Drug Class Review

Drugs to Treat Asthma and Chronic Obstructive Pulmonary Disease (COPD)

Final Original Report

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STRUCTURED ABSTRACT

Purpose

To compare the efficacy and safety of inhaled corticosteroids (ICSs), long-acting beta-2 agonists (LABAs), leukotriene modifiers (LMs), long-acting anticholinergics, phosphodiesterase-4 inhibitors, and combination products for people with persistent asthma or chronic obstructive pulmonary disease.

Data Sources

To identify published studies, we searched MEDLINE, The Cochrane Library, International Pharmaceutical Abstracts, and reference lists of included studies through September 2013. We also requested dossiers of information from pharmaceutical manufacturers. This streamlined update is limited to direct comparisons and did not include placebo-controlled trials.

Review Methods

Study selection, data abstraction, validity assessment, grading the strength of the evidence, and data synthesis were all carried out according to standard Drug Effectiveness Review Project methods.

Results

Efficacy studies provided moderate-strength evidence that equipotent doses of ICSs administered through comparable delivery devices do not differ in their ability to control asthma symptoms, prevent asthma exacerbations, or reduce the need for additional rescue medication. There was also moderate-strength evidence that equipotent doses of ICS do not differ in the overall incidence of adverse events or withdrawals due to adverse events in patients with asthma There was no evidence comparing different ICS in patients with chronic obstructive pulmonary disease (COPD) except in subgroups.

There was moderate-strength evidence that LABAs do not differ in ability to prevent exacerbations, hospitalizations, or emergency visits or improve quality of life in patients with persistent asthma not controlled with ICS alone. There was also no difference in tolerability or adverse events between formoterol and salmeterol. In patients with COPD, there was low-strength evidence that arformoterol and formoterol are associated with similar exacerbation rates and improvements in quality of life, that formoterol and indacaterol have similar impacts on exacerbations and quality of life, and that indacaterol has a small transient advantage over salmeterol in its effects on quality of life, but differences disappear over time.

Low-strength evidence also did not support a difference between montelukast and zafirlukast in their ability to improve quality of life in patients with asthma. There was no evidence comparing LMs in patients with COPD.

There was moderate-strength evidence of no difference between combination products fluticasone/salmeterol and either budesonide/formoterol or mometasone furoate/formoterol in quality of life, exacerbations or asthma deteriorations, withdrawals due to adverse events, or serious adverse events in patients with asthma (when high doses of mometasone

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furoate/formoterol and fluticasone propionate/salmeterol were used, strength of evidence was low). Low-strength evidence did not support a difference between fluticasone/salmeterol and fluticasone/vilanterol in quality of life in treating asthma. There were no prospective, randomized, head-to-head clinical trials of ICS/LABA combination products available in the United States in patients with COPD.

Efficacy studies up to 56 weeks in duration provided consistent evidence of greater benefit for asthma patients treated with ICS monotherapy compared with those treated with LM monotherapy (high-strength evidence). Direct evidence suggested no difference in tolerability or overall adverse events between ICSs and LMs when used to treat asthma (moderate-strength evidence). Specific adverse events reported with ICSs, such as cataracts and decreased growth velocity, were not found among patients taking LMs. Evidence was insufficient to determine if long-term treatment with ICSs leads to a reduction in final adult height. There were no head-to-head studies of ICS compared with LM in patients with COPD.

Overall evidence indicated that ICSs and leukotriene receptor antagonists (LTRAs) are safer than LABAs for use as monotherapy (high-strength evidence). LABAs were not recommended or approved for use as monotherapy for persistent asthma because they may increase the risk of asthma-related deaths (high-strength evidence). In a pooled analysis of 7 studies, asthmatics treated with LABAs had an increased occurrence of exacerbations compared with those treated with ICS. However, in patients with COPD there was moderate-strength evidence of no difference between ICS and LABAs in exacerbations or hospitalizations due to exacerbations and low-strength evidence of no difference between treatments in mortality. Although there was low-strength evidence of no difference in risk of having any adverse event between ICS and LABAs, serious pneumonia was more frequent with ICS.

Low-strength evidence did not support a difference in patients with asthma between tiotropium and salmeterol in exacerbations, quality of life, withdrawals due to adverse events, or proportion of patients with serious harms. In patients with COPD, there was moderate-strength evidence that fewer patients experience an exacerbation or a nonfatal serious adverse event with tiotropium compared with salmeterol and low-strength evidence of no difference between tiotropium and salmeterol in hospitalizations and in proportions of patients with clinically significant improvement in quality of life. However, fewer patients withdrew due to adverse events with tiotropium. For the comparison of indacaterol and tiotropium, there was low-strength evidence that in patients with *severe* COPD, indacaterol provided less protection from exacerbations, but similar mortality and improved quality of life. In a broader patient population of *moderate to severe* COPD, tiotropium was associated with significantly lower proportions of patients with clinically significant improvement in quality of life, but the 2 drugs did not differ in hospitalizations or exacerbations. Tiotriopium and formoterol had similar effects on exacerbations (low-strength evidence). Additionally, there was no difference between tiotropium and indacaterol or formoterol in withdrawals due to adverse events and no difference between tiotropium and indacaterol or formoterol in proportion of patients with nonfatal serious harms (low-strength evidence).

Low-strength evidence from 1 trial suggested that more asthma patients taking roflumilast than beclomethasone experienced exacerbations and withdrew from the study due to adverse events. There were no trials comparing ICS with phosphodiesterase-4 inhibitors in patients with COPD.

Results from large trials up to 12 months in duration in patients with persistent asthma provided moderate-strength evidence of greater efficacy with the addition of a LABA to an ICS

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than with a higher-dose ICS (high-strength evidence for ≥12, low-strength for <12) with no difference in overall adverse events (with the exception of tremor which was increased in those taking ICS/LABA vs. higher-dose ICS). There were no head-to-head studies comparing ICS/LABA vs. a higher-dose ICS in patients with COPD.

When comparing an ICS/LABA with a different ICS in patients with asthma, low-strength evidence suggested no difference in exacerbations, adverse events, or withdrawals due to adverse events between fluticasone furoate plus vilanterol and fluticasone propionate. There was also low-strength evidence that risk of experiencing any adverse events is greater with ciclesonide compared with fluticasone plus salmeterol. No trials of ICS/LABA compared with a different ICS were identified in patients with COPD.

There was no apparent difference in symptoms, exacerbations, rescue medicine use, overall adverse events, or withdrawals due to adverse events between asthma patients treated with ICSs plus LTRAs compared with increased dose of ICSs (moderate-strength evidence for ≥12 years of age, low-strength for <12 years). There were no similar head-to-head studies in COPD patients.

High-strength evidence from a meta-analysis of 5 randomized controlled trials indicated that fluticasone plus salmeterol was more efficacious than montelukast for the treatment of persistent asthma in patients at least 12 years of age (moderate-strength evidence of greater efficacy with fluticasone propionate/salmeterol in children). There was low-strength evidence for similar rates of overall adverse events and withdrawals due to adverse events between treatments in patients with asthma. There were no trials of this comparison in patients with COPD.

Results provided strong evidence that the addition of a LABA to ICS therapy is more efficacious than the addition of a LTRAs to ICS therapy in patients with persistent asthma (high-strength evidence for ≥12, low-strength for <12). We found no difference in overall adverse events or withdrawals due to adverse events between ICS/LABA and ICS/LTRA (moderate-strength evidence for ≥12, insufficient for <12). There were no trials of ICS/LABA compared with ICS/LTRA in COPD patients.

In patients with persistent asthma, low-strength evidence did not support a difference between tiotropium plus ICS compared with a higher-dose ICS in exacerbations, improvements in quality of life, or withdrawals due to harms. There were no head-to-head studies comparing tiotropium/ICS with a higher-dose of the same ICS in COPD patients.

In patients with COPD, treatment with fluticasone plus salmeterol was associated with decreased mortality but higher risk of hospitalization and greater improvement in quality of life compared with treatment with tiotropium (low-strength evidence). There was also low-strength evidence of no difference in mortality between tiotropium and fluticasone/vilanterol or umeclidinium bromide/vilanterol. Tiotropium and umeclidinium bromide/vilanterol had similar effects on quality of life (low-strength evidence). However, low-strength evidence supported reduced risk of serious harms with tiotropium compared with fluticasone/salmeterol, although there was no difference in withdrawal due to adverse events. Tiotropium and fluticasone/vilanterol also did not differ in proportion of patients with serious adverse events and tiotropium and umeclidinium bromide/vilanterol did not differ in proportion of patients who withdraw due to harms (low-strength evidence). There were no trials of these comparisons in patients with asthma.

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Conclusions

Overall findings did not suggest that 1 medication within any of the classes evaluated is significantly more effective or harmful than the other medications within the same class. Our results supported the general clinical practice of starting initial treatment for persistent asthma with an ICS. For people with poorly-controlled persistent asthma taking an ICS, our findings suggested that the addition of a LABA is most likely to provide the greatest benefit as the next step in treatment. For patients with COPD, our results indicated that monotherapy with ICS and LABAs are similarly effective and have similar risk of experiencing any adverse event. However, there was low-strength evidence that treatment with ICS increases the risk of serious pneumonia. In general the evidence for newer asthma and COPD medications is of insufficient or low strength for most benefit and harms outcomes.

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EVIDENCE TABLES

Published in 2 separate documents: Original and Update 1 Report Evidence Tables and Streamlined Report Evidence Tables . References throughout this report identify the respective documents as Evidence Tables A or B.

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INTRODUCTION

Asthma is a chronic lung disease characterized by reversible airway obstruction, inflammation, and increased airway responsiveness. As a result of inflammation, individuals with asthma may experience symptoms such as wheezing, difficulty breathing, or coughing. The airway obstruction which occurs with asthma is generally reversible spontaneously or with treatment. Asthma is thought to have a genetic, inheritable component, often begins early in life, and consists of variable symptoms regardless of asthma classification.[1] The Expert Panel of the National Asthma Education and Prevention Program (NAEPP) reclassified asthma categories most recently in 2007; the mild intermittent category was eliminated (now called intermittent) and the persistent category was subdivided into mild, moderate, or severe.[1] The change was partly done to acknowledge that exacerbations can be severe in any asthma category. Table 1 lists the criteria used to classify asthma severity.

Table 1. Classification of asthma severity[1]

	Daytime symptoms	Nighttime symptoms	Short-Acting Beta-2 Agonist use	Interference with daily activity	FEV_1 percent predicted	FEV_1/FVC
Intermittent	≤ 2 days/week	≤ 2 nights/month	≤ 2 days/week	None	> 80%	Normal
Persistent						
Mild	> 2/week but < 1/day	3-4 nights/month	> 2 days/week	Minor	≥ 80%	Normal
Moderate	Daily	> 1 night/week but < 1/night	Daily	Some	> 60% - < 80%	Reduced 5%
Severe	Continual	Frequent	Several times daily	Extreme	≤ 60%	Reduced > 5%

Asthma outcomes have improved over the past several years but the burden remains substantial. Asthma is estimated to affect 300 million individuals worldwide with 25.9 million of those individuals living in the United States (2011 data).[2-4] It is the cause of 250,000 worldwide deaths annually with over 3000 of them in the United States (2010 data).[2-4] The World Health Organization estimates 15 million disability-adjusted life years lost annually due to asthma.[2]

Chronic obstructive pulmonary disease (COPD) is another chronic lung disease, characterized primarily by persistent airflow limitation. Smoking is the most common risk factor, interacting with genetic predisposition. COPD is more common over the age of 40 and is usually progressive, becoming more severe over time, and usually associated with an increased inflammatory response to smoke and other airborne particles. Chronic inflammation may destroy lung tissue, causing emphysema, and/or lead to small airway damage and obstruction. However, the current COPD definition from the Global Initiative for Chronic Obstructive Lung Disease (GOLD) does not describe emphysema and chronic bronchitis as COPD subtypes, as has been done in the past. Emphysema is 1 of several pathologic changes in the lungs that may occur in COPD patients. Chronic bronchitis is a clinical term describing 2 of the symptoms (cough and sputum production) also associated with COPD; however, chronic bronchitis may develop before or after the changes in airflow that characterize COPD.[5] Dyspnea (shortness of breath) is the

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third major symptom associated with COPD. As in asthma, exacerbations may also occur. Table 2 shows the GOLD classification of COPD severity.[5]

Table 2. Classification of COPD severity[5]

In patients with $FEV_1/FVC < 0.70$		
Airflow limitation	**GOLD Classification**	**Percent of predicted FEV_1**
Mild	GOLD 1	≥ 80%
Moderate	GOLD 2	≥ 50% to < 80%
Severe	GOLD 3	≥ 30% to < 50%
Very severe	GOLD 4	<30%

The estimated prevalence of physician-diagnosed COPD in the United States is 14.8 million, with an estimated 12 million additional undiagnosed cases. Death rates from COPD increased steadily from a rate of 2.1 per 100,000 in 1950, leveling off around 42 per 100,000 in 2000; in 2008 the death rate was 45.3 per 100,000. Asthma and COPD together impose substantial economic costs, estimated in 2008 at $68.0 billion in the United States, 53.7 in direct healthcare costs and 14.3 indirect costs from lost productivity. Direct costs associated with asthma and COPD can be further divided into hospitalization ($13.1 billion), ER visits ($3.1 billion), office visits ($13.2 billion), home health care ($4.0 billion) and prescription drugs ($20.4 billion).[6]There are currently 2 categories of medications used in asthma treatment: controller medications and quick relief (or rescue) medications. Although all patients with persistent asthma should have a short-acting relief medication on hand for treatment of exacerbations and a controller medication for long-term control, this report focuses on the following currently available controller medications: inhaled corticosteroids (ICSs), long-acting beta-2 agonists (LABAs), leukotriene modifiers (LMs), fixed-dose combination products, long-acting anticholinergics, and phosphodiesterase-4 inhibitors. Leukotriene modifiers and phosphodiesterase-4 inhibitors are oral agents; the remaining drugs are inhaled and delivered through a variety of devices including metered dose inhalers (MDIs), dry powder inhalers (DPIs), and nebulizers. In the past, MDI products contained chlorofluorocarbons (CFCs) which were found to be detrimental to atmospheric ozone and have now been banned from use. They were replaced with alternative administration devices including hydrofluoroalkane (HFA) propellant MDIs and dry powder inhalers. Inhaled corticosteroids and LABAs are used to treat COPD as well as asthma. Tiotropium and roflumilast are controller medications used to treat COPD, but not approved for the treatment of asthma.[5,7] Table 3 lists the trade names, manufacturers, available formulations, and age indications for controller medications for persistent asthma and COPD.

Inhaled corticosteroids are the preferred agents for long-term control of persistent asthma according to expert panel recommendations.[1] They are one of several current medications available to treat persistent asthma that target the inflammatory process caused by multiple inflammatory cells and mediators including lymphocytes, mast cells, and eosinophils, among others.[1] The inhaled route of administration serves to directly target the inflammation while minimizing systemic effects which can result from oral administration. These agents have been approved as first line therapy for asthma control in all stages of persistent asthma.[1] The 8 ICSs currently available include: beclomethasone dipropionate, budesonide, ciclesonide, flunisolide, fluticasone propionate, fluticasone furoate, mometasone furoate, and triamcinolone acetonide.

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Table 3. Long-term controller medication class, trade names, manufacturers, formulations, and indications[8-36]

Medication class	Generic name	Trade name	Manufacturer	Dosage form/device	Strength	Approved indication in US
Inhaled corticosteroids	Beclomethasone dipropionate	QVAR®	Teva	Aerosol, Metered; Inhalation	40 mcg/puff 80 mcg/puff	Asthma only (age ≥ 5)
	Budesonide	Pulmicort Flexhaler®	AstraZeneca	Powder, Inhalation	90 mcg/puff 180 mcg/puff	Asthma only (age ≥ 6)
		Pulmicort Respules®	AstraZeneca	Suspension; Inhalation	0.25 mg/2 ml 0.50 mg/2 ml 1.00 mg/2 ml	Asthma only (age 1-8)
		Pulmicort Turbuhaler®	AstraZeneca	Powder; Inhalation	200 mcg/puff	Asthma only (age ≥ 6) No longer available in US Not approved for use in US
	Ciclesonide	Alvesco®	Takeda GMBH	Aerosol, Metered; Inhalation	80 mcg/puff 160 mcg/puff	Asthma only (age ≥ 12)
	Flunisoide	Aerospan™ HFA	Meda	Aerosol, Metered; Inhalation	80 mcg/puff	Asthma only (age ≥ 6)
	Fluticasone propionate	Flovent® HFA	GlaxoSmithKline	Aerosol, Metered; Inhalation	44 mcg/puff 110 mcg/puff 220 mcg/puff	Asthma only (age ≥ 4)
		Flovent Diskus®	GlaxoSmithKline	Powder; Inhalation	50 mcg/puff 100 mcg/puff 250 mcg/puff	Asthma only (age ≥ 4)
	Mometasone furoate	Asmanex® Twisthaler®	Merck	Powder; Inhalation	110 mcg/puff 220 mcg/puff	Asthma only (age ≥ 4)
Leukotriene modifiers Leukotriene receptor antagonists	Montelukast	Singulair® (generic)	Merck	Tablet, Chewable Tablet, Granule; Oral	4 mg/packet 4 mg/chew tab 5 mg/chew tab 10 mg/tablet	Asthma only (age ≥ 1)
	Zafirlukast	Accolate®	AstraZeneca	Tablet; Oral	10 mg 20 mg	Asthma only (age ≥ 5)
	Zileuton	Zyflo®	Cornerstone Therapeutics	Tablet; Oral	300 mg[a] 600 mg	Asthma only (age ≥ 12)

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Medication class	Generic name	Trade name	Manufacturer	Dosage form/device	Strength	Approved indication in US
5-lipoxygenase Inhibitor		Zyflo CR®	Cornerstone Therapeutics	Tablet, Extended Release; Oral	600 mg	Asthma (age ≥ 12)
Long-Acting Beta-2 Agonists	Arformoterol	Brovana®	Sunovion	Solution; Inhalation	0.015 mg/base/2 ml	Not approved for asthma (COPD only)
	Formoterol fumarate	Perforomist®	Mylan	Solution; Inhalation	0.02 mg/2 ml	Not approved for asthma (COPD only)
	Formoterol fumarate/ Eformoterol	Foradil® Aerolizer® Foradil®	Novartis	Powder; Inhalation	12 mcg/puff	Asthma (age ≥ 5)
	Salmeterol xinafoate	Serevent®	GlaxoSmithKline	Powder; Inhalation	50 mcg base/puff	Asthma (age ≥ 4) COPD
	Indacaterol maleate	Arcapta™	Novartis	Powder; Inhalation	75 mcg/base	Not approved for asthma (COPD only)
Long-acting anticholinergics	Aclidinium bromide	Tudorza™ Pressair™	Forest	Powder, Metered; Inhalation	0.375 mg/puff	Not approved for asthma (COPD only)
	Tiotropium bromide monohydrate	Spiriva®	Boehringer Ingelheim	Powder; Inhalation	18 mcg base/puff	Not approved for asthma (COPD only)
Fixed-dose combination products (LABA+ICS)	Fluticasone propionate/ Salmeterol xinafoate	Advair Diskus®	GlaxoSmithKline	Powder; Inhalation	100 mcg/puff; 50 mcg base/puff 250 mcg/puff; 50 mcg base/puff 500 mcg/puff; 50 mcg base/puff	Asthma (age ≥ 4)[b] COPD[c]
		Advair® HFA	GlaxoSmithKline	Aerosol, Metered; Inhalation	45 mcg/puff; 21 mcg base/puff 115 mcg/puff; 21 mcg base/puff 230 mcg/puff; 21 mcg base/puff	Asthma (age ≥ 12)
	Formoterol/ Budesonide	Symbicort®	AstraZeneca	Aerosol, Metered; Inhalation	80 mcg/puff; 4.5 mcg/puff 160 mcg/puff; 4.5 mcg/puff	Asthma (age ≥ 12) COPD[d]

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Table 3. Long-term controller medication class, trade names, manufacturers, formulations, and indications[8-36]

Medication class	Generic name	Trade name	Manufacturer	Dosage form/device	Strength	Approved indication in US
		Symbicort® Turbuhaler	AstraZeneca	Powder; Inhalation	100 mcg/puff; 6 mcg/puff 160 mcg/puff; 4.5 mcg/puff 200 mcg/puff; 6 mcg/puff 400 mcg/puff; 12 mcg/puff	Asthma (age ≥ 12) Not approved for use in the US Approved in Canada, New Zealand
	Formoterol/ Mometasone furoate	Dulera®	Merck	Aerosol, Metered; Inhalation	100 mcg/puff; 5.0 mcg/puff 200 mcg/puff; 5.0 mcg/puff	Asthma (age ≥ 12)
	Vilanterol/Fluticasone Furoate	Breo® Ellipta™	GlaxoSmithKline	Powder; Inhalation	100 mcg/puff; 25 mcg base/puff	Not approved for asthma (COPD only)
Fixed-dose combination product (Anticholinergic + LABA)	Umeclidinium/Vilanterol	Anoro™Ellipta™	GlaxoSmithKline	Powder; Inhalation	62.5mcg/puff; 25mcg base/puff	Not approved for asthma (COPD only)
Phosphodiesterase-4	Roflumilast	Daliresp®	Forest	Tablet; Oral	500 mcg	Not approved for asthma (COPD only)

[a] This dosing level has been discontinued by the manufacturer, but was available previously.
[b] For children 4-11 years, only the 100 mcg/puff; 50 mcg base/puff dose is approved.
[c] In COPD, only the 250 mcg/puff; 50 mcg base/puff dose is approved.
[d] Symbicort 160/4.5 mcg is the only approved dose for COPD.

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. The ICSs often have different kinetic and side effect profiles with similar numerical doses depending on the delivery device and the product.[1] Since there are insufficient head-to-head trials comparing all of the various ICSs, determining equivalency among products is sometimes difficult. Table 4i and ii lists comparative dosing of the available products based on the recently updated GINA guidelines.[37]

Long-acting beta-2 agonists are agents used in combination with ICSs to obtain control in persistent asthma. The mechanism of action of these agents is through relaxation of airway smooth muscles to reverse bronchoconstriction.[1,38] In contrast to short-acting beta-2 agonists, which are used for quick relief of acute symptoms due to their quick onset and short duration of action, LABAs provide long-acting bronchodilation for 12 hours allowing for twice daily administration;[1] the newest agent, indacaterol, has a 24 hour duration of action for once-daily dosing. The NAEPP expert panel advocates the use of LABAs as the preferred adjunct therapy for patients ≥ 12 years old with persistent asthma not controlled on ICSs alone.[1] In addition, LABAs are useful in the prevention of exercise-induced bronchospasm (EIB).[1,38] These agents are not used for relief of acute asthma symptoms and are contraindicated for use as monotherapy for persistent asthma (see Key Question 2 for details).[1] Currently there are 5 available LABAs: arformoterol (ARF), formoterol (FM) (formerly known as eformoterol in the UK), indacaterol (IC), vilanterol (VI), and salmeterol (SM). Arformoterol, vilanterol and indacaterol are currently approved only for COPD (Table 3). The main clinical difference in the 2 agents available to treat asthma is that formoterol has a quicker onset of action than salmeterol.[1]

The LMs are another class of controller medications used in the treatment of asthma and comprise 2 classes of medications: leukotriene receptor antagonists (LTRAs) and 5-lipoxygenase inhibitors (Table 3). The more general term "leukotriene modifier" (LM) will be used throughout this report to refer to any of the 3 drugs in this class. Leukotrienes cause contraction of smooth muscles, mucous secretion, and inflammation contributing to asthma symptoms.[1,38] The LTRAs (montelukast and zafirlukast) bind to cell receptors to prevent these actions from occurring.[1] Montelukast is approved for children ≥ 1 year old and zafirlukast for children ≥ 5 years old in the United States and ≥ 12 years old in Canada. They are approved for mild persistent asthma and as adjunct therapy with ICSs.[1,38] Montelukast is also approved for EIB.[38]

Zileuton's mechanism of action is through the inhibition of 5-lipoxygenase which is involved in the production of leukotrienes.[1] This medication is indicated for use in patients ≥ 12 years old.[1,38] Metabolism of this drug is through the CYP 450 1A2, 2C9, and 3A4 isoenzymes which are responsible for a variety of drug-drug interactions.[38] In addition, liver function monitoring is required with zileuton therapy[1,38] due to the involvement of the CYP 450 system and potential adverse events, which has limited the use of this product.

Combination controller medications including both an ICS and a LABA available for the treatment of asthma include fluticasone/salmeterol, budesonide/formoterol, and mometasone furoate/formoterol (Table 3). These fixed-dose combination products are recommended for patients not adequately controlled on a long-term asthma-control medication, such as an ICS, or whose disease severity clearly warrants initiation of treatment with both an ICS and LABA.[1,38] These agents are available as DPI or HFA products (Table 2).

Pharmacotherapy recommendations for COPD differ from those for asthma, though the drugs used overlap. Either a LABA or long-acting anticholinergic, rather than an ICS, is used as first-line therapy in COPD[5,7] Guidelines from the American College of Physicians and collaborating organizations base treatment recommendations on spirometry alone, with treatment initiated with long-acting bronchodilators for FEV_1 less than 60% of that predicted.[7] GOLD

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guidelines consider symptoms and exacerbations in addition to spirometry. They recommend a treatment sequence for patients with disease of increasing severity of (1) LABA or long-acting anticholinergic, (2) ICS/LABA *or* long-acting anticholinergic, and (3) ICS/LABA *and/or* long-acting anticholinergic.[39] ACP guidelines consider evidence for combination therapy in COPD weaker than that for monotherapy and state only that clinicians may consider combination therapy, again for patients with FEV_1 less than 60% of predicted.[7] Finally, GOLD guidelines also include roflumilast as an option to prevent exacerbations, given in conjunction with long-acting bronchodilators.[5]

Tiotropium and roflumilast are 2 drugs approved for treatment of COPD, but not for asthma. Tiotropium is an inhaled long-acting anticholinergic, also known as a long-acting muscarinic antagonist (LAMA); it blocks binding of acetylcholine to muscarinic receptors that mediate bronchoconstriction, with a duration of action more than 24 hours.[5] Aclidinium bromide is another LAMA, approved for use as a single agent in the United States. Umeclidinium is also a LAMA, FDA-approved only in combination with vilanterol (Anoro™ Ellipta™). Roflumilast, an oral agent, is the only phosphodiesterase-4 (PDE-4) inhibitor available in the United States. PDE-4 metabolizes cyclic AMP in lung tissue, and its inhibition leads to accumulation of cyclic AMP, though the downstream effects of cAMP accumulation are not clearly defined.[17]

The most recent update of the asthma report was completed in 2011. The most recent update of the inhaled corticosteroid report was completed in 2006. This review is an update of these 2 reports in patients with asthma or COPD with the addition of new medications. While the previous reports included placebo-controlled trials, because this is a streamlined report, placebo-controlled trials are not included and have been removed from previously included evidence. The scope of the report has also changed and no longer includes comparisons to short-acting medications for asthma patients and no longer includes comparisons of a combination product with its individual elements unless the dosage is significantly changed. This review includes 6 new drugs or drug combinations not present in either prior report.

