 (NR), NR	
			Levalbuterol 0.63mg	43	NR	NR	10.8 (NR), NR	
			Levalbuterol 1.25mg	43	NR	NR	15.9 (NR), NR	
	Milgrom, 2001	Heart rate, day 1, change (BPM) at 30 min	Albuterol 1.25mg	338	NR	NR	NR	QTc: lev 0.31mg & alb 2.5mg caused a significantly greater prolongation of the QTc on day 0 (p<0.0001) and day 21 (p=0.054)
			Albuterol 2.5mg	338	NR	NR	11.3 (NR), NR	
			Levalbuterol 0.31mg	338	NR	NR	0.7 (NR), NR	
			Levalbuterol 0.63mg	338	NR	NR	NR	
		Heart rate, day 21, change (bpm) at 30 min	Albuterol 1.25mg	338	NR	NR	NR	
			Albuterol 2.5mg	338	NR	NR	6.0 (NR), NR	
			Levalbuterol 0.31mg	338	NR	NR	0.2 (NR), NR	
			Levalbuterol 0.63mg	338	NR	NR	NR	
Qureshi, 2005	Pulse rate, median change (bpm) at 5th nebulization	Albuterol	129	NR	NR	18 (NR), NR		
		Levalbuterol	129	NR	NR	18 (NR), NR		
Cardiovascular: Other								
Adult Asthma	Gumbhir-Shah, 1999	QTc interval, AUC (number) at 0-10 hrs	Albuterol 2.5mg QID	13	NR	21.9 (24.5)	NR	
			Levalbuterol 1.25mg QID	13	NR	23.0 (31.4)	NR	
Cardiovascular: Palpitations								
	Lotvall, 2001	Palpitations (number) at 1 day	Albuterol 12.5 to 3200 ug	20	NR	7 (35%)	NR	
			Levalbuterol 6.25 to 1600 ug	20	NR	8 (40%)	NR	
Cardiovascular: Tachycardia								
Mixed Asthma	Nelson, 1998; Pleskow, 2004	Tachycardia (number) at 4 weeks	Albuterol 1.25mg	362	NR	0 (0%)	NR	
			Albuterol 2.5mg	362	NR	2 (2.7%)	NR	

Population	Author, Year	Outcome (unit) at time point	Intervention	n	Baseline, Mean(SD) or No(%)	Follow-Up, Mean(SD) or No(%)	Change from Baseline, Mean (SD), p-value	Comments
<u>Albuterol vs Levalbuterol</u>								
Cardiovascular: Tachycardia								
Mixed Asthma	Nelson, 1998; Pleskow, 2004	Tachycardia (number) at 4 weeks	Levalbuterol 0.63mg	362	NR	2 (2.8%)	NR	
			Levalbuterol 1.25mg	362	NR	2 (2.7%)	NR	
Cardiovascular: Ventricular Arrhythmias								
Adult Asthma	Lotvall, 2001	Ventricular, tachyarrhythmias (number) at 1 day	Albuterol 12.5 to 3200 ug	20	NR	3 (15%)	NR	
			Levalbuterol 6.25 to 1600 ug	20	NR	2 (10%)	NR	
Pediatric Asthma	Skoner, 2005	Mean change after 30 min (bpm) at day 0	Albuterol 1.25mg-2.5mg TID	211	NR	NR	3.6 (8.9), NR	
			Levalbuterol 0.31mg TID	211	NR	NR	0.4 (14.1), NR	
			Levalbuterol 0.63mg TID	211	NR	NR	3.4 (11.0), NR	
		Mean change after 30 min (bpm) at day 21	Albuterol 1.25mg-2.5mg TID	211	NR	NR	5.5 (11.0), NR	
			Levalbuterol 0.31mg TID	211	NR	NR	2.3 (11.0), NR	
			Levalbuterol 0.63mg TID	211	NR	NR	6.0 (10.7), NR	
Gastrointestinal: Nausea								
	Carl, 2003	Nausea and vomiting (number) at NR	Albuterol 2.5mg	547	NR	1 (0.37%)	NR	
			Levalbuterol 1.25mg	547	NR	1 (0.35%)	NR	
	Qureshi, 2005	Nausea and vomiting (number) at up to 1 hr.	Albuterol	129	NR	11 (17%)	NR	
			Levalbuterol	129	NR	5 (8%)	NR	
Metabolic: Glucose								
Adult Asthma	Gumbhir-Shah, 1999	Serum glucose, AUC at 10h follow-up (number) at 10 hrs	Albuterol 2.5mg QID	13	NR	35.5 (22.0)	NR	
			Levalbuterol 1.25mg QID	13	NR	33.3 (18.1)	NR	
	Nowak, 2004	Glucose, maximum change (mg/dl) at 60 minutes	Albuterol	91	NR	NR	15.9-62.4 (NR), NR	

Population	Author, Year	Outcome (unit) at time point	Intervention	n	Baseline, Mean(SD) or No(%)	Follow-Up, Mean(SD) or No(%)	Change from Baseline, Mean (SD), p-value	Comments
<u>Albuterol vs Levalbuterol</u>								
Metabolic: Glucose								
Adult Asthma	Nowak, 2004	Glucose, maximum change (mg/dl) at 60 minutes	Levalbuterol	91	NR	NR	46.4-57.1 (NR), NR	
Mixed Asthma	Nelson, 1998; Pleskow, 2004	Mean serum glucose (mg/ml) at Day 28	Albuterol 2.5mg TID	362	NR	NR	4.9 (NR), NR	
			Levalbuterol 0.63mg TID	362	NR	NR	2.4 (NR), NR	
Pediatric Asthma	Gawchik, 1999	Glucose (mg/dl) at 60 minutes	Albuterol 1.25mg	43	NR	NR	16.2 (NR), NR	
			Albuterol 2.5mg	43	NR	NR	19.6 (NR), NR	
			Levalbuterol 0.16mg	43	NR	NR	14.8 (NR), NR	
			Levalbuterol 0.31mg	43	NR	NR	-0.5 (NR), NR	
			Levalbuterol 0.63mg	43	NR	NR	21.2 (NR), NR	
			Levalbuterol 1.25mg	43	NR	NR	30.5 (NR), NR	
Metabolic: Potassium								
Adult Asthma	Gumbhir-Shah, 1999	K+, mean AUC at 10h follow-up (number) at 10 hrs	Albuterol 2.5mg QID	13	NR	2.18 (1.2)	NR	
			Levalbuterol 1.25mg QID	13	NR	3.32 (2.74)	NR	
	Lotvall, 2001	K+, change from baseline in highest dosage (mmol/L) at 1 day	Albuterol 12.5 to 3200 ug	20	NR	NR	-0.24 (NR), NR	
			Levalbuterol 6.25 to 1600 ug	20	NR	NR	-0.26 (NR), NR	
		K+, change from baseline in highest dosage (number) at 1 day	Albuterol 12.5 to 3200 ug	20	NR	NR	-0.24 (NR), NR	
			Levalbuterol 6.25 to 1600 ug	20	NR	NR	-0.26 (NR), NR	
	Nowak, 2004	K+, maximum change (mEq/L) at 60 minutes	Albuterol	91	NR	NR	-0.52 to -0.62 (NR), NR	
			Levalbuterol	91	NR	NR	-0.29 to -0.91 (NR), NR	
Mixed Asthma	Nelson, 1998; Pleskow, 2004	Change in mean K+ (meq/ml) at Day 28, 60min after dose	Albuterol 2.5mg TID	362	NR	NR	-0.3 (NR),	
			Levalbuterol 0.63mg TID	362	NR	NR	-0.2 (NR),	

Population	Author, Year	Outcome (unit) at time point	Intervention	n	Baseline, Mean(SD) or No(%)	Follow-Up, Mean(SD) or No(%)	Change from Baseline, Mean (SD), p-value	Comments			
<u>Albuterol vs Levalbuterol</u>											
Metabolic: Potassium											
Pediatric Asthma	Gawchik, 1999	K+ (mEq/L) at 60 minutes	Albuterol 1.25mg	43	NR	NR	-0.4 (NR), NR				
			Albuterol 2.5mg	43	NR	NR	-0.6 (NR), NR				
			Levalbuterol 0.16mg	43	NR	NR	-0.2 (NR), NR				
			Levalbuterol 0.31mg	43	NR	NR	-0.2 (NR), NR				
			Levalbuterol 0.63mg	43	NR	NR	-0.5 (NR), NR				
			Levalbuterol 1.25mg	43	NR	NR	-0.5 (NR), NR				
	Milgrom, 2001	K+, % pts w/level decreased >= 0.8mEq/ml, day 0 (number) at 30 Min	Albuterol 1.25mg	338	NR	NR	7 (NR), NR	Glucose also measured: alb 2.5mg caused significantly larger increases than lev			
			Albuterol 2.5mg	338	NR	NR	25 (NR), NR	0.31mg & lev 0.63mg, p=.043			
			Levalbuterol 0.31mg	338	NR	NR	5 (NR), NR	alb 1.25mg on day 21, p<0.05			
			Levalbuterol 0.63mg	338	NR	NR	6 (NR), NR				
			Qureshi, 2005	K+, drop of <3.0 meq/L (number) at After 5th treatment in emergency department	Albuterol	129	NR	3 (5%)	NR		
					Levalbuterol	129	NR	3 (5%)	NR		
Musculoskeletal											
Mixed Asthma	Nelson, 1998; Pleskow, 2004	Leg cramps (number) at up to 4	Albuterol 1.25mg	362	NR	0 (0%)	NR				
			Albuterol 2.5mg	362	NR	0 (0%)	NR				
			Levalbuterol 0.63mg	362	NR	0 (0%)	NR				
			Levalbuterol 1.25mg	362	NR	2 (2.7%)	NR				
Neurologic: Headache											
Pediatric Asthma	Qureshi, 2005	Headache (number) at up to 4	Albuterol 1.25mg	362	NR	2 (2.9%)	NR				
			Albuterol 2.5mg	362	NR	2 (2.7%)	NR				
			Levalbuterol 0.63mg	362	NR	3 (4.2%)	NR				
			Levalbuterol 1.25mg	362	NR	4 (5.5%)	NR				
			Pediatric Asthma	Qureshi, 2005	Headache (number) at up to 1 hr.	Albuterol	129	NR	4 (6%)	NR	
						Levalbuterol	129	NR	8 (12%)	NR	

