Beta$_2$-Agonists

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The Health Resources Commission
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Health Resources Commission

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

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

Overview

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

In the summer of 2007 the Oregon Health Resources Commission (HRC) appointed a subcommittee to perform an evidence-based review of the use of $Beta_2$-agonists. Members of the subcommittee consisted of physicians, a pharmacist, and a nurse practitioner. The subcommittee had XXX meetings. All meetings were held in public

with appropriate notice provided. The HRC director worked with the Center for Evidence-based Policy (Center) and the Oregon Health and Science University's (OHSU) Evidence-based Practice Center (EPC) to develop and finalize key questions for this drug class review, specifying patient populations, medications to be studied and outcome measures for analysis, considering both effectiveness and safety. Evidence was specifically sought for subgroups of patients based on race, ethnicity and age, demographics, other medications and co-morbidities. Using standardized methods, the EPC reviewed systematic databases, the medical literature and dossiers submitted by pharmaceutical manufacturers. Inclusion and exclusion criteria were applied to titles and abstracts, and each study was assessed for quality according to predetermined criteria. The EPC's report," Drug Class Review on Beta $_2$ Agonists" was completed in September 2006, circulated to subcommittee members and posted on the web. The subcommittee met to review the document and this report is the consensus result of those meetings. Time was allotted for public comment, questions and testimony.
This report does not recite or characterize all the evidence that was discussed by the OHSU EPC, the Subcommittee or the HRC. This report is not a substitute for any of the information provided during the subcommittee process, and readers are encouraged to review the source materials. This report is prepared to facilitate the HRC in providing recommendations to the Department of Human Services. The HRC, working together with the EPC, the Center for Evidence Based Policy, DMAP, and the Oregon State University College of Pharmacy, will monitor medical evidence for new developments in this drug class. Approximately once per year new pharmaceuticals will be reviewed and if appropriate, a recommendation for inclusion in the PMPDP will be made. For pharmaceuticals on the plan, significant new evidence will be assessed and Food and Drug Administration changes in indications and safety recommendations will be evaluated. The Beta$_2$-Agonists report will be updated if indicated. Substantive changes will be brought to the attention of the Health Resources Commission, who may choose to approve the report, or reconvene a subcommittee.

The full OHSU Evidence-based Practice Center's report, "Drug Class Review on Beta$_2$-Agonists" is available via the Office for Oregon Health Policy & Research, Practitioner-Managed Prescription Drug Plan website:
www.oregon.gov/DAS/OHPPR/ORRX/HRC/evidence_based_reports.shtml
Information regarding the Oregon Health Resources Commission and its subcommittee policy and process can be found on the Office for Oregon Health Policy & Research website: http://www.oregon.gov/DAS/OHPPR/HRC/index.shtml
You may request more information including copies of the draft report, and minutes of subcommittee meetings, from:
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Information dossiers submitted by pharmaceutical manufacturers are available upon request from the OHSU Center for Evidence-based Policy by contacting:
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There will be a charge for copying and handling in providing documents from both the Office of Oregon Health Policy & Research and the Center for Evidence Based Policy.

Critical Policy

Senate Bill 819

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

Health Resources Commission

– "Clinical outcomes are the most important indicators of comparative effectiveness"
– "If evidence is insufficient to answer a question, neither a positive nor a negative association can be assumed."

Clinical Overview

Asthma

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 nonallergic (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 beta$_2$-agonists (LABAs).[2] Medications for quick relief of bronchoconstriction and acute symptoms include short-acting beta$_2$-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.

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 Europe[7] 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 men[5] 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 function[7] 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.

Definition of Beta$_2$-Agonists

Inhaled beta$_2$-agonists

Beta$_2$-agonists act primarily to relax airway smooth muscle by stimulating beta$_2$-receptors, which in turn increase cyclic AMP and produce functional antagonism to bronchoconstriction. Beta$_2$-agonists may also have anti-inflammatory properties, as suggested by in vitro experiments.[6] The long-acting inhaled beta$_2$-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 asthma[2] 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 short acting beta$_2$-agonists (SABAs) relax airway smooth muscle and increase airflow within 30 minutes[1] and last 4 to 5 hours. They are the drug of choice for treating acute asthma symptoms and exacerbations and are used for preventing EIB. The SABAs are not recommended for regularly scheduled, daily use. 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. Numerous clinical studies have demonstrated that albuterol (hydrofluoroalkane 134a (HFA) formulations have comparable safety and efficacy to CFC albuterol formulations.