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Table 4a. Low, medium, and high daily doses of inhaled corticosteroids

Drug	Daily Dose (mcg)		
	Low	Medium	High
Adults and adolescents (12 years and older)[37]			
Beclometasone dipropionate (CFC)[a]	200-500	>500-1000	>1000
Beclometasone dipropionate (HFA)	100-200	>200-400	>400
Budesonide (DPI)	200-400[a]	>400-800	>800
Ciclesonide (HFA)	80-160	>160-320	>320
Fluticasone propionate (DPI)	100-250	>250-500	>500
Fluticasone propionate (HFA)	100-250	>250-500	>500
Mometasone furoate	110-220	>220-440	>440
Triamcinolone acetonide	400-1000	>1000-2000	>2000
Children 6-11 years			
Beclometasone dipropionate (CFC)[a]	100-200	>200-400	>400
Beclometasone dipropionate (HFA)	50-100	>100-200	>200
Budesonide (DPI)	100-200	>200-400	>400
Budesonide (nebules)	250-500	>500-1000	>1000
Ciclesonide (HFA)	80	>80-160	>160
Fluticasone propionate (DPI)	100-200	>200-400	>400
Fluticasone propionate (HFA)	100-200	>200-500	>500
Mometasone furoate	110	≥220-≤440	≥440
Triamcinolone acetonide	400-800	>800-1200	>1200

CFC: Chlorofluorocarbon propellant; DPI: dry powder inhaler; HFA: hydrofluoroalkaline propellant.
[a] Beclomethasone dipropionate CFC is included for comparison with older literature.

Table 4b. Low daily doses of inhaled corticosteroids for children 5 years and younger[37]

Drug	Low daily dose (mcg)
Beclomethasone dipropionate (HFA)	100
Budesonide pMDI+ spacer	200
Budesonide nebulized	500
Fluticasone propionate (HFA)	100
Ciclesonide	160
Mometasone furoate	Not studies below 4 years of age
Triamcinolone acetonide	Not studies below 4 years of age

HFA: hydrofluoroalkaline propellant; pMDI: pressurized metered dose inhaler.
This is not a table of clinical equivalence. A low daily dose is defined as the dose that has not been associated with clinically adverse effects in trials that included measures of safety.

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Scope and Key Questions

The purpose of this review is to assist healthcare providers, researchers, and policy makers in making clinical decisions, creating formularies, and developing policies regarding long-term control medications for asthma and COPD based on the most current available literature. We compare the efficacy, effectiveness, and tolerability of controller medications used in the treatment of persistent asthma and COPD, and also look for subgroups that may differ in these areas. We compare efficacy and tolerability both within and between the major classes of controller drugs. The Pacific Northwest Evidence-based Practice Center (EPC) 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 approved the following key questions to guide this review:

1. What is the comparative *within-class* and *across-class* efficacy and effectiveness of long-acting beta agonists, long-acting anticholinergics, inhaled corticosteroids, fixed dose combination products and long-acting oral (non-inhaled) medications used to treat outpatients with persistent or chronic asthma or chronic obstructive pulmonary disease (COPD)?

2. What is the comparative *within-class* and *across-class* tolerability and frequency of adverse events of long-acting beta agonists, long-acting anticholinergics, inhaled corticosteroids, fixed dose combination products and long-acting oral (non-inhaled) medications used to treat outpatients with persistent or chronic asthma or chronic obstructive pulmonary disease (COPD)?

3. Are there subgroups of patients based on demographics (age, racial groups, gender), asthma or COPD severity, comorbidities (drug-disease interactions, including obesity), other medications (drug-drug interactions), smoking status, genetics, or pregnancy for which asthma or COPD controller medications differ in efficacy, effectiveness, or frequency of adverse events?

Inclusion Criteria

This review includes pediatric (12 months to 18 years) or adult outpatients with persistent asthma or adult outpatients with COPD treated with any of the following agents: ICSs (beclomethasone, budesonide, ciclesonide, flunisolide, fluticasone propionate, triamcinolone acetonide, mometasone furoate), LABAs (formoterol, arformoterol, indacaterol, salmeterol), LMs (montelukast, zafirlukast, zileuton), combination products (fluticasone propionate/salmeterol xinafoate, budesonide/formoterol, mometasone furoate/formoterol, fluticasone furoate/vilanterol), long-acting anticholinergics (tiotropium, aclidinium), or PDE-4 inhibitors (roflumilast).

For efficacy and effectiveness outcomes of interest we included randomized controlled trials (RCTs) of at least 12 weeks duration and a sample size of at least 100 which evaluate control of symptoms, functional capacity and quality of life, urgent care services, adherence, hospitalization, or mortality. We also included comparative good-quality systematic reviews. For

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adverse events outcomes, we included observational studies of at least 6 months duration and a sample size of at least 100 (Table 5). Further details related to inclusion criteria are provided below in the Methods section under Study Selection. Boxed warnings associated with these products are provided in Appendix B. Dosing equivalency of the agents was based on the 2014 GINA guidelines.[37]

Table 5. Outcome measures and study eligibility criteria

Outcome	Outcome measures	Study eligibility criteria
Efficacy / Effectiveness	• Asthma control - Asthma exacerbations - Days/nights frequency of symptoms - Frequency of rescue medication use - Courses of oral steroids • Quality of life • Ability to participate in work, school, sports, or physical activity, improved sleep • Adherence • Emergency department / urgent medical care visits • Hospitalization • Mortality	• Randomized controlled clinical trials of at least 12 weeks duration and n ≥ 100 • Head-to-head trials only (placebo-controlled trials excluded). • Comparative good-quality systematic reviews
Adverse Events/Safety	• Overall adverse events reported • Withdrawals due to adverse events • Serious adverse events • Specific adverse events including: - *Growth suppression* - *Bone mineral density* - *Osteoporosis/fractures* - *Ocular toxicity* - *Suppression of HPA axis* - *Anaphylaxis* - *Death*	• Randomized controlled clinical trials of at least 12 weeks duration and n ≥ 100 • Head-to-head trials only • Comparative good-quality systematic reviews • Observational studies of at least 6 months duration and n ≥ 100

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METHODS

Literature Search

To identify relevant citations, we searched MEDLINE®, the Cochrane Database of Systematic Reviews®, the Cochrane Central Register of Controlled Trials® through January week 5, 2014 using terms for included drugs, indications, and study designs (see Appendix C for complete search strategies). We limited the electronic searches to "human" and "English language." We attempted to identify additional studies through hand searches of reference lists of included studies and reviews. In addition, we searched the FDA's Center for Drug Evaluation and Research for medical and statistical reviews. Finally, we requested dossiers of published and unpublished information from the relevant pharmaceutical companies for this review. All received dossiers were screened for studies or data not found through other searches. All citations were imported into an electronic database (Endnote® X4, Thompson Reuters).

Study Selection

All citations were reviewed for inclusion using the criteria shown in Table 6. One reviewer assessed titles and abstracts and a second reviewer assessed excluded titles and abstracts for inclusion. If both reviewers agreed that the trial did not meet eligibility criteria, it was excluded. Full-text articles of potentially relevant citations were retrieved and again were assessed for inclusion by 2 reviewers. Disagreements were resolved by consensus. Results published *only* in abstract form and unpublished data were not included unless adequate details were available for quality assessment.

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Table 6. Study inclusion criteria

Populations
- Adult or pediatric outpatients with persistent asthma
- Persistent asthma is defined using the NAEPP classification[1] (see Table 1)
- Outpatients with chronic obstructive pulmonary disease (COPD)

Interventions/Treatments

Inhaled corticosteroids:
- Beclomethasone
- Budesonide
- Ciclesonide
- Flunisolide
- Fluticasone propionate
- Triamcinolone acetonide
- Mometasone furoate

Long-acting beta-2 agonists (LABAs)
- Formoterol
- Arformoterol
- Salmeterol
- Indacaterol

Leukotriene modifiers
- Montelukast
- Zafirlukast
- Zileuton

Combination products – ICS/LABA
- Fluticasone propionate/salmeterol
- Budesonide/formoterol
- Futicasone furoate/vilanterol
- Mometasone furoate/formoterol

Combination products-LAMA/LABA
- Umeclidinium /vilanterol

Phosphodiesterase-4 inhibitor
- Roflumilast

Long-acting anticholinergics
- Tiotropium
- Aclidinium

Efficacy and effectiveness outcomes
- Control of symptoms (e.g., days/nights/frequency of symptoms, rate of asthma exacerbations, frequency of rescue medication use, courses of oral steroids)
- Functional capacity and quality of life (missed school and missed work days, ability to participate in work/school/sports/physical activity, activity limitation, improved sleep/sleep disruption)
- Urgent care services (Emergency department visits/urgent medical care visits)
- Persistence
- Hospitalization
- Mortality

Adverse events/safety outcomes
- Overall adverse events
- Withdrawals due to adverse events
- Serious adverse events (e.g., acute adrenal crisis, fractures, mortality)
- Specific adverse events (e.g. growth suppression, bone mineral density/osteoporosis, ocular toxicity, suppression of the HPA axis, tachycardia, anaphylaxis, death)

Study designs
- For efficacy and effectiveness, head-to-head RCTs of at least 12 weeks duration (N ≥100) and good-quality systematic reviews
- For adverse events/safety, RCTs of at least 12 weeks (N ≥ 100) and observational studies of at least 6 months duration (N ≥ 100)

For efficacy and effectiveness, we initially included randomized controlled trials (RCTs) of 6 weeks duration and a sample size n ≥ 40 but later changed these criteria to 12 weeks duration and a sample size ≥ 100 to reduce the number of small studies of short duration (which

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would likely have less meaningful results than would larger studies of longer duration). We removed previously included studies no longer meeting the updated criteria or conducted sensitivity analysis to determine if their inclusion in meta-analyses significantly changed the outcome. Due to the streamlined nature of this review, we included only head-to-head studies for efficacy and effectiveness and did not include any placebo-controlled trials for effectiveness or harms. We also did not update, and removed from this report, the prior sections on inhaled corticosteroids (ICSs) plus long-acting beta-2 agonists (LABAs) compared with ICS at the same dose. We felt this was similar to a placebo controlled trial and any trial with this design (any 2 drugs vs. 1 of the drugs at the same dose, including ICS plus leukotriene modifier (LM) compared with same-dose ICS) was excluded from this review. We also did not update, and removed from the previous report, trials of therapy with anti-IgE medications as well as therapy with short-acting products. In addition, we did not include studies that compared a class of drugs with another class of drugs without stratifying the evidence by individual drug comparisons. For efficacy and effectiveness we focused on mortality, exacerbations, hospitalizations, emergency department visits, and quality of life. For harms we focused on withdrawals due to adverse events, total patients experiencing any adverse events, and total patients experiencing any serious adverse event. We considered these outcomes potentially more objective than other outcomes (e.g., symptom scores, activity limitation).

We reviewed the literature using a hierarchy of evidence approach, where the best evidence is the focus of our synthesis for each question, population, intervention and outcome addressed. Results from well-conducted, systematic reviews and head-to-head trials provide the strongest evidence to compare drugs with respect to effectiveness, efficacy, and adverse events; head-to-head trials were defined as those comparing 1 included treatment of interest (those listed in Table 6) with another treatment of interest. We did not include studies that compare step-down therapy for people with stable asthma, different doses of the same medication, or the same drug therapies in 2 versus 1 inhaler. We did not include studies evaluating adjustable dosing strategies unless there was another eligible comparator arm.

A review was considered to be systematic if it presented a systematic approach to reviewing the literature through a comprehensive search strategy, provided adequate data from included studies, and evaluated the methods of included studies (with quality review/critical appraisal).

Data Abstraction

We abstracted information on population characteristics, interventions, subject enrollment, and discontinuation and results for efficacy, effectiveness, and harms outcomes for trials, observational studies, and systematic reviews. We recorded intent-to-treat results when reported. If true intent-to-treat results were not reported, but loss to follow-up was very small, we considered these results to be intent-to-treat results. In cases where only per protocol results were reported, we calculated intent-to-treat results if the data for these calculations were available.

Validity Assessment (Quality Assessment)

We assessed the internal validity (quality) of trials based on the predefined criteria of the Drug Effectiveness Review Project.[40] We rated the internal validity of each trial based on the methods used for randomization, allocation concealment, and blinding; the similarity of compared groups

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at baseline; adequate reporting of dropouts, attrition, and the use of intention-to-treat analysis. Trials that had a fatal flaw were rated poor quality; trials that met all criteria were rated good quality; the remainder were 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 *possibly* valid. A poor-quality trial is not valid—the results are at least as likely to reflect flaws in the study design as a true difference between the compared drugs. A fatal flaw is reflected by failing to meet combinations of items of the quality assessment checklist.

The criteria we used to rate observational studies of adverse events reflected aspects of the study design that were particularly important for assessing adverse event rates (patient selection methods, degree to which all patients were included in analysis, *a priori* specification and definition of adverse events, method of identification and ascertainment of events, adequate duration of follow-up for identifying specified events, and degree to which and methods used to control for potentially confounding variables in analyses).

Included systematic reviews were also rated for quality based on predefined criteria: clear statement of the questions(s), inclusion criteria, adequacy of search strategy, validity assessment, adequacy of detail provided for included studies, and appropriateness of the methods of synthesis.

Grading the Strength of Evidence

We graded strength of evidence based on the guidance established for the Evidence-based Practice Center Program of the Agency for Healthcare Research and Quality.[41] Developed to grade the overall strength of a body of evidence, this approach incorporates 4 key domains: risk of bias (includes study design and aggregate quality), consistency, directness, and precision of the evidence. We also considered other domains that may be relevant for some scenarios, such as equipotency (for inhaled corticosteroids), a dose-response association, plausible confounding that would decrease the observed effect, strength of association (magnitude of effect), and publication bias. Table 7 describes the grades of evidence that can be assigned. Due to time and resource constraints we set priorities for grading the strength of evidence for only a subset of the outcomes deemed to be of greatest importance to decision makers., For the current update, we graded the following outcomes: exacerbations, quality of life, mortality, hospitalizations, functional capacity, number of people with serious adverse events, and withdrawals due to adverse events.

Table 7. Definitions of the grades of overall strength of evidence[42]

Grade	Definition
High	High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of the effect and may change the estimate.
Low	Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate.
Insufficient	Evidence either is unavailable or does not permit estimation of an effect.

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Data Synthesis

We constructed evidence tables showing the study characteristics, quality ratings, and results for all included studies. We reviewed studies using a hierarchy of evidence approach, where the best evidence is the focus of our synthesis for each question, population, intervention, and outcome addressed. Trials that evaluated 1 included medication against another provided direct evidence of comparative effectiveness and adverse event rates.

In addition to discussion of the findings of the studies overall, quantitative analyses were conducted using meta-analyses on outcomes for which a sufficient number of studies reported and for studies which they were homogeneous enough such that combining their results can be justified. For the current update, we set priorities for conducting meta-analyses only for the same subset of outcomes for which we graded the strength of the evidence: exacerbations, quality of life, mortality, hospitalizations, functional capacity, number of people with serious adverse events, and withdrawals due to adverse events. In updating meta-analyses from the 2011 asthma report and the 2006 inhaled corticosteroid report, in addition to adding new evidence, we either removed data from studies that no longer met our revised eligibility criteria (≥ 12 weeks' duration; ≥ 100 patients) or conducted sensitivity analyses based on related variation in sample size and duration. We did not update meta-analyses from the 2011 asthma report and the 2006 inhaled corticosteroid report on outcomes that were not among the prespecified highest priority subset for this update. Random effects models were used for the estimation of pooled effects.[43] Forest plots are presented to graphically summarize the study results and the pooled results.[44] The I^2 statistic (the proportion of variation in study estimates due to heterogeneity) was calculated to assess heterogeneity between the effects from the studies.[45,46] Potential sources of heterogeneity were examined with subgroup analysis by factors such as study design, study quality, variations in interventions, and patient population characteristics. Meta-analyses were conducted using Stats Direct Cam Code, Altrincham UK) software, STATA 10.1 (StataCorp, College Station, Texas), or Comprehensive Meta Analysis V2.exe. When meta-analyses could not be performed, the data are summarized qualitatively.

Peer Review

We requested and received peer review of the report from 2 experts. Their comments were reviewed and, where possible, incorporated into the final document. All comments and the authors' proposed actions were reviewed by representatives of the participating organizations of the Drug Effectiveness Review Project before finalization of the report. Names of peer reviewers for the Drug Effectiveness Review Project are listed at www.ohsu.edu/drugeffectiveness.

Public Comment

This report was posted to the Drug Effectiveness Review Project website for public comment. We received comments from 4 pharmaceutical companies.

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RESULTS

Overview

This streamlined update is limited only to direct comparisons and did not include placebo controlled trials or studies that compared a class of drug with another. Owing to the streamlined focus, some studies included previously have been taken out of this update because they did not meet the streamlined inclusion criteria. A total of 197 studies from the asthma and inhaled corticosteroids report that were already included previously have been retained in this report.

For this update, a total of 2314 citations were identified from searching electronic databases, reviews of reference lists, pharmaceutical manufacturer dossier submissions, hand searching and public comment. By applying the eligibility and exclusion criteria to titles and abstracts of all identified citations, we identified 469 potentially includable citations. After reapplying the criteria for inclusion to the full texts of these citations, we ultimately included 72 publications representing 58 studies and 14 companion publications. Fifty were head-to head trials (+14 companion publications), 3 were observational studies (+1 companion publication) and 5 were systematic reviews. We received dossiers from 7 pharmaceutical manufacturers: AstraZeneca LP, Boehringer Ingelheim Pharmaceuticals, Inc., Forest Research Institute, Glaxo Smithkline, USA, Merck & Co., Inc, Sunovion Pharmaceutical Inc and Teva Pharmaceuticals, Inc. In total, we included 10 studies[47-56] and 2 companion publications that were submitted in the dossiers.[57,58]

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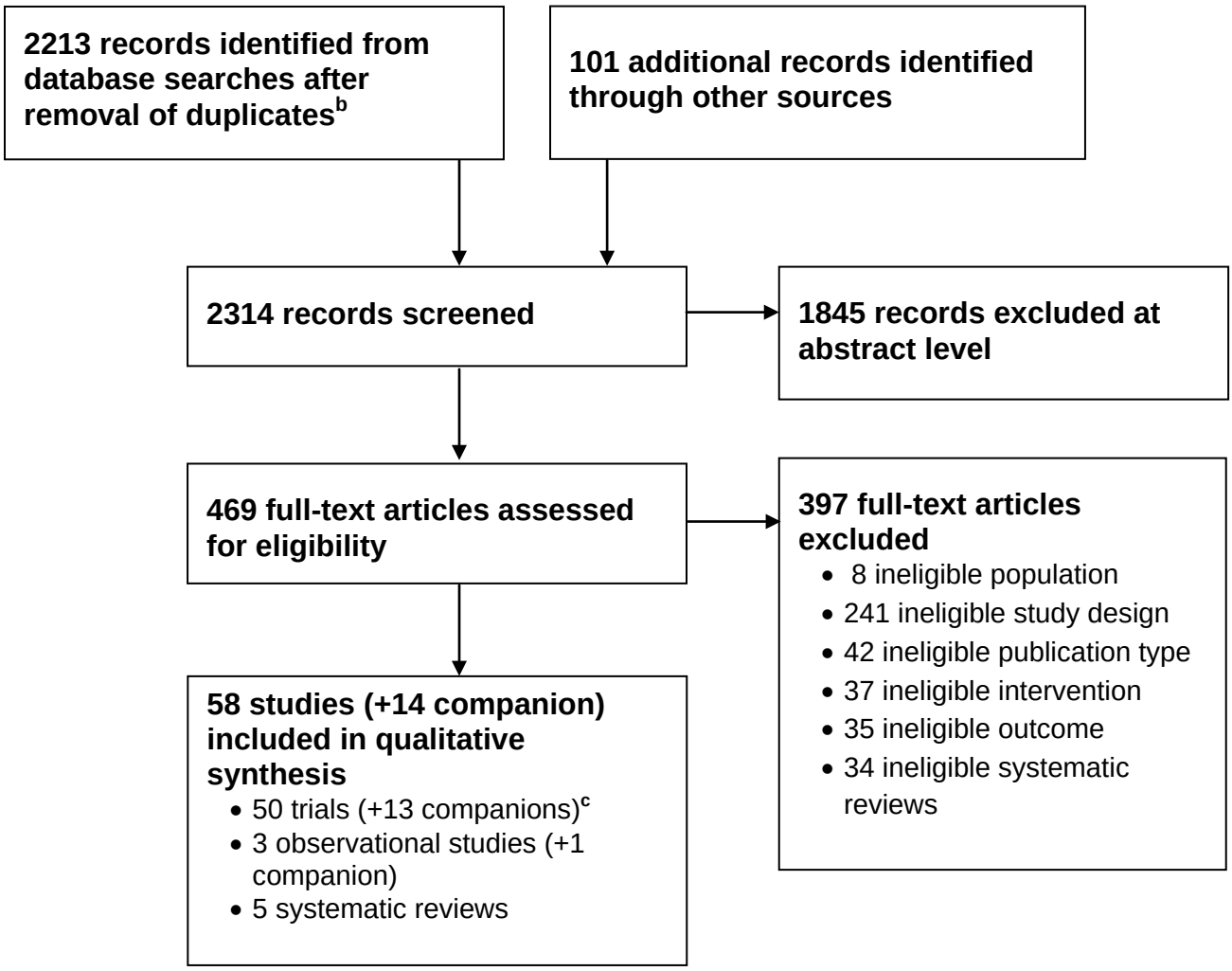
Figure 1. Results of literature search[a]



[a] DERP uses a modified PRISMA flow diagram.[59]
[b] The numbers in the flow chart pertain to streamlined original report.
[c] Of the included trials, 3 trials and 4 companion publications have not been synthesized separately as they are included as part of the systematic reviews.

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Key Question 1. Efficacy and Effectiveness

What is the comparative efficacy and effectiveness of controller medications used to treat outpatients with persistent asthma or COPD?

I. Intra-class Comparisons (within a class)

A. Inhaled Corticosteroids

Asthma. We found 3 systematic reviews with meta-analyses[60-62] and 32 head-to-head randomized controlled trials (RCTs)[63-109] (Table 8). Five head-to-head RCTs included children < 12 years (Table 9).[79,82,99,100,106] No study was characterized as an effectiveness trial; all included efficacy studies were conducted in narrowly defined populations.

Overall, efficacy studies provide moderate evidence that inhaled corticosteroids (ICSs) do not differ in their ability to control asthma symptoms, prevent exacerbations, and reduce the need for additional rescue medication at equipotent doses administered through comparable delivery devices (Appendix E, Table E-1, E-11). Relatively few studies reported exacerbations, healthcare utilization (hospitalizations, emergency visits), or quality of life outcomes. Long-term data beyond 12 weeks is lacking for most of the comparisons. In children, head-to-head trials support the conclusion that ICSs do not differ in their impact on health outcomes, but data were only available for 5 comparisons (3 systematic reviews and 5 RCTs): beclomethasone dipropionate (BDP) compared with budesonide (BUD), BDP compared with fluticasone propionate (FP), BUD compared with ciclesonide (CIC), BUD compared with FP, and CIC compared with FP. We conducted meta-analyses for comparisons within this section when sufficient data were available and a recent meta-analysis was not already published. There were often too few trials comparing equipotent ICS doses reporting similar outcomes measures to allow quantitative synthesis.

COPD. Currently no ICS monotherapy is approved by the FDA for the treatment of COPD. We did not find any head-to-head trials comparing an ICS with another.

Detailed assessment

Description of studies

One systematic review with meta-analysis and 2 RCTs compared BDP with BUD; 2 systematic reviews with meta-analyses and 7 RCTs compared BDP with FP; 2 RCTs compared BDP with mometasone furoate (MF); 5 RCTs compared BUD with CIC; 1 meta-analysis and 5 RCTs compared BUD with FP; 1 RCT compared BUD with MF; 1 RCT compared BUD with triamcinolone acetonide (TAA); 8 RCTs compared CIC with FP; 2 RCTs compared FP with MF; and 3 RCTs compared FP with TAA in patients with asthma (Table 8).

Based on National Asthma Education and Prevention Program equipotent dose estimates (Table 4), 35 head-to-head RCTs included equipotent comparisons for some arms (6 of these had multiple arms, with both equipotent and non-equipotent comparisons)[47,63,72,85,92,95,97,110] and 10 RCTs (compared only non-equipotent doses.[71,75,77,83,87,89,103,105,111] Of the 22 head-to-head trials that compared equivalent doses, 6 compared high dose to high dose, 5 compared medium dose to medium dose, 6 compared low dose to low dose. The most commonly used delivery devices were MDIs and DPIs; 12 studies (38%) compared MDI to MDI; 8 studies (25%) compared DPI

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to DPI; 11 studies (34%) compared MDI to DPI; 1 study (3%) compared both DPI to DPI and MDI to DPI.[80]

Study populations

The 32 head-to-head RCTs included a total of 14,429 asthma patients. Most studies were conducted in adult populations. Five studies[79,82,99,100,106] were conducted primarily in pediatric populations. Seven studies (22%) were conducted in the United States, 5 (16%) in Europe, 1 in India (3%), and 19 (59%) were other multinational combinations often including Europe, Canada, or the United States. Asthma severity ranged from mild persistent to severe persistent: 4 studies (13%) were conducted in patients with mild to moderate persistent asthma, 8 (25%) in patients with mild to severe persistent asthma, 5 (16%) in patients with moderate persistent asthma, 7 (22%) in patients with moderate to severe persistent asthma, and 3 (9%) in patients with severe persistent asthma. Five studies did not report the severity or severity could not be determined.

Other asthma medications were often allowed if maintained at a constant dose; all trials allowed the use of a short-acting beta-agonist. Most trials enrolled patients who were currently being treated with ICS.

Methodologic quality

The overall quality of the head-to-head trials included in our review was rated fair to good. Most trials received a quality rating of fair. The method of randomization and allocation concealment were rarely reported.

Sponsorship

Of the 32 head-to-head trials, 30 (94%) were funded by pharmaceutical companies; 1 study was funded by the government (3%), and 1 study (3%) did not report funding sources

Head-to-head comparisons

Beclomethasone dipropionate (BDP) compared with budesonide (BUD)

One good systematic review[60] and 2 fair head-to-head RCTs[94,109] comparing BDP to BUD met our inclusion criteria.

The systematic review[60] included 24 studies (1174 subjects); 18 of these were in adults. Twelve studies (50%) had treatment periods of between 2 and 4 weeks, 10 studies (42%) had treatment periods of between 6 and 12 weeks. The longest study had an effective treatment period of 2 years. As an inclusion criterion for the review, all studies had to assess equal nominal daily doses of BDP and BUD. Results were distinguished by whether patients were not treated with regular oral corticosteroids (OCS) (20 studies) or were dependent on regular OCS. Studies were further divided by parallel and crossover designs. The majority of crossover trials had significant design flaws, so the results should be viewed with caution.