Population	Author, Year	Outcome (unit) at time point	Intervention	n	Baseline, Mean(SD) or No(%)	Follow-Up, Mean(SD) or No(%)	Change from Baseline, Mean (SD), p-value	Comments
Albuterol vs Levalbuterol								
Neurologic: Light-headedness								
Mixed Asthma	Nelson, 1998; Pleskow, 2004	Dizziness (number) at up to 4 wks	Albuterol 1.25mg	362	NR	0 (0%)	NR	
			Albuterol 2.5mg	362	NR	0 (0%)	NR	
			Levalbuterol 0.63mg	362	NR	1 (1.4%)	NR	
			Levalbuterol 1.25mg	362	NR	2 (2.7%)	NR	
Pediatric Asthma	Qureshi, 2005	Light-headedness (number) at up to 1 hr.	Albuterol	129	NR	3 (5%)	NR	
			Levalbuterol	129	NR	9 (14%)	NR	
Neurologic: Anxiety								
Adult Asthma	Cockcroft, 1997	Restlessness, number with any reported (number) at 20 min	Albuterol 2.5mg	12	0 (NR%)	11 (92%)	NR	Increased for racemic salb & lev @ 20 min (p<0.01); NSD for other at 180min;
			Levalbuterol 1.25mg	12	0 (NR%)	11 (92%)	NR	
		Restlessness, number with any reported (number) at 3 hrs	Albuterol 2.5mg	12	0 (NR%)	2 (17%)	NR	Most restlessness was severe.
			Levalbuterol 1.25mg	12	0 (NR%)	3 (25%)	NR	
Mixed Asthma	Nelson, 1998; Pleskow, 2004	Anxiety (number) at up to 4 wks	Albuterol 1.25mg	362	NR	0 (0%)	NR	
			Albuterol 2.5mg	362	NR	0 (0%)	NR	
			Levalbuterol 0.63mg	362	NR	0 (0%)	NR	
			Levalbuterol 1.25mg	362	NR	2 (2.7%)	NR	
		Nervousness (number) at up to 4 Wks	Albuterol 1.25mg	362	NR	3 (4.4%)	NR	lev 0.63mg + alb 1.25m.g < lev 1.25mg+ alb 2.5mg , p=0.003; lev 0.63mg vs alb
			Albuterol 2.5mg	362	NR	6 (8.1%)	NR	2.5mg, p=0.098
			Levalbuterol 0.63mg	362	NR	2 (2.8%)	NR	
			Levalbuterol 1.25mg	362	NR	7 (9.6%)	NR	
Pediatric Asthma	Skoner, 2005	Number of patients reporting (number) at study duration	Albuterol 1.25mg-2.5mg TID	211	NR	0 (NR%)	NR (NR), NR	
			Levalbuterol 0.31mg TID	211	NR	1 (NR%)	NR (NR), NR	
			Levalbuterol 0.63mg TID	211	NR	0 (NR%)	NR (NR), NR	

Population	Author, Year	Outcome (unit) at time point	Intervention	n	Baseline, Mean(SD) or No(%)	Follow-Up, Mean(SD) or No(%)	Change from Baseline, Mean (SD), p-value	Comments
<u>Albuterol vs Levalbuterol</u>								
Neurologic: Other								
Pediatric Asthma	Skoner, 2005	Hyperkinesia (number of pts reporting) (number) at study	Albuterol 1.25mg-2.5mg TID	211	NR	1 (NR%)	NR (NR), NR	
			Levalbuterol 0.31mg TID	211	NR	0 (NR%)	NR (NR), NR	
			Levalbuterol 0.63mg TID	211	NR	1 (NR%)	NR (NR), NR	
Neurologic: Tremor								
Adult Asthma	Lotvall, 2001	Tremor (number) at 1 day	Albuterol 12.5 to 3200 ug	20	NR	9 (45%)	NR	
			Levalbuterol 6.25 to 1600 ug	20	NR	7 (35%)	NR	
Adult COPD	Datta, 2003	Tremor, 0=no tremor; 6=severe tremor (score) at 1 hr	Albuterol	30	NR	NR	0.50 (NR), NR	NSD between groups
			Levalbuterol	30	NR	NR	0.30 (NR), NR	
		Tremor, 0=no tremor; 6=severe tremor (score) at 2 hrs	Albuterol 2.5mg	30	NR	NR	0.46 (NR), NR	
			Levalbuterol 1.25mg	30	NR	NR	0.26 (NR), NR	
		Tremor, 0=no tremor; 6=severe tremor (score) at 30 min	Albuterol	30	NR	NR	0.43 (NR), NR	
			Levalbuterol	30	NR	NR	0.30 (NR), NR	
Mixed Asthma	Nelson, 1998; Pleskow, 2004	Tremor (number) at up to 4 wks	Albuterol 1.25mg	362	NR	0 (0%)	NR	
			Albuterol 2.5mg	362	NR	2 (2.7%)	NR	
			Levalbuterol 0.63mg	362	NR	0 (0%)	NR	
			Levalbuterol 1.25mg	362	NR	5 (6.8%)	NR	
Pediatric Asthma	Qureshi, 2005	Tremor (number) at up to 1 hr.	Albuterol	129	NR	21 (33%)	NR	
			Levalbuterol	129	NR	24 (37%)	NR	
Respiratory								
	Skoner, 2005	Asthma exacerbation (number of pts reporting) (number) at study	Albuterol 1.25mg-2.5mg TID	211	NR	2 (NR%)	NR (NR), NR	
			Levalbuterol 0.31mg TID	211	NR	1 (NR%)	NR (NR), NR	

Population	Author, Year	Outcome (unit) at time point	Intervention	n	Baseline, Mean(SD) or No(%)	Follow-Up, Mean(SD) or No(%)	Change from Baseline, Mean (SD), p-value	Comments
<u>Albuterol vs Levalbuterol</u>								
Respiratory								
Pediatric Asthma	Skoner, 2005	Asthma exacerbation (number of pts reporting) (number) at study	Levalbuterol 0.63mg TID	211	NR	1 (NR%)	NR (NR), NR	
		Serious asthma AE (number of patients reporting) (number) at study duration	Albuterol 1.25mg-2.5mg TID	211	NR	1 (NR%)	NR (NR), NR	
			Levalbuterol 0.31mg TID	211	NR	0 (NR%)	NR (NR), NR	
			Levalbuterol 0.63mg TID	211	NR	0 (NR%)	NR (NR), NR	

Population	Author, Year	Outcome (unit) at time point	Intervention	n	Baseline, Mean(SD) or No(%)	Follow-Up, Mean(SD) or No(%)	Change from Baseline, Mean (SD), p-value	Comments
<u>Albuterol vs Metaproterenol</u>								
Adverse Events: Other								
Adult COPD	Berezuk, 1983	Minor, see comments (number) at 6 hrs		11	NR	NR	NR	
Cardiovascular: Blood Pressure								
Pediatric Asthma	Milner, 1971	DBP, AUC (mm/min) at 150 min	Albuterol	12	NR	214 (NR)	NR	
			Metaproterenol	12	NR	94 (NR)	NR	
		DBP, duration (min) at 150 min	Albuterol	12	NR	28 (NR)	NR	
			Metaproterenol	12	NR	22 (NR)	NR	
		DBP, increase from baseline (mmHg) at 150 min	Albuterol	12	60 (NR)	63 (NR)	3 (NR), NR	
			Metaproterenol	12	63 (NR)	66 (NR)	3 (NR), NR	
		DBP, time to peak (min) at 150 min	Albuterol	12	NR	10 (NR)	NR	
			Metaproterenol	12	NR	26 (NR)	NR	
		SBP, AUC (mm/min) at 150 min	Albuterol	12	NR	409 (NR)	NR	
			Metaproterenol	12	NR	555 (NR)	NR	
		SBP, increase from baseline (mmHg) at 150 min	Albuterol	12	97 (NR)	106 (NR)	9 (NR), NR	
			Metaproterenol	12	98 (NR)	111 (NR)	13 (NR), NR	
		SBP, time to peak (min) at 150 min	Albuterol	12	NR	29 (NR)	NR	
			Metaproterenol	12	NR	10 (NR)	NR	
Cardiovascular: Heart Rate								
Adult Asthma	Choo-Kang, 1969	Heart rate, mean % change (%) at 1 min	Albuterol 200ug	24	NR	NR	3.5 (NR), NR	

Population	Author, Year	Outcome (unit) at time point	Intervention	n	Baseline, Mean(SD) or No(%)	Follow-Up, Mean(SD) or No(%)	Change from Baseline, Mean (SD), p-value	Comments
<u>Albuterol vs Metaproterenol</u>								
Cardiovascular: Heart Rate								
Adult Asthma	Choo-Kang, 1969	Heart rate, mean % change (%) at 1 min	Metaproterenol 1500ug	24	NR	NR	1.6 (NR), NR	
		Heart rate, mean % change (%) at 20 min	Albuterol 200ug	24	NR	NR	0.5 (NR), NR	
Pediatric Asthma	Milner, 1971	Heart rate, mean % change (%) at 6 min	Metaproterenol 1500ug	24	NR	NR	1.1 (NR), NR	
			Albuterol 200ug	24	NR	NR	4.1 (NR), NR	
		Pulse rate, AUC (bpm) at 20 min	Metaproterenol 1500ug	24	NR	NR	-0.6 (NR), NR	
			Albuterol	12	NR	908 (NR)	NR	
		Pulse rate, increase from baseline (bpm) at 20 min	Metaproterenol	12	NR	1427 (NR)	NR	
			Albuterol	12	101 (NR)	118 (NR)	17 (NR), NR	
		Pulse rate, mean duration of increase (min) at 20 min	Metaproterenol	12	107 (NR)	135 (NR)	28 (NR), NR	
			Albuterol	12	NR	45 (NR)	NR	
Pulse rate, time to peak (min) at 20 min	Metaproterenol	12	NR	42 (NR)	NR			
	Albuterol	12	NR	20 (NR)	NR			
Neurologic: Light-headedness								
		Dizziness (number) at NR		12	NR	1 (8.3%)	NR	
<u>Albuterol vs Pirbuterol</u>								
Cardiovascular: Other								
	Volkl, 1991	Cardiac side effect (number) at end of study	Albuterol 0.1mg	17	0 (NR%)	0 (NR%)	NR	
			Pirbuterol 0.2mg	17	0 (NR%)	0 (NR%)	NR	