Table 1. Pharmacokinetics, indications and dosing of included drugs[8]

Drug Trade Name(s)	How supplied	Half-life and other relevant pharmacokinetic features**	FDA labeled indications	Dosing (inhaled doses)	Dose adjustments for special populations
Long-acting beta-agonists (LABAs)					
Salmeterol *Serevent Discus*®	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 halflife: 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 Exercise induced asthma; Prophylaxis: 1 inhalation (50 mcg) 30 minutes prior to exercise	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
Formoterol *Foradil Aerolizer*® (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 halflife: 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 Exerciseinduced 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)
Short-acting beta-agonists (SABAs)					
Albuterol *Ventolin HFA*®, *Proventil*® (also available	Inhalation Aerosol Powder: 0.09 MG/Actuation Kit: 0.09	Absorption: Time to peak concentration, 3 to 4 h Elimination	Asthma; Treatment and Prophylaxis Exercise-induced asthma;	Asthma; Treatment and Prophylaxis: 2 inhalations every 4-6 h or	Pediatric patients: Asthma; Treatment and Prophylaxis: 4 y and older, 2 inhalations every 4-

generically)	MG/Actuation	halflife: 3-6.5 hrs	Prophylaxis	1 inhalation every 4 h Exerciseinduced asthma; Prophylaxis: 2 inhalations 15 min before exercise	6 h or 1 inhalation every 4 h Exercise-induced asthma; Prophylaxis: 4 y and older, 2 inhalations 15 min before exercise
Levalbuterol *Xopenex®* *Xopenex HFA®*	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 halflife: 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 *Alupent®* (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 *Exirel®, Maxair®*	Inhalation Aerosol Powder: 0.2 MG/Actuation	Elimination halflife: 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

******* *Time to peak concentration does not necessarily correlate with time to peak effect.*

Quality of the Evidence

For quality of evidence the EPC assessed the internal validity (quality) of controlled clinical trials using a quality assessment tool found based on criteria 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.
The EPC assessed observational and other study designs with adverse event data based on nonbiased selection of patients, loss to follow-up, non-biased and accurate ascertainment of events, and control for potential confounders. 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 remaining studies 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 may be 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 the EPC 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 predefined criteria (as above): 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.

Weighing the Evidence
Please refer to the section on inclusion and exclusion criteria (page 11). For a detailed description of the process used to select included documents please refer to the full report of the Oregon EPC (reference on page 3).
A particular randomized trial might receive two different ratings: one for efficacy and another for adverse events. The overall strength of evidence for a particular key question reflects the quality, consistency, and power of the body of evidence relevant to that question.
The subcommittee's task was to evaluate the comparative benefits and harms of different pharmacologic treatments for beta$_2$-agonists. For the purposes of this report, the drug fenoterol, and inhaler dosed terbutaline which are not available in the United States were not considered.

Scope and Key Questions
The purpose of this review is to compare the benefits and harms of different pharmacologic treatments for beta$_2$-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) including the Health Resources Commission Director. 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 $beta_2$-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 $beta_2$-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 $beta_2$-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 $beta_2$-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 $beta_2$-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 $beta_2$-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 $beta_2$-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 $beta_2$-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 $beta_2$-agonists is more efficacious, effective, or associated with fewer adverse events than another inhaled $beta_2$-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 beta$_2$-agonists is more efficacious, effective, or associated with fewer adverse events: albuterol, levalbuterol, pirbuterol, and metaproterenol?