For asthma patients not treated with OCS, crossover studies showed no significant difference between treatments for symptom measures (variety of symptom scores reported) or rescue medication use. There was no significant difference between BDP and BUD for daytime breathlessness, morning breathlessness, and daily symptom scores (6 studies, 256 subjects; standardized mean difference (SMD 0.06, 95% CI: -0.18, 0.31). Nor was there a significant difference in night-time breathlessness and evening breathlessness scores (3 studies, 134 subjects; SMD -0.09, 95% CI: -0.43, 0.25). Similarly, for asthma patients not treated with OCS,

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parallel group studies showed no significant differences in rescue medication use or withdrawals due to asthma exacerbations.

For asthma patients treated with OCS, 1 crossover study assessed OCS-sparing effects and 3 evaluated other outcomes. The outcomes for those that did not assess OCS-sparing effects were pooled (3 studies, 144 subjects) and found no significant difference between BDP and BUD for daytime or night-time breathlessness scores, sleep disturbance scores, or rescue medication use.

There were no RCTs comparing BDP with BUD in number of patients experiencing an exacerbation. One open-label RCT (6 months, n=225) of adult patients with mild to severe persistent asthma enrolled steroid naïve patients receiving equipotent low doses of FP 125 mcg per day, BDP 200 mcg per day and BUD 200 mcg per day via MDI according to their disease severity based on GINA guidelines.[110] Number of exacerbations were comparable with 44 versus 48 exacerbations reported in BUD versus BDP-treated patients, respectively. The same trial reports significant difference in quality-of-life between the 3 drugs on the St. George Respiratory Questionnaire (SGRQ) at 6 months (endpoint, p=0.006).[110] Mean changes from baseline for BDP and BUD were -58 and -56.8 with greater improvement with BDP (p-value NR). The strength of evidence was insufficient to draw any conclusion for this outcome due to unknown consistency and imprecision. It should be noted that although SGRQ is designed to measure quality-of-life in both asthma and COPD patients, it is primarily used in COPD. The study reports that SGRQ was used for the first time to measure quality of life in asthmatics.[110]

One non-inferiority 12-week parallel group trial (N = 460), with stratification for LABA use, compared treatment with 3 inhaled corticosteroids: BDP extrafine aerosol (Qvar Autohaler 800 mcg/d, N = 149), BUD Turbuhaler (1600 mcg/d, N = 162), and FP Diskus (1000 mcg/d, N = 149).[94] Overall asthma control was improved in all groups with no significant difference between groups, establishing non-inferiority of BDP Qvar Autohaler versus BUD, (-1.0 compared to -0.8, 95% CI -0.30 to 0.07).[94] There was low-strength evidence that BDP extrafine aerosol was statistically superior to BUD in nocturnal awakening on the Juniper asthma control questionnaire (-1.0 compared with -0.7, 95% CI -0.43 to -0.05).

Beclomethasone dipropionate (BDP) compared with ciclesonide (CIC)
We did not identify any good- or fair-quality systematic reviews or head-to-head trials that compared BDP with CIC.

Beclomethasone dipropionate (BDP) compared with flunisolide (FLUN)
We did not identify any good- or fair-quality systematic reviews or head-to-head trials that compared BDP to FLUN.

Beclomethasone dipropionate (BDP) compared with fluticasone propionate (FP)
Two systematic reviews and 11 head-to-head RCTs comparing FP to BDP met our inclusion criteria. One systematic review[61] included studies comparing FP with either BDP or BUD. Of the 71 studies included in this review, 33 compared FP to BDP (9 of those 33 were included in our review). Comparisons were stratified by FP: BDP/BUD dose ratios of 1:2 or 1:1. The pooled treatment effect of FP was compared to the pooled treatment effect for BDP and BUD. For the studies conducted at dose ratios of 1:2, pooled estimates indicate that FP-treated patients had fewer symptoms, required less rescue medication, and had a higher likelihood of pharyngitis (see Key Question 2) than those treated with BDP or BUD. There was no difference in exacerbations.

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For the studies conducted at dose ratios of 1:1, individual studies and pooled estimates suggest no difference in symptoms, rescue medicine use, or the number of asthma exacerbations. Although we rated the quality of this review as good, the comparison of FP to the combined effect of BDP and BUD limits possible conclusions regarding the *specific* comparison of BDP to FP.

The other systematic review[62] compared either CFC or HFA-propelled FP with HFA-propelled extrafine BDP. The review included 9 studies (1265 participants) and found no statistically significant difference between treatments for symptom scores and quality of life.

Of the 7 RCTs that compared BDP to FP,[69,79,80,91,94,98,101,110] only 1was conducted exclusively in a population of children and adolescents aged 4-11.[79] Asthma severity ranged from mild- to severe-persistent. Doses ranged from low to high; all studies included comparisons of equipotent doses of BDP and FP. Study duration ranged from 6 to 52 weeks. All but 2 trials[91,98,110] assessed asthma symptoms and rescue medicine use.

Two fair-quality RCTs[80,91] of 1 year duration compared high doses of FP to BDP in adult patients with moderate to severe asthma. One compared BDP 1500 mcg/day and FP 1500 mcg/day taken via MDI[80] while the other compared 1000 mcg FP/day to 2000 mcg per day BDP via MDI.[91] Exacerbations defined as increase in asthma symptoms leading to change in therapy other than beta$_2$-agonist occurred in 16% and 28% of patients taking FP and BDP ($p<0.05$)[80] and in 39% and 48% of patients respectively (*P*=NS).[91] There is low-strength evidence in adults that FP is better than BDP in proportion of patients with exacerbation (RR 0.71; 95% CI 0.51 to 0.99). Two studies of 3[69] and 6[110] months duration in adults reported higher number of exacerbations in FP versus BDP. Evidence for exacerbations is insufficient in children (16% treated with FP experienced an exacerbation versus 19% of children treated with BDP) based on a single study.[79] There is also insufficient-strength evidence to draw any conclusions regarding comparative efficacy of FP or BDP in quality-of-life outcomes. Only 1 study reported on quality of life in adult patients with mild to severe asthma. Treatment with FP resulted in improved St. George's Respiratory Questionnaire (SGRQ) total score at 6 months versus BDP.[110] The mean change from baseline in total SGRQ total score was -59.3, -58 for FP, and BDP respectively.

There was moderate-strength evidence from two 12 week trials that FP is similar to BDP in nighttime awakening. One study of non-smoking adults compared low and medium doses of FP 88 mcg, 200 mcg or BDP 168 mcg and 336 mcg/day in patients with mild to and severe asthma.[101] Comparison of combined drug effect of FP vs BDP found no significant difference between groups. The second trial compared high doses of BDP extrafine aerosol, Qvar Autohaler 800 mcg/day, BUD Turbuhaler 1600 mcg/day and FP Diskus 1000 mcg/day with stratification for LABA use (2:1 yes:no) indicated non-inferiority for BDP versus FP in nocturnal awakening assessed by French Version of Juniper Asthma Control Questionnaire (95% CI -0.30 to 0.80) [94]

There is insufficient evidence that FP is associated with higher mortality than BDP. A 12 month study of patients with moderate to severe asthma receiving high dose 1500 mcg FP/day MDI reported 2 deaths compared to 1 death on patients taking 1500 mcg BDP/day MDI (RR 1.86; 95% CI 0.25 to 14.11).[80]

Beclomethasone dipropionate (BDP) compared with mometasone furoate (MF)

Two fair-quality RCTs[68,95] compared treatment with BDP and MF for 12 weeks. Both compared medium-dose BDP MDI (336 mcg/d) and multiple doses of MF DPI (low-dose 200 mcg/d and medium-dose 400 mcg/d in both studies, and high-dose 800 mcg/d in 1 study),[68] in patients at least 12 years old with persistent asthma. Both studies found no statistically significant

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differences between BDP and MF for symptoms, nocturnal awakenings, and rescue medicine use.

Beclomethasone dipropionate (BDP) compared with triamcinolone acetonide (TAA)
We did not identify any good- or fair-quality systematic reviews or head-to-head trials that compared BDP with TAA.

Budesonide (BUD) compared with ciclesonide (CIC)
Five fair-quality multicenter RCTs meeting our inclusion criteria compared BUD with CIC.[71,85,103,106,112] All 5 were 12 weeks in duration. One was conducted in children age 6-11[106] and 1 in adolescents 12-17 years old.[112] One was conducted using subjects with mild to moderate persistent asthma, 2 with mild to severe, 1 with moderate to severe, and 1 with severe persistent asthma. Two trials only compared nonequivalent doses with CIC given at a higher relative dose than BUD.[71,103] The 3 studies comparing equivalent doses were non-inferiority trials. All studies used dry powder formulations of BUD and HFA-MDI for CIC. All 5 trials evaluated outcomes for asthma symptoms and rescue medicine use and all but 1[85] reported exacerbations. All 5 trials were funded by pharmaceutical companies.

Overall, the evidence from the 3 studies comparing equivalent doses (low versus low or medium versus medium doses of ICSs) was consistent, finding CIC to be non-inferior to BUD. All 3 studies reported similar improvement in symptoms,[85,106,112] rescue medication use,[85,106,112] and quality of life [106,112] for subjects treated with CIC and those treated with BUD.

Budesonide (BUD) compared with flunisolide (FLUN)
We did not identify any good- or fair-quality systematic reviews or head-to-head trials that compared BUD to FLUN.

Budesonide (BUD) compared with fluticasone propionate (FP)
One previously-described systematic review and 8 head-to-head RCTs comparing FP to BUD met our inclusion criteria. The systematic review[61] included studies comparing FP with BDP or BUD. Of the 71 studies included in this review, 37 compared FP to BUD. Comparisons were stratified by FP: BDP/BUD dose ratios of 1:2 or 1:1. The pooled treatment effect of FP was compared to the pooled treatment effect for BDP and BUD. For the studies conducted at dose ratios of 1:2, pooled estimates indicate that FP-treated patients had fewer symptoms, required less rescue medication, and had a higher likelihood of pharyngitis (see Key Question 2) than those treated with BDP or BUD. There was no difference in exacerbations. For the studies conducted at dose ratios of 1:1, individual studies and pooled estimates suggest no difference in symptoms, rescue medicine use, or the number of asthma exacerbations. Although we rated the quality of this review as good, the comparison of the effectiveness of BUD and FP cannot be clearly ascertained from this systematic review[61] because the comparator group contains both BUD and BDP.

Five fair-rated head-to-head RCTs meeting our inclusion criteria compared BUD to FP.[82,87,94,102,110] Trial duration ranged from 12 to 26 weeks. One was conducted in children and adolescents; [82,88]4 were conducted in patients with moderate and/or severe persistent asthma,[82,87,94,102] while 1 was conducted in patients with mild, moderate and severe asthma.[110] Two trials compared nonequivalent doses with FP given at a higher relative dose than BUD.

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[87,88,111] All but 1 study[111] used dry powder formulations of both medications. Four trials evaluated outcomes for asthma symptoms and rescue medicine use.[63,76,82,87,88,90,94,102]

Two fair-quality RCTs compared high doses of FP to high doses of BUD[87,102] in adult patients with moderate to severe asthma. The duration of studies ranged between 12 and 24 weeks. There is insufficient evidence to draw conclusions for exacerbations in adults. A higher proportion of exacerbations was reported in the 24-week study in patients taking FP compared to BUD. [87] However, in the 12 week study, more patients taking BUD reported exacerbations compared to FP.[102] None of the studies reported any significant difference between groups (pooled relative risk 1.01, 95% CI 0.70 to 1.45). It should be noted that in the 24 week study, although both groups received 2000µg/day FP or BUD DPI high doses, the relative potency of FP is greater at the given dose. A 20-week double blind, double dummy trial in children 4-12 years with moderate to severe asthma receiving medium doses of FP 400 mcg/day DPI or BUD 800 mcg/day DPI reported similar results with no statistically significant difference between 2 groups in exacerbations (RR 0.25, 95% CI 0.06 to 1.03) although the point estimate favored FP.[82] Evidence for exacerbations in both adults and children is insufficient to support any conclusions about comparative effectiveness of BUD and FP.

Another trial of 6 months duration in 225 patients experiencing mild to severe asthma reported number of exacerbations.[110] Patients received FP 125 mcg/day or 200 mcg/day, BDP or BUD via MDI according to the disease severity based on GINA guidelines. Higher number of exacerbations were reported in patients taking BUD compared to FP (44 vs 34, p=NR). The same study reported quality of life using SGQL and found greater improvement with FP versus BUD. (p=NR between groups). [110] This evidence was insufficient to draw conclusions on the comparative efficacy of FP and BUD regarding quality of life.

A 24-week study in adults comparing FP 2000 mcg/day DPI to BUD 2000 mcg/ day DPI reported significantly fewer number of days absent from work when patients were treated with FP compared to BUD (p=0.012).[87] Evidence is low-strength that FP is associated with better functional capacity compared to BUD in adults.

Three trials comparing equipotent doses of FP and BUD did not find any difference between drugs in symptoms and rescue medication use.[82,94,102] A fourth trial[87] compared non-equivalent doses (relative potency of FP was greater at the doses given) and found FP to be superior to BUD for symptoms, rescue medicine use.

Budesonide (BUD) compared with mometasone furoate (MF)

One fair-quality 12-week RCT[72] compared BUD and MF. The study randomized 730 persons 12 years and older with moderate persistent asthma to medium dose (800 mcg/day) BUD or low-, medium-, or high-dose (200, 400, 800 mcg/day, respectively) MF.[72] There were no statistically significant differences between medium-dose BUD and medium-dose MF for symptoms or nocturnal awakenings, but patients treated with medium-dose MF had a greater decrease in rescue medicine use than those treated with medium-dose BUD (-90.66 mcg/d compared with -33.90 mcg/d; $P < 0.05$).

Budesonide (BUD) compared with triamcinolone acetonide (TAA)

One fair-rated 52-week RCT[108] met our inclusion/exclusion criteria for this comparison. The trial randomized 945 adults ≥18 with mild, moderate, or severe persistent asthma to BUD DPI (mean dose at start and end: 941.9 and 956.8 mcg/d) or TAA pMDI (1028.2 and 1042.9 mcg/d, respectively). On average, patients were treated with medium doses, but starting doses and dose

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adjustments were left to the discretion of the clinical investigator. Patients treated with BUD had greater improvements in symptom- and episode-free days ($P<0.001$), daytime and nighttime asthma symptom scores ($P<0.001$), and quality of life ($P<0.001$) than those treated with TAA.

Ciclesonide (CIC) compared with flunisolide (FLUN)
We did not identify any good- or fair-quality systematic reviews or head-to-head trials that compared CIC to FLUN.

Ciclesonide (CIC) compared with fluticasone propionate (FP)
Eight fair-quality RCTs meeting our inclusion criteria compared CIC with FP.[66,70,74,78,89,93,99,100] Six were 12 weeks in duration, 1 was 24 weeks,[78] and 1 was 6 months.[66] Two enrolled children.[99,100] Three were conducted in subjects with mild to severe persistent asthma; 2 in subjects with moderate persistent asthma;[70,74] and 1 each in mild to moderate[78] and moderate to severe persistent asthma.[66] One trial did not report sufficient information to determine the severity of persistent asthma.[89] All but 1 trial compared equipotent doses of ICSs. [89] Five of the trials comparing equipotent doses compared low dose CIC with low dose FP; 1 compared medium doses [70] and 1 compared high doses.[66] All but 1 trial used HFA-MDI for delivery of both medications.[70] All 8 RCTs were funded by pharmaceutical companies producing CIC.

Overall, the evidence from these studies supports the conclusion that there is no difference in the outcomes of interest between equipotent doses of CIC and FP. All 7 trials comparing equipotent doses reported non-inferiority of CIC compared to FP or no statistically significant difference for the outcomes of interest with 1 exception. All of the trials used some measure to assess symptoms and rescue medication use; all but 1 assessed exacerbations; and 4 assessed quality of life. The 1 exception was reported in a 12-week trial of 474 subjects, which found greater improvement in quality of life with CIC versus FP (mean change from baseline in AQLQ: 0.29 vs. 0.11, $P = 0.005$ for 1-sided superiority).[70] The same trial reported non-inferiority or no statistically significant difference between medications for symptoms.

We conducted meta-analyses of these studies for exacerbations, symptoms, and rescue medication use and found no statistically significant differences between CIC and FP (Appendix E). There was no statistically significant difference between CIC and FP for exacerbations requiring treatment with oral steroids (OR 0.97, 95% CI: 0.50 to 1.88), improvement in symptom scores (SMD 0.016, 95% CI: -0.05 to 0.08), or change in rescue medication use (SMD 0.03, 95% CI: -0.03 to 0.09). There was no significant statistical heterogeneity for any of these analyses ($I^2 = 0$ for all).

Ciclesonide (CIC) compared with mometasone furoate (MF)
We did not identify any good- or fair-quality systematic reviews or head-to-head trials that compared CIC with MF.

Ciclesonide (CIC) compared with triamcinolone acetonide (TAA)
We did not identify any good or fair-quality systematic reviews or head-to-head trials that compared CIC with TAA.

Flunisolide (FLUN) compared with fluticasone propionate (FP)
We did not identify any good- or fair-quality systematic reviews or head-to-head trials that compared FLUN to fluticasone propionate.

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Flunisolide (FLUN) compared with mometasone furoate (MF)
We did not identify any good- or fair-quality systematic reviews or head-to-head trials that compared BDP to FLUN.

Flunisolide (FLUN) compared with triamcinolone acetonide (TAA)
We did not identify any good- or fair-quality systematic reviews or head-to-head trials that compared BDP to FLUN.

Fluticasone propionate (FP) compared with mometasone furoate (MF)
Two fair-rated trials comparing FP with MF met our inclusion/exclusion criteria.[86,97,107] One fair-rated dose-ranging study (N = 733) conducted in 60 study centers compared medium-dose FP (500 mcg/day) to low-, medium-, and high-dose MF (200, 400, and 800 mcg/day, respectively) in 733 patients 12 years and older with moderate persistent asthma.[97] The investigators found no statistically significant differences at endpoint between patients treated with medium-dose FP and those treated with medium- and high-dose MF with respect to wheeze and cough scores, nighttime awakenings, or rescue medication use ($P>0.05$ for all). However, patients treated with medium-dose FP had significantly greater improvement in the number of nighttime awakenings ($P < 0.05$) than did those treated with low-dose MF. In addition, patients on medium-dose FP had significantly better morning difficulty breathing scores than did patients on either low- or medium-dose MF ($P<0.05$).

A second study was a multinational trial (N=203) that compared high dose MF (800 mcg/day) with high dose FP (1000 mcg/day) for 12 weeks.[86] The investigators found no statistically significant differences at endpoint with respect to rescue medication use, symptoms, and exacerbations.

Fluticasone propionate (FP) compared with triamcinolone acetonide (TAA)
Three fair-rated trials comparing FP to TAA met our inclusion/exclusion criteria.[64,75,83] Only 1 of the 3 trials comparing equipotent doses[64] found greater improvements in subjects treated with FP. The other 2 trials comparing non-equipotent doses[75,83] reported greater improvements for FP-treated subjects for some outcomes and no difference for the others.

The trial comparing equipotent doses[64] was a 12-week, multicenter RCT (N = 680) comparing medium-dose FP MDI (440 mcg/d), medium-dose TAA MDI (1200 mcg/d), and the combination of FP (196 mcg/d) and salmeterol (SM). Subjects were at least 12 years of age and were poorly controlled on ICS therapy. Fluticasone propionate-treated subjects had better improvements in symptoms, nighttime awakenings, and rescue medicine use.

The 2 studies comparing non-equipotent doses were similarly designed fair-quality RCTs[75,83] conducted in 24 outpatient centers. Subjects in both were randomized to medium-dose FP (500 mcg/day by DPI), low-dose TAA (800 mcg/day by MDI with spacer), or placebo for 24 weeks. Both were conducted in subjects 12 years or older previously treated with ICS. No differences were found in symptom scores or in the percentage of symptom-free days. Subjects treated with FP had greater improvements in rescue medicine requirements in both studies than those treated with TAA. One of the trials reported greater improvement in nighttime awakenings[83] for those treated with FP, but the other reported no difference.[75] One reported significantly better improvements in quality of life for FP-treated patients compared to TAA-treated patients.[83]

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Table 8. Characteristics of head-to-head studies comparing inhaled corticosteroids in children and adults

Study	Study Design N Duration	Country Population Setting	Comparison (total daily dose in mcg)	Quality Rating
Beclomethasone compared with budesonide				
Adams et al. 2000[60]	Systematic review with meta-analysis 24 studies (1174 subjects), 5 parallel, 19 cross-over (2 had a washout) Range 2 weeks to 2 years; 50% were 2-4 weeks	Majority in Europe 24 trials (6 trials in children, 18 in adults)	BDP compared with BUD all studies assessed equal nominal daily doses of BDP and BUD	Good
Molimard et al. 2005[94]	RCT, open-label 460 12 weeks	France Age 18-60, moderate to severe persistent, not controlled on ICS, smoking status NR Multicenter, subspecialty clinics (69 pulmonologists)	BDP MDI (800) compared with BUD DPI (1600) compared with FP DPI (1000)	Fair
Padukudru et al[110]	RCT, open label 225 6 months	India Mean Age 35.8 years, mild to severe, steroid naïve	BDP MDI(200) BUD MDI (200)	Fair
Beclomethasone compared with ciclesonide				
No systematic reviews or head-to-head trials found				
Beclomethasone compared with flunisolide				
No systematic reviews or head-to-head trials found				

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Table 8. Characteristics of head-to-head studies comparing inhaled corticosteroids in children and adults

Study	Study Design N Duration	Country Population Setting	Comparison (total daily dose in mcg)	Quality Rating
Beclomethasone compared with fluticasone				
Adams et al. 2007[61]	Systematic review with meta-analysis 71 trials (14,602 participants), 59 parallel, 14 cross-over (4 had a washout) Majority of studies (47) were between 6 weeks and 5 months; 14 were ≤4 weeks	Multinational (most in Europe) Severity ranged from mild to severe persistent	FP compared with BDP (33 trials) FP compared with BUD (37) FP compared with BDP/BUD (2) 38 studies had FP:BDP/BUD dose ratio of 1:2; 22 had dose ratio 1:1; remainder had multiple dose ratio comparisons or ratio was unclear	Good
Lasserson et al. 2010[62]	Systematic review with meta-analysis 9 trials (1265 participants) 3 to 12 weeks	Multinational (most in Europe) Severity ranged from mild to severe persistent	FP compared with extrafine HFA BDP	Good
Boe et al. 1994[69]	RCT, DB 134 12 weeks	Norway Age ≥ 18, poorly controlled, 34% smokers Multicenter	FP DPI (1600) compared with BDP DPI (2000)	Fair
de Benedictis et al. 2001[79]	RCT, DB 434 52 weeks	Multinational (7 countries: Holland, Hungary, Italy, Poland, Argentina, Chile, South Africa) Age 4-11, prepubertal, severity and smoking status NR Multicenter (32)	FP DPI (400) compared with BDP DPI (400)	Fair

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Table 8. Characteristics of head-to-head studies comparing inhaled corticosteroids in children and adults

Study	Study Design N Duration	Country Population Setting	Comparison (total daily dose in mcg)	Quality Rating
Fabbri et al. 1993[80]	RCT, DB 274 12 months (daily symptom outcomes collected for initial 12 weeks)	Multinational (10 European) Age 12-80, moderate to severe, not controlled on ICS, 11% smokers Multicenter (25)	FP MDI (1500) compared with BDP MDI (1500)	Fair
Lorentzen et al. 1996[91]	RCT, DB 213 12 months	Multinational (7, Europe) Age 18-77, severe, well controlled on high dose ICS, 19% smokers Multicenter (20 outpatient clinics)	FP MDI (1000) compared with BDP MDI (2000)	Fair
Molimard et al. 2005[94]	RCT, open-label 460 12 weeks	France Age 18-60, moderate to severe persistent, not controlled on ICS, smoking status NR Multicenter, subspecialty clinics (69 pulmonologists)	BDP MDI (800) compared with BUD DPI (1600) compared with FP DPI (1000)	Fair
Padukudru et al[110]	RCT, open label 225 6 months	India Mean Age 35.8 years, mild to severe, steroid naïve	BDP MDI(200) FP MDI (125)	Fair
Raphael et al. 1999[101]	RCT, DB, DD 399 12 weeks	US Age ≥ 12 years, mild to severe, not controlled on ICS, smokers excluded Multicenter, specialty asthma and primary care centers (23)	FP MDI (164) compared with FP MDI (440) compared with BDP MDI (336) compared with BDP MDI (672)	Fair

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Table 8. Characteristics of head-to-head studies comparing inhaled corticosteroids in children and adults

Study	Study Design N Duration	Country Population Setting	Comparison (total daily dose in mcg)	Quality Rating
Beclomethasone compared with mometasone furoate				
Bernstein et al. 1999[68]	RCT, DB, DD 365 12 weeks	US Age ≥12, mild to moderate, on ICS, smokers excluded Multicenter (20)	Mometasone furoate DPI (200) vs. Mometasone furoate DPI (400) vs. Mometasone furoate DPI (800) vs. BDP MDI (336) vs. placebo	Fair
Nathan et al. 2001[95]	RCT, DB, DD 227 12 weeks	US Age ≥ 12, moderate, on ICS, smokers excluded Multicenter (15)	Placebo vs. Mometasone furoate DPI (200) vs. Mometasone furoate DPI (400) vs. BDP MDI (336)	Fair
Beclomethasone compared with triamcinolone acetonide				
No systematic review or head- to- head trials found				
Budesonide compared with ciclesonide				
Boulet et al. 2006[71]	RCT, DB, DD 359 12 weeks	Multinational - Canada and Europe Age 12-75, mild to moderate, on ICS, heavy smokers or ex-smokers excluded (>10 cigarettes/day) Multicenter	CIC HFA-MDI (320) vs. BUD DPI (320)	Fair
Hansel et al. 2006[85]	RCT 554 12 weeks	Multinational - Europe Age 12-75, mild to severe, on ICS, 9% smokers Multicenter	CIC HFA-MDI (80) vs. CIC HFA-MDI (320) vs. BUD DPI (400)	Fair

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Table 8. Characteristics of head-to-head studies comparing inhaled corticosteroids in children and adults

Study	Study Design N Duration	Country Population Setting	Comparison (total daily dose in mcg)	Quality Rating
Ukena et al. 2007[103]	RCT, DB, DD 399 12 weeks	Germany Age 12-75, mild to severe, smokers excluded Multicenter	CIC HFA-MDI (320) vs. BUD DPI (400)	Fair
Vermeulen et al. 2007[112]	RCT, DB, DD 403 12 weeks	Multinational - Hungary, Poland, Serbia/Montenegro, South Africa, Spain Age 12-17, severe, not controlled on ICS, excluded smokers Multicenter	CIC HFA-MDI (320) vs. BUD DPI (800)	Fair
von Berg et al. 2007[106]	RCT, DB, DD 621 12 weeks	Multinational - Australia, Germany, Hungary, Poland, Portugal, Serbia and Montenegro, South Africa and Spain Age 6-11, moderate to severe, smoking status NR Multicenter	CIC HFA-MDI (160) vs. BUD DPI (400)	Fair
Budesonide compared with flunisolide				
No systematic review or head-to-head trials found				
Budesonide compared with fluticasone				
Adams et al. 2007[61]	Systematic review with meta-analysis 71 trials (14,602 participants), 59 parallel, 14 cross-over (4 had a washout) Majority of studies (47) were between 6 weeks and 5 months; 14 were ≤4 weeks	Multinational (most in Europe) Severity ranged from mild to severe persistent	FP vs. BDP (33 trials) FP vs. BUD (37) FP vs. BDP/BUD (2) 38 studies had FP:BDP/BUD dose ratio of 1:2; 22 had dose ratio 1:1; remainder had multiple dose ratio comparisons or ratio was unclear	Good