Population	Author, Year	Outcome (unit) at time point	Intervention	n	Baseline, Mean(SD) or No(%)	Follow-Up, Mean(SD) or No(%)	Change from Baseline, Mean (SD), p-value	Comments	
<u>Metaproterenol vs Pirbuterol</u>									
Adverse Events: Rate									
Adult COPD	Chodosh, 1989	Diverse, non-serious adverse events (number) at NR	Metaproterenol	26	NR	4 (15.4%)	NR	4 pts: chest pain/tightness/pressure, headache	
			Pirbuterol	26	NR	3 (12%)	NR	3 pts: dizziness, blurred vision, rash, itching	
Cardiovascular: Tachycardia									
Adult Asthma	Tinkelman, 1990	Tachycardia (number) at up to 12 wks.	Metaproterenol	133	NR	2 (3.0%)	NR	P< 0.05 for all AEs; 42% of pirb 31% of meta reported AEs.	
			Pirbuterol	133	NR	2 (3.0%)	NR		
Gastrointestinal: Diarrhea									
		Diarrhea (number) at up to 12 wks.	Metaproterenol	133	NR	1 (1.5%)	NR	AEs include: personality change hyperkinesia, chest pain/tightness, abdom pain/cramps, glossitis, stomatitis, bruising, weakness, paresthesia, rash, fatigue,, flatulence, palpitations, appetite increase, malaise, hoarseness.	
			Pirbuterol	133	NR	2 (3.0%)	NR		
Gastrointestinal: Nausea									
		Nausea (number) at up to 12 wks.	Metaproterenol	133	NR	1 (1.5%)	NR		
			Pirbuterol	133	NR	4 (6.1%)	NR		
Gastrointestinal: Other									
		Dry mouth (number) at up to 12	Metaproterenol	133	NR	2 (3.0%)	NR		
			Pirbuterol	133	NR	2 (3.0%)	NR		
Neurologic: Headache									
		Headache (number) at up to 12	Metaproterenol	133	NR	3 (4.5%)	NR		
			Pirbuterol	133	NR	3 (4.5%)	NR		
Neurologic: Light-headedness									
		Dizziness (number) at up to 12	Metaproterenol	133	NR	0 (0%)	NR		
			Pirbuterol	133	NR	2 (3.0%)	NR		
Neurologic: Anxiety									
		Nervousness (number) at up to 12 wks.	Metaproterenol	133	NR	7 (10.4%)	NR		
			Pirbuterol	133	NR	14 (21.2%)	NR		
Neurologic: Other									
		Drowsiness (number) at up to 12 wks.	Metaproterenol	133	NR	2 (3.0)	NR		
			Pirbuterol	133	NR	1 (1.5)	NR		
Neurologic: Tremor									
		Tremor (number) at up to 12 wks.	Metaproterenol	133	NR	2 (3.0%)	NR		
			Pirbuterol	133	NR	3 (4.5%)	NR		

Population	Author, Year	Outcome (unit) at time point	Intervention	n	Baseline, Mean(SD) or No(%)	Follow-Up, Mean(SD) or No(%)	Change from Baseline, Mean (SD), p-value	Comments
<u>Albuterol vs Fenoterol</u>								
Adverse Events: Rate								
Adult COPD	Tandon, 1980	Side effects (number) at end of	Albuterol 100ug	15	NR	5 (33%)	NR	
			Fenoterol 160ug	15	NR	13 (87%)	NR	
Cardiovascular: Blood Pressure								
Adult Asthma	Hockley, 1983	SBP (mmHg) at up to 8 hrs.	Albuterol 5mg	10	NR	129 (NR)	NR	SBP only "significant" AE
			Fenoterol 5mg	10	NR	122 (NR)	NR	
	Lipworth, 1995	DBP, mean change (mmHg) at NR	Albuterol 200ug	18	NR	NR	0 (NR), NR	Changes measure after 200 & 4000ug cumulative dose, time interval between doses NR
			Albuterol 4,000ug	18	NR	NR	-5 (NR), NR	
			Fenoterol 200ug	18	NR	NR	-1 (NR), NR	
			Fenoterol 4,000ug	18	NR	NR	-7 (NR), NR	
		SBP, mean change from baseline (mmHg) at NR	Albuterol 200ug	18	NR	NR	-3 (NR), NR	
			Albuterol 4,000ug	18	NR	NR	5 (NR), NR	
			Fenoterol 200ug	18	NR	NR	1 (NR), NR	
			Fenoterol 4,000ug	18	NR	NR	7 (NR), NR	
	Newhouse, 1996	DBP (mmHg) at 10-60 mins	Albuterol 100 Microgram	257	78.3 (NR)	NR	4.7 (NR), NR	Reported change in HR & BP pooled for both interventions.
			Fenoterol 200 microgram	257	81.0 (NR)	NR	2.4 (NR), NR	
		SBP (mmHg) at 10-60 mins	Albuterol 100 microgram	257	123.1 (NR)	NR	2.9 (NR), NR	
			Fenoterol 200 microgram	257	128.4 (NR)	NR	5.9 (NR), NR	
	Windom, 1990	SBP, mean change (mmHg) at 1 hr	Albuterol 400ug	12	118.7 (7.27)	NR	2.5 (NR), NR	Figures interpolated from graph in text
			Fenoterol 400ug	12	119.3 (9.01)	NR	-1.5 (NR), NR	
		SBP, mean change (mmHg) at 35 min	Albuterol 400ug	12	118.7 (7.27)	NR	-5.0 (NR), NR	
			Fenoterol 400ug	12	119.3 (9.01)	NR	-1.5 (NR), NR	

Population	Author, Year	Outcome (unit) at time point	Intervention	n	Baseline, Mean(SD) or No(%)	Follow-Up, Mean(SD) or No(%)	Change from Baseline, Mean (SD), p-value	Comments
<u>Albuterol vs Fenoterol</u>								
Cardiovascular: Blood Pressure								
Adult Asthma	Windom, 1990	SBP, mean change (mmHg) at 5 min	Albuterol 400ug	12	118.7 (7.27)	NR	-1.5 (NR), NR	Figures interpolated from graph in text
			Fenoterol 400ug	12	119.3 (9.01)	NR	-2.6 (NR), NR	
Adult Asthma/Bronchitis	Tang, 1984	DBP (mmHg) at 1 hr	Albuterol 100ug	24	79.6 (13.72)	76.4 (9.8)	3.2 (NR), NR	
			Fenoterol 100ug	24	80.6 (10.29)	79.0 (14.21)	1.6 (NR), NR	
		DBP (mmHg) at 15 min	Albuterol 100ug	24	79.6 (13.72)	78.1 (7.84)	-1.5 (NR), NR	
			Fenoterol 100ug	24	80.6 (10.29)	79.0 (10.29)	-1.6 (NR), NR	
		DBP (mmHg) at 2 hrs	Albuterol 100ug	24	79.6 (13.72)	77.3 (6.86)	-2.3 (NR), NR	
			Fenoterol 100ug	24	80.6 (10.29)	78.8 (12.74)	-1.8 (NR), NR	
		DBP (mmHg) at 30 min	Albuterol 100ug	24	79.6 (13.72)	80.1 (8.33)	-0.5 (NR), NR	
			Fenoterol 100ug	24	80.6 (10.29)	76.3 (11.76)	-4.3 (NR), NR	
		SBP (mmHg) at 1 hr	Albuterol 100ug	24	135.3 (24.98)	126.3 (19.6)	-9.0 (NR), NR	
			Fenoterol 100ug	24	129.5 (20.58)	124.0 (21.56)	-5.5 (NR), NR	
		SBP (mmHg) at 15 min	Albuterol 100ug	24	135.3 (24.98)	128.6 (19.6)	-6.7 (NR), NR	
			Fenoterol 100ug	24	129.5 (20.58)	127.3 (20.58)	-2.2 (NR), NR	
		SBP (mmHg) at 2 hrs	Albuterol 100ug	24	135.3 (24.98)	131.5 (23.03)	-3.8 (NR), NR	
			Fenoterol 100ug	24	129.5 (20.58)	128.9 (20.09)	-0.6 (NR), NR	
		SBP (mmHg) at 30 min	Albuterol 100ug	24	135.3 (24.98)	129.5 (19.6)	-5.8 (NR), NR	

Population	Author, Year	Outcome (unit) at time point	Intervention	n	Baseline, Mean(SD) or No(%)	Follow-Up, Mean(SD) or No(%)	Change from Baseline, Mean (SD), p-value	Comments
<u>Albuterol vs Fenoterol</u>								
Cardiovascular: Blood Pressure								
Adult Asthma/Bronchitis	Tang, 1984	SBP (mmHg) at 30 min	Fenoterol 100ug	24	129.5 (20.58)	124.9 (21.07)	-4.6 (NR), NR	
Cardiovascular: Heart Rate								
Adult Asthma	Huhti, 1978	Heart rate, mean increase (bpm) at 1 hr	Albuterol 0.1mg	12	93 (13.86)	87 (6.93)	-6 (NR), ≤ 0.001	AEs reported after 2 doses
			Fenoterol 0.2mg	12	90 (10.39)	95 (6.93)	5 (NR), ≤ 0.001	
		Heart rate, mean increase (bpm) at 15 min	Albuterol 0.1mg	12	93 (13.86)	90 (10.39)	-3 (NR), ≤ 0.05	
			Fenoterol 0.2mg	12	90 (10.39)	93 (6.93)	3 (NR), NR	
		Heart rate, mean increase (bpm) at 2 hrs	Albuterol 0.1mg	12	93 (13.86)	85 (10.39)	-8 (NR), ≤ 0.001	
			Fenoterol 0.2mg	12	90 (10.39)	93 (10.39)	3 (NR), ≤ 0.001	
		Heart rate, mean increase (bpm) at 4 hrs	Albuterol 0.1mg	12	93 (13.86)	90 (6.93)	-3 (NR), NR	
			Fenoterol 0.2mg	12	90 (10.39)	89 (10.39)	-1 (NR), NR	
	Lipworth, 1995	Heart rate, mean change (bpm) at NR	Albuterol 200ug	18	NR	NR	0 (NR), NR	
			Albuterol 4,000ug	18	NR	NR	19 (NR), NR	
			Fenoterol 200ug	18	NR	NR	-2 (NR), NR	
			Fenoterol 4,000ug	18	NR	NR	29 (NR), NR	
	Newhouse, 1994	Heart rate (bpm) at 250ug cumulative dose		12	NR	NR	NR	Reported change in HR & BP pooled in both interventions.
		Heart rate (bpm) at 54 min	Albuterol 2500ug	12	NR	NR	-6 (NR), NR	
			Fenoterol 2500ug	12	NR	NR	NR	
	Newhouse, 1996	Heart rate (bpm) at 10-60 mins	Albuterol 100 microgram	257	96.5 (NR)	NR	3.3 (NR), NR	
			Fenoterol 200 microgram	257	96.7 (NR)	NR	2.9 (NR), NR	
	Windom, 1990	Heart rate, mean change (bpm) at 1 hr	Albuterol 400ug	12	61.8 (9.01)	NR	4.0 (NR), NR	Figures interpolated from graph in text.
			Fenoterol 400ug	12	68.2 (9.7)	NR	6.0 (NR), NR	
		Heart rate, mean change (bpm) at 35 min	Albuterol 400ug	12	61.8 (9.01)	NR	2.0 (NR), NR	