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

1. Salmeterol xinofoate = Serevent Discus
2. Formoterol fumarate = Foradil, Oxeze, others

Short-acting

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

Method of delivery

1. 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

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

Safety outcomes

1. Overall adverse effects
2. Withdrawals due to adverse effects
3. Serious adverse events
4. Specific adverse events or withdrawals due to specific adverse events

Study designs

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

Comparisons

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

Exclusion criteria

Populations or conditions

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

Summary of Results

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 beta$_2$-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 beta$_2$-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 beta$_2$-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 beta$_2$-agonists when used in the outpatient setting: albuterol, fenoterol, levalbuterol, pirbuterol, metaproterenol and terbutaline?

Long Acting Agents

Salmeterol vs. formoterol

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.

No differences were found between formoterol and salmeterol for the outcomes of symptoms, use of rescue medications, healthcare utilization[9]), and quality of life in the fair-quality studies examining these outcomes. Campbell and colleagues[10] 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.

Children with asthma

One open-label trial presented effectiveness data 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 adverse effects (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).[11,12]

Adults or children with EIA

Only one study was identified which examined EIA. Richter and colleagues[13] examined acute protection against exercise-induced bronchoconstriction in 25 adults. 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. 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 colleagues[14] 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 study[15] 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.

Short Acting Agents

Albuterol vs. levalbuterol

Adult asthma

Nelson and colleagues[16] and Pleskow et al.[17] 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 trial[18] (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. Two of these studies took place in the ER. Qureshi and colleagues[19] 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 colleagues[20] (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 collegues[21] 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 colleagues[22] 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 levalabuteral 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. These all took place in the emergency department, and were similarly-designed RCTs, with blinding of the patient and treating physician. Qureshi and colleagues[19] (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[20], 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.[23] 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 colleagues[23] 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
No data was found on comparative effectiveness outcomes.

Albuterol vs. metaproterenol
There were no effectiveness data for any of the five fair-quality studies which were evaluated.
In an exercise-challenge study of adolescents with exercise-induced bronchospasm,[24] albuterol and metaproterenol were equally efficacious in blocking exercise-induced bronchospasm initially. The duration of action of albuterol was significantly longer than for metaproterenol ($p<0.05$).

Albuterol vs. pirbuterol
Of the three studies (in four publications) which provided direct comparative data on these drugs, two were of poor quality, and one was of fair quality.[25] None of these studies provided data on effectiveness outcomes.

Metaproterenol vs. pirbuterol
There were no data on effectiveness outcomes in two identified studies of COPD and in one study of asthma in adults.

KQ 1 Consensus:
KQ1. 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?
1. There was no significant difference found between salmeterol and formoterol (delivered via dry powder systems) for:
A) In adult asthmatics for symptoms, rescue medication usage, healthcare utilization and quality of life.
B) In COPD patients for respiratory symptoms
C) In EIA patients (one single dose study) for maximum FEV_1 fall.

KQ 2 Consensus:
KQ2. 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?
A) Please note: fenoterol and inhaled terbutaline are not currently available in the US.
B) There is no evidence of comparative difference in efficacy or effectiveness
1. One RCT showed a statistically significant decrease in rescue medication use for levabuterol (no between group statistics reported).
2. A controlled clinical trial in the emergency room reported a decrease in additional therapy with levalbuterol compared to comparable albuterol dosages. Hospital admission rates were reported as similar between the two groups. No statistical comparisons were provided for these groups.
3. No effectiveness data were found for albuterol vs. metaproterenol, albuterol vs. pirbuterol, and metaproterenol vs. pirbuterol.

KQ 3 Consensus:
KQ3. 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?
1.There is insufficient evidence to determine relative differences in efficacy or effectiveness.

KQ 4 Consensus:
KQ4. 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?
A) Please Note: fenoterol and inhaled terbutaline are not currently available in the US.
1. There is insufficient evidence to determine relative efficacy or effectiveness for albuterol vs. levalbuterol in this group.
2. There is no data available for the other medications in this group regarding efficacy or effectiveness for this group.
3. In emergency room patients there was NSD found in two studies for hospital admissions between the two drugs, however a third, larger study of primarily African-American males age 1-18 found a significant (p=0.02) reduction in hospital admissions for levalbuterol 1.25 mg 3 doses vs. albuterol 2.5mg 3 doses.
4. There is insufficient evidence to determine relative efficacy or effectiveness of Albuterol vs. metaproterenol for blocking EIA. There was no data for pirbuterol or levalbuterol in EIA.