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Table 8. Characteristics of head-to-head studies comparing inhaled corticosteroids in children and adults

Study	Study Design N Duration	Country Population Setting	Comparison (total daily dose in mcg)	Quality Rating
Ferguson et al. 1999[82]	RCT, DB, DD 333 20 weeks	Multinational (6 countries worldwide) Ages 4-12, moderate to severe, on ICS, smoking status NR Multicenter	FP DPI (400) vs. BUD DPI (800)	Fair
Heinig et al. 1999[87]	RCT, DB, DD 395 24 weeks	Multinational (Belgium, Canada, Denmark, Netherlands) Age 18-75, severe, not controlled on ICS, 15% current smokers Multicenter (47)	FP DPI (2000) vs. BUD DPI (2000)	Fair
Molimard et al. 2005[94]	RCT, open-label 460 12 weeks	France Age 18-60, moderate to severe persistent, not controlled on ICS, smoking status NR Multicenter, subspecialty clinics (69 pulmonologists)	BDP MDI (800) vs. BUD DPI (1600) vs. FP DPI (1000)	Fair
Padukudru et al[110]	RCT, open label 225 6 months	India Mean Age 35.8 years, mild to severe, steroid naïve	BUD MDI(200) FP MDI (125)	Fair
Ringdal et al. 1996[102]	RCT, DB, DD 518 12 weeks	Multinational Age 18-75, moderate to severe, not controlled on ICS, 19% smokers Multicenter	FP DPI (800) vs. BUD DPI (1600)	Fair

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Table 8. Characteristics of head-to-head studies comparing inhaled corticosteroids in children and adults

Study	Study Design N Duration	Country Population Setting	Comparison (total daily dose in mcg)	Quality Rating
Budesonide compared with mometasone furoate				
Bousquet et al. 2000[72]	RCT, single-blind 730 12 weeks	Multinational (17) Age ≥ 12, moderate, on ICS, smokers excluded Multicenter (57)	Mometasone furoate DPI (200) vs. Mometasone furoate DPI (400) vs. Mometasone furoate DPI (800) vs. Budesonide DPI (800)	Fair
Budesonide compared with triamcinolone acetonide				
Weiss et al. 2004[108]	RCT 945 52 weeks	US Age ≥ 18, mild to severe, smoking status NR Multicenter, patients from 25 managed care plans	BUD DPI (mean dose at start and end: 941.9 and 956.8 mcg/d) vs. TAA pMDI (1028.2/1042.9 mcg/d)	Fair
Ciclesonide compared with flunisolide				
No systematic reviews or head-to-head trials found				
Ciclesonide compared with fluticasone				
Bateman 2008[66]	RCT 528 6 months	Multinational - Europe, North America, South Africa Age 12-75, moderate to severe, on ICS, 33% ex-smokers or current smokers Multicenter	CIC HFA-MDI (640) vs. FP HFA-MDI (660)	Fair
Boulet 2007[70]	RCT 474 12 weeks	Multinational - Austria, Canada, Germany, Hungary, South Africa, Spain Age 12-75, moderate, 30% ex-smokers or current smokers Multicenter	CIC HFA-MDI (320) vs. FP DPI (400)	Fair

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Table 8. Characteristics of head-to-head studies comparing inhaled corticosteroids in children and adults

Study	Study Design N Duration	Country Population Setting	Comparison (total daily dose in mcg)	Quality Rating
Buhl 2006[74]	RCT 529 12 weeks	Multinational - Germany, Austria, The Netherlands, Spain, Hungary, Poland, South Africa Age 12-75, moderate, on ICS, smoking status NR Multicenter	CIC HFA-MDI (160) vs. FP HFA-MDI (176)	Fair
Dahl 2010[78]	RCT, DB, DD 480 24 weeks	Multinational – Austria, Canada, Germany, Poland, and South Africa Age 12-75, on ICS, mild to moderate, excluded current and ex-smokers with ≥ 10 pack-year history, 22-31% current or ex-smokers enrolled Multicenter	CIC HFA-MDI (80) vs. FP HFA-MDI (200)	Fair
Knox 2007[89]	RCT 111 12 weeks	United Kingdom, Belgium Age 17-75, on ICS, severity NR, 2-3% smokers Multicenter	CIC HFA-MDI (160) vs. FP HFA-MDI (500)	Fair
Magnussen 2007[93]	RCT 808 12 weeks	Multinational - Germany, Poland, Czech Republic, France, Italy, The Netherlands, Slovakia, Spain Age >12, mild to severe, 21-24% ex- and current smokers Multicenter	CIC HFA-MDI (80) vs. CIC HFA-MDI (160) vs. FP HFA-MDI (176)	Fair
Pedersen 2009[99]	RCT 744 12 weeks	Multinational - Brazil, Germany, Hungary, Poland, Portugal, South Africa Age 6-11, mild to severe, smoking status NR Multicenter	CIC HFA-MDI (80) vs. CIC HFA-MDI (160) vs. FP HFA-MDI (176)	Fair

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Table 8. Characteristics of head-to-head studies comparing inhaled corticosteroids in children and adults

Study	Study Design N Duration	Country Population Setting	Comparison (total daily dose in mcg)	Quality Rating
Pedersen 2006[100]	RCT 556 12 weeks	Multinational - 8 countries Age 6-15, mild to severe, excluded current smokers Multicenter	CIC HFA-MDI (160) vs. FP HFA-MDI (176)	Fair
Ciclesonide compared with mometasone furoate				
No systematic reviews or head-to-head trials found				
Ciclesonide compared with triamcinolone acetonide				
No systematic reviews or head-to-head trials found				
Flunisolide compared with fluticasone				
No systematic reviews or head-to-head trials found				
Flunisolide compared with mometasone furoate				
No systematic reviews or head-to-head trials found				
Flunisolide compared with triamcinolone acetonide				
No systematic reviews or head-to-head trials found				
Fluticasone compared with mometasone furoate				
Harnest et al. 2008[86]	RCT 203 12 weeks	Multinational Age ≥18, moderate to severe, on ICS, smoking status NR Multicenter	MF DPI (800) vs. FP DPI (1000)	Fair
O'Connor et al. 2001 [97]	RCT, DB 733 12 weeks	Multinational (20) Age ≥12, moderate, on ICS, excluded smokers Multicenter, University hospitals	MF DPI (200) vs. MF DPI (400) vs. MF DPI (800) vs. FP DPI (500)	Fair

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Table 8. Characteristics of head-to-head studies comparing inhaled corticosteroids in children and adults

Study	Study Design N Duration	Country Population Setting	Comparison (total daily dose in mcg)	Quality Rating
Fluticasone compared with triamcinolone acetonide				
Baraniuk et al. 1999[64]	RCT, DB, triple- dummy 680 12 weeks	US Age ≥12, not controlled on ICS, excluded smokers Multicenter, Pulmonary/allergy medicine clinics (50)	FP MDI (196) + Salmeterol (84) vs. FP MDI (440) vs. TAA MDI (1200)	Fair
Condemi et al. 1997[75]	RCT, DB, DD 291 24 weeks	US Age ≥12, persistent asthma, on ICS, excluded smokers Multicenter (24 outpatient centers)	FP DPI (500) vs. TAA MDI (800) vs. placebo	Fair
Gross et al. 1998[83]	RCT, DB, DD 304 24 weeks	US Age ≥12, mild to moderate, on ICS, excluded smokers Multicenter (24 respiratory care or allergy University Clinics)	FP DPI (500) vs. TAA MDI (800) vs. placebo	Fair

Abbreviations: AQLQ = Asthma Quality of Life Questionnaire; BDP = beclomethasone dipropionate; BUD = Budesonide; CI =confidence interval; CIC = ciclesonide; DB = double-blind; DD = double dummy; DPI = dry powder inhaler; FLUN = Flunisolide; FP = Fluticasone Propionate; FrACQ = French version of the Juniper Asthma Control Questionnaire; ICS = Inhaled Corticosteroids; MA=meta-analysis; MDI = metered dose inhaler; NR = not reported; NS = not statistically significant; OR= odds ratio; QOL = quality of life; RCT= randomized controlled trial; SMD = standard mean difference; SR=systematic review; TAA = Triamcinolone Acetonide.

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Table 9. Characteristics of head-to-head studies comparing inhaled corticosteroids that included children

Study	Study Design N Duration	Study Population	Comparison (total daily dose)	Quality Rating
Beclomethasone compared with budesonide				
Adams, N et al. 2000[60]	Systematic review with meta-analysis 24 studies (1174 subjects), 5 parallel, 19 cross-over (2 had a washout) Range 2 weeks to 2 years; 50% were 2-4 weeks	Majority in Europe 24 trials (6 trials in children, 18 in adults)	BDP vs. BUD all studies assessed equal nominal daily doses of BDP and BUD	Good
Beclomethasone compared with fluticasone				
Adams, et al. 2007[61]	Systematic review with meta-analysis 71 trials (14,602 participants), 59 parallel, 14 cross-over (4 had a washout) Majority of studies (47) were between 6 weeks and 5 months; 14 were ≤ 4 weeks	Multinational (most in Europe) Severity ranged from mild to severe persistent	FP vs. BDP (33 trials) FP vs. BUD (37) FP vs. BDP/BUD (2) 38 studies had FP: BDP/BUD dose ratio of 1:2; 22 had dose ratio 1:1; remainder had multiple dose ratio comparisons or ratio was unclear	Good
Lasserson et al. 2010[62]	Systematic review with meta-analysis 9 trials (1265 participants) 3 to 12 weeks	Multinational (most in Europe) Severity ranged from mild to severe persistent 2/9 trials in children	FP compared with extrafine HFA BDP	Good
De Benedicts et al. 2001[79]	RCT, DB 434 52 weeks	Multinational (7 countries: Holland, Hungary, Italy, Poland, Argentina, Chile, South Africa) Age 4-11, prepubertal, severity and smoking status NR Multicenter (32)	FP DPI (400) vs. BDP DPI (400)	Fair

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Table 9. Characteristics of head-to-head studies comparing inhaled corticosteroids that included children

Study	Study Design N Duration	Study Population	Comparison (total daily dose)	Quality Rating
Budesonide compared with ciclesonide				
von Berg et al. 2007[106]	RCT, DB, DD 621 12 weeks	Multinational - Australia, Germany, Hungary, Poland, Portugal, Serbia and Montenegro, South Africa and Spain Age 6-11, moderate to severe, smoking status NR Multicenter	CIC HFA-MDI (160) vs. BUD DPI (400)	Fair
Budesonide compared with fluticasone				
Adams et al. 2007[61]	Systematic review with meta-analysis 71 trials (14,602 participants), 59 parallel, 14 cross-over (4 had a washout) Majority of studies (47) were between 6 weeks and 5 months; 14 were ≤ 4 weeks	Multinational (most in Europe) Severity ranged from mild to severe persistent	FP vs. BDP (33 trials) FP vs. BUD (37) FP vs. BDP/BUD (2) 38 studies had FP:BDP/BUD dose ratio of 1:2; 22 had dose ratio 1:1; remainder had multiple dose ratio comparisons or ratio was unclear	Good
Ferguson et al. 1999[82]	RCT, DB, DD 333 20 weeks	Multinational (6 countries worldwide) Ages 4-12, moderate to severe, on ICS, smoking status NR Multicenter	FP DPI (400) vs. BUD DPI (800)	Fair
Ciclesonide compared with fluticasone				
Pedersen 2009[99]	RCT 744 12 weeks	Multinational - Brazil, Germany, Hungary, Poland, Portugal, South Africa Age 6-11, mild to severe, smoking status NR Multicenter	CIC HFA-MDI (80) vs. CIC HFA-MDI (160) vs. FP HFA-MDI (176)	Fair

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Table 9. Characteristics of head-to-head studies comparing inhaled corticosteroids that included children

Study	Study Design N Duration	Study Population	Comparison (total daily dose)	Quality Rating
Pedersen 2006[100]	RCT 556 12 weeks	Multinational - 8 countries Age 6-15, mild to severe, excluded current smokers Multicenter	CIC HFA-MDI (160) vs. FP HFA-MDI (176)	Fair

Abbreviations: AQLQ = Asthma Quality of Life Questionnaire; BDP = beclomethasone dipropionate; BUD = Budesonide; CI = confidence interval; CIC = ciclesonide; DB = double-blind; DD = double dummy; DPI = dry powder inhaler; FP = Fluticasone Propionate; MA = meta-analysis; MDI = metered dose inhaler; NR = not reported; NS = not statistically significant; OR= odds ratio; QOL = quality of life; RCT= randomized controlled trial; SMD = standard mean difference; SR=systematic review.

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B. Leukotriene Modifiers (LMs)

Summary of findings

Asthma. We found 2 fair-rated head-to-head trials comparing a leukotriene modifier (LM) with another that met most inclusion/exclusion criteria for our updated review (Table 10).[113,114] One trial compared montelukast (ML) and zafirlukast at recommended doses in adults with mild persistent asthma, and reported no statistically significant differences between groups in rescue medicine use and quality of life (Appendix E, Table E-2). Because this study included only 40 subjects, it would not have met inclusion criteria for this streamlined update. However, because of limited evidence available for this drug class, we felt the data were still useful to include. Another trial comparing ML to zileuton (ZIL) in 227 adults in India with mild to moderate asthma suggested slightly greater improvement in symptoms with ZIL, but did not show differences in rescue medicine use. We found no head-to-head trials comparing zafirlukast to ZIL. In addition, we found no head-to-head trials in children, or any trials of LMs in patients with COPD.

Overall, limited head-to-head evidence from 2 short-term studies (12 weeks) does not support differences between LMs in ability to decrease rescue medicine use or improve quality of life in patients with asthma, though symptoms improved slightly more with ZIL than ML in patients in India.

COPD. Leukotriene modifiers are approved for asthma only, and we found no evidence comparing a LM to another in patients with COPD.

Detailed assessment

Head-to-head comparisons

Montelukast (ML) compared with zafirlukast (ZAF)
One fair-quality, 12-week,[113] head-to-head trial comparing ML to zafirlukast in patients with asthma met the inclusion/exclusion criteria for our review. The trial compared the effect of ML (10 mg/day) and zafirlukast (40 mg/day) on quality of life and rescue medication use and enrolled 40 adults with mild persistent asthma from a subspecialty respiratory pathophysiology center in Italy. At endpoint, improvement in beta-agonist use was not significantly different between ML- and zafirlukast-treated patients. Improvements in asthma-related quality of life (AQLQ) also appeared similar between the 2 treatment groups, but a statistical comparison was not reported and given the small sample size evidence was insufficient to compare quality of life between the 2 drugs (Appendix E, Table E-2).

Montelukast (ML) compared with zileuton (ZIL)
A somewhat larger, fair-quality trial[114] compared ML with ZIL in adults in India with mild to moderate chronic asthma. Effects of 12 weeks of treatment with ML (10 mg/d, 1 daily dose) or ZIL (2,400 mg/d, two 600 mg tablets twice daily) on symptoms and the use of rescue medications were assessed. The effect of symptoms on activities and sleep was measured on a 4-point scale for each of 4 asthma symptoms, with an overall score summed across symptoms (range 0 to 16 points, where 0 indicates no symptoms). Between baseline and 12 weeks, overall scores for subjects treated with ZIL dropped 5.0 points (95% CI 4.6-5.4), and those for ML 4.2 points (95% CI 3.8-4.7); though CIs overlapped (p= 0.018). Decline in rescue medicine use did not differ between the 2 treatment groups (p=0.445).

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Zafirlukast (ZAF) compared with zileuton (ZIL)
We did not identify any good- or fair-quality systematic reviews or head-to-head trials that compared zafirlukast (ZAF) to ZIL in subjects with asthma or COPD.

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Table 10. Characteristics of head-to-head studies comparing leukotriene modifiers in children and adults with asthma

Study	Study design N Duration	Country Study population Setting	Comparison (total daily dose in mg/day)	Quality rating
Montelukast compared with zafirlukast				
Riccioni et al.[113]	RCT 40 12 weeks	Italy Age ≥12, mild, smoking status NR Respiratory Pathophysiology Center	ML (10) compared with ZAF (40)	Fair
Montelukast compared with zileuton				
Kubavat et al[114]	RCT 227 12 weeks	India Age 18-65, smoking NR 6 centers, not described	ML (10) compared with ZIL (2,400)	Fair
Zafirlukast compared with zileuton				
No systematic reviews or head-to-head trials found				

Abbreviations: AQLQ = Asthma Quality of Life Questionnaire; ML = Montelukast; NR = not reported; NS = not statistically significant; RCT= randomized controlled trial; ZAF = Zafirlukast.; ZIL = Zileuton
Symbol use: Drug X > Drug Y = statistically significant difference in outcomes favoring Drug X;
Drug X > Drug Y trend = point estimate favors Drug X, but the difference is not statistically significant or tests of statistical significance were NR;
No difference = no statistically significant difference or tests of statistical significance were not reported and outcomes are similar.

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C. Long-Acting Beta-2 Agonists (LABAs)

Summary of findings

We found 3 fair-quality RCTs in patients with asthma[115-118] that included head-to-head comparisons of 1 LABA with another LABA and met our inclusion/exclusion criteria (Table 11). All were published before 2010, when the FDA issued a boxed warning against use of LABAs as monotherapy in patients with asthma (see Key Question 2). Two compared eformoterol (eFM) with SM[115,116] and 1 compared formoterol (FM) with SM.[117,118] (Of note, FM was formerly known as eFM in the UK and these are generally considered the same drug.) Overall, results from 3 efficacy studies provide moderate evidence (Appendix E, Table E-3) that LABAs do not differ in their ability to control asthma symptoms, prevent exacerbations, improve quality of life, and prevent hospitalizations or emergency visits in patients with persistent asthma not controlled on ICSs alone.

For this update we found no additional trials comparing LABAs in patients with asthma, but did find 6 new trials in patients with COPD.[119-123] Three trials[122-124] compared the new LABA indacaterol (IC) (FDA-approved in 2011) with SM, and another compared IC with FM.[119] One trial[125] compared arformoterol (ARF) with FM, and the final trial compared FM delivered with a nebulizer to FM via dry powder inhaler. Few deaths occurred in these trials, and none provided sufficient evidence to compare mortality across LABAs. There were no statistically significant differences between drugs in risk of exacerbations or improvements in quality of life with 1 exception: quality of life favored IC at the midpoint of 1 trial,[123] but by the end of the trial the difference was not statistically significant. There was also a trend towards improved exacerbation and quality of life outcomes for FM versus ARF.

Detailed assessment

Description of studies

Of the 3 asthma trials, 2 compared eFM with SM and 1 compared FM with SM (Table 11). Study duration ranged from 8 weeks to 6 months. The most commonly used delivery devices were MDIs and DPIs: 2 studies compared DPI to DPI; 1 study compared DPI to DPI and to MDI (eFM DPI compared with SM DPI compared with SM MDI).[116]

Two of the 6 COPD trials used nebulizers; the only trial including ARF delivered both doses via a nebulizer, and 1 trial compared nebulized FM to FM via DPI.[120] All other drugs in the COPD trials were delivered via DPI. The durations of the COPD trials ranged from 12 weeks to 1 year. Another trial, with open-label design comparing FM and SM over 6 months, was rated poor for efficacy but fair for harms and is discussed in Key Question 2 below.[126]

Study populations

The 3 head-to-head asthma RCTs included a total of 1,107 subjects. Two were conducted primarily in adult populations,[115,117,118] and 1[116] in a pediatric and adolescent population (age 6-17) (Table 11). Two trials were conducted in the UK and Republic of Ireland[115,116] and 1 was conducted in France, Italy, Spain, Sweden, Switzerland and the UK.[117,118] Asthma severity ranged from mild to severe persistent: 1 study was conducted in patients with mild to moderate persistent asthma,[115] 1 in patients with moderate persistent,[116] and 1 in patients with moderate to severe persistent.[117,118] All 3 trials enrolled subjects that were not adequately controlled on ICSs. Smoking status was not reported for the pediatric/adolescent trial.[116] The other 2 studies (66%) allowed smokers and reported that 14% to 24% in each group smoked.

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The 6 COPD trials included a total of 3,957 patients treated with a LABA. One of the COPD trials recruited subjects age 35 and older,[125] and the other 5 RCTs enrolled subjects age 40 and older. Many patients were current smokers, ranging from 45% to 52% of subjects in the 4 studies that reported these data. Two trials were conducted in the United States, 1 in Japan,[124] and the other 3 were multinational, 1 including patients in the United States.[119,122,123]

Sponsorship

Of the 3 head-to-head trials in patients with asthma, 2 were funded by pharmaceutical companies; 1 trial did not report the source of funding, but at least 1 author had a primary affiliation with a pharmaceutical company. All 6 studies in COPD patients were funded by pharmaceutical companies.

Head-to-head comparisons

Arformoterol (ARF) compared with formoterol (FM)

Asthma. We did not identify any good- or fair-quality systematic reviews or head-to-head trials that compared ARF to FM in patients with asthma.

COPD. One fair-quality trial[125] compared ARF with FM in patients with COPD. The trial recruited 444 patients age 35 and older from 62 centers in the United States. During 6 months of treatment subjects received ARF 30 mcg daily or 50 mcg daily, administered with a nebulizer, or 24 mcg of FM via DPI. The trial provided low-strength evidence that exacerbation rates were similar between ARF and FM patients (Appendix E, Table E-12). Patients taking ARF had a somewhat higher risk of 1 or more exacerbations than those taking FM, with RR 1.44 (95% CI 0.99 to 2.10) for 30 mcg and RR 1.36 (95% CI 0.93 to 2.01) for 50 mcg of ARF; however, differences were not statistically significant. Quality of life, measured by the St George's Respiratory Questionnaire, improved between baseline and the end of treatment by 6.8 points for patients taking FM and 3.7 points for those taking either ARF dose, but CIs overlapped between the 3 arms. Rescue medicine use declined and dyspnea symptoms improved to a similar degree in all 3 treatment arms. The trial provided insufficient evidence to compare mortality between the groups; only 1 death occurred in the study, in a patient taking 50 mcg ARF (Appendix E, Table E-12).

Arformoterol (ARF) compared with salmeterol (SM)

We did not identify any good or fair-quality systematic reviews or head-to-head trials that compared ARF to SM in patients with asthma or COPD.

Eformoterol (eFM) compared with salmeterol (SM)

Asthma. Two fair-quality RCTs meeting our inclusion/exclusion criteria compared eFM with SM.[115,116] Both enrolled patients not adequately controlled on ICSs and were conducted in the UK and Republic of Ireland. The first was an 8-week trial that enrolled 469 adolescents and adults ≥12 years of age with mild to moderate persistent asthma.[115] The other was a 12-week trial that enrolled 156 children and adolescents between 6 and 17 years of age with moderate persistent asthma.[116]

Both trials assessed asthma symptoms, nocturnal awakenings, and exacerbations. One trial also reported hospital admission or visits to A&E (accident and emergency departments)[115]

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while the other study also reported rescue medication use, quality of life, missed work, missed school, and compliance.[116] The trials found no difference between those treated with eFM and those treated with SM for all outcomes except for rescue medicine use: 1 trial[116] found a greater decrease in rescue medicine use in those treated with eFM than in those treated with SM.

COPD. We did not identify any good- or fair-quality systematic reviews or head-to-head trials that compared eFM to SM in patients with COPD.

Formoterol (FM): nebulized compared with dry powder inhaler

Asthma. We did not identify any good- or fair-quality systematic reviews or head-to-head trials that compared FM administered via nebulizer versus DPI in subjects with asthma.

COPD. A 12-week fair-quality trial[120] in 237 United States COPD patients compared FM administered with a nebulizer to FM via dry powder inhaler, and provided low-strength evidence that the efficacy of the 2 formulations is comparable. The trial administered 40 mcg daily of FM via nebulizer or 24 mcg via DPI. Exacerbations occurred in 5 patients using nebulizers (4.1%) and 7 using DPIs (6.1%). Quality of life improved in both treatment arms, with SGRQ scores declining by about 5.5 points with nebulized FM and 4.1 points with the DPI, and the difference was not statistically significant. No deaths occurred in either group. Results were similar between the 2 groups for rescue medication use, which declined from baseline in both groups.

Formoterol (FM) compared with indacaterol (IC)

Asthma. We did not identify any good or fair-quality systematic reviews or head-to-head trials that compared FM to IC in patients with asthma.

COPD. The INVOLVE Study[119] is a multinational randomized trial of COPD patients comparing 2 doses of the new LABA IC with FM. This fair-quality trial was funded by a pharmaceutical company and recruited 1,300 patients from outpatient sites in 25 countries, not including the United States. Patients were randomized to 52 weeks of treatment with either 24 mcg/day of FM, 300 mcg/day of IC, or 600 mcg/day of IC, all via DPI. The study provided low-strength evidence that the efficacy of IC is comparable to that of FM for exacerbations and quality of life, with some clinical outcomes favoring IC.

The INVOLVE trial reported mortality, exacerbations, quality of life and other outcomes. Exacerbations occurred in 126 patients taking FM, 133 taking 300 mcg of IC, and 116 taking 600 mcg IC; differences were not statistically significant, and the results provide low-strength evidence that FM and IC are comparable for preventing exacerbations. Quality of life scores were also very similar between the 3 groups, with SGRQ scores of 37.3 for FM, 36.6 for IC 300 mcg, and 36.7 for IC 600 mcg (differences not statistically significant), again providing low-strength evidence that FM and IC have comparable effects. At 12 weeks, dyspnea scores were better with IC than with FM, but at 52 weeks differences were not statistically significant. Rescue medication use decreased from baseline more with IC than with FM, and IC patients had fewer days when they needed salbutamol. Patients taking IC also had more nights with no awakenings than did FM patients, with the difference statistically significant for the higher IC dose. The trial provided insufficient evidence on comparative mortality

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Formoterol (FM) compared with salmeterol (SM)

Asthma. One fair-quality open-label 6-month RCT meeting our inclusion/exclusion criteria compared FM with SM in 482 adults ≥ 18 years of age with moderate to severe persistent asthma.[117,118] This trial reported symptoms, rescue medicine use, quality of life, missed days of work, ER visits, and hospitalizations. There were no statistically significant differences in these outcomes between those treated with FM than those treated with SM.

COPD. We did not identify any good or fair-quality systematic reviews or head-to-head trials that compared FM to SM in patients with COPD.

Indacaterol (IC) compared with salmeterol (SM)

Asthma. We did not identify any good or fair-quality systematic reviews or head-to-head trials that compared IC with SM in patients with asthma.