Population	Author, Year	Outcome (unit) at time point	Intervention	n	Baseline, Mean(SD) or No(%)	Follow-Up, Mean(SD) or No(%)	Change from Baseline, Mean (SD), p-value	Comments
Albuterol vs Fenoterol								
Cardiovascular: Heart Rate								
Adult Asthma	Windom, 1990	Heart rate, mean change (bpm) at 35 min	Fenoterol 400ug	12	68.2 (9.7)	NR	-1.0 (NR), NR	Figures interpolated from graph in text.
		Heart rate, mean change (bpm) at 5 min	Albuterol 400ug	12	61.8 (9.01)	NR	-0.25 (NR), NR	
Adult Asthma/Bronchitis	Wong, 1990	Heart rate, mean maximum change from baseline (bpm) at 90 min - 3	Fenoterol 400ug	12	68.2 (9.7)	NR	0.0 (NR), NR	
			Albuterol 100ug	10	NR	NR	8 (9), NR	
		Fenoterol 200ug	10	NR	NR	29 (24), NR		
		Terbutaline 250ug	10	NR	NR	8 (14), NR		
	Tang, 1984	Pulse rate (bpm) at 1 hr	Albuterol 100ug	24	92.0 (13.23)	88.3 (12.74)	-3.7 (NR), NR	
			Fenoterol 100ug	24	88.7 (10.78)	84.5 (10.78)	-4.2 (NR), NR	
		Pulse rate (bpm) at 15 min	Albuterol 100ug	24	92.0 (13.23)	89.0 (12.25)	-3.0 (NR), NR	
			Fenoterol 100ug	24	88.7 (10.78)	85.6 (10.78)	-3.1 (NR), NR	
		Pulse rate (bpm) at 2 hrs	Albuterol 100ug	24	92.0 (13.23)	88.3 (13.23)	-3.7 (NR), NR	
			Fenoterol 100ug	24	88.7 (10.78)	83.9 (11.76)	-4.8 (NR), NR	
Adult COPD	Tandon, 1980	Heart rate, change from baseline (bpm) at 1 puff	Albuterol 100ug	15	NR	NR	-2 (NR), <0.02	HR change from baseline only reported when change was statistical significant
			Fenoterol 160ug	15	NR	NR	NR	
		Heart rate, change from baseline (bpm) at 11 puffs	Albuterol 100ug	15	NR	NR	NR	Alb reported at 1 & 3 puffs Fen reported at 7-13 puffs
			Fenoterol 160ug	15	NR	NR	9 (NR), <0.05	
Heart rate, change from baseline (bpm) at 13 puffs	Albuterol 100ug	15	NR	NR	NR			
	Fenoterol 160ug	15	NR	NR	6.25 (NR), <0.05			

Population	Author, Year	Outcome (unit) at time point	Intervention	n	Baseline, Mean(SD) or No(%)	Follow-Up, Mean(SD) or No(%)	Change from Baseline, Mean (SD), p-value	Comments
<u>Albuterol vs Fenoterol</u>								
Cardiovascular: Heart Rate								
Adult COPD	Tandon, 1980	Heart rate, change from baseline (bpm) at 3 puffs	Albuterol 100ug	15	NR	NR	-2.5 (NR), <0.05	
			Fenoterol 160ug	15	NR	NR	NR	
		Heart rate, change from baseline (bpm) at 7 puffs	Albuterol 100ug	15	NR	NR	NR	
			Fenoterol 160ug	15	NR	NR	7.25 (NR), <0.05	
Pediatric Asthma	Blackhall, 1976	Pulse rate (bpm) at 1 hr	Albuterol 100ug	15	NR	NR	NR	
			Fenoterol 160ug	15	NR	NR	8 (NR), <0.05	
			Albuterol 2mg	30	89.5 (NR)	99.9 (NR)	10.4 (NR), NR	
			Fenoterol 2mg	30	92.7 (NR)	101.6 (NR)	8.9 (NR), NR	
	Dawson, 1985	Heart rate, % increase from baseline (%) at end of study	Albuterol 400ug (Inhalator)	40	NR	NR	6 (NR), NR	
			Albuterol 400ug (Rotahaler)	40	NR	NR	-2 (NR), NR	
			Fenoterol 200ug (Rotahaler)	40	NR	NR	2 (NR), NR	
			Fenoterol 400ug (Inhalator)	40	NR	NR	0 (NR), NR	
	Graff-Lonnevig, 1976	Heart rate, mean change (bpm) at 1 hr	Albuterol 200ug	16	NR	NR	-3.8 (NR), NR	Measure of change in HR not clear, assume bpm.
			Fenoterol 100ug	16	NR	NR	-3.9 (NR), NR	
		Heart rate, mean change (bpm) at 2 hrs	Albuterol 200ug	16	NR	NR	-3.7 (NR), NR	
			Fenoterol 100ug	16	NR	NR	-8.2 (NR), NR	
Heart rate, mean change (bpm) at 4 hrs		Albuterol 200ug	16	NR	NR	-2.0 (NR), NR		
		Fenoterol 100ug	16	NR	NR	-5.7 (NR), NR		
Heart rate, mean change (bpm) at 5 min	Albuterol 200ug	16	NR	NR	2.1 (NR), NR			
	Fenoterol 100ug	16	NR	NR	1.7 (NR), NR			
Heart rate, mean change (bpm) at 6 hrs	Albuterol 200ug	16	NR	NR	-8.0 (NR), NR			
	Fenoterol 100ug	16	NR	NR				

Population	Author, Year	Outcome (unit) at time point	Intervention	n	Baseline, Mean(SD) or No(%)	Follow-Up, Mean(SD) or No(%)	Change from Baseline, Mean (SD), p-value	Comments
<u>Albuterol vs Fenoterol</u>								
Cardiovascular: Heart Rate								
Pediatric Asthma	Graff-Lonnevig, 1976	Heart rate, mean change (bpm) at 6 hrs	Fenoterol 100ug	16	NR	NR	-6.8 (NR), NR	
			Albuterol 5mg	21	NR	NR	22%, NR	
	Scalabrin, 1996	Heart rate, % change from baseline (%) at 1 hr	Fenoterol 0.083mg/kg	21	NR	NR	7%, NR	
			Terbutaline 0.1mg/kg	21	NR	NR	0%, NR	
			Albuterol 5mg	21	NR	NR	12%, NR	
			Fenoterol 0.083mg/kg	21	NR	NR	8%, NR	
			Terbutaline 0.1mg/kg	21	NR	NR	0%, NR	
			Albuterol 5mg	21	NR	NR	24%, NR	
	Scalabrin, 1996	Heart rate, % change from baseline (%) at 2 hrs	Fenoterol 0.083mg/kg	21	NR	NR	10%, NR	
			Terbutaline 0.1mg/kg	21	NR	NR	-8%, NR	
Albuterol 5mg			21	NR	NR	24%, NR		
Fenoterol 0.083mg/kg			21	NR	NR	10%, NR		
Scalabrin, 1996	Heart rate, % change from baseline (%) at 5 min	Albuterol 5mg	21	NR	NR	24%, NR		
		Fenoterol 0.083mg/kg	21	NR	NR	10%, NR		
Scalabrin, 1996	Heart rate, % change from baseline (%) at 5 min	Terbutaline 0.1mg/kg	21	NR	NR	-8%, NR		
		Fenoterol 0.083mg/kg	21	NR	NR	10%, NR		
Cardiovascular: Palpitations								
Adult Asthma	Hockley, 1983	Palpitations (number) at up to 8	Albuterol 5mg	10	NR	0 (0%)	NR	
			Fenoterol 5mg	10	NR	1 (10%)	NR	
	Wong, 1990	Palpitations (number) at 3 hrs	Albuterol 100ug	10	NR	1 (10%)	NR	
			Fenoterol 200ug	10	NR	3 (30%)	NR	
			Terbutaline 250ug	10	NR	3 (30%)	NR	
			Fenoterol 200ug	10	NR	3 (30%)	NR	
Cardiovascular: Ventricular Arrhythmias								
Adult COPD	Tandon, 1980	Ventricular, dysrhythmia (number) at end of study	Albuterol 100ug	15	NR	0 (0%)	NR	
			Fenoterol 160ug	15	NR	4 (27%)	NR	
Metabolic: Potassium								
Adult Asthma	Windom, 1990	K+, plasma concentration, mean change (mmol/L) at 1 hr	Albuterol 400ug	12	3.9 (0.35)	NR	-0.1 (NR), NR	Figures interpolated from graph in text.
			Fenoterol 400ug	12	3.9 (0.35)	NR	-0.5 (NR), NR	
		K+, plasma concentration, mean change (mmol/L) at 35 min	Albuterol 400ug	12	3.9 (0.35)	NR	0.0 (NR), NR	
			Fenoterol 400ug	12	3.9 (0.35)	NR	-0.1 (NR), NR	