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 beta$_2$-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 beta$_2$-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 beta$_2$-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 beta$_2$-agonists, when used in the outpatient setting: albuterol, fenoterol, levalbuterol, pirbuterol, metaproterenol and terbutaline?

Overview of adverse events
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. There were no apparent differences between the various drugs being compared in this review.

Long Acting Agents
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%. 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 study[26] and a poor-quality study. Cazzola and colleagues[27] 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, 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.[9] 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.[28] Cazzola and

colleagues[27] 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.[27] There were no significant changes in potassium 1 hour after treatment in a poor-quality study examining this outcome.
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. 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).

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.[11] 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. Tremor was reported in 1 of 68 patients taking formoterol 36mg and none with lower dosages or with salmeterol 50ug.[29] 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.[11,12]

Short Acting Agents
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 weeks[16]) among the four studies reporting these data.[16,18,30,31] 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.[32,19,31] 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) ($p<0.05$).[16]
In the only study examining blood pressure, there were no significant changes in either group.[32] Palpitations[31] and tachycardia[16] 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.[32,16,19] 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.[33,16,31]

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.[16] 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.[18]

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.[18,19,30]

Children

Study withdrawal rates in pediatric studies were inconsistent in the two studies that reported these data. [21, 22] 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%.[22] 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.[34,21, 22] There was no significant difference between groups in the degree of increased heart rate between treatment groups.[23,34] Skoner and colleagues[22] noted a greater increase in heart rate ($p<0.04$) with levalbuterol 0.63 mg three times daily (4.1 beats 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.[19] Tremulousness was reported in 37% and 33% of pediatric patients using levalbuterol and racemic albuterol, respectively[19] with no significant difference between groups.

Milgrom and colleagues[21] 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 colleagues[22] 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 poorquality study of children aged 3 to 11 years,[34] 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.[19] 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.[21] Skoner and colleagues[22] 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).[34]

Albuterol vs metaproterenol

No data on withdrawals were provided in the included studies. A single study[35] 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.[36]

Metaproterenol vs pirbuterol

Rates of withdrawals were similarly low in both treatment groups in the only available study.[37] 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 a 2 patients taking metaproterenol (n= 67) and 2 taking pirbuterol (n= 66).[37] Headache, dizziness, tremors, nausea occurred in ≤ 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 ($p>0.05$).

KQ 5 Consensus:

KQ5. 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?

1. There is insufficient evidence to determine comparative differences in safety or rates of adverse events in this group.
    a. There was NSD between salmeterol and formoterol at approved dose levels for heart rate , headache, and tremor.

KQ 6 Consensus:
KQ6. 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 fenoterol, levalbuterol, pirbuterol, metaproterenol and terbutaline?

1. There was NSD found between albuterol and levalbuterol in studies evaluating: blood pressure, palpitations, tachycardia, increased blood glucose, dizziness, nervousness, anxiety, and tremor, serum potassium decrease.
2. In the one study evaluating albuterol vs metaproterenol: there was NSD in blood pressure or heart rate.
3. There was one study comparing adverse effects of metaproterenol vs pirbuterol which found NSD in headache, dizziness, tremors, nausea, or nervousness.
4. There was no comparative data on adverse events for albuterol vs. pirbuterol

KQ 7 Consensus:
KQ7. 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?

1. There is insufficient evidence to determine comparative differences in safety or rates of adverse events in this group.

KQ 8 Consensus:
KQ8. 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?
1.When comparing albuterol with levalbuterol:
A) There is insufficient evidence to determine a difference between the two drugs for increased heart rate, lightheadedness, dizziness, or nervousness or changes in serum K^+, or clinically relevant changes in blood glucose.
B) There is no data comparing the effect of these two drugs on blood pressure in this population.
2. There is no comparative data for albuterol vs metaproterenol, albuterol vs pirbuterol, or metaproterenol vs pirbuterol.