COPD. Three fair-quality RCTs in COPD patients compared the effects of IC with those of SM. The INSIST Study[122] recruited 1,123 patients from 144 centers in 8 countries including the United States. Patients received either 150 mcg of IC or 100 mcg of SM daily via DPI for 12 weeks. The INFLIGHT-2 Study[123] was smaller (N=667) but of longer duration (26 weeks). Patients from outpatient sites and clinical research centers in 15 non-US countries participated, and the same daily doses of IC and SM as in the INSIST Study were given via DPI. The third trial was a small, unpublished study of 186 patients at 37 centers in Japan, comparing a higher daily dose of IND (300 mcg) to the same dose of SM (100 mcg) used in the larger trials.

None of the 3 trials reported exacerbations or hospitalizations. All 3 did report mortality, but there were few deaths in any trial and evidence was insufficient to establish a difference between the 2 drugs.

INFLIGHT-2 also reported quality of life, and reported that SGRQ scores improved more for IC than for SM after 12 weeks' treatment ($p<0.05$). The minimum clinically important difference is 4 points on the SGRQ scale, and at 12 weeks IC patients were more likely to achieve this clinically-important improvement than were SM patients (OR1.59, 95% CI: 1.12-2.25).By 26 weeks, the gap between SGRQ scores had narrowed and was no longer statistically significant. Dyspnea scores were better in IC than SM patients at 12 weeks in both studies (statistically significant in both trials), but by the end of the 26-week INFLIGHT-2 trial differences were no longer significant. In both studies IC patients had fewer days requiring salbutamol as a rescue medication; INSIST also showed fewer puffs per day of salbutamol, though INFLIGHT-2 did not.

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Table 11. Characteristics of head-to-head studies comparing long-acting beta-2 agonists in children and adults

Study	Study Design N Duration	Country Study population Setting	Comparison (total daily dose in mcg)	Quality rating
Asthma (LABA monotherapy contraindicated since 2010)				
Eformoterol compared with Salmeterol				
Campbell et al. 1999[115]	RCT, cross-over 469 8 weeks	UK & Republic of Ireland Age≥ 12, mild to moderate, not controlled on ICS, 20-24% current smokers in each group General practice & hospital centers	eFM DPI (24) vs. SM DPI (100) vs. SM MDI (100)	Fair
Everden et al. 2004[116]	RCT, open 156 12 weeks	UK & Republic of Ireland Children and adolescents age 6-17, moderate persistent, not controlled on ICS, smoking status=NR General practice outpatient clinics	eFM DPI (24) vs. SM DPI (100)	Fair
Formoterol compared with Salmeterol				
Vervloet et al. 1998[117] *AND* Rutten-van Molken et al. 1998[118]	RCT, open 482 6 months	France, Italy, Spain, Sweden, Switzerland & UK Age ≥ 18, moderate-severe, not controlled on ICS, 14-16% current smokers Outpatient centers	FM DPI (24) vs. SM DPI (100)	Fair
COPD				
Arformoterol compared with Formoterol				
Hanania et al. 2010[125]	RCT 444 6 months	US Age ≥ 35, 45% current smokers Multicenter (62), setting NR	ARF NEB (30) vs. ARF NEB (50) vs. FM DPI (24)	Fair
Formoterol fumarate (nebulized) compared with Formoterol fumarate (DPI)				
Gross et al. 2008[120]	RCT 237[a] 12 weeks	US Age ≥ 40, 52% current smokers Multicenter (38), setting NR	FM NEB (40) vs. FM DPI (24)	Fair

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Study	Study Design N Duration	Country Study population Setting	Comparison (total daily dose in mcg)	Quality rating
Formoterol compared with Indacaterol				
Dahl et al. 2010[119] INVOLVE Study	RCT 1,300[a] 52 weeks	25 non-US countries Age ≥ 40, 40.0 pack-year smoking history[a] Outpatient clinics and physicians' offices	FM DPI (24) vs. IC DPI (300) vs. IC DPI (600)	Fair
Indacaterol compared with Salmeterol				
Korn et al. 2011[122] INSIST study	RCT 1,123 12 weeks	8 countries including US Age ≥ 40, 44.5% current smokers Multicenter (144), setting NR	IC DPI (150) vs. SM DPI (100)	Fair
Kornmann et al. 2011[123] INFLIGHT-2 study	RCT 667[a] 26 weeks	15 non-US countries Age ≥ 40, 46% current smokers[a] Multicenter (142); respiratory outpatient clinics, physicians' offices and clinical research centers.	IC DPI (150) vs. SM DPI (100)	Fair
Novartis, 2011 [124]	RCT 186 52 weeks	Japan Age ≥ 40, smoking history ≥ 20 pack-years Multicenter (37), setting NR	IC DPI (300) vs. SM DPI (100)	Fair

[a]Excludes placebo arm.

Abbreviations: AQLQ = Asthma Quality of Life Questionnaire; CI = confidence interval; DPI = dry powder inhaler; eFM = Eformoterol; FM = Formoterol; MDI = metered dose inhaler; NEB = nebulized; NR = not reported; NS = not statistically significant; QOL = quality of life; RCT= randomized controlled trial; SM = Salmeterol; SMD = standard mean difference.

Symbol use: Drug X > Drug Y = statistically significant difference in outcomes favoring Drug X; Drug X > Drug Y trend = point estimate favors Drug X, but the difference is not statistically significant or tests of statistical significance were NR; No difference = no statistically significant difference or tests of statistical significance were not reported and outcomes are similar.

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D. Combination Products

1. Inhaled corticosteroid (ICS) and long-acting beta-2 agonist (LABA) compared with inhaled corticosteroid and long-acting beta-2 agonist

We found 7 RCTs with 11 publications[47,48,57,127-134] that compared the combination of an ICS plus a LABA with another ICS/LABA combination for controller therapy treatment of asthma (Table 12). Four trials compared fixed- dose combination inhalers containing BUD/FM to fixed-dose combination inhalers of FP/SM.[127,129,130,132] Two compared fixed- dose combination inhalers containing FP/SM to fixed- dose combination inhalers of MF/FM.[47,133] A single study compared fixed-dose combination inhalers containing FP/SM to fixed-dose combination inhalers of (fluticasone furoate [FF]/vilanterol [VI]).[48]

Overall, results from 4 large trials up to 6 months in duration provide moderate-strength evidence that there is no significant difference in efficacy between fixed-dose combination treatment with BUD/FM and FP/SM. (Appendix E, Table E-5) The results of our meta-analysis show no statistically significant difference between the risk of exacerbations requiring oral steroids (OR 1.11; 95% CI 0.95 to 1.3) or exacerbations requiring emergency visits or hospital admissions (OR 0.74; 95% CI 0.53 to 1.03) (Appendix F). Quality of life measures specific to asthma also found no differences between these treatments. Moderate-strength evidence from 2 trials (12 and 52 weeks) indicated no difference in asthma deteriorations (emergency visits, hospitalizations or requiring additional medications) between MF/FM and FP/SM at medium doses. Low-strength evidence from only the 52-week study also suggests no difference between MF/FM and FP/SM at high doses. Other eligible outcomes were not reported. A single study of FP/SM compared with FF/VI provides low-strength evidence of no difference in quality of life between the treatments.

A single 48-week RCT of a fixed-dose combination of BPD/FM compared with a fixed dose combination of BUD/FM in patients with COPD was found.[135] Results from this trial did not suggest differences between the drug combinations in exacerbations, hospitalizations, quality of life or adverse events. This evidence is low strength due to lack of ability to assess consistency and precision of estimates without pre-established minimal important differences in exacerbation rates and improvement in quality of life measures.

Description of studies

In patients with asthma, 4 RCTs (Table 12) compared BUD/FM with FP/SM, 2 compared FP/SM with MF/FM and 1 compared FP/SM with FF/VI. Study duration ranged from 12 to 52 weeks.

Within-trial equipotency of daily ICS dose varied for the trials of BUD/FM compared with FP/SM. All 4 trials administered the same total daily dose of FP/SM (500/100), which is considered a medium daily dose of ICS when delivered via DPI and a high daily dose when delivered via pMDI (Table 3). In 2 trials, 500 mcg of FP was compared with an equipotent daily dose of BUD,[127,128,130] while 2 studies medium daily doses of BUD were compared with a high dose of FP.[129,131,132,134]

A 52-week trial of MF/FM and FP/SM randomized patients to moderate (200 mcg MF per day, 250 mcg FP via MDI) or high (400 mcg MF per day, 500 mcg FP via MDI based on their prior dosing of ICS,[133] while a 12-week trial randomized to medium doses of MF/FM using a MDI and medium doses of FP/SM using a DPI.[47] The 52-week trial was designed specifically to assess long-term harms, and measured only minimal benefits outcomes.

Lastly, FF/VI 100/25 mcg once daily using a DPI was compared with FP/SM 150/50 mcg twice daily using a MDI in patients with asthma.[48]

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A 48-week, multi-country RCT of BDP/FM 200mg/12mg pMDI, BUD/FM 400mg/12mg DPI, or FM 12mg DPI alone (all BID) enrolled 718 patients with severe COPD according to the GOLD guidelines, including at least 1 serious exacerbation in the last year. [135]

Study populations

The 4 head-to-head RCTs of BUD/FM compared with FP/SM included a total of 5818 subjects. All studies were conducted in adolescent and/or adult populations. None included children < 12 years of age. All trials were multinational. All enrolled subjects that were not adequately controlled on current therapy. Three were conducted in subjects with moderate to severe persistent asthma; 1 did not report the severity classification.[132,134] Three trials (75%) excluded smokers with at least a 10 pack-year history; 1 (25%) allowed some smokers and reported that 5% to 7% of subjects in each group were current smokers.

The 2 trials of MF/FM and FP/SM included a total of 1,126 patients ≥ 12 years old, 1 conducted at sites in North America and the other at sites in South America. The 52-week study included stable patients using moderate to high doses of ICS, while the 12 week study included patients on a stable regimen with moderate dose ICS, but with ≥2 exacerbations in the last year. Both studies excluded current and ex-smokers.

The trial of FF/VI compared with FP/SM enrolled 806 patients (> 12 years old) with stable asthma, taking medium doses of an ICS, and with FEV1 reversibility of > 12% and > 200 mL after albuterol administration. The study excluded current and ex-smokers, and was conducted in multiple countries worldwide.

The single study of patients with COPD enrolled 718 patients with severe COPD according to the GOLD guidelines, including at least 1 serious exacerbation in the last year. [135] The study population had 37% current smokers, and a mean of 38 pack-years of smoking for all patients enrolled. The mean percent predicted normal FEV_1 pre-bronchodilator was 42%.

Sponsorship

Of the 8 trials, 7 (88%) were funded by pharmaceutical companies; 1 trial did not report the source of funding but at least 1 author had a primary affiliation with a pharmaceutical company. No trials were funded primarily by a source other than a pharmaceutical company.

Head-to-head comparisons

Asthma

Budesonide (BUD)/formoterol (FM) compared with fluticasone (FLUN)/salmeterol (SM)

Based on meta-analysis, 4 trials provided moderate-strength evidence of no statistically significant difference between BUD/FM and FP/SM in the number of asthma patients with an exacerbations requiring oral steroids: OR 1.11 (95% CI 0.95 to 1.3) or exacerbations requiring emergency visit or hospital admission: OR 0.74 (95% CI 0.53 to 1.03) (Appendix F, Evidence Tables A and B).[127,129,130,132] Post hoc subgroup analyses of data in patients 16 years old or greater in 2 studies indicated similar findings.[128,131]

All the trials reported use of rescue medication, with 3 finding no differences between fixed-dose combination treatments.[127,129,130] The only study finding a small difference was a 6 month trial (N=3,335), where the total daily dose of BUD delivered by DPI is considered medium and the total daily dose of FP delivered by pMDI is considered high.[132,134] The authors reported greater improvement in the number of rescue puffs used per day for those treated with FP/SM (mean difference, 95% CI: 0.10, 0.01-0.19). This study also reported a lower rate of

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hospitalizations or emergency visits per 100 patients per 6 months for those treated with BUD/FM (5 compared with 8, $P = 0.013$). The total number of hospitalizations or emergency visits was not analyzed for statistical significance, but there were fewer such events in the BUD/FM arm compared with the FP/SM arm (72 and 106, respectively). A post-hoc analysis of the original study that was limited to participants ages 16 and above yielded similar results. Other outcomes reported in the study did not indicate statistically significant differences between groups. Although statistical analysis was not reported, a study using equipotent doses[127] reported numerically fewer hospitalizations/ER visits in patients treated with BUD/FM.

Two trials reported change in the AQLQ scale.[129,132] One reported the proportion with meaningful improvement (≥ 0.5 from baseline) as 63% with BUD/FM MDI and 61.9% with FP/SM DPI,[129] while the other reported that an increase in AQLQ score of 0.76–0.78 was seen across groups.[132] These studies did not interpret these differences as clinically meaningful although statistical analyses were not reported.

Fluticasone (FLUN)/salmeterol (SM) compared with mometasone furoate (MF)/formoterol (FM)
Based on 2 studies, low-strength evidence suggests no difference in the rate of exacerbations between MF/FM and FP/SM at medium or high doses in patients with asthma. (Appendix F, Evidence Tables A and B). The 2 studies differed in duration by 40 weeks, so data were not pooled. Additionally, both studies reported "asthma deterioration" defined as emergency visits, hospitalizations or the need for additional medications (e.g. steroids) as a combined outcome rather than exacerbations specifically. In the 12-week trial comparing medium doses of each combination product, the rates were the same between groups: MF/FM 5.7% and FP/SM 5.7%.[47] In the 52-week trial, the rates with the medium doses of each combination product were greater than in the shorter trial, but similar to each other; MF/FM 9.9% versus FP/SM 8.8%.[133] However, in this trial the rates with the higher doses of the combination products were much greater than the medium doses; MF/FM 17.7%% versus FP/SM 20.0%, although not statistically significantly different to each other (our calculated P = 0.58). Other eligible effectiveness outcomes were not reported in either study.

Fluticasone (FLUN)/salmeterol (SM) compared with fluticasone/vilanterol (VI)
In a single good-quality trial (N = 806), after 24 weeks of treatment, there were no differences found between FP/SM and FF/VI in mean improvement in the AQLQ+12 scale in patients with asthma.[48] The difference in final score was 0.09 (95% CI -0.03 to 0.21). Similarly there was no difference between groups in the EQ-5D scores on any dimension or the overall visual analogue score. No exacerbations occurred during the trial. This study provides only low-strength evidence of no differences between the treatments on quality of life outcomes, due to the limitations of not being able to assess consistency, and having an imprecise estimate of effect. The evidence is insufficient for other outcomes.

COPD

Budesonide (BUD)/formoterol (FM) compared with beclomethasone (BDP)/formoterol
In a single good-quality, 48-week multi-country trial (N = 718), no differences were found BUD/FM and BDP/FM in total exacerbations, exacerbations requiring an emergency department visit or hospitalization, exacerbations requiring corticosteroid treatment, or improvement in quality of life (as measured using the St. George Respiratory Questionnaire). It was noted that the overall number of exacerbations was lower than expected in this study, given that the

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enrollment was patients with severe COPD. Post-hoc subgroup analyses were conducted due to concerns over variation across countries in management of exacerbations, and while the rates were slightly lower for BDP/FM (0.162 events per patient year) than with BUD/FM (0.180 events per patient year), these did not affect the results in that these differences were not statistically significant. It would be difficult to discern a clinically meaningful difference between the 2 combination products based on these data.

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Table 12. Characteristics of head-to-head randomized controlled trials comparing inhaled corticosteroids and long-acting beta-2 agonists with inhaled corticosteroids and long-acting beta-2 agonists in patients with asthma

Study	N Duration	Country Population Setting	Comparison (total daily ex-mouthpiece dose in mcg)	Equipotent steroid component	Quality rating
Budesonide/formoterol compared with fluticasone/salmeterol					
Aalbers et al. 2004[127] AND Aalbers et al. 2010[128a]	658 1 month double-blind (+6 months open)	Multinational (Denmark, Finland, Germany, Norway, Sweden and The Netherlands) Age ≥ 12 years, asthma ≥ 6 months, not controlled on ICS alone, moderate to severe, excluded smokers with ≥ 10 pack-year history	BUD/FM (640/18) DPI vs. FP/SM (500/100) DPI	Yes	Fair
Dahl et al. 2006[130] EXCEL trial	1397 24 weeks	Multinational Age ≥ 18 years with asthma for a minimum of 6 months, not controlled on 1000-2000 BDP or equivalent, moderate to severe, excluded smokers with ≥ 10 pack-year history	BUD/FM (640/18) DPI vs. FP/SM (500/100) DPI	Yes	Good
Kuna et al. 2007[132] AND Price et al. 2007[134] AND Kuna 2010[131b]	3335 6 months	Multinational Age ≥12, not controlled, taking ICS at entry (46-47% also taking LABA at entry), 5-7% were current smokers	BUD/FM (640/18) DPI vs. FP/SM (500/100) pMDI	No (medium compared with high)	Good
Busse 2008[129] AND O'Connor[57]	1225 6 months	Multicenter US Age ≥ 12 years, asthma ≥ 6 months, in stable condition on medium dose of ICS or LABA for ≥ 12 weeks, excluded smokers with ≥ 20 pack-year history	BUD/FM (640/18) DPI vs. FP/SM (500/100) pMDI	No (medium compared with high)	Fair

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Table 12. Characteristics of head-to-head randomized controlled trials comparing inhaled corticosteroids and long-acting beta-2 agonists with inhaled corticosteroids and long-acting beta-2 agonists in patients with asthma

Study	N Duration	Country Population Setting	Comparison (total daily ex-mouthpiece dose in mcg)	Equipotent steroid component	Quality rating
Fluticasone/salmeterol compared with mometasone furoate/formoterol					
Maspero[133]	404 52 weeks	Multinational Age ≥ 12 years with stable asthma, taking moderate to high doses of ICS. Excluded current smokers or ≥ 10 pack-year history	Medium doses: MF/FM (200/10) Vs FP/SM (250/50) High doses: MF/FM (400/10) Vs FP/SM (500/50) All via MDI	Yes	Fair
Bernstein[47]	722 12 weeks	Multinational Age > 12 years on a stable regimen with moderate dose ICS, but with >2 exacerbations in the last year. Excluded current smokers or ≥ 10 pack-year history	MF/FM (400/20) pMDI FP/SM (500/100) DPI	Yes	Fair
Fluticasone/salmeterol compared with fluticasone/vilanterol					
Woodcock[48]	806 24 weeks	Multinational Age > 12 years with stable asthma, taking medium doses of an ICS, and with FEV1 reversibility of > 12% and > 200 mL after albuterol.	FP/SM (500/100) pMDI Vs FF/VI (100/25)DPI	Yes	Fair

Abbreviations: AD= adjustable dosing; BUD+FM= budesonide and formoterol in separate inhalers; BUD/FM= budesonide and formoterol in 1 inhaler; DPI= dry powder inhaler; FP = fluticasone propionate; FP+SM= fluticasone and salmeterol in separate inhalers; FP/SM= fluticasone and salmeterol in 1 inhaler; ICS = inhaled corticosteroid; LABA = long-acting beta-2 agonist; NS= not statistically significant; pMDI= pressurized metered dose inhaler; SR = systematic review; RCT= randomized controlled trial.

[a] Post-hoc analysis of ages ≥ 16 (N = 644) from the full study population.

[b] Post-hoc analysis of ages ≥ 16 (N = 2854) from the full study population.

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E. Long-Acting Muscarinic Antagonists (LAMAs)

We found no reviews or head-to-head RCTs comparing a LAMA with another LAMA in patients with either COPD or asthma.

II. Inter-class Comparisons (between classes)

A. Monotherapy

1. Inhaled corticosteroids (ICSs) compared with leukotriene modifiers (LMs)

We found 3 systematic reviews with meta-analyses[136-138] and 23 RCTs[139-164] (Tables 13 and 14) comparing ICSs with LMs in patients with asthma. Fifteen of the RCTs were in adolescents and adults ≥12 years of age and 8 (11 articles) were in children < 12.[139,141,146,147,154,157,159,160,164,165] We found no evidence comparing ICSs with LMs in patients with COPD.

Overall, efficacy studies up to 56 weeks in duration provide consistent evidence favoring ICSs over LMs for the treatment of asthma as monotherapy for both children and adults for exacerbations and quality of life (high-strength evidence, Appendix E, Table E-4 and meta-analysis results in Appendix F). Low-strength evidence suggests that emergency department visits and missed school days were also fewer on fluticasone than ML for children age 6 to 14. Results for rescue medicine use and asthma symptoms also favored ICSs.

We found no review or head-to-head studies comparing ICS with LM in patients with COPD.

Description of studies

Of the 23 RCTs (Tables 13 and 14), 6 RCTs compared ML with BDP; 10 RCTs compared ML with FP; 4 compared ZAF with FP; and 3 RCTs compared ML with BUD. Study duration ranged from 6 weeks to 56 weeks. Three trials included extension phases ranging 36-48 weeks in duration.[151,152,166]

Study populations

The 23 RCTs included a total of 10,556 patients. Most studies were conducted in adult populations. Eight studies (11 articles)[58,139,141,146,147,154,157,159-161,165,166] were conducted primarily in pediatric populations. Fourteen studies (61%) were conducted in the United States, 3 (9%) in Europe or the UK, and 6 (26%) were other multinational combinations often including Europe, Canada, or the United States. Asthma severity ranged from mild persistent to severe persistent: 6 studies (26%) were conducted in patients with mild persistent asthma, 11 (48%) in patients with mild to moderate persistent asthma, 3 (13%) in patients with mild to severe persistent asthma, and 3 (13%) did not report the severity or it was unable to be determined.

Methodologic quality

The 23 RCTs included in our review were rated fair quality for internal validity. The method of randomization and allocation concealment was rarely reported.

Sponsorship

Of the 23 RCTs, 18 (78%) were funded by pharmaceutical companies; only 3 studies (13%) were funded primarily by sources other than pharmaceutical companies; 2 studies (9%) did not report any source of funding.

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Head-to-head comparisons

We conducted meta-analyses for 2 outcomes that were reported with sufficient data in multiple trials (Appendix F). Those treated with ICSs had less frequent exacerbations (SMD -0.17, 95% CI: -0.22, -0.12, 13 studies) and a greater improvement in quality of life (AQLQ scores; SMD -0.19, 95% CI: -0.27, -0.12, 7 studies) than those treated with LMs. For both meta-analyses, sensitivity analyses indicate no difference in overall conclusions with removal of any single study. In addition, there was no significant heterogeneity between studies (Appendix F). Patients treated with ICSs also showed a greater increase in the proportion of days free from rescue medication use (12 studies), greater reduction in rescue medicine use per day (13 studies), greater increase in percent of symptom-free days (13 studies), and greater improvement in symptom score (10 studies).

When looking at ML alone compared with ICSs, our meta-analysis again shows that patients treated with ICSs had fewer exacerbations and greater improvement in quality of life than those treated with ML (Appendix F). Results for rescue medication use and asthma symptoms also favored ICSs. Comparing ZAF alone with ICSs, patients treated with ICSs once more had fewer exacerbations than those treated with ZAF (Appendix F), as well as less rescue medicine use and fewer symptoms.

A previously published good-quality systematic review included 18 RCTs (N = 3,757), 13 of which compared ICS therapy to ML therapy in children and adolescents 18 years and younger diagnosed with asthma at least 6 months prior to enrollment.[136] Six of the included trials also met our inclusion criteria[147,154,158-160,166]; 7 did not. Duration of studies varied but ranged from 4-12 weeks, 24-28 weeks, and 48-56 weeks, and 1 study was 112 weeks long. While most of the studies included patients age 6-18, 1 study included children younger than 6 (2-8 years) for which a nebulizer was used for ICS administration.[159] Intervention drugs included oral ML (4 to 10 mg) compared to either inhaled BDP 200-400 mcg/day (0.5 mg nebulized), FP 200 mcg/day, BUD 200-800 mcg/day or TAA 400 mcg/day.

Seven trials (N = 2,429) contributed to the primary outcome, with ICS-treated patients showing a significantly lower risk of developing an exacerbation requiring systemic corticosteroids (RR 0.83, 95% CI: 0.72 – 0.96; NNT 24). However, no statistically significant difference was noted between groups with respect to withdrawals due to exacerbations (N=680, RR 0.73, 95% CI: 0.36 – 1.48) and hospitalizations due to exacerbations (N = 533, RR 0.33, 95% CI: 0.03 – 3.15). Additional data were pooled based on secondary outcomes of interest and found ICS significantly improved mean change from baseline of symptom score (N = 575, SMD 0.18, 95% CI 0.01 – 0.34]), rescue inhaler use (puffs/24 hours: N = 1823, SMD 0.34 puffs/day, 95% CI 0.16 – 0.53]), and rescue-free days (N = 1904, SMD 0.16, 95% CI 0.07 – 0.25).

Another good-quality systematic review with meta-analysis compared licensed doses of LTRAs with ICSs.[137] It included 3 trials testing a higher ICS dose; 3 trials testing a lower ICS dose; and the 21 remaining trials using equal nominal daily doses of ICS. It included 27 studies (9,100 subjects), 3 of these in children and 24 in adults. Nine of these included trials also met our inclusion criteria.[140,142-145,148-150,152,153,162] Eighteen of the included studies in this systematic review did not meet our inclusion/exclusion criteria. Duration of studies varied but ranged from 4-8 weeks, 12-16 weeks, and 24-37 weeks. The intervention drugs included ML (5 to 10 mg) and ZAF (20 mg twice daily). The ICS dose was uniform across 21 trials; 7 of those used BDP 400 mcg/day, 1 used BDP 400-500 mcg/day, and 11 used FP 200 mcg/day. Three trials tested a high dose of ICS (BUD 800 mcg/day), 1 trial failed to report the dose used, and 3 trials used low dose

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BDP or equivalent. Eight trials enrolled patients who had mild asthma; 19 enrolled patients with moderate asthma; 3 trials did not report baseline FEV1.

Eighteen trials contributed to the primary outcome showing a 65% increased risk of exacerbations requiring systemic steroids for any LTRA (10 trials in ML and 5 trials in ZAF) compared to any ICS dosing regimen. The pediatric trials (3) could not be pooled due to a lack of exacerbations. However, 5 trials were pooled for exacerbations requiring hospitalization and there was no significant difference. Data at 12 weeks were pooled according to outcome and found ICS significantly improved change in symptom score (6 trials, SMD 0.29, 95% CI: 0.21 to 0.37), nocturnal awakenings (6 trials, SMD 0.21, 95% CI: 0.13 to 0.30), daily use of beta-2-agonists (6 trials, WMD 0.28 puffs/day, 95% CI: 0.20 to 0.36), symptom-free days (3 trials, WMD -12, 95% CI: -16 to -7), rescue-free days (3 trials, WMD -14%, 95% CI: -18, -10), and quality of life (2 trials, WMD -0.3, 95% CI: -0.4, -0.2). Similarly, ICS significantly improved asthma control days (3 trials, WMD -8 %, 95% CI: -15, -1]) and rescue-free days (2 trials, WMD -9%, 95% CI: -14, -03). LTRAs significantly increased the risk of study withdrawal (19 trials, RR 1.3, 95% CI: 1.1, 1.6) which was attributable to poor asthma control (17 trials, RR 2.6, 95% CI: 2.0, 3.4).