Population	Author, Year	Outcome (unit) at time point	Intervention	n	Baseline, Mean(SD) or No(%)	Follow-Up, Mean(SD) or No(%)	Change from Baseline, Mean (SD), p-value	Comments
<u>Albuterol vs Fenoterol</u>								
<u>Metabolic: Potassium</u>								
Adult Asthma	Windom, 1990	K+, plasma concentration, mean change (mmol/L) at 5 min	Albuterol 400ug	12	3.9 (0.35)	NR	-0.1 (NR), NR	Figures interpolated from graph in text.
			Fenoterol 400ug	12	3.9 (0.35)	NR	-0.1 (NR), NR	
	Wong, 1990	K+, concentration change from baseline (Mmol/L) at 2 puffs	Albuterol 100ug	10	NR	NR	0.10 (NR), NR	
			Fenoterol 200ug	10	NR	NR	0.06 (NR), NR	
			Terbutaline 250ug	10	NR	NR	0.03 (NR), NR	
		K+, concentration change from baseline (Mmol/L) at 26 puffs	Albuterol 100ug	10	NR	NR	-0.42 (NR), NR	
			Fenoterol 200ug	10	NR	NR	-0.73 (NR), NR	
			Terbutaline 250ug	10	NR	NR	-0.45 (NR), NR	
	K+, concentration change from baseline (Mmol/L) at 8 puffs	Albuterol 100ug	10	NR	NR	-0.01 (NR), NR		
		Fenoterol 200ug	10	NR	NR	-0.42 (NR), NR		
Terbutaline 250ug		10	NR	NR	-0.20 (NR), NR			
Adult COPD	Yang, 1996	K+, plasma (mEq) at after exercise	Albuterol 2mg	13	3.44 (0.5)	3.55 (0.43)	NR	
			Fenoterol 2mg	13	3.44 (0.32)	3.24 (0.29)	NR	
<u>Mortality</u>								
Mixed Asthma	Spitzer, 1992	Death only, adjusted odds ratio (number) at study exit	Albuterol	12,301	NR	0.9 (NR)	NR	Combined baseline characteristics for both: death and/or near fatal event: 129 cases (54% M), 655 controls (56% M). Death only: 44 cases (64% M), 233 controls (56%M)
			Fenoterol	12,301	NR	5.3 (NR)	NR	
		Death only, crude odds ratio (number) at study exit	Albuterol	12,301	NR	0.9 (NR)	NR	
			Fenoterol	12,301	NR	5.3 (NR)	NR	
		Death, odds ratio, high usage* (number) at study exit	Albuterol	12,301	NR	29.4 (NR)	NR	
			Fenoterol	12,301	NR	90.0 (NR)	NR	
Death, odds ratio, low usage* (number) at study exit	Albuterol	12,301	NR	3.4 (NR)	NR			

Population	Author, Year	Outcome (unit) at time point	Intervention	n	Baseline, Mean(SD) or No(%)	Follow-Up, Mean(SD) or No(%)	Change from Baseline, Mean (SD), p-value	Comments	
<u>Albuterol vs Fenoterol</u>									
Mortality									
Mixed Asthma	Spitzer, 1992	Death, odds ratio, low usage* (number) at study exit	Fenoterol	12,301	NR	3.1 (NR)	NR		
		Death, odds ratio, medium usage* (number) at study exit	Albuterol	12,301	NR	10.0 (NR)	NR		
			Fenoterol	12,301	NR	9.0 (NR)	NR		
		Near-fatal event/ death, adjusted odds ratio (number) at study exit	Albuterol	12,301	NR	1.5 (NR)	NR		
			Fenoterol	12,301	NR	3.7 (NR)	NR		
		Near-fatal event/death, crude odds ratio (number) at study exit	Albuterol	12,301	NR	1.5 (NR)	NR		
			Fenoterol	12,301	NR	3.7 (NR)	NR		
		Near-fatal event/death, odds ratio, high usage* (number) at study exit	Albuterol	12,301	NR	24.0 (NR)	NR		
			Fenoterol	12,301	NR	22.7 (NR)	NR		
		Near-fatal event/death, odds ratio, low usage* (number) at study exit	Albuterol	12,301	NR	4.4 (NR)	NR		
			Fenoterol	12,301	NR	3.2 (NR)	NR		
		Near-fatal event/death, odds ratio, medium usage* (number) at study exit	Albuterol	12,301	NR	8.0 (NR)	NR		
		Fenoterol	12,301	NR	7.8 (NR)	NR			
	Suissa, 1994	Death, asthma, beta agonist use vs non-use (number) at 12 mos	Albuterol	12,301	NR	NR	NR	NR	Most frequent use of drugs associated w/higher death rates.
			Fenoterol	12,301	NR	NR	NR	NR	After adjusting for dose equivalence quad coeff for the square of the dose:
		Death, asthma-related (number) at 12 mos	Albuterol	12,301	NR	9.8 (NR%)	NR	NR	albuterol 3.1 (CI: 1.1-1.5) vs fenoterol 5.9 (CI: 2.9-8.9), p=0.40
			Fenoterol	12,301	NR	61.5 (NR%)	NR	NR	
		Death, non-asthma related (number) at 12 mos	Albuterol	12,301	NR	28.7 (NR%)	NR	NR	

Population	Author, Year	Outcome (unit) at time point	Intervention	n	Baseline, Mean(SD) or No(%)	Follow-Up, Mean(SD) or No(%)	Change from Baseline, Mean (SD), p-value	Comments
<u>Albuterol vs Fenoterol</u>								
Mortality								
Mixed Asthma	Suissa, 1994	Death, non-asthma related (number) at 12 mos	Fenoterol	12,301	NR	21.4 (NR%)	NR	
Neurologic: Headache								
Adult Asthma	Wong, 1990	Headache (number) at following max dose	Albuterol 100ug	10	NR	3 (30%)	NR	
			Fenoterol 200ug	10	NR	5 (50%)	NR	
			Terbutaline 250ug	10	NR	2 (20%)	NR	
Neurologic: Tremor								
	Hockley, 1983	Tremor (number) at up to 8 hrs.	Albuterol 5mg	10	NR	1 (10%)	NR	
			Fenoterol 5mg	10	NR	2 (20%)	NR	
	Newhouse, 1996	Tremor (number) at duration of	Albuterol 100 Microgram	257	10 (NR%)	25 (NR%)	NR	Other AEs: headache & dizziness, rate was alb: 43%, feno 56%, p=0.029
			Fenoterol 200 microgram	257	20 (NR%)	51 (NR%)	NR	
	Wong, 1990	Tremor (number) at following max dose	Albuterol 100ug	10	NR	4 (40%)	NR	
			Fenoterol 200ug	10	NR	6 (60%)	NR	
Adult Asthma/Bronchitis	Tang, 1984	Tremor (number) at NA	Albuterol 100ug	24	2 (8.3%)	5 (20.8%)	3 (NR), NR	
			Fenoterol 100ug	24	3 (12.5%)	7 (29.2%)	4 (NR), NR	
Pediatric Asthma	Scalabrin, 1996	Tremor, % change from baseline (%) at 1 hr	Albuterol 5mg	21	NR	NR	93 (NR), NR	
			Fenoterol 0.083mg/kg	21	NR	NR	86 (NR), NR	
			Terbutaline 0.1mg/kg	21	NR	NR	104 (NR), NR	
		Tremor, % change from baseline (%) at 2 hrs	Albuterol 5mg	21	NR	NR	106 (NR), NR	
			Fenoterol 0.083mg/kg	21	NR	NR	34 (NR), NR	
			Terbutaline 0.1mg/kg	21	NR	NR	90 (NR), NR	
		Tremor, % change from baseline (%) at 30 min	Albuterol 5mg	21	NR	NR	151 (NR), NR	
			Fenoterol 0.083mg/kg	21	NR	NR	93 (NR), NR	

Population	Author, Year	Outcome (unit) at time point	Intervention	n	Baseline, Mean(SD) or No(%)	Follow-Up, Mean(SD) or No(%)	Change from Baseline, Mean (SD), p-value	Comments
<u>Albuterol vs Fenoterol</u>								
Neurologic: Tremor								
Pediatric Asthma	Scalabrin, 1996	Tremor, % change from baseline (%) at 30 min	Terbutaline 0.1mg/kg	21	NR	NR	62 (NR), NR	
		Tremor, % change from baseline (%) at 5 min	Albuterol 5mg	21	NR	NR	175 (NR), NR	
			Fenoterol 0.083mg/kg	21	NR	NR	167 (NR), NR	
			Terbutaline 0.1mg/kg	21	NR	NR	119 (NR), NR	

Population	Author, Year	Outcome (unit) at time point	Intervention	n	Baseline, Mean(SD) or No(%)	Follow-Up, Mean(SD) or No(%)	Change from Baseline, Mean (SD), p-value	Comments
Albuterol vs Terbutaline								
Adverse Events: Other								
	Oldaeus, 1995	Adverse events (score 0-3), day (score) at up to 2 wks.	Albuterol 0.4mg TID	20	NR	0.15 (0.49)	NR	
			Terbutaline 0.5mg TID	20	NR	0.09 (0.28)	NR	
		Adverse events (score 0-3), night (score) at up to 2 wks.	Albuterol 0.4mg TID	20	NR	0.05 (0.22)	NR	
			Terbutaline 0.5mg TID	20	NR	0.05 (0.22)	NR	
Adverse Events: Rate								
Adult Asthma	Malinen, 2000	No. of patients reported adverse events (number) at NR	Albuterol 100ug	29	NR	4 (14%)	NR	Headache: 1 alb pt & 1 terb pt Cough: 2 terb, Bronchospasm: 1 terb
			Terbutaline 250ug	29	NR	5 (17%)	NR	
Mixed Asthma	Munzenberger, 1989	Total adverse events (number) at up to 7 days	Albuterol 400ug	20	NR	16 (80%)	NR	NSD between drugs. 10 pts reported reported AEs, 1 accounted for 15 AEs
			Terbutaline 360ug	20	NR	13 (65%)	NR	
Cardiovascular: Blood Pressure								
	Capecchi, 1978	DBP (mmHg) at 1 hr	Albuterol 0.2mg	14	88.60 (20.2)	87.50 (13.47)	NR	No side effects of significance observed.
			Terbutaline 0.5mg	14	87.50 (22.82)	90.70 (17.21)	NR	
		DBP (mmHg) at 15 min	Albuterol 0.2mg	14	88.60 (20.2)	91.80 (20.58)	NR	
			Terbutaline 0.5mg	14	87.50 (22.82)	88.20 (21.33)	NR	
		DBP (mmHg) at 4 hrs	Albuterol 0.2mg	14	88.60 (20.2)	83.20 (20.58)	NR	
			Terbutaline 0.5mg	14	87.50 (22.82)	85.40 (20.95)	NR	
		SBP (mmHg) at 1 hr	Albuterol 0.2mg	14	149.60 (35.55)	147.90 (30.68)	NR	
			Terbutaline 0.5mg	14	148.60 (37.79)	146.40 (26.57)	NR	
		SBP (mmHg) at 15 min	Albuterol 0.2mg	14	149.60 (35.55)	148.20 (35.92)	NR	
			Terbutaline 0.5mg	14	148.60 (37.79)	146.80 (35.92)	NR	
		SBP (mmHg) at 4 hrs	Albuterol 0.2mg	14	149.60 (35.55)	141.10 (35.92)	NR (NR), <0.05	
			Terbutaline 0.5mg	14	148.6(37.8)	148.60 (33.67)	NR	