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 beta$_2$-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 beta$_2$-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,[15] albuterol vs. fenoterol,[38] albuterol vs levalbuterol,[33] and metaproterenol vs terbutaline[25] The age range was up to 80 years in two studies comparing formoterol to salmeterol.[39,14] Consistent with the epidemiology of COPD, male participants dominated these trials and in a number of these, more than 80% of participants were male. Several trials examined predominantly male asthmatics. No study examined a predominantly female population either as part of the main study or as a subgroup, for either asthma or COPD.

Long Acting Agents

Salmeterol vs formoterol

Cazzola and colleagues[39] 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 males[40] salmeterol was equally as effective, but longer acting, than formoterol. Celik and colleagues[41] 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 colleagues[14] 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 colleagues[15] 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.

Short Acting Agents

Albuterol vs levalbuterol

Datta and colleagues[33] 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.

Albuterol vs metaproterenol

Four inhaled beta$_2$-agonists were compared[25] 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.[42]

Albuterol vs pirbuterol vs metaproterenol

Peacock and colleagues[25] 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.

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,[19,23] and one study examined asthmatic adults.[18]

Albuterol vs levalbuterol

In an RCT in the emergency department,[23] 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,[19] 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.[26] 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 colleagues[26] 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.

KQ 9 Consensus:
KQ9. 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$_2$-agonsts is more efficacious, effective, or associated with fewer adverse events than another inhaled beta$_2$-agonst?
1 There is insufficient evidence to determine comparative efficacy, or effectiveness between salmeterol and formoterol in this group.
2. There is insufficient evidence to determine comparative differences in adverse events between salmeterol and formoterol in this group.
3. There was no data on race or comorbidities or pregnancy.

KQ 10 Consensus:
KQ 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?
A) Efficacy and Effectiveness
1. There is insufficient evidence to determine comparative differences in efficacy or effectiveness for albuterol vs. levalbuterol, albuterol vs. pirbuterol, or metaproteronol vs. pirbuterol.
B) Adverse Events
1. There is insufficient evidence to determine a comparative difference in heart rate or tremor for albuterol vs. levalbuterol in older predominantly male populations.
2. There is no data on race or comorbidities.

Conclusions:

Long Acting Beta$_2$-Agonists

1. In adult asthmatics there was no significant difference found between salmeterol and formoterol for symptoms, rescue medication usage, healthcare utilization and quality of life.
2. In adults with COPD there was no significant difference between salmeterol and formoterol for respiratory symptoms.
3. In children with asthma there is insufficient evidence to determine relative differences in efficacy or effectiveness.
4. In Adults with Asthma or COPD there is insufficient evidence to determine comparative differences in safety or rates of adverse events.
5. In children with asthma there is insufficient evidence to determine comparative differences in safety or rates of adverse events.
6. There is insufficient evidence to determine comparative efficacy, or effectiveness or adverse events for subgroups of patients based on demographic characteristics (age or gender) or other medications (drug-drug interactions). There was no data on race, comorbidities or pregnancy.
7. Data suggests that there may be a difference in onset of action of formoterol vs. salmeterol; further evaluation is needed before a comparative difference can be determined.

Short Acting Beta$_2$-Agonists

1. In adults and children with asthma and adults with COPD there is insufficient evidence to determine relative differences in efficacy or effectiveness between albuterol or levalbuterol.
2. In adults or children with asthma or adults with COPD; no effectiveness data were found for albuterol vs. metaproterenol, albuterol vs. pirbuterol, and metaproterenol vs. pirbuterol.
3. In adults and children with asthma and adults with COPD; there is insufficient evidence to determine a relative difference in safety or adverse events with these medications. There was no comparative data for adverse events for albuterol vs. pirbuterol in adults and for albuterol vs metaproterenol, albuterol vs pirbuterol, or metaproterenol vs pirbuterol in children.
4. There is insufficient evidence to determine comparative differences in efficacy or effectiveness in subgroups of patients based on demographic characteristics (age, racial groups, gender), other medications (drug-drug interactions), comorbidities (drug-disease interactions), or pregnancy for albuterol vs. levalbuterol, albuterol vs. pirbuterol, or metaproteronol vs. pirbuterol.
5. There is insufficient evidence to determine comparative differences in heart rate or tremor for predominantly older male patients for albuterol vs. levalbuterol. There is no data for race or comorbidities.

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