A third and final fair-quality meta-analysis compared LTRAs to ICSs.[138] It included 6 studies (5,278 subjects); 5 retrospective cohort studies and 1 prospective trial. None of these 6 studies met our inclusion criteria. The analysis included trials of subjects with a diagnosis of asthma, without restriction to severe asthma patients or children. Duration of studies was at least 6 months. The pooling of the 6 studies showed a significantly higher annual rate of emergency department visits in the LTRA group ($P < 0.005$). The rate of hospitalizations was shown to decrease significantly with the use of ICSs compared to LTRAs (2.23% compared with 4.3%; $P < 0.05$).

Fluticasone propionate (FP) compared with montelukast (ML)

We found 10 fair-quality RCTs (14 publications) that compared ML with FP [139,144,146,147,153-157,160,161,164,166]in patients with asthma that met our inclusion criteria. Our meta-analyses of outcomes from these trials show that patients treated with FP had greater improvement in quality of life (AQLQ scores: SMD -0.15, 95% CI: -0.25, -0.06, 4 studies) and fewer exacerbations (OR 0.70, 95% CI 0.57-0.86, 5 studies), than those treated with ML (Appendix F). Patients treated with FP also had a greater increase in the proportion of days free from rescue medication use (7 studies), greater reduction in rescue medicine use per day (5 studies), greater increase in the proportion of symptom-free days (6 studies), greater improvement in symptom score (4 studies), and fewer nocturnal asthma symptoms requiring albuterol (1 study, median 2.0 for FP vs. 6.5 for ML, p=0.005).[165] An analysis of a subset of participants[161] from 1 trial[157] of children age 6 to 14 found that participants treated with FP had fewer emergency department visits and missed school days than those taking ML, and differences were statistically significant (Table E-4). Differences between FP and ML for physician's visits and missed work were not statistically significant, though patients taking FP appeared to miss fewer days of work (p=0.06). (It was not clear in this population of children under 15 whether it was participants or their caregivers whose work was analyzed). This study included only the monotherapy arms of the larger trial, and also excluded subjects who did not complete the trial or had missing cost-effectiveness data (19.4% excluded from the 2 treatment arms), which could bias its results. Baseline age and sex were comparable, though smoking was not reported. Details of the characteristics of the 10 individual RCTs[139,144,146,147,153-157,160,164,166] are summarized in Tables 13 and 14.

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Beclomethasone (BDP) compared with montelukast (ML)
Six fair-quality RCTs[140,141,148,150-152,162] meeting inclusion criteria compared ML with BDP (Tables 13 and 14). Most of the outcomes reported favored BDP over ML or found no difference between groups. In general, the results comparing BDP with ML appear to be consistent with the overall results comparing ICSs with LTRAs. Our meta-analysis shows that compared to ML-treated patients, those treated with BDP had fewer exacerbations (SMD -0.15, 95% CI: -0.30, -0.002, Appendix F). The 6 trials also showed a trend toward more rescue free days and symptom-free days with BDP than with ML.

Details of the individual RCTs are summarized in Tables 13 and 14. The only trial enrolling children < 12 years of age was a fair-rated multinational, multi-center RCT in children (N = 360) comparing ML 5 mg/day (N = 120) with medium dose BDP 400 mcg/day (N = 119) for 56 weeks.[141] Subjects with mild persistent asthma, age 6.4 – 9.4 for boys and 6.4 – 8.4 for girls were enrolled worldwide. The primary objective of the trial was to assess the effects of ML and BDP on linear growth; however, some of our primary outcomes of interest were also reported. Fewer subjects treated with ML or BDP had asthma reported as an adverse experience compared to those treated with placebo, but the difference between groups was not statistically significant (36.7% compared with 42.9% compared with 50.4%, *P* = NS for ML compared with BDP). There were no statistically significant differences in the percentage of patients requiring oral steroids (25% compared with 23.5%), the percentage requiring more than 1 course of oral steroids (5.8% compared with 5.9%), or the percentage of days of beta-agonist use (10.55% compared with 6.65%) between those treated with ML and those treated with BDP.

Budesonide (BUD) compared with montelukast (ML)
We found 3 fair-quality RCTs comparing BUD with ML[158,159,163] that met most of our inclusion criteria in patients with asthma (Tables 13 and 14). Two of the three studies enrolled less than the 100 subjects our update inclusion criteria required, but we retained these data since limited evidence was available for this comparison. Too few studies reported sufficient data for meta-analysis of our included outcomes. Of the 3 RCTs, 1 enrolled adult populations,[163] 1[158] enrolled children and adolescents ages 6-18, and 1[58,159] enrolled children ages 2-8. Most subjects in these trials had mild persistent asthma. Study duration ranged from 12 to 52 weeks. The reported outcomes of interest were either not statistically significantly different between the 2 groups or favored BUD. For symptoms, 2 trials[158,163] reported no statistically significant differences between groups. Two trials reporting exacerbations found more favorable results for those treated with BUD than those treated with ML,[159,163] including results in patients ages 2 to 4 years (see Key Question 3).[58] The single trial reporting quality of life found no difference between the treatments for overall quality of life measures in patients age 2-8.[159]

Fluticasone (FLUN) compared with zafirlukast (ZAF)
We found 4 fair-quality RCTs comparing FP with ZAF[142,143,145,149] that met our inclusion criteria. All 4 trials show similar results favoring FP over ZAF for symptoms, rescue medicine use, and quality of life. Our meta-analysis again shows that subjects treated with FP had fewer exacerbations (SMD 0.21, 95% CI: -0.31, -0.11, 4 studies) than those treated with ZAF (Appendix F).

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Table 13. Characteristics of head-to-head studies comparing inhaled corticosteroids with leukotriene receptor antagonists in children and adults with asthma

Study	Study design N Duration	Country Study population Setting	Comparison (total daily dose)	Quality rating
Inhaled corticosteroids compared with leukotriene receptor antagonists				
Castro-Rodriguez et al. 2010[136]	Systematic review with meta-analysis 18 RCTs (3,757 subjects total); 13 studies compared ICSs with ML ≥ 4 weeks treatment with ICS or ML	Children < 18 yrs, diagnosed > 6 months before study entry	ICS vs. ML and/or vs. ICS/ML	Good
Ducharme et al. 2004[137]	Systematic review with meta-analysis 27 studies (91,00 subjects)	3 trials in children, 24 trials in adults	Licensed doses of LTRA vs. ICS (3 trials tested a higher dose; 3 trials tested a lower dose; remaining tested equal to baseline daily doses of ICS)	Good
Halpern et al. 2003[138]	Meta-analysis 6 studies (5278 subjects)	United States 5 retrospective cohort, 1 prospective trial	ICS vs. LTRA	Fair
Fluticasone compared with montelukast				
Busse et al. 2001[144]	RCT 533 24 weeks	United States Age 15 and older, moderate to severe persistent asthma, excluded current smokers within the past year and those with ≥ 10 pack-year history Multicenter (52)	FP (176 mcg) vs. ML (10 mg) Low dose ICS	Fair
Garcia et al. 2005[147] MOSAIC Study	RCT 994 52 weeks	Multinational (24 including Asia, Africa, North and South America) Children age 6 – 14, mild persistent asthma, smoking status NR Multicenter (104) Primary care	FP (200 mcg) via MDI vs. ML (5 mg) Medium to Low (12-14 years of age) dose ICS	Fair

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Table 13. Characteristics of head-to-head studies comparing inhaled corticosteroids with leukotriene receptor antagonists in children and adults with asthma

Study	Study design N Duration	Country Study population Setting	Comparison (total daily dose)	Quality rating
Meltzer et al. 2002[153]	RCT 522 24 weeks	United States Age 15 and older, moderate to severe persistent asthma, excluded current smokers within the past year and those with ≥ 10 pack-year history Multicenter	FP (176 mcg) vs. ML (10 mg) Low dose ICS	Fair
Ostrom et al. 2005[154]	RCT 342 12 weeks	United States Children age 6-12, mild to moderate persistent asthma, smoking status NR Multicenter (46) Outpatient clinics	FP (100 mcg) vs. ML (5 mg) Low dose ICS	Fair
Peters et al. 2007[139]	RCT 500 16 weeks	United States Age 6 and older, mild to moderate asthma, smoking status NR Multicenter	FP (200 mcg) vs. FP (200 mcg)/ SM (100 mcg) vs. ML (5 – 10 mg) Low dose ICS	Fair
Price et al. 2013[155]	RCT 683 6 months	UK Age 18 to 55, chronic asthma, all subjects active cigarette smokers Multicenter (131)	FP (500 mcg) vs. ML (10 mg)	Fair
Sorkness et al. 2007[146,157,165] Pediatric Asthma Controlled Trial (PACT) Wang et al. 2011 [161]	RCT 285 48 weeks 254[a]	United States Children age 6-14, mild to moderate persistent asthma, excluded current smokers within the past year Childhood Asthma Research and Education Centers	FP (200 mcg) vs. FP (100 mcg)/ SM (50 mcg) QAM plus SM (50 mg) QPM vs. ML (5 mg) Low dose ICS	Fair

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Table 13. Characteristics of head-to-head studies comparing inhaled corticosteroids with leukotriene receptor antagonists in children and adults with asthma

Study	Study design N Duration	Country Study population Setting	Comparison (total daily dose)	Quality rating
Szefler et al. 2005[160]	RCT 144 16 weeks	United States Children age 6-17, mild to moderate persistent asthma, smoking status NR University Clinics	FP (200 mcg) vs. ML (5 – 10 mg) Low dose ICS	Fair
Zeiger et al. 2005[156,164] MIAMI Trial	RCT 400 12 weeks 36-week open label extension	United States Age 15 – 85, mild persistent asthma, smoking status NR Multicenter (39)	ML (10 mg) vs. FP (176 mcg) Low dose ICS	Fair
Zeiger et al. 2006[166] CARE Network Trial	RCT 144 (127 in analysis) 16 weeks (8 weeks, crossover, 8 weeks); additionally, only included data from the last 4 weeks of each treatment period	United States Children age 6-17, mild to moderate persistent asthma, smoking status NR Multicenter	FP (200 mcg) vs. ML (5 – 10 mg) Low dose ICS	Fair
Beclomethasone compared with montelukast				
Bau mgartner et al. 2003[140]	RCT 730 6 weeks	Multinational (Canada and South America) Age 15 and older, mild to severe persistent asthma, excluded current smokers within past year and those with > 7 pack-year history Multicenter (16)	BDP (400 mcg) vs. ML (10 mg) vs. placebo Medium Dose ICS	Fair
Becker et al. 2006[141]	RCT 360 56 weeks	Multinational (North and South America, Europe, Asia, Africa) Boys age 6.4-9.4 and girls age 6.4-8.4 years, mild to moderate persistent asthma, smoking status NR Multicenter (30)	ML (5 mg) vs. BDP (400 mcg) vs. placebo High dose ICS	Fair

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Table 13. Characteristics of head-to-head studies comparing inhaled corticosteroids with leukotriene receptor antagonists in children and adults with asthma

Study	Study design N Duration	Country Study population Setting	Comparison (total daily dose)	Quality rating
Israel et al. 2002[148]	RCT 782 6 weeks	United States Age 15 and older, mild to severe persistent asthma, excluded current smokers within the past year and those with > 7 pack-year history Multicenter (64)	ML (10 mg) vs. BDP (400 mcg) vs. placebo Medium dose ICS	Fair
Laviolette et al. 1999[150]	RCT 642 16 weeks	Multinational (18 including Europe, Asia, Africa, Australia, North America) Age 15 and older, mild to severe persistent asthma, excluded current or former smoker Multicenter (70)	BDP (400 mcg) plus ML (10 mg) vs. BDP (400 mcg) vs. ML (10 mg) vs. placebo Low dose ICS	Fair
Lu et al. 2009[151]	RCT, 3-part 2x2 crossover study 406 (126 in extension) 12 weeks 48 week open label extension study[b]	United States Adults age 15-65, ≥ 1 year clinical history of mild to severe persistent asthma Multicenter (42 total, 30 extension)	ML 10 mg daily vs. Loratadine 10 mg daily vs. ML 10 mg + loratadine 10 mg daily vs. BDP 400 mcg Medium dose ICS	Fair
Malmstrom et al. 1999[152,162]	RCT 895 (436 in extension) 12 weeks plus a 3 week placebo washout period where patients were switched from treatment to placebo 37 week double-blind extension phase	Multinational (19 in Europe, Africa, Australia, Central and South America) Age 15 and older, mild to severe persistent asthma, excluded current on former smokers Multicenter (36), clinical centers	ML 10 mg vs. BDP 400 mcg vs. placebo (extension: ML vs. BDP in pre-assigned groups) Medium dose ICS	Fair

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Table 13. Characteristics of head-to-head studies comparing inhaled corticosteroids with leukotriene receptor antagonists in children and adults with asthma

Study	Study design N Duration	Country Study population Setting	Comparison (total daily dose)	Quality rating
Budesonide compared with montelukast				
Stelmach et al. 2005[158]	RCT 51 24 weeks	Poland Children age 6-18, newly diagnosed asthma with sensitivity to house dust mites, smoking status NR University clinics	BUD (400 mcg) vs. BUD (800 mcg) vs. ML (5 – 10 mg) Low to Medium Dose ICS	Fair
Szefler et al. 2007[159] Szefler et al. 2013[58]	RCT, open label 395 52 weeks 203	United States Children 2-8, mild persistent asthma, smoking status NR Multicenter Subgroup analysis: Children ages 2-4	BUD inhalation suspension (BIS) (0.5 mg) vs. ML (4 or 5 mg) Low dose ICS	Fair
Yurdakul et al. 2003[163]	RCT 74 12 weeks	Turkey Adults age 23 – 45, mild persistent asthma, excluded smokers Research hospital	BUD (400 mcg) vs. ML (10 mg) Low dose ICS	Fair
Fluticasone compared with zafirlukast				
Bleecker et al. 2000[142]	RCT 451 12 weeks	Multinational Age 12 and older, mild to severe persistent asthma, excluded current smokers within the past year and those with ≥ 10 pack-year history Multicenter (41)	FP (176 mcg) vs. ZAF (40 mg) Low dose ICS	Fair

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Table 13. Characteristics of head-to-head studies comparing inhaled corticosteroids with leukotriene receptor antagonists in children and adults with asthma

Study	Study design N Duration	Country Study population Setting	Comparison (total daily dose)	Quality rating
Brabson et al. 2002[143]	RCT 440 6 weeks	United States Age 12 and older, mild to moderate persistent asthma, smoking status NR Multicenter (44)	FP (176 mcg) vs. ZAF (40 mg) Low dose ICS	Fair
Busse et al. 2001[145]	RCT 338 12 weeks	United States Age 15 and older, mild to severe persistent asthma, excluded current smokers within the past year and those with ≥ 10 pack-year history Multicenter 50% primary care	FP (176 mcg) vs. ZAF (40 mg) vs. placebo Low dose ICS	Fair
Kim et al. 2000[149]	RCT 437 6 weeks	United States Age 12 and older, mild to severe persistent asthma, excluded current smokers within the past year and those with ≥ 10 pack-year history Multicenter Allergy and Asthma centers	FP (176 mcg) vs. ZAF (40 mg) Low dose ICS	Fair

Abbreviations: AQLQ = Asthma Quality of Life Questionnaire; BDP = beclomethasone dipropionate; BUD = Budesonide; CI = confidence interval; FP = Fluticasone Propionate; ICS = Inhaled Corticosteroids; LTRAs = Leukotriene receptor antagonists; ML = Montelukast; NR = not reported; NS = not statistically significant; QOL = quality of life; WMD = weighted mean difference; ZAF = Zafirlukast.
Symbol use: Drug X > Drug Y = statistically significant difference in outcomes favoring Drug X; Drug X > Drug Y trend = point estimate favors Drug X, but the difference is not statistically significant or tests of statistical significance were NR; No difference = no statistically significant difference or tests of statistical significance were not reported and outcomes are similar.
[a] Includes only FP and ML arms, and patients completing the trial and with no missing data for cost-effectiveness (19.4% excluded from 2 arms).
[b]Extension study: ML 10 mg + loratadine 10 mg daily vs. BDP 400 mcg

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Table 14. Characteristics of head-to-head studies comparing inhaled corticosteroids with leukotriene receptor antagonists in children < 12 with asthma

Study	Study design N Duration	Country Study population Setting	Comparison (total daily dose)	Quality rating
Inhaled corticosteroids compared with montelukast				
Castro-Rodriguez et al. 2010[136]	Systematic review with meta-analysis 18 RCTs (3,757 subjects total); 13 studies compared ICSs with ML ≥ 4 weeks treatment with ICS or ML	Children < 18 yrs, diagnosed > 6 months before study entry	ICS vs. ML and/or vs. ICS/ML	Good
Fluticasone compared with montelukast				
Garcia et al. 2005[147] MOSAIC Study	RCT 994 52 weeks	Multinational (24 including Asia, Africa, North and South America) Children age 6-14, mild persistent asthma, smoking status NR Multicenter (104) Primary care	FP (200 mcg) via MDI vs. ML (5 mg) Medium to Low (12-14 years of age) dose ICS	Fair
Ostrom et al. 2005[154]	RCT 342 12 weeks	United States Children age 6-12, mild to moderate persistent asthma, smoking status NR Multicenter (46) Outpatient clinics	FP (100 mcg) vs. ML (5 mg) Low dose ICS	Fair
Peters et al. 2007 [139]	RCT 500 16 weeks	United States Age ≥ 6, mild to moderate asthma, smoking status NR Multicenter	FP (200 mcg) vs. FP (200 mcg)/ SM (100 mcg) vs. ML (5 – 10 mg) Low dose ICS	Fair

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Table 14. Characteristics of head-to-head studies comparing inhaled corticosteroids with leukotriene receptor antagonists in children < 12 with asthma

Study	Study design N Duration	Country Study population Setting	Comparison (total daily dose)	Quality rating
Sorkness et al. 2007[146,157,165] Pediatric Asthma Controller Trial (PACT) Wang et al. 2011 [161]	RCT 285 48 weeks 254[a]	United States Children age 6-14, mild to moderate persistent asthma, Excluded current smokers within the past year Childhood Asthma Research and Education Centers	FP (200 mcg) vs. FP (100 mcg)/SM (50 mcg) QAM plus SM (50 mg) QPM vs. ML (5 mg) Low dose ICS	Fair
Szefler et al. 2005[160]	RCT 144 16 weeks	United States Children age 6-17, mild to moderate persistent asthma, smoking status NR University Clinics	FP (200 mcg) vs. ML (5 – 10 mg) Low dose ICS	Fair
Zeiger et al. 2006[166] CARE Network Trial	RCT 144 (127 in analysis) 16 weeks (8 weeks, crossover, 8 weeks); additionally, only included data from the last 4 weeks of each treatment period	United States Children age 6-17, mild to moderate persistent asthma, smoking status NR Multicenter	FP (200 mcg) vs. ML (5 – 10 mg) Low dose ICS	Fair
Beclomethasone compared with montelukast				
Becker et al. 2006[141]	RCT 360 56 weeks	Multinational (North and South America, Europe, Asia, Africa) Boys age 6.4-9.4 and girls age 6.4-8.4 years, mild to moderate persistent asthma, smoking status NR Multicenter (30)	ML (5 mg) vs. BDP (400 mcg) vs. placebo High dose ICS	Fair

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Table 14. Characteristics of head-to-head studies comparing inhaled corticosteroids with leukotriene receptor antagonists in children < 12 with asthma

Study	Study design N Duration	Country Study population Setting	Comparison (total daily dose)	Quality rating
Budesonide compared with montelukast				
Szefler et al. 2007[159]	RCT, open label 395 52 weeks	United States Children 2-8, mild persistent asthma, smoking status NR Multicenter	BUD inhalation suspension (BIS) (0.5 mg) vs. ML (4 or 5 mg)	Fair
Szefler et al. 2013 [58]	203	Subgroup analysis: Children age 2-4	Low dose ICS	

Abbreviations: AQLQ = Asthma Quality of Life Questionnaire; BIS = Budesonide inhalation suspension; BDP = beclomethasone dipropionate; BUD = Budesonide; CI = confidence interval; FP = Fluticasone Propionate; MDI = metered dose inhaler; ML = Montelukast; NR = not reported; NS = not statistically significant; PAQLQ = Pediatric Asthma Quality of Life Questionnaire; QOL = quality of life; RCT= randomized controlled trial; RR = relative risk.

Symbol use: Drug X > Drug Y = statistically significant difference in outcomes favoring Drug X; Drug X > Drug Y trend = point estimate favors Drug X, but the difference is not statistically significant or tests of statistical significance were NR; No difference = no statistically significant difference or tests of statistical significance were not reported and outcomes are similar

[a] Includes only FP and ML arms, and patients completing the trial and with no missing data for cost-effectiveness (19.4% excluded from 2 arms).

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2. Inhaled corticosteroids (ICSs) compared with long-acting beta-2 agonists (LABAs)

We found 16 fair- or good-quality RCTs[167-185] that included head-to-head comparisons of 1 ICS with 1 LABA in patients with asthma meeting our inclusion/exclusion criteria. Twelve of these were multi-arm trials that compared an ICS/LABA combination product with the individual ICS and LABA components (Table 15).[167-176,182-185]

Overall, efficacy studies provide consistent evidence favoring ICSs over LABAs for the treatment of asthma as monotherapy for children and adults (high-strength evidence, Appendix E, Table E-8). Those treated with LABAs had significantly higher odds of experiencing an exacerbation (as defined by each study) than those treated with ICSs (OR = 2.12; 95% CI = 1.53, 2.95; 7 studies). Although our meta-analyses found no statistically significant differences in measures of symptoms or rescue medicine use, the majority of individual RCTs included in this review reported no differences or favorable results for those treated with ICSs compared to those treated with LABAs for almost all outcomes. Of note, LABAs are not recommended nor approved for use as monotherapy for persistent asthma.[1]

We identified 1 good-quality systematic review of ICS versus LABA in patients with COPD.[186] The review included 7 RCTs (combined n=5997) and all met inclusion criteria for this report. All studies were rated unclear to low risk of bias on randomization, allocation concealment, blinding, completeness of data and selective reporting. All studies were multicenter, double-blind RCTs with durations of 6 months to 3 years. The mean age of participants was 64 years with 62% to 78% males. Four studies compared FP with SM. Three studies compared BUD with FM. Fluticasone propionate was associated with increased mortality versus SM (OR 1.23, 95% CI 1.01 to 1.51, 2 studies) but BUD was not so associated when compared with FM (OR 0.62, 95% CI 0.31 to 1.22, 3 studies). Exacerbation risk ratios for combined LABA and ICS and individual comparisons were similar (combined OR 0.96, 95% CI 0.89 to 1.02, 4 studies). Quality of life scores were significantly improved with FP versus SM (mean difference -0.77, 95% CI -1.49 to -0.04, 2 studies) and when the 2 LABAs versus the 2 ICS were combined (mean difference -0.74, 95% CI -1.42 to -0.06, 3 studies) but there was no difference in quality of life scores between BUD and FM (Mean difference -0.51, 95% CI -2.63 to 1.61, 1 study).

Two multicenter, double-blind RCTs published since this systematic review compared MF with FM in 26 week trials with 26 week extensions.[187,188] There was no difference in quality of life scores between groups in either study.

Description of studies

Of the 16 trials of patients with asthma, 7 (44%) compared FP with SM, 3 (19%) compared BDP with SM, 2 (13%) compared MF with FM, 1 (7%) compared TAA with SM, 2 (14%) compared BUD with FM, and 1 (7%) compared FP with FM (Table 15). Study duration ranged from 12 weeks to 12 months. The most commonly used delivery devices were MDIs and DPIs; 6 studies (38%) compared DPI to DPI; 8 studies (50%) compared MDI to MDI, and 2 studies (13%) compared pMDI to DPI.

Study populations

The 16 head-to-head RCTs included a total of 5199 subjects. Most were conducted primarily in adult populations. Three studies[180,181 183] were conducted in pediatric and adolescent populations. Most trials were conducted in North America or Europe. Asthma severity ranged from mild to severe persistent but was most commonly not reported: 4 studies (25%) were conducted in

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patients with mild to moderate persistent asthma, 1 (6%) in patients with moderate to severe persistent, and the severity was not reported in 11 (69%) trials.

Smoking status was not reported for the 2 pediatric/adolescent trials and 1 of the adolescent/adult trials.[168] Among the others, 12 (92%) excluded current smokers or those with a recent history of smoking and 1 (8%) allowed smokers and reported that 12-17% in each group were smokers.

Sponsorship

Of the 16 head-to-head trials, 13 (81%) were funded by pharmaceutical companies; 1 study was funded primarily by a source other than a pharmaceutical company and 2 did not report funding source.

Head-to-head comparisons

Inhaled corticosteroid (ICS) (any) compared with long-acting beta-2 agonist (LABA) (any) for monotherapy in patients with asthma

We conducted meta-analyses for 5 outcomes that were reported with sufficient data in multiple similar trials (Appendix F). These included percentage improvement in symptom-free days, change in symptom scores, exacerbations, percentage improvement in rescue-free days, and change in rescue medicine use. We found no statistically significant differences in the percentage improvement in symptom-free days (SMD = 0.05; 95% CI = -0.10, 0.21; 7 studies), change in symptom scores (SMD = 0.14; 95% CI = -0.05, 0.34; 6 studies), percentage improvement in rescue-free days (SMD = -0.14; 95% CI = -0.35, 0.07; P = 0.186; 5 studies), and change in rescue medicine use (as number of puffs per day) (SMD = 0.14; 95% CI = -0.11, 0.40; 7 studies). We found that those treated with LABAs had a significantly higher odds of experiencing an exacerbation than those treated with ICSs (OR = 2.12; 95% CI = 1.53, 2.95; 7 studies). The measure of statistical heterogeneity was high in the analysis of rescue puffs per day (I^2 78.4). For all analyses except percentage of rescue free days, sensitivity analyses indicate no difference in overall meta-analysis conclusions with single studies removed. For the percent rescue free days analysis, removal of Lundback et al caused the difference between ICS and LABA to reach statistical significance (favoring LABA) (point estimate = -0251; 95% CI: -0.390, -0.113; P < 0.001).

Fluticasone propionate (FP) compared with salmeterol (SM)

Asthma. Seven fair-quality RCTs compared FP with SM for monotherapy.[167,169-173,175,176,182] None included children ≤ 12 years of age. All 7 also included comparisons with an FP/SM combination product. Study duration was 12 weeks for 6 trials and 12 months for 1 trial.[169] Four compared SM with low-dose FP and 3 compared SM with medium-dose FP. Six of the 7 were conducted in the United States; 1 was conducted in Sweden.[169]

The majority of trials assessed asthma symptoms, nocturnal awakenings, exacerbations, and rescue medicine use. Two trials[172,175] reported quality of life. The majority of trials found no difference or a trend toward better outcomes in those treated with FP than those treated with SM (Evidence Tables A and B).