Population	Author, Year	Outcome (unit) at time point	Intervention	n	Baseline, Mean(SD) or No(%)	Follow-Up, Mean(SD) or No(%)	Change from Baseline, Mean (SD), p-value	Comments
<u>Albuterol vs Terbutaline</u>								
Cardiovascular: Heart Rate								
Adult Asthma	Eryonucu, 2001	Heart rate (bpm) at 15 min	Albuterol 200ug	20	74 (4)	85 (4)	NR (NR), <0.01	
			Terbutaline 500ug	20	74 (3)	85 (4)	NR (NR), <0.01	
		Heart rate (bpm) at 30 min	Albuterol 200ug	20	74 (4)	78 (5)	NR (NR), >0.05	
			Terbutaline 500ug	20	74 (3)	77 (3)	NR (NR), >0.05	
	Heart rate (bpm) at 5 min	Albuterol 200ug	20	74 (4)	81 (3)	NR (NR), <0.05		
		Terbutaline 500ug	20	74 (3)	79 (3)	NR (NR), <0.05		
	Wong, 1990	Heart rate, mean maximum change from baseline (bpm) at 90 min - 3	Albuterol 100ug	10	NR	NR	8 (9), NR	
			Fenoterol 200ug	10	NR	NR	29 (24), NR	
			Terbutaline 250ug	10	NR	NR	8 (14), NR	
	Mixed Asthma	Capecchi, 1978	Pulse rate (bpm) at 1 hr	Albuterol 0.2mg	14	82.80 (12.35)	83.10 (13.84)	NR
Terbutaline 0.5mg				14	86.00 (11.97)	80.40 (10.85)	NR	
Pulse rate (bpm) at 15 min			Albuterol 0.2mg	14	82.80 (12.35)	85.60 (11.97)	NR	
			Terbutaline 0.5mg	14	86.00 (11.97)	87.60 (13.1)	NR	
Pulse rate (bpm) at 4 hrs		Albuterol 0.2mg	14	82.80 (12.35)	84.20 (9.35)	NR		
		Terbutaline 0.5mg	14	86.00 (11.97)	85.30 (11.6)	NR		
Munzenberger, 1989		Heart rate, mean peak increase (bpm) at 5 min	Albuterol 400ug	20	78.8 (12.5)	83.6 (NR)	4.8 (NR), >0.05	No significant change in PR, SBP or DBP.
Pediatric Asthma		Chandra, 2004	Heart rate (bpm) at 30 min	Terbutaline 360ug	20	75.4 (8.6)	78.2 (NR)	2.8 (NR), >0.05
	Albuterol 100ug			60	96 (NR)	102 (NR)	NR	
	Hung, 2001		Terbutaline 250ug	60	90 (NR)	98 (NR)	NR	
			Albuterol 0.125mg/kg	30	131.58 (8.53)	132.75 (9.32)	NR (NR), >0.05	
			Terbutaline 0.125mg/kg	30	123.50 (7.72)	121.50 (8.13)	NR (NR), >0.05	

Population	Author, Year	Outcome (unit) at time point	Intervention	n	Baseline, Mean(SD) or No(%)	Follow-Up, Mean(SD) or No(%)	Change from Baseline, Mean (SD), p-value	Comments	
<u>Albuterol vs Terbutaline</u>									
Cardiovascular: Heart Rate									
Pediatric Asthma	Scalabrin, 1996	Heart rate, % change from baseline (%) at 1 hr	Albuterol 5mg	21	NR	NR	22%, NR		
			Fenoterol 0.083mg/kg	21	NR	NR	7%, NR		
	Heart rate, % change from baseline (%) at 2 hrs	Albuterol 5mg	Terbutaline 0.1mg/kg	21	NR	NR	0%, NR		
			Fenoterol 0.083mg/kg	21	NR	NR	12%, NR		
		Heart rate, % change from baseline (%) at 5 min	Albuterol 5mg	Terbutaline 0.1mg/kg	21	NR	NR	8%, NR	
				Fenoterol 0.083mg/kg	21	NR	NR	0%, NR	
	Terbutaline 0.1mg/kg	Albuterol 5mg	21	NR	NR	24%, NR			
		Fenoterol 0.083mg/kg	21	NR	NR	10%, NR			
Terbutaline 0.1mg/kg	Fenoterol 0.083mg/kg	21	NR	NR	-8%, NR				
	Fenoterol 0.083mg/kg	21	NR	NR					
Cardiovascular: Palpitations									
Adult Asthma	Anani, 1989	Palpitations (number) at 3 wks	Albuterol 400ug QID	30	NR	1 (80%)	NR		
			Terbutaline 500ug QID	30	NR	1 (80%)	NR		
	Wong, 1990	Palpitations (number) at 3 hrs	Albuterol 100ug	10	NR	1 (10%)	NR		
			Fenoterol 200ug	10	NR	3 (30%)	NR		
			Terbutaline 250ug	10	NR	3 (30%)	NR		
			Albuterol 400ug	20	NR	3 (15%)	NR	NSD between drugs	
Mixed Asthma	Munzenberger, 1989	Palpitations (number) at 1 week	Terbutaline 360ug	20	NR	1 (5%)	NR		
			Albuterol 400ug	20	NR	1 (3%)	NR		
Pediatric Asthma	Chandra, 2004	Palpitations (number) at 30 min	Terbutaline 250ug	60	NR	2 (6%)	NR		
			Albuterol 400ug	60	NR	2 (10%)	NR		
Gastrointestinal: Nausea									
Mixed Asthma	Munzenberger, 1989	Nausea (number) at up to 7 days	Albuterol 400ug	20	NR	2 (10%)	NR	NSD between drugs	
			Terbutaline 360ug	20	NR	1 (5%)	NR		
Gastrointestinal: Other									
		Bad taste (number) at up to 7	Albuterol 400ug	20	NR	1 (5%)	NR		
			Terbutaline 360ug	20	NR	2 (10%)	NR		

Population	Author, Year	Outcome (unit) at time point	Intervention	n	Baseline, Mean(SD) or No(%)	Follow-Up, Mean(SD) or No(%)	Change from Baseline, Mean (SD), p-value	Comments
<u>Albuterol vs Terbutaline</u>								
Gastrointestinal: Other								
Mixed Asthma	Munzenberger, 1989	Vomiting (number) at up to 7 days	Albuterol 400ug	20	NR	0 (0%)	NR	NSD between drugs
			Terbutaline 360ug	20	NR	1 (5%)	NR	
Metabolic: Other								
	Capecchi, 1978	pH (number) at 30 min	Albuterol 0.2mg	14	7.45 (0.03)	7.47 (0.04)	NR (NR), <0.05	
			Terbutaline 0.5mg	14	7.43 (0.03)	7.45 (0.03)	NR (NR), <0.01	
Metabolic: Potassium								
Adult Asthma	Wong, 1990	K+, concentration change from baseline (Mmol/L) at 2 puffs	Albuterol 100ug	10	NR	NR	0.10 (NR), NR	
			Fenoterol 200ug	10	NR	NR	0.06 (NR), NR	
			Terbutaline 250ug	10	NR	NR	0.03 (NR), NR	
		K+, concentration change from baseline (Mmol/L) at 26 puffs	Albuterol 100ug	10	NR	NR	-0.42 (NR), NR	
			Fenoterol 200ug	10	NR	NR	-0.73 (NR), NR	
			Terbutaline 250ug	10	NR	NR	-0.45 (NR), NR	
		K+, concentration change from baseline (Mmol/L) at 8 puffs	Albuterol 100ug	10	NR	NR	-0.01 (NR), NR	
			Fenoterol 200ug	10	NR	NR	-0.42 (NR), NR	
			Terbutaline 250ug	10	NR	NR	-0.20 (NR), NR	
Pediatric Asthma	Hung, 2001	K+, serum level (mEq/L) at 30 min	Albuterol 0.125mg/kg	30	3.74 (0.51)	3.12 (0.85)	NR (NR), <0.05	
			Terbutaline 0.125mg/kg	30	3.69 (0.52)	3.22 (0.48)	NR (NR), <0.05	
Musculoskeletal								
	Chandra, 2004	Accessory muscle score: 0 (number) at 30 min	Albuterol 100ug	60	23 (79%)	26 (90%)	NR	
			Terbutaline 250ug	60	28 (90%)	29 (94%)	NR	
		Accessory muscle score: 1 (number) at 30 min	Albuterol 100ug	60	6 (21%)	3 (10%)	NR	
			Terbutaline 250ug	60	3 (10%)	2 (6%)	NR	
Neurologic: Headache								
Adult Asthma	Wong, 1990	Headache (number) at following max dose	Albuterol 100ug	10	NR	3 (30%)	NR	
			Fenoterol 200ug	10	NR	5 (50%)	NR	

Population	Author, Year	Outcome (unit) at time point	Intervention	n	Baseline, Mean(SD) or No(%)	Follow-Up, Mean(SD) or No(%)	Change from Baseline, Mean (SD), p-value	Comments
<u>Albuterol vs Terbutaline</u>								
Neurologic: Headache								
Adult Asthma	Wong, 1990	Headache (number) at following max dose	Terbutaline 250ug	10	NR	2 (20%)	NR	
Mixed Asthma	Munzenberger, 1989	Headache (number) at up to 7 days	Albuterol 400ug	20	NR	4 (20%)	NR	NSD between drugs
			Terbutaline 360ug	20	NR	3 (15%)	NR	
Neurologic: Anxiety								
Adult Asthma	Vilsvik, 1993	Irritation symptoms (number) at up to 2 wks.	Albuterol 0.1mgX2	159	NR	44 (27.6%)	NR	23 pts reported same AEs; 8 alb, 14 in both periods, mild to moderate, tremors & palpitations.
			Terbutaline 0.5mg	159	NR	18 (11.3%)	NR	9.4% diff in favor of albuterol, p<0.05
Mixed Asthma	Munzenberger, 1989	Nervousness (number) at up to 7 days	Albuterol 400ug	20	NR	1 (5%)	NR	NSD between drugs
			Terbutaline 360ug	20	NR	2 (10%)	NR	
Pediatric Asthma	Oldaeus, 1995	Restlessness (number) at up to 2 wks.	Albuterol 0.4mg TID	20	NR	3 (15%)	NR	
			Terbutaline 0.5mg TID	20	NR	3 (15%)	NR	
Neurologic: Other								
Adult Asthma	Vilsvik, 1993	Coordination problems (number) at up to 2 wks.	Albuterol 0.1mgX2	159	NR	12 (7.5%)	NR	
			Terbutaline 0.5mg	159	NR	4 (2.5%)	NR	
Mixed Asthma	Lindsay, 1994	Sleep disturbance, symptom score (number) at 4 wks	Albuterol 0.1mg BID	46	0.4 (0.67)	0.3 (0.67)	NR	No differences detected in occurrence of AEs. Terb, 51% pts; Alb, 54% pts reported AEs (asthma & upper respiratory tract infection)
			Terbutaline 0.5mg BID	46	0.4 (0.67)	0.3 (0.67)	NR	
	Munzenberger, 1989	Insomnia (number) at up to 7 days	Albuterol 400ug	20	NR	0 (0%)	NR	NSD between drugs
			Terbutaline 360ug	20	NR	1 (5%)	NR	
		Vertigo (number) at up to 7 days	Albuterol 400ug	20	NR	2 (10%)	NR	
			Terbutaline 360ug	20	NR	1 (5%)	NR	
Neurologic: Tremor								
Adult Asthma	Anani, 1989	Tremor (number) at 3 wks	Albuterol 400ug QID	30	NR	0 (0%)	NR	
			Terbutaline 500ug QID	30	NR	1 (80%)	NR	
	Wong, 1990	Tremor (number) at following max dose	Albuterol 100ug	10	NR	4 (40%)	NR	

Population	Author, Year	Outcome (unit) at time point	Intervention	n	Baseline, Mean(SD) or No(%)	Follow-Up, Mean(SD) or No(%)	Change from Baseline, Mean (SD), p-value	Comments
<u>Albuterol vs Terbutaline</u>								
Neurologic: Tremor								
Adult Asthma	Wong, 1990	Tremor (number) at following max dose	Fenoterol 200ug	10	NR	6 (60%)	NR	
			Terbutaline 250ug	10	NR	4 (40%)	NR	
Mixed Asthma	Munzenberger, 1989	Tremor (number) at up to 7 days	Albuterol 400ug	20	NR	3 (15%)	NR	NSD between drugs
			Terbutaline 360ug	20	NR	1 (5%)	NR	
Pediatric Asthma	Chandra, 2004	Tremor (number) at 30 min	Albuterol 100ug	60	NR	4 (14%)	NR	
			Terbutaline 250ug	60	NR	3 (10%)	NR	
	Scalabrin, 1996	Tremor, % change from baseline (%) at 1 hr	Albuterol 5mg	21	NR	NR	93 (NR), NR	
			Fenoterol 0.083mg/kg	21	NR	NR	86 (NR), NR	
			Terbutaline 0.1mg/kg	21	NR	NR	104 (NR), NR	
		Tremor, % change from baseline (%) at 2 hrs	Albuterol 5mg	21	NR	NR	106 (NR), NR	
			Fenoterol 0.083mg/kg	21	NR	NR	34 (NR), NR	
			Terbutaline 0.1mg/kg	21	NR	NR	90 (NR), NR	
		Tremor, % change from baseline (%) at 30 min	Albuterol 5mg	21	NR	NR	151 (NR), NR	
			Fenoterol 0.083mg/kg	21	NR	NR	93 (NR), NR	
			Terbutaline 0.1mg/kg	21	NR	NR	62 (NR), NR	
		Tremor, % change from baseline (%) at 5 min	Albuterol 5mg	21	NR	NR	175 (NR), NR	
			Fenoterol 0.083mg/kg	21	NR	NR	167 (NR), NR	
			Terbutaline 0.1mg/kg	21	NR	NR	119 (NR), NR	
Respiratory: Cough								
Mixed Asthma	Lindsay, 1994	Cough, symptom score (number) at 4 wks	Albuterol 0.1mg BID	46	0.4 (0.67)	0.3 (0.67)	NR	
			Terbutaline 0.5mg BID	46	0.3 (0.67)	0.3 (0.67)	NR	

Population	Author, Year	Outcome (unit) at time point	Intervention	n	Baseline, Mean(SD) or No(%)	Follow-Up, Mean(SD) or No(%)	Change from Baseline, Mean (SD), p-value	Comments
<u>Fenoterol vs Metaproterenol</u>								
Cardiovascular: Blood Pressure								
Adult Asthma	Burgess, 1990	DBP, mean change (mmHg) at 1.5 Hrs	Fenoterol	12	NR	NR	-7.7 (8.66), NR	Plasma K+ also measured: fen significant decreased level 65 and 90 min
			Metaproterenol	12	NR	NR	-3.9 (9.01), NR	
		DBP, mean change (mmHg) at 35 min	Fenoterol	12	NR	NR	-4.9 (5.54), NR	
			Metaproterenol	12	NR	NR	-3.6 (5.89), NR	
		DBP, mean change (mmHg) at 5 min	Fenoterol	12	NR	NR	-1.2 (3.12), NR	
			Metaproterenol	12	NR	NR	-0.9 (5.54), NR	
		SBP, mean change (mmHg) at 1.5 hrs	Fenoterol	12	NR	NR	7.8 (6.93), NR	
			Metaproterenol	12	NR	NR	3.9 (9.7), NR	
		SBP, mean change (mmHg) at 35 min	Fenoterol	12	NR	NR	3.3 (10.39), NR	
			Metaproterenol	12	NR	NR	1.1 (8.31), NR	
		SBP, mean change (mmHg) at 5 min	Fenoterol	12	NR	NR	-1.2 (8.66), NR	
			Metaproterenol	12	NR	NR	2.6 (7.97), NR	
<u>Metaproterenol vs Terbutaline</u>								
Cardiovascular: Blood Pressure								
	Roth, 1977	DBP (mmHg) at NR	Metaproterenol 650ug	21	NR	NR	NR	
			Terbutaline 125ug	21	NR	NR	NR	
Cardiovascular: Heart Rate								
	Roth, 1977	Heart rate (NR) at 5 min	Metaproterenol 650ug	21	NR	NR	NR	
			Terbutaline 125ug	21	NR	NR	NR	

Population	Author, Year	Outcome (unit) at time point	Intervention	n	Baseline, Mean(SD) or No(%)	Follow-Up, Mean(SD) or No(%)	Change from Baseline, Mean (SD), p-value	Comments
<u>Fenoterol vs Terbutaline</u>								
<u>Cardiovascular: Heart Rate</u>								
	Carmichael, 1980	Heart rate, mean increase following max dose (bpm) at up to	Fenoterol 2mg	12	NR	NR	4 bpm (NR), NR	
			Terbutaline 10mg	12	NR	NR	9 bpm (NR), NR	
	Gray, 1982	Heart rate, mean maximum increase (bpm) at 1 puff	Fenoterol 100ug	12	85 (NR)	NR	6.3 (NR), 0.001	
			Terbutaline 250ug	12	84 (NR)	NR	2.4 (NR), 0.05	
		Heart rate, mean maximum increase (bpm) at 15 puffs	Fenoterol 100ug	12	85 (NR)	NR	25 (NR), 0.001	
			Terbutaline 250ug	12	84 (NR)	NR	15 (NR), 0.001	
	Wong, 1990	Heart rate, mean maximum change from baseline (bpm) at 90 min - 3	Albuterol 100ug	10	NR	NR	8 (9), NR	
			Fenoterol 200ug	10	NR	NR	29 (24), NR	
			Terbutaline 250ug	10	NR	NR	8 (14), NR	
Pediatric Asthma	Lin, 2002	Heart rate (bpm) at 15 min	Fenoterol 1.25mg	108	108.68 (17.5)	113.09 (14.9)	4.41 (NR), NR	

Population	Author, Year	Outcome (unit) at time point	Intervention	n	Baseline, Mean(SD) or No(%)	Follow-Up, Mean(SD) or No(%)	Change from Baseline, Mean (SD), p-value	Comments
<u>Fenoterol vs Terbutaline</u>								
Cardiovascular: Heart Rate								
Pediatric Asthma	Lin, 2002	Heart rate (bpm) at 15 min	Terbutaline 5.0mg	108	113.18 (18.20)	102.51 (18.20)	7.33 (NR), NR	
		Heart rate, % change from baseline (%) at 1 hr	Albuterol 5mg	21	NR	NR	22%, NR	
	Fenoterol 0.083mg/kg		21	NR	NR	7%, NR		
	Terbutaline 0.1mg/kg		21	NR	NR	0%, NR		
	Heart rate, % change from baseline (%) at 2 hrs		Albuterol 5mg	21	NR	NR	12%, NR	
			Fenoterol 0.083mg/kg	21	NR	NR	8%, NR	
	Terbutaline 0.1mg/kg		21	NR	NR	0%, NR		
	Heart rate, % change from baseline (%) at 5 min		Albuterol 5mg	21	NR	NR	24%, NR	
			Fenoterol 0.083mg/kg	21	NR	NR	10%, NR	
	Terbutaline 0.1mg/kg	21	NR	NR	-8%, NR			
Cardiovascular: Other								
Adult Asthma	Anderson, 1979	Chest pain (number) at duration of study	Fenoterol 0.4mg	17	NR	1 (6%)	NR	
			Terbutaline 0.5mg	17	NR	2 (12%)	NR	
Cardiovascular: Palpitations								
Pediatric Asthma	Gray, 1982	Palpitations (number) at up to 5 hrs	Fenoterol 100ug	12	NR	6 (50%)	NR	
			Terbutaline 250ug	12	NR	1 (8.3%)	NR	
	Wong, 1990	Palpitations (number) at 3 hrs	Albuterol 100ug	10	NR	1 (10%)	NR	
			Fenoterol 200ug	10	NR	3 (30%)	NR	
	Terbutaline 250ug	10	NR	3 (30%)	NR			
		Lin, 2002	Palpitations (number) at 30 mins	Fenoterol 1.25mg	108	NR	4 (7.0%)	NR
Terbutaline 5.0mg	108	NR	3 (5.9%)	NR				
Gastrointestinal: Diarrhea								
Adult Asthma	Anderson, 1979	Fainting and diarrhea (number) at duration of study	Fenoterol 0.4mg	17	NR	0 (0%)	NR	
			Terbutaline 0.5mg	17	NR	1 (6%)	NR	