COPD. We identified 1 good-quality systematic review of ICS versus LABA in patients with COPD.[186] The review included 4 RCTs (combined n=4527) that compared FP with SM. The daily SM dose for all studies was 100 mcg; for 3 studies, including the largest study, the daily FP

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dose was 1000 mcg, with a daily dose of 500 mcg in the fourth study. All studies were multicenter, double-blind RCTs from 6 months to 3 years duration. The mean age of participants was 64 years with 62% to 76% males. In a meta-analysis of 2 studies, mortality was increased with FP versus SM (OR 1.23, 95% CI 1.01 to 1.51). There were no deaths reported in the other 2 studies. Three studies reported exacerbation rates and found no difference between fluticasone groups and SM groups (risk ratio 0.97, 95% CI 0.91 to 1.05) with no difference in hospitalizations due to exacerbations (risk ratio 1.07, 95% CI 0.91 to 1.26). However, there was significant improvement in SGRQ quality of life scores with fluticasone (mean difference -0.77, 95% CI -1.49 to -0.06, 2 studies).

Beclomethasone (BDP) compared with salmeterol (SM)
Asthma. Three fair-quality RCTs compared BDP with SM.[179-181] One[179] enrolled adolescents and adults ≥ 12 years of age; the other 2 studies enrolled children and adolescents aged 6-14[180] or 6-16.[181] Study duration ranged from 26 weeks to 12 months. All 3 compared SM with medium-dose BDP.

All 3 trials reported exacerbations and rescue medicine use; 2 reported symptoms[179,181] and nocturnal awakenings;[179,180] 1 reported missed school.[180] With the exception of 1 trial that reported greater improvement in the percentage of rescue-free days for those treated with SM (36% compared with 28%, $P = 0.016$),[179] all 3 trials reported no differences or better outcomes for those treated with BDP than for those treated with SM (Evidence Tables A).

COPD. There were no reviews or head-to head studies comparing BDP with SM in patients with COPD.

Triamcinolone acetonide (TAA) compared with salmeterol (SM)
Asthma. One good-rated 16-week multicenter RCT[177,178] (SOCS Trial) compared TAA with SM in 164 adolescents and adults aged 12-65. The trial reported fewer exacerbations and a lower treatment failure rate for those treated with TAA, but no statistically significant difference in symptoms, rescue medicine use, or quality of life (Evidence Tables A).

COPD. There were no reviews or head-to-head studies comparing TAA with SM in patients with COPD.

Budesonide (BUD) compared with formoterol (FM)
Asthma. Two fair-rated 12-week multicenter RCTs[168,174] compared BUD with FM in adolescents and adults aged ≥ 12. The results showed trends toward fewer exacerbations and greater improvements in symptoms, nocturnal awakenings, and rescue medicine use for those treated with BUD (Evidence Tables A). Whether these trends were statistically significantly different was not reported (the studies focused on comparing BUD/FM with the other treatments).

COPD. We identified 1 good-quality systematic review of ICS versus LABA in patients with COPD.[186] The review included 3 RCTs (combined n=1470) that compared BUD with FM. The daily FM dose for all studies was 18 mcg; for 2 studies the daily BUD dose was 800 mcg, with a daily dose of 640 mcg in the third study. All studies were multicenter, double-blind RCTs from 6 months to 1 year duration. The mean age of participants was 64 years with 67% to 78% males. In a meta-analysis of 2 studies, there was no difference in mortality between groups, although the

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pooled estimate favored a reduction with BUD (OR 0.62, 95% CI 0.31 to 1.22). There was also no difference in exacerbation rates also based on the results from 2 studies (RR 0.86, 95% CI 0.73 to 1.03) and a non-significant improvement in SGRQ quality of life scores with BUD (Mean difference -0.51, 95% CI -2.63 to 1.61, 1 study) but a non-significant improvement in symptom scores with FM (MD -0.22, 95% CI -0.47 to 0.03, 3 studies).

Mometasone furoate (MF) compared with formoterol (FM)
Asthma. Two fair-quality RCTs compared MF 100 mcg[184] or 200 mcg[185] twice daily with FM 10 mcg twice daily for 26 weeks in patients with asthma. Both studies included patients in over 150 sites in North America, Latin America, Europe, and Asia. In 1 trial (n=394, mean age=42, 39% male) 34% of MF patients experienced an asthma deterioration at some point in the study versus 54% of FM patients (RR 0.63, 95% CI 0.50 to 0.79, p<0.001).[185] Additionally, MF was superior to FM on the 7-point asthma quality of life questionnaire (mean change 0.50 versus 0.31, p=0.04) and in proportion of nights with nocturnal awakenings due to asthma requiring SABA use (0.11 for MF and 0.17 for FM, p<0.001) but there was no difference between groups on a 7-point asthma control questionnaire (p=0.13).

In the second trial (n=376, mean age=39, 44% male), treatment with MF was associated with reduced clinically judged deteriorations (hospitalizations, emergency treatment or treatment with corticosteroids) versus FM (RR 0.34, 95% CI 0.17 to 0.67, p=0.002).[184]

COPD. One good-quality[188] and 1 fair-quality RCT[187] of 26 weeks duration compared MF 400 mcg with FM 10 mcg (combined n=915). Combined, the mean age of subjects was 60 years and 77% were male. Approximately 48% were current smokers. There was no difference between mometasone and FM in mean change in SGRQ quality of life scores in either study (exact values not reported). Thirty-three percent of patients treated with MF experienced a COPD exacerbation versus 40% of patients treated with FM in 1 study (RR 0.82, 95% CI 0.65 to 1.04, p=0.10).[187]

Fluticasone propionate (FP) compared with formoterol (FM)
Asthma. We identified 1 good-quality 12-week RCT (n=239) comparing FP 100 mcg with FM 10 mcg in patients with mild to moderate asthma.[183] Patients were ≥ 12 years with a mean age of 39 and equally spit between males and females. Current smokers were excluded, as well as those with a smoking history of at least 10 pack-years. Documented ICS use within the 4 weeks preceding screening was required. Exacerbations were similar with fluticasone versus FM (RR 0.84, 95% CI 0.55 to 1.30, p=0.43). There was little difference in rescue medication-free days (43.3% vs 41.9%) and symptom-free days (37.3% vs 38.0%) when treated with fluticasone versus FM, respectively.

COPD. There were no reviews or head-to-head studies comparing fluticasone with FM in patients with COPD.

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Table 15. Characteristics of head-to-head studies comparing inhaled corticosteroids with long-acting beta-2 agonists in patients with asthma[a]

Study	Study design N Duration	Country Population Setting	Comparison (total daily dose in mcg)	Quality rating
Fluticasone propionate compared with salmeterol				
Kavuru et al. 2000[167] AND Nathan et al. 2003[176]	RCT, DB 356 12 weeks	US Age ≥12yr, asthma ≥ 6 months, patients well controlled on current therapy (stratified into 2 eligible groups: group 1 had to be on ICS for ≥3 months; group 2 was taking SM for ≥1 week), severity NR, smokers excluded Multicenter (42)	Placebo vs. FP/SM DPI (200/100) vs. SM DPI (100) vs. FP DPI (200)	Fair
Lundback et al. 2006[169]	RCT, DB 282 12 months	Sweden Age 18 to 70, mild or moderate persistent, uncontrolled on current medication,12-17% smokers in each group Patients recruited from ~4000 individuals with asthma who had participated in large epidemiologic studies	FP/SM DPI (500/100) vs. FP DPI (500) vs. SM DPI (100)	Fair
Murray et al. 2004[170]	RCT, DB 267 12 weeks	US Age ≥12yr, asthma ≥6 months, not controlled severity NR, smokers excluded Multicenter (33 sites)	SM DPI (100) vs. FP DPI (200) vs. FP/SM DPI (200/100)	Fair
Nathan et al. 2006[171] AND Edin et al. 2009[172]	RCT, DB 365 12 weeks	US Age ≥12yr, asthma ≥6 months, not controlled on ICS, severity NR, smokers excluded Multicenter (45)	FP/SM MDI (440/84) vs. FP MDI (440) vs. SM MDI (84) vs. Placebo	Fair
Nelson et al. 2003[173]	RCT, DB 283 12 weeks	US Age ≥12, persistent asthma not controlled, severity NR, smokers excluded Multicenter (33)	FP/SM MDI (176/84) vs. FP MDI (176) vs. SM MDI (84)	Fair

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Table 15. Characteristics of head-to-head studies comparing inhaled corticosteroids with long-acting beta-2 agonists in patients with asthma[a]

Study	Study design N Duration	Country Population Setting	Comparison (total daily dose in mcg)	Quality rating
Shapiro et al. 2000[175] AND Nathan et al. 2003[176]	RCT, DB 349 12 weeks	US Age ≥12, asthma ≥6 months, previously treated with low to medium ICS, severity NR, smokers excluded Multicenter (42)	Placebo vs. FP/SM DPI (500/100) vs. SM DPI (100) vs. FP DPI (500)	Fair
Pearlman et al. 2004[182] AND Edin et al. 2009[172]	RCT, DB 360 12 weeks	US Age ≥12yr, asthma ≥ 6 months, patients well controlled on current therapy (stratified into 2 eligible groups: group 1 had to be on ICS for ≥3 months; group 2 was taking SM for ≥1 week), severity NR, smokers excluded Multicenter (36)	FP/SM MDI (176/84) vs. FP MDI (176) vs. SM MDI (84) vs. Placebo	Fair
Beclomethasone compared with salmeterol				
Nathan et al. 1999[179]	RCT, DB 386 26 weeks	US Age ≥12yr, on SABAs, not on inhaled or oral corticosteroids, severity NR, smokers excluded Multicenter (25)	SM MDI (84) vs. BDP MDI (336) vs. placebo	Fair
Simons et al. 1997[180]	RCT, DB 241 52 weeks	Canada Age 6-14, clinically stable asthma, not currently on ICS, severity NR, smoking status NR Multicenter	BDP DPI (400) vs. SM DPI (100) vs. placebo	Fair
Verberne et al. 1997[181]	RCT, DB 67 54 weeks	Netherlands Age 6-16, on ICS ≥3 months, mild to moderate persistent asthma, smoking status NR Multicenter (18)	SM DPI (100) vs. BDP DPI (400)	Fair

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Table 15. Characteristics of head-to-head studies comparing inhaled corticosteroids with long-acting beta-2 agonists in patients with asthma[a]

Study	Study design N Duration	Country Population Setting	Comparison (total daily dose in mcg)	Quality rating
Lazarus et al. 2001[177] AND Deykin et al. 2005[178] SOCS Trial	RCT, triple-blind 164 16 weeks	North America Age 12-65, persistent asthma, well controlled on TAA, severity NR, smokers excluded Multicenter (6)	TAA MDI (800) vs. SM MDI (84) vs. placebo	Good
Budesonide compared with formoterol				
Noonan et al. 2006[174]	RCT; DB 596 12 weeks	US Age ≥12, moderate to severe persistent asthma not controlled, on moderate to high dose ICS for ≥4 weeks, patients with >10 pack-year smoking history excluded Multicenter (84)	BUD/FM pMDI (640/18) vs. BUD pMDI (640) vs. FM DPI (18) vs. BUD pMDI (640) + FM DPI (18) vs. placebo	Fair
Corren et al. 2007[168]	RCT, DB 480 12 weeks	US Age ≥12, mild to moderate persistent asthma, treated with low to medium dose ICS for ≥4 weeks, patients with >10 pack-year smoking history excluded Multicenter (56)	BUD/FM pMDI (320/18) vs. BUD pMDI (320) vs. FM DPI (18) vs. placebo	Fair
Fluticasone propionate compared with formoterol				
Nathan, 2012[183]	RCT, DB 239 12 weeks	North America and Europe Age ≥12, mild to moderate persistent asthma, smokers excluded	FP (400) vs, FM (40)	Good
Mometasone furoate compared with formoterol				
Nathan, 2010	RCT, DB, DD 394 26 weeks	North America, Latin America, Europe, Asia Age ≥12, adolescents (12-17) were not enrolled in countries permitting only adult patients, smokers excluded	MF (400) vs. FM (20)	Fair

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Table 15. Characteristics of head-to-head studies comparing inhaled corticosteroids with long-acting beta-2 agonists in patients with asthma[a]

Study	Study design N Duration	Country Population Setting	Comparison (total daily dose in mcg)	Quality rating
Meltzer, 2012	RCT, DB 376 26 weeks	North America, Latin America, Europe, Asia Age ≥12, smokers excluded	MF (200) vs. FM (20)	Fair

Abbreviations: BDP = beclomethasone dipropionate; BUD = Budesonide; DD= double dummy; DPI = dry powder inhaler; FM = Formoterol; FP = Fluticasone Propionate; ICS = Inhaled Corticosteroids; LABAs = Long-Acting Beta-2 Agonists; MA=meta-analysis; MDI = metered dose inhaler; NR = not reported; NS = not statistically significant; RCT= randomized controlled trial; SM = Salmeterol; SR=systematic review; TAA = Triamcinolone Acetonide

[a]LABA monotherapy contraindicated since 2010 in patients with asthma (see Key Question 2).

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3. Leukotriene modifiers (LMs) compared with long-acting beta-2 agonists (LABAs)

We found 2 fair-quality RCTs[189,190] that included head-to-head comparisons of 1 LM with 1 LABA meeting our inclusion/exclusion criteria in patients with asthma. One trial compared ML with SM[189] and 1 compared ML with eFM (Table 16).[190]

Overall, the 2 small trials do not provide sufficient evidence to draw any firm conclusions about the comparative efficacy of LMs and LABAs for use as monotherapy for persistent asthma (Appendix E, Table E-6). Of note, LABAs are neither recommended nor approved for use as monotherapy for persistent asthma.[1] As discussed previously, we did not remove trials published before the FDA's 2010 boxed warning on LABAs in asthma. We found no head-to-head trials comparing LMs with LABAs in patients with COPD.

Description of studies

We found 2 fair-quality RCTs[189,190] that included head-to-head comparisons of 1 LM with 1 LABA meeting our inclusion/exclusion criteria (Table 16). One 8-week trial compared ML with SM[189] and one 18-week trial compared ML with eFM.[190]

Study populations

The 2 RCTs included a total of 249 subjects. Both were conducted primarily in adult populations. One was conducted in the United States[189] and 1 in Australia.[190] One trial included patients with moderate to severe asthma,[190] while asthma severity was not reported in the second trial.[189] Both trials excluded current smokers or those with more than a 10 to 15 pack-year history.

Sponsorship

One trial was funded by a pharmaceutical company,[189] and the other by a combination of industry and federal government sources.[190]

Head-to-head comparisons

Montelukast (ML) compared with salmeterol (SM)

One fair-rated RCT (N = 191) compared ML 10 mg/day (N = 97) with SM 100 mcg/day (N = 94) as monotherapy for 8 weeks.[189] Subjects with chronic asthma and evidence of exercise-induced bronchoconstriction age 15 to 45 were enrolled from multiple centers in the United States. The trial was designed to evaluate exercise-induced bronchoconstriction and most of the outcomes reported were intermediate outcomes that are not included in our report. The trial also reported mortality as an outcome, with no deaths in the ML group and 1 in the SM group (*P* = NR).

b. Montelukast (ML) compared with eformoterol (eFM)

One fair-quality cross-over RCT (N = 58) compared eFM 24 mcg/day with ML 10 mg/day (6 weeks of treatment, 1-week washout, 6 weeks of treatment with the other medication, 1-week washout, then all subjects received FP 500 mcg/day for 6 weeks).[190] Subjects age 16 to 75 with mild to moderate persistent asthma previously treated with or without ICS were enrolled from multiple research centers in Australia. We only report results of the ML and eFM comparison because the fluticasone portion of the study does not have a comparison. Over the 12 weeks of treatment, subjects treated with eFM had fewer symptoms (percentage of symptom-free days: 23 compared with 0; *P* = 0.01; symptom scores: 1.2 compared with 1.6; *P* = 0.02), less rescue

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medicine use (percentage of rescue-free days: 40 compared with 30; $P = 0.008$), and better quality of life (QUALITY OF LIFE score: 0.4 compared with 0.6; $P=0.001$) compared to those treated with ML.

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Table 16. Characteristics of head-to-head studies comparing leukotriene modifiers with long-acting beta-2 agonists for monotherapy in asthma[a]

Study	Study design N Duration	Country Study population Setting	Comparison (total daily dose)	Quality rating
Montelukast compared with salmeterol				
Edelman et al.[189]	RCT 191 8 weeks	United States Age 15-45, severity NR, excluded current smokers and those with ≥15 pack-year history Multicenter (17), research centers	ML (10 mg) vs. SM (100 mcg)	Fair
Montelukast compared with eformoterol				
Jenkins et al. 2005[190]	RCT, cross-over 58 20 weeks (eFM and ML were compared for first 13 weeks, with 1 week washout in between 6 week treatment periods)	Australia Age 16-75, mild to moderate persistent asthma, excluded current smokers and those with ≥10 pack-year history Research centers	eFM DPI (24 mcg) vs. ML (10 mg) After the first 14 weeks, all subjects were treated with FP 500 mcg/day + placebo	Fair

Abbreviations: eFM = eFormoterol; ML = Montelukast; NR = not reported; NS = not statistically significant; QOL = quality of life; SM = Salmeterol.

Symbol use: Drug X > Drug Y = statistically significant difference in outcomes favoring Drug X; Drug X > Drug Y trend = point estimate favors Drug X, but the difference is not statistically significant or tests of statistical significance were NR; No difference = no statistically significant difference or tests of statistical significance were not reported and outcomes are similar.

[a]LABA monotherapy contraindicated since 2010 (see Key Question 2)

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4. Long-acting beta-2 agonists (LABAs) compared with long-acting muscarinic antagonists (LAMAs)

Asthma. We included 2 fair-quality RCTs[68,95,191,192] that compared step-up therapy with either tiotropium (TIB) or SM in patients whose asthma was not controlled by inhaled corticosteroids alone. These RCTs provided low-strength evidence that step-up therapy with either TIB or SM does not differ in its effects on exacerbations or quality of life. Evidence was insufficient to support conclusions about mortality and hospitalizations.

COPD. We included a good-quality Cochrane review[193] that studied the effects of TIB 18 mcg/d compared with SM 50 mcg/d (4 RCTs in 3 publications with 8936 participants),[194-196] FM 10 mcg/d 150-300 mcg/d (1 RCT with 431 participants),[197] and IC (2 studies with 2856 participants).[198,199] Evidence for mortality is insufficient to support any conclusions about the comparative effects of TIB and LABAs. Compared with SM, there is moderate-strength evidence that TIB is associated with fewer patients experiencing 1 or more exacerbations and low-strength evidence that TIB and SM do not differ in hospitalizations and proportions of patients with clinically significant improvement in quality of life. For the comparison of IC and TIB, there is low-strength evidence that in patients with *severe* COPD, IC provided less protection from exacerbations, but similar mortality and improved quality of life; and in a broader patient population of *moderate to severe* COPD, TIB was associated with significantly lower proportions of patients with clinically significant improvement in quality of life, but the 2 drugs did not differ in hospitalizations or exacerbations. There is low-strength evidence that TIB and FM do not differ in exacerbations and insufficient evidence to draw conclusions about hospitalizations and quality of life.

Formoterol (FM) compared with tiotropium (TIB)

Asthma. We found no reviews or head-to-head studies comparing FM with TIB in patients with asthma.

COPD. We included a good-quality Cochrane review[193] that studied the effects of TIB 18 mcg/d compared with FM 10 mcg/d 150-300 mcg/d (1 RCT with 431 participants).[197] The end date of the Cochrane review search was February 2012 and we did not identify any new trials published since then. The Cochrane review authors judged the risk of bias as low to unclear for the majority of domains. Duration of follow-up was 6 months. We relied on the meta-analyses performed by the Cochrane reviewers for exacerbations. As noted by the Cochrane reviewers, due to the limited number of events, we did not conduct a meta-analysis of mortality. There is low-strength evidence of no statistically significant difference between TIB and FM in proportion of patients with 1 or more exacerbations (10% compared with 8.1%; OR 1.32; 95% CI, 0.68 to 2.55). There is insufficient evidence to draw conclusions about comparative effects on hospitalization and quality of life outcomes due to a lack of data on those outcomes.

Indacaterol (IC) compared with tiotropium (TIB)

Asthma. We found no reviews or head-to head studies comparing IC with TIB in patients with asthma.

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COPD. The longest-term data on the comparison of IC (150 mcg) and TIB (18 mcg) comes from the fair-quality INVIGORATE trial (Indacaterol: Providing Opportunity to Re-engage Patient With Life), which was a 52-week noninferiority trial of 3444 patients with *severe* COPD and a history of at least 1 moderate to severe exacerbation in the past 12 months.[200] INVIGORATE provided low-strength evidence that IC provided less protection from exacerbations (≥ 1 exacerbations: 40% vs 35%; RR 1.11; 95% CI 1.03 to 1.19), but similar mortality (1.4% compared with 1.5%) and chance of St. George's Respiratory Questionnaire improvement ≥ 4 units (49% vs 49%; OR 1.03; 95% CI, 0.88, 1.21).

We also included a good-quality Cochrane review[193] that studied the effects of TIB 18 mcg/d compared with IC in 2 earlier studies done in a broader population of 2856 participants with COPD ranging in severity from moderate to severe.[198,199] Duration of follow-up was 12 weeks[199] and 26 weeks.[198,201] The Cochrane review authors judged the risk of bias as low to unclear for the majority of domains. We relied on the meta-analyses performed by the Cochrane reviewers for exacerbations and quality of life. We supplemented the Cochrane review findings with additional meta-analyses for all-cause hospitalizations. As noted by the Cochrane reviewers, due to the limited number of events, we did not conduct a meta-analysis of mortality. Evidence was low-strength across all outcomes. The only statistically significant difference was that TIB was associated with a lower proportion of patients with a clinically significant improvement in quality of life (42% compared with 50%; RD -0.08; 95% CI, -0.13 to -0.03). Otherwise, there were no significant differences between TIB and IC in hospitalizations (4.8% compared with 4.9%; OR 1.14; 95% CI, 0.80 to 1.62) or proportion of patients with 1 or more exacerbations (11.9% compared with 14.1%; OR 0.92; 95% CI, 0.66 to 1.28).

Salmeterol (SM) compared with tiotropium (TIB)

Asthma. Two fair-quality RCTs[191,192] compared the addition of treatment with TIB or SM in patients whose asthma was not controlled by inhaled corticosteroids alone. The TALC RCT (Tiotropium Bromide as an alternative to Increased Inhaled Glucocorticoid in Patient Inadequately Controlled on a Lower Dose of Inhaled Corticosteroid) compared 14 weeks of treatment with TIB 18 mcg/d or SM 50 mcg/d when added to BDP 80 mcg/d.[192] The second RCT compared 16 weeks of treatment with TIB 5 mcg/d or SM 50 mcg/d when added to 400 to 1000 mcg/d of BUD or equivalent in patients with the B16-Arg/Arg genotype.[191] Both RCTs provide low-strength evidence that TIB is noninferior to SM for exacerbations and quality of life outcomes. Exacerbations occurred in 4.3% and 2.4% of patients taking TIB and SM, respectively, in TALC[192] and in 12.5% and 12.7% of patients with the B16-Arg/Arg genotype, respectively. Mean improvement from baseline was similar for TIB and SM on the Asthma Quality-of-Life Questionnaire score (mean difference, -0.13; 95% CI, -0.28 to 0.02) in TALC[192] and on the Mini-Asthma Quality of Life Questionnaire in patients with the B16-Arg/Arg genotype (estimated treatment difference, -0.149; 95% CI, -0.320 to 0.022).[191] There was 1 death (0.5%) in the SM group and 1 hospitalization (0.5%) in the TIB group in the TALC RCT, but due to unknown consistency and imprecision, we did not draw conclusions about the comparative effectiveness of TIB and SM on these outcomes. Tiotropium was noninferior to SM on various symptom measures in both RCTs.

COPD. We included a good-quality Cochrane review[193] that studied the effects of TIB 18 mcg/d compared with SM 50 mcg/d (4 RCTs in 3 publications with 8936 participants).[194-196] The end

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date of the Cochrane review search was February 2012 and we did not identify any new trials published since then.

The Cochrane review authors judged the risk of bias as low to unclear for the majority of domains across all RCTs. Study duration ranged from 12 weeks,[194] to 6 months,[195] to 12 months.[196] We relied on the meta-analyses performed by the Cochrane reviewers for hospitalizations, quality of life, and exacerbations. For mortality, the Cochrane review only evaluated the comparison of TIB versus long-acting beta2-agonists as a group (1.2% compared with 1.4%; OR 0.82; 95% CI, 0.60 to 1.13), as the number of events in each group were be too few to evaluate subgroup differences based on individual long-acting beta2-agonist type. For this reason, we did not pursue supplemental meta-analyses of individual long-acting beta2-agonists and considered the evidence for mortality to be insufficient to support any conclusions. There is moderate-strength evidence that TIB is associated with fewer participants experiencing 1 or more exacerbations compared with SM (32% compared with 36%; OR 0.84, 95% CI, 0.77 to 0.92). Tiotropium also reduced days unable to perform paid work (0.67 days compared with 0.97 days; *P* not reported) during the 1-year POET-COPD trial (Prevention Of Exacerbations with Tiotropium).[201] There is low-strength evidence of no statistically significant difference between TIB and SM in hospitalizations (2.4% compared with 5.2%; OR 0.45, 95% CI, 0.19 to 1.06) or proportions of patients with a clinically significant improvement in quality of life (at least 4 units on St. George's Respiratory Questionnaire; 49% compared with 43%; RD 0.06; 95% CI, -0.02 to 0.13).

5. Inhaled corticosteroids (ICSs) compared with phosphodiesterase-4 (PDE-4) inhibitors

One trial comparing an ICS to a PDE-4 inhibitor in patients with asthma met our inclusion/exclusion criteria (Table 17).[202] The trial included adolescents and adults ages 12 to 70 years in Europe and the UK. Patients taking BDP had fewer exacerbations than those taking RF; we calculated an exacerbation risk 3 times greater for RF than BDP, but the confidence interval was wide. The investigators concluded that RF was noninferior to BDP for asthma symptoms and rescue medicine use. We did not find any trials of PDE-4 inhibitors in patients with COPD.

Overall, limited head-to-head evidence from 1 trial[202] suggests RF is noninferior to BDP in reducing symptoms and rescue medicine use in patients with asthma, though there was a trend towards more exacerbations in patients taking RF compared to those taking BDP.

Beclomethasone (BDP) compared with roflumilast (RF)

One fair-rated trial comparing BDP with roflumilast (RF) met our inclusion/exclusion criteria.[202] The trial had a noninferiority design and enrolled 499 patients ages 12 to 70 years with moderate persistent asthma, according to the trial's reported inclusion and exclusion criteria, from centers in Europe and the UK. Effects of 500 mcg/day of RF or 400 mcg/day BDP on exacerbations, symptoms, and rescue medication use were reported.

Fewer patients taking BDP experienced asthma exacerbations, with 4 exacerbations in the BDP group (2% of these patients) and 13 in the RF arm (5%), for a relative risk of 3.2 comparing RF with BDP (95% CI 1.1 to 9.1, calculated for this review). Improvements in asthma symptom scores and rescue medication use were similar between the 2 treatment arms. BDP reduced rescue medicine use from baseline by 1.15 puffs/day, compared with a decrease of 1.00 puffs/day for RF (p=0.0171), but the investigators did not consider the difference clinically meaningful. Asthma symptoms during the day and night were scored on scales from 0 to 4, with higher scores for symptoms disrupting activities and sleep. Symptom scores declined more from

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baseline for BDP than RF (-1.00 vs. -0.82), but the difference was not statistically significant (p=0.09) The study investigators concluded that RF was noninferior to BDP for asthma symptoms and rescue medicine use, though they did not comment on the difference in exacerbations reported and whether they would consider it clinically meaningful.

Table 17. Characteristics of head-to-head studies comparing inhaled corticosteroids and phosphodiesterase-4 inhibitors in children and adults with asthma

Study	Study design N Duration	Country Study population Setting	Comparison (total daily dose in mcg/day)	Quality rating
Beclomethasone diproprionate compared with roflumilast				
Bousquet et al. 2006 [202]	RCT 499 12 weeks	France, Germany, Great Britain, and Spain Age 12-70, moderate asthma, 70% non-smokers, 30% ex-smokers Multicenter, setting NR	BDP (400) compared with RF (500)	Fair

Abbreviations: BDP = beclomethasone dipropionate; NR = not reported; RCT= randomized controlled trial.

B. Combination Therapy

1. Inhaled corticosteroid (ICS) and long-acting beta-2 agonist (LABA) compared with higher-dose inhaled corticosteroid (addition of LABA to ICS compared with increasing the dose of ICS)

We found 4 systematic reviews with meta-analysis[203-206] and 35 RCTs (39 publications)[64,104,139,207-242] that included head-to-head comparisons between an ICS/LABA with a higher-dose ICS in patients with asthma meeting our inclusion/exclusion criteria. These trials compared the addition of a LABA to an ICS with increasing the dose of the ICS. Twenty-three of the 35 (66%) administered the ICS and LABA in a single inhaler and 12 (34%) administered the ICS and LABA in separate inhalers. Nine trials[139,210,215,216,229,233,238,240,241] included children, and 2 enrolled an exclusively pediatric population under 12 years of age.[210,215,238] (Table 18)

Overall, results from large trials up to 12 months in duration support greater efficacy with the addition of a LABA to an ICS than with a higher-dose ICS for adults and adolescents with persistent asthma (high-strength evidence, Appendix E, Table E-11). Our meta-analysis shows statistically significantly greater improvement in percent symptom-free days (SMD -0.20, 95% CI: -0.25, -0.14; 15 studies), symptom scores (SMD = -0.22, 95% CI: -0.34, -0.11; 10 studies), percent rescue-free days (SMD = -0.24, 95% CI: -0.31, -0.16; 11 studies), and rescue medicine use (SMD = -0.22, 95% CI: -0.28, -0.16; 16 studies) for subjects treated with ICS/LABA. Despite a trend toward fewer subjects with exacerbations in the ICS/LABA group, the difference was not statistically significant in our analysis (OR = 0.91, 95% CI: 0.81, 1.02; 23 studies). Just 1 trial exclusively enrolled children under 12 (4 included some subjects < 12) and results are not necessarily generalizable to pediatric populations.

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We identified no reviews or head-to-head trials of ICS/LABA compared with higher dose of the same ICS in patients with COPD.

Description of studies

Four large systematic reviews with meta-analyses[203-206] compared the addition of any LABA to any ICS (ICS/LABA) with increasing the ICS dose. The largest review by Ducharme et al.[205] was an update to Greenstone, 2005.[243] It included 48 trials (47 publications) (6 of them in pediatric populations). Twenty-three of those trials met our inclusion/exclusion criteria. One of the reviews included studies only in children aged 2 to 18 years.[204]

Of the 35 RCTs we included (Table 18), 15 (44%) compared FP/SM with fluticasone; 7 (21%) compared BUD/FM with BUD, 6 (18%) compared BDP/SM with BDP, 3 (9%) compared BDP/FM with BDP, 2 (6%) compared FP/SM with BUD, 1 (3%) compared BUD/FM with fluticasone, 1 (3%) compared FP/SM with TAA, and 1 compared MF/FM with MF (the total number of comparisons, 35, does not equal the number of trials because 1 trial contributed comparisons to both FP/SM compared with FP and to FP/SM compared with TAA).[64]

Study duration ranged from 8 weeks to 12 months. The most commonly used delivery devices were DPIs: 23 studies (68%) delivered all medicines via DPIs, 9 studies (26%) delivered all via MDIs, and 3 studies (9%) used MDIs for the ICSs in both groups and DPIs for the LABAs.[217,218,230] Twenty-three of the 3-53 (66%) administered the ICS and LABA in a single inhaler and 12 (34%) administered the ICS and LABA in separate inhalers.

Study populations

The 35 head-to-head RCTs included a total of 18,784 subjects (Table 19). Most were conducted primarily in adult populations. Nine studies (26%) included pediatric populations under 12 years of age.[139,210,215,216,229,233,238,240] Eighteen trials (51%) were multinational, 8 (24%) were conducted in the United States, 3 in the Netherlands, 2 in Germany, and 1 each in Greece, Australia, the Netherlands, and the United Kingdom.

Asthma severity ranged from mild to severe persistent: 3 studies (9%) were conducted in patients with mild persistent asthma, 8 (24%) in patients with mild to moderate persistent asthma, 4 (12%) in patients with moderate persistent asthma, 6 (18%) in patients with moderate to severe persistent, and the severity was not reported in 14 (40%) trials. Smoking status was not reported for 15 trials (44%). Eleven (33%) excluded current smokers or those with greater than a 10 pack-year history. Eight (24%) allowed active smokers and reported that between 5 and 33% of subjects were active smokers

Almost all trials required use of ICS prior to randomization for all subjects. There were 2 exceptions: 1 trial enrolled previously steroid naïve patients that achieved good control on FP/SM[208] and 1 trial enrolled patients that were uncontrolled on previous therapy (80% had been on ICS).[223] The vast majority enrolled subjects that were not controlled on ICS therapy. Just 4 trials enrolled subjects that were described as controlled on ICS therapy.[139,212,221,240]

Sponsorship

Of the 35 head-to-head trials, 32 (91%) were funded by pharmaceutical companies; 1 trial (3%) did not report the source of funding but at least 1 author had a primary affiliation with a pharmaceutical company. Two studies (6%) were funded primarily by a source other than a pharmaceutical company.

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Head-to-head comparisons

Using data from the head-to-head RCTs that met our inclusion criteria, we conducted meta-analyses for 5 outcomes that were reported with sufficient data in multiple trials (Appendix F). These included percent symptom-free days, symptom scores, exacerbations, percent rescue-free days, and rescue medicine use (puffs/day). Subjects treated with ICS/LABA had greater improvement in the percentage of symptom-free days (SMD = -0.20. 95% CI: -0.25, -0.14, 14 studies contributing 15 comparisons), greater improvement in symptom scores (SMD = -0.22, 95% CI: -0.34, -0.11, 9 studies contributing 10 comparisons), greater improvement in the percentage of rescue-free days (SMD = -0.24, 95% CI: -0.31, -0.16, 10 studies contributing 11 comparisons), and greater reduction in rescue medicine use (SMD = -0.22, 95% CI: -0.28, -0.16, 15 studies contributing 16 comparisons) than those treated with a higher-dose ICS alone. However, there was no statistically significant difference in the odds of experiencing an exacerbation, but the pooled odds ratio favored those treated with ICS/LABA (OR = 0.91, 95% CI: 0.81, 1.02, 23 studies). For all of the meta-analyses except the analysis for exacerbations, sensitivity analyses indicate no significant difference in overall meta-analysis conclusions with any single study removed. With the exception of the analysis for symptom score, there was no significant heterogeneity between studies for these outcomes (Appendix F). The statistical heterogeneity for the symptom score analysis was substantial ($I^2 = 70.5$, $P < 0.001$) with the inclusion of the FP arm of the Baraniuk et al, 1999 study, but was no longer significant ($I^2 = 40.8$, $P = 0.095$) when this was removed from the analysis. Additional sensitivity analyses removing studies enrolling subjects that were well controlled on current therapy[208,212,221,240] found no difference in overall meta-analysis conclusions.

One good systematic review[205] compared the addition of any LABA to any ICS (ICS/LABA) with increasing the ICS dose (Table 18). The review included 48 trials (6 of them in pediatric populations) that included a total of 15,155 subjects. The systematic review reported fewer exacerbations requiring treatment with oral corticosteroids with LABA plus ICS versus a higher dose of ICS (RR 0.88, 95% CI: 0.78, 0.98, N = 25). They reported no significant difference in exacerbations requiring hospitalization. Results from meta-analyses for some measures of symptoms (change in daytime symptom score, overall 24-hour symptom score, change in percent symptom free days, and % nighttime awakenings) were statistically significant with a trend toward favoring ICS/LABA therapy. Analyses of rescue medicine use (change in daytime rescue inhalations, change in nighttime inhalations, change in rescue inhalations over 24 hours, and change in mean percent of rescue free days) also showed a statistically significant trend toward improvement with ICS/LABA therapy. However, there was no significant group difference in percent symptom-free days at endpoint or percent overall rescue free days.

Another good systematic review with meta-analysis[203] compared the impact of numerous asthma therapies on exacerbations. They found that combination therapy with ICSs/LABAs was associated with fewer exacerbations than was increasing the dose of ICSs (RR 0.86; 95% CI: 0.76, 0.96; $P = 0.65$ for heterogeneity; 10 studies) (full details available in Evidence Tables A and B).

One recent good-quality systematic review with meta-analyses compared the addition of any LABA to any ICS (ICS/LABA) with increasing the ICS dose in children aged 2 to 18 years.[204] The review included 6 studies for this comparison and the mean age of participants across the studies was 10 years. A meta-analysis of the primary outcome (exacerbations requiring oral steroids) included only 2 studies and found no statistically significant difference between the ICS/LABA or higher-dose ICS groups (RR = 1.5, 95% CI 0.65 to 3.48). The review

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did not report results for outcomes such as daytime rescue inhalations, nighttime awakenings, and daytime or nighttime symptoms because of insufficient data. (Evidence Tables B)

A fair-quality systematic review by Jaeschke et al.[206] included 31 studies with 14,409 patients that compared ICS/LABA to higher-dose ICS. The review analyzed studies of SM and FM separately. The meta-analysis results for both medications for asthma related hospitalizations were not statistically significant [(FM/ICS vs. ICS): OR = 0.68, 95% CI 0.38, 1.24 (N = 6); (SM/ICs vs. ICS): OR = 1.12, 95% CI 0.54 to 2.35 (N = 13)]. The results of analyses for total mortality were also not statistically significant for either group [(FM/ICS vs. ICS): OR = 0.71, 95% CI 0.13 to 3.91 (N= 2); (SM/ICs vs. ICS): OR = 3.12, 95% CI 0.30 to 25.49 (N = 2)]. The authors noted that asthma-related mortality could not be assessed because of low frequency of events.

An additional systematic review by Rodrigo et al.[244] analyzed 57 studies with 34,747 patients; 32 of these studies compared LABA/ICS to a higher dose of ICS. This review combined studies of ICS/LABA compared with same dose ICS and ICS/LABA compared with a higher-dose ICS in the analyses, therefore it is not considered in our assessment of ICS/LABA compared with higher-dose ICS. The results of the combined analysis for exacerbations requiring systemic steroids showed a statistically significant result in favor of LABA/ICS (RR = 0.73, 95% CI 0.67 to 0.79, N = 30).

Fluticasone propionate (FP)/salmeterol (SM) compared with fluticasone propionate

Fifteen fair-quality RCTs (7249 subjects) compared FP/SM with a higher dose of FP[64,139,208,209,212-216,220,221,229,237-239] (Table 18). Twelve administered FP/SM in a single inhaler device[139,208,209,212,213,215,216,220,221,229,237,238] and 3 tested the combination delivered by separate inhalers. Four studies[139] included children ≤ 12 years of age. Study duration was 8 weeks for 1 trial, 12 weeks for 6 trials, 16 weeks for 2 trials, 24-26 weeks for 5 trials, and 52 weeks for 1 trial.

The majority of trials assessed asthma symptoms and rescue medicine use. Nine trials also reported exacerbations and 2 reported quality of life. For these outcomes, most of the trials either reported no difference or outcomes favoring FP/SM combination therapy over the increased dose of FP. One trial, comparing FP twice daily with FP/SM once daily, reported a statistically significant difference in favor of FP alone for mean daily asthma symptom score.[213] For subjects treated with FP/SM compared to those treated with FP alone, 7 trials reported fewer symptoms or better improvement in symptoms,[208,209,214,216,220,237,239] 9 trials reported a greater decrease or less frequent use of rescue medicine,[64,208,209,212,214-216,220,239] 1 trial reported a trend toward fewer exacerbations,[209] and 1 trial reported greater improvement in nocturnal awakenings.[214] The 2 trials reporting quality of life found no statistically significant difference in overall quality of life measures[139,237] (Evidence Tables A and B). One trial reported no differences in children age 6-16 on symptom free days or the occurrence of exacerbations.[238]

Meta-analyses of 9 trials show no statistically significant difference in exacerbations, but the pooled odds ratio favors those treated with FP/SM (OR = 0.90, 95% CI: 0.71, 1.14; 9 studies). Sensitivity analyses indicate that the removal of any 1 study does not change the overall conclusion. There was no significant heterogeneity between studies ($I^2 = 0$). Additional meta-analyses for symptom-free days, symptom scores, rescue-free days, and rescue medicine use show a trend toward results similar to those in the overall meta-analysis for ICS/LABA compared with higher-dose ICS.

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Budesonide (BUD)/formoterol (FM) compared with budesonide
Seven fair-quality RCTs (6460 patients) compared BUD/FM with a higher dose of BUD[210,225,227,228,233,235,236] (Table 18). Five administered BUD/FM in a single inhaler device[210,227,228,233] and 2 tested the combination delivered by separate inhalers. Two of the trials[210,233] included children ≤ 12 years of age. One enrolled children with mild to moderate persistent asthma between the ages of 4 and 11.[210] The other enrolled subjects with moderate persistent asthma between the ages of 4 and 80.[233] Study duration was 12 months for 6 trials and 12 weeks for 1 trial.[228]

All trials assessed asthma symptoms, exacerbations, and rescue medicine use. Four trials also reported nocturnal awakenings. For these outcomes, the majority of trials reported no difference or outcomes favoring BUD/FM combination therapy. For subjects treated with BUD/FM compared to those treated with BUD alone, 5 of 6 trials reported fewer symptoms or better improvement in symptoms,[210,225,228,233,235,236] 1 trial (of 5 reporting) found greater reduction in nocturnal awakenings,[228] and 4 trials reported a greater decrease or less frequent use of rescue medicine.[225,228,233,235,236] Four trials found no difference in exacerbations.[210,227,228,233] One study found that the number of asthma exacerbations per patient-treatment year was significantly lower with BUD/FM (0.185) compared with a higher dose of BUD alone (0.315) ($P = 0.049$).[236]The remainder of trials reported no difference for these outcomes except for 1 trial reporting a trend toward fewer exacerbations in subjects treated with the increased dose of BUD than those treated with BUD/FM.[225,235]

Meta-analyses of 7 trials found trends consistent with the overall ICS/LABA compared with higher-dose ICS meta-analyses. Subjects treated with BUD/FM had greater improvement in the percentage of symptom-free days (SMD = -0.19, 95% CI: -0.27, -0.11, 6 studies), greater improvement in symptom scores (SMD = -0.18, 95% CI: -0.28, -0.07; 2 studies), greater improvement in the percentage of rescue-free days (SMD = -0.21, 95% CI: -0.36, -0.05, 3 studies), and greater reduction in rescue medicine use (SMD = -0.16, 95% CI: -0.26, -0.06 , 5 studies) than those treated with a higher-dose BUD alone. There was no statistically significant difference in exacerbations (OR = 0.98, 95% CI: 0.72, 1.34, 5 studies).

Beclomethasone (BDP)/salmeterol (SM) compared with beclomethasone
Six fair-quality RCTs (2,574 subjects) compared BDP/SM with a higher dose of BDP[104,217,219,226,231,240,242,245] (Table 18). All 6 administered BDP/SM in separate inhalers. One trial[240] enrolled children and adolescents between the ages of 4 and 18. The remainder were conducted in populations ≥ 12 years of age. Study duration was 12 weeks for 1 trial,[104] 21-24 weeks for 4 trials,[217,219,226,231,242,245] and 1 year for 1 trial.[240]

All trials assessed asthma symptoms, exacerbations, and rescue medicine use. Four trials also reported nocturnal awakenings and 2 reported quality of life outcomes. For each of these outcomes, the majority of trials reported no difference or outcomes favoring BDP/SM combination therapy; none reported a statistically significantly greater improvement for those treated with BDP alone. For symptoms, 3 trials reported no difference[104,217,219,240] and 3 found results favoring BDP/SM.[226,231,242,245] For nocturnal awakenings, 1 trial reported no difference[231] and 3 found results favoring BDP/SM.[217,219,226,242,245] For exacerbations, 5 trials reported no difference[104,217,219,226,231,242,245] and 1 reported a trend toward fewer exacerbations requiring steroids for those treated with BDP alone.[240] All but 1 trial[217,219] reported a greater decrease or less frequent use of rescue medicine for those treated with BDP/SM than for those treated with

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BDP alone. The 2 trials reporting quality of life found no significant difference between the groups.[104,217,219]

Meta-analyses of these 6 trials showed trends consistent with the overall ICS/LABA compared with higher-dose ICS meta-analyses. Subjects treated with BDP/SM had statistically significantly greater reduction in rescue medicine use (SMD = 0.18, 95% CI: 0.05, 0.31; 4 studies) and trended toward greater improvement in the percentage of symptom-free days (SMD = 0.14, 95% CI: -0.01, 0.28; 2 studies) than those treated with a higher-dose BDP alone. There was no statistically significant difference in the percentage of subjects with exacerbations (SMD = -0.019, 95% CI: -0.095, 0.058; 5 studies contributing 6 comparisons).

Beclomethasone (BDP)/formoterol (FM) compared with beclomethasone
Three fair RCTs (982 subjects) meeting our inclusion/exclusion criteria compared BDP/FM with a higher dose of BDP alone.[211,218,230] All 3 enrolled adults ≥18 that were not controlled on ICSs. Two compared BDP/FM in a single inhaler device[211] and 1 tested the combination delivered by separate inhalers.[230] Two studies[211,230] reported statistically significantly better symptom and rescue medicine use outcomes for subjects treated with BDP/FM than those treated with FM alone (Evidence Tables A and B). Huchon et al.[218] reported that a reduction in rescue medication use was statistically significant from baseline for the BDP/FM group and did not change for the BDP alone group, but did not report whether the difference between the groups was significant. Two studies found a trend toward fewer exacerbations in those treated with BDP/FM.[218,230]

Fluticasone propionate (FP)/ salmeterol (SM) compared with budesonide (BUD)
One good 12-week RCT (N = 349)[223] and 1 fair 24-week RCT (N = 353)[222,224] meeting our inclusion/exclusion criteria compared FP/SM with a higher relative dose of BUD alone. The 12-week trial compared FP/SM (200/100) with BUD (800) and the 24-week trial compared FP/SM (500/100) with BUD (1600). Both were multinational trials that enrolled subjects ≥ 12 years of age. Both administered FP/SM in a single inhaler device. The 2 trials reported some conflicting results. The 12-week trial found no statistically significant difference between treatment groups in symptoms, exacerbations, or rescue medicine use. The 24-week trial reported fewer symptoms, less rescue medicine use, and greater improvement in quality of life for those treated with FP/SM than those treated with BUD alone, but no significant difference in exacerbations.

Budesonide (BUD)/formoterol (FM) compared with fluticasone propionate (FP)
One 12-week fair RCT meeting our inclusion/exclusion criteria compared BUD/FM in a single inhaler with a higher relative dose of FP alone in 344 adults with moderate persistent asthma.[207] The trial reported no statistically significant difference in symptoms or nocturnal awakenings. But, those treated with BUD/FM had fewer mild exacerbations and required less rescue medicine compared to those treated with FP alone.

Fluticasone propionate (FP)/salmeterol (SM) compared with triamcinolone acetonide (TAA)
We found 1 fair RCT meeting our inclusion/exclusion criteria that compared FP/SM (in separate inhalers) with a higher relative dose of TAA alone.[64] This trial is also included above in this section for the FP/SM compared with FP comparison because there was an FP-only arm as well. It enrolled 680 adults and adolescents ≥ 12 years of age with persistent asthma not adequately controlled on ICS. They reported greater improvement in symptoms, nocturnal awakenings, and rescue medicine use for those treated with FP/SM than for those treated with TAA alone.

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Mometasone furoate (MF)/formoterol (FM) compared with mometasone furoate
We found 1 fair-quality RCT meeting inclusion/exclusion criteria that compared MF/FM with a higher dose of MF in patients with asthma.[241] This 12-week trial randomized 473 patients (233 in the MF/FM group) ≥ 12 years of age (mean age 48) with a history of asthma deteriorations within the preceding 2-12 months requiring treatment with corticosteroids with or without a LABA to MF/FM 200/10 mcg or MF 400 mcg twice daily. There were significantly fewer asthma deterioration in the MF/FM group compared with the MF higher dose group (29 vs 40, p=0.038). Fifteen MF/F patients experienced a clinically judged deterioration (emergency treatment or treatment with additional asthma medication) compared with 11 in the MF/FM group (p-value not reported). There was no difference in mean change in AQLS quality of life scores between the MF/FM group and the MF group (0.61 vs. 0.50; p=0.84).[246]

2. Inhaled corticosteroid (ICS) and long-acting beta-2 agonist (LABA) compared with inhaled corticosteroid (different drug)

We identified 3 RCTs which compared the combination of an ICS and LABA to a different ICS (at any dose). One trial compared FM/SM with CIC and 2 compared FF/VI with FP in patients with asthma. We identified no reviews or head-to-head studies of this comparison in patients with COPD.

Fluticasone propionate (FP) and salmeterol (SM) compared with ciclesonide (CIC)
We identified 1 fair-quality RCT (n=432) in patients with mild persistent asthma who were randomized to CIC 160 mcg once daily or FP/SM 200/100 twice daily.[247] Patients were ≥ 12 years of age (mean age 30), 43% male, non- or ex-smokers with a smoking history of < 10 pack years. Quality of life scores on the AQLQ were significantly improved with CIC versus FM/SM (mean change 0.36 vs 0.27, p<0.0001) although there was no difference between treatments on asthma symptom-free days or asthma symptom scores (p=0.06, p=0.75, respectively. The probability of experiencing a severe asthma exacerbation was 0.30 in the CIC group compared with 0.18 in the FM/SM group (p-values not reported).

Fluticasone furoate (FF) and vilanterol (VI) compared with fluticasone propionate (FP)
We identified 1 good-quality[248] and 1 fair-quality, RCT[249] that compared FF/VI with FP via DPI. The good-quality study (n=503, mean age = 39, 37% male, duration=52 weeks) primarily evaluated safety but did report that there was no difference in risk of severe exacerbations based on treatment with FF/VI (200/25 mcg or 100/25 mcg once daily) versus FP (500 mcg) twice daily (RR 0.74, 95% CI 0.21 to 2.70, p=0.65). The frequency of mild and moderate exacerbations was not reported.

The fair-quality, unpublished study (n=392, mean age 47, 41% male, duration=24 weeks) randomized patients to FF/VI 200/25 mcg once daily or FP 500 mcg twice daily via DPI. Information on exacerbations was not provided. Change from baseline on the AQLQ quality of life measure were identical between groups at 12 weeks (0.74) and similar at 24 weeks (.93 in the FF/VI group vs. 0.90 in the FP group, p-values not reported). Differences in rescue-free days and symptom-free days were improved with FF/VI but the difference was not statistically significant (p=0.07, p=0.14, respectively).

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Table 18. Characteristics of head-to-head studies comparing inhaled corticosteroid and long-acting beta-2 agonist (in one or separate inhalers) with higher-dose inhaled corticosteroid

Study	Study Design N Duration	Country Population Setting	Comparison (total daily dose in mcg)	Quality Rating
Fluticasone propionate + salmeterol compared with fluticasone propionate				
Baraniuk et al. 1999[64]	RCT, DB, triple-dummy 680 12 weeks	US Age ≥ 12, uncontrolled with low-dose ICS, severity NR, smokers excluded Pulmonary/allergy medicine clinics (50)	FP MDI (196) + SM (84) compared with FP MDI (440) compared with TAA MDI (1200)	Fair
Bateman et al. 2006[208]	RCT, DB 484 12 weeks	Multinational Age 12 to 80, previously steroid naïve patients that achieved good control on FP/SM (500/100), smokers excluded Multicenter	FP/SM (200/100) compared with FP (500) All delivery devices=DPIs	Fair
Bergmann et al. 2004[209]	RCT, DB 365 12 weeks	Germany Age 18-70, moderate persistent asthma, poorly controlled on ICS, smokers excluded Multicenter, private practice and outpatient clinics	FP/SM DPI (500/100) compared with FP DPI (1000)	Fair
Busse et al. 2003[212]	RCT, DB 558 24 weeks	US Age ≥ 12, mild to moderate persistent asthma, had to be controlled on FP (500) during the third run-in, smoking status NR Multicenter	FP/SM DPI (200/100) compared with FP DPI (500)	Fair
Chuchalin,et al 2008[213]	RCT, DD 2258 1 year	Ages 12-79, ≥6 month history of mild asthma receiving SABA only, allowed smokers if <10 pack-year history,	FP/SM DPI (100/50) vs FP DPI (200) vs Placebo	Fair

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Table 18. Characteristics of head-to-head studies comparing inhaled corticosteroid and long-acting beta-2 agonist (in one or separate inhalers) with higher-dose inhaled corticosteroid

Study	Study Design N Duration	Country Population Setting	Comparison (total daily dose in mcg)	Quality Rating
Condemi et al. 1999[214]	RCT, DB, DD 437 24 weeks	US age ≥12, uncontrolled on ICS, severity NR, smokers excluded Multicenter (36)	FP MDI (196) +SM MDI (84) compared with FP MDI (440)	Fair
de Blic et al. 2009[215]	RCT, DB, DD 321 12 weeks	12 European Countries Children, aged 4–11 yrs, with a clinical history of asthma for at least 6 months and uncontrolled on ICS Multicenter	FP (100) + SM (200) Vs. FP (400) All delivery devices - DPI	Fair
Gappa et al. 2009[216]	RCT, DB, DD 281 8 weeks	Germany Age 4-16; symptomatic persistent mild to moderate seasonal or perennial asthma and currently using low-dose ICS Multicenter	FP/SM DPI (100/ 200) Vs. FP (400) All delivery devices - DPI	Fair
Ind et al. 2003[220]	RCT, DB, DD 502 24 weeks	Multinational (UK, Italy, Canada, Denmark, Iceland, Republic of Ireland) Age 16 to 75, moderate to severe persistent asthma, uncontrolled on ICS, 13-24% smokers in each group Multicenter (100) - Hospitals and primary care centers	FP/SM MDI (500/100) vs. FP MDI (500) vs. FP MDI (1000)	Fair

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Table 18. Characteristics of head-to-head studies comparing inhaled corticosteroid and long-acting beta-2 agonist (in one or separate inhalers) with higher-dose inhaled corticosteroid

Study	Study Design N Duration	