Population	Author, Year	Outcome (unit) at time point	Intervention	n	Baseline, Mean(SD) or No(%)	Follow-Up, Mean(SD) or No(%)	Change from Baseline, Mean (SD), p-value	Comments
<u>Fenoterol vs Terbutaline</u>								
Metabolic: Potassium								
Adult Asthma	Wong, 1990	K+, concentration change from baseline (Mmol/L) at 2 puffs	Albuterol 100ug	10	NR	NR	0.10 (NR), NR	
			Fenoterol 200ug	10	NR	NR	0.06 (NR), NR	
			Terbutaline 250ug	10	NR	NR	0.03 (NR), NR	
		K+, concentration change from baseline (Mmol/L) at 26 puffs	Albuterol 100ug	10	NR	NR	-0.42 (NR), NR	
			Fenoterol 200ug	10	NR	NR	-0.73 (NR), NR	
			Terbutaline 250ug	10	NR	NR	-0.45 (NR), NR	
		K+, concentration change from baseline (Mmol/L) at 8 puffs	Albuterol 100ug	10	NR	NR	-0.01 (NR), NR	
			Fenoterol 200ug	10	NR	NR	-0.42 (NR), NR	
			Terbutaline 250ug	10	NR	NR	-0.20 (NR), NR	
Neurologic: Headache								
Pediatric Asthma	Lin, 2002	Headache (number) at following max dose	Albuterol 100ug	10	NR	3 (30%)	NR	
			Fenoterol 200ug	10	NR	5 (50%)	NR	
			Terbutaline 250ug	10	NR	2 (20%)	NR	
		Headache (number) at up to 30 mins.	Fenoterol 1.25mg	108	NR	1 (1.8%)	NR	
			Terbutaline 5.0mg	108	NR	2 (3.9%)	NR	
			Fenoterol 0.4mg	17	NR	2 (12%)	NR	
Neurologic: Light-headedness								
Adult Asthma	Anderson, 1979	Light-headedness (number) at duration of study	Terbutaline 0.5mg	17	NR	2 (12%)	NR	
			Terbutaline 10mg	12	NR	1 (8.3%)	NR	
			Terbutaline 5mg	12	NR	1 (8.3%)	NR	
Pediatric Asthma	Lin, 2002	Dizziness (number) at up to 30	Fenoterol 1.25mg	108	NR	6 (10.5%)	NR	
			Terbutaline 5.0mg	108	NR	6 (11.8%)	NR	
Neurologic: Anxiety								
Adult Asthma	Anderson, 1979	Difficulty focusing (number) at duration of study	Fenoterol 0.4mg	17	NR	1 (6%)	NR	

Population	Author, Year	Outcome (unit) at time point	Intervention	n	Baseline, Mean(SD) or No(%)	Follow-Up, Mean(SD) or No(%)	Change from Baseline, Mean (SD), p-value	Comments
<u>Fenoterol vs Terbutaline</u>								
Neurologic: Anxiety								
Adult Asthma	Anderson, 1979	Difficulty focusing (number) at duration of study	Terbutaline 0.5mg	17	NR	0 (0%)	NR	
Neurologic: Other								
Pediatric Asthma	Lin, 2002	Weakness of extremities (number) at up to 30 mins.	Fenoterol 1.25mg	108	NR	1 (1.8%)	NR	
			Terbutaline 5.0mg	108	NR	1 (2.0%)	NR	
Neurologic: Tremor								
Adult Asthma	Anderson, 1979	Tremor (number) at duration of	Fenoterol 0.4mg	17	NR	1 (6%)	NR	
			Terbutaline 0.5mg	17	NR	0 (0%)	NR	
		Tremor, tinnitus (number) at duration of study	Fenoterol 0.4mg	17	NR	0 (0%)	NR	
			Terbutaline 0.5mg	17	NR	1 (6%)	NR	
	Carmichael, 1980	Tremor (number) at duration of	Fenoterol 1mg	12	NR	1 (8.3%)	NR	
			Fenoterol 2mg	12	NR	5 (41.7%)	NR	
			Terbutaline 10mg	12	NR	3 (25%)	NR	
			Terbutaline 5mg	12	NR	1 (8.3%)	NR	
	Gray, 1982	Tremor (number) at up to 5 hrs.	Fenoterol 100ug	12	NR	3 (25%)	NR	
			Terbutaline 250ug	12	NR	1 (8.3%)	NR	
	Wong, 1990	Tremor (number) at following max dose	Albuterol 100ug	10	NR	4 (40%)	NR	
			Fenoterol 200ug	10	NR	6 (60%)	NR	
			Terbutaline 250ug	10	NR	4 (40%)	NR	
Pediatric Asthma	Lin, 2002	Tremor (number) at up to 30 mins.	Fenoterol 1.25mg	108	NR	3 (5.3%)	NR	
			Terbutaline 5.0mg	108	NR	3 (5.9%)	NR	
	Ribeiro, 1990	Tremor (number) at up to 2 wks.	Fenoterol 0.2mg TID	36	NR	2 (5.6%)	NR	
			Terbutaline 0.5mg TID	36	NR	0 (0%)	NR	
	Scalabrin, 1996	Tremor, % change from baseline (%) at 1 hr	Albuterol 5mg	21	NR	NR	93 (NR), NR	
			Fenoterol 0.083mg/kg	21	NR	NR	86 (NR), NR	
			Terbutaline 0.1mg/kg	21	NR	NR	104 (NR), NR	

Population	Author, Year	Outcome (unit) at time point	Intervention	n	Baseline, Mean(SD) or No(%)	Follow-Up, Mean(SD) or No(%)	Change from Baseline, Mean (SD), p-value	Comments	
<u>Fenoterol vs Terbutaline</u>									
Neurologic: Tremor									
Pediatric Asthma	Scalabrin, 1996	Tremor, % change from baseline (%) at 2 hrs	Albuterol 5mg	21	NR	NR	106 (NR), NR		
			Fenoterol 0.083mg/kg	21	NR	NR	34 (NR), NR		
		Tremor, % change from baseline (%) at 30 min	Terbutaline 0.1mg/kg	21	NR	NR	90 (NR), NR		
			Albuterol 5mg	21	NR	NR	151 (NR), NR		
		Tremor, % change from baseline (%) at 5 min	Fenoterol 0.083mg/kg	21	NR	NR	93 (NR), NR		
			Terbutaline 0.1mg/kg	21	NR	NR	62 (NR), NR		
		Tremor, % change from baseline (%) at 5 min	Albuterol 5mg	21	NR	NR	175 (NR), NR		
			Fenoterol 0.083mg/kg	21	NR	NR	167 (NR), NR		
		Tremor, % change from baseline (%) at 5 min	Albuterol 5mg	Fenoterol 0.083mg/kg	21	NR	NR	167 (NR), NR	
				Terbutaline 0.1mg/kg	21	NR	NR	119 (NR), NR	
Respiratory: Cough									
Adult Asthma	Anderson, 1979	Cough (number) at duration of	Fenoterol 0.4mg	17	NR	1 (6%)	NR		
			Terbutaline 0.5mg	17	NR	0 (0%)	NR		
Respiratory: Other									
Adult Asthma	Anderson, 1979	Husky voice (number) at duration of study	Fenoterol 0.4mg	17	NR	1 (6%)	NR		
			Terbutaline 0.5mg	17	NR	0 (0%)	NR		

Appendix F. Abbreviations

(cyclic) AMP, cyclic adenosine monophosphate
AEs, adverse events
AUC, area under curve
B₂, beta-2
bpm, beats per minute
CAS, composite asthma score
CFC, Chlorofluorocarbon(s)
CI, 95% confidence interval
COPD, chronic obstructive pulmonary disease
CT, controlled trial
d, day
DB, double blind
ECG,
ED, emergency department
EIA, exercise-induced asthma
EKG,
ER, emergency room
FEF₂₅₋₇₅, mean forced expiratory flow during the middle of FVC
FEV₁, force expiratory volume in 1 second
FVC, forced vital capacity
g, grams
GP, general practice
H2H, head-to-head
HRQL, health-related quality of life
L, liter
LABA, long-acting beta-agonist
m(os), month(s)
mcg, micrograms
mg, milligram(s)
min, minute(s)
mL, milliliter(s)
mmol, millimole(s)
n, sample size
NA, not applicable
No, number
NR, not reported
NS, not significant
NSD, no significant difference
OR, odds ratio
PaCO₂, partial pressure of arterial CO₂
PaO₂, partial pressure of arterial O₂
PEF(R), peak expiratory flow
Pt(s), patient(s)

PVCO₂, partial pressure of mixed venous carbon dioxide

PVO₂, partial pressure of mixed venous oxygen

QoL, quality of life

RCT, randomized controlled trial

SABA, short-acting beta-agonist

SB, single blind

SD, standard deviation

SE, standard error

ug, micro-grams

US(A), United States (of America)

VC, vital capacity

VPB, ventricular premature beats

vs, versus

V_T, tidal volume

wk(s), week(s)

y(r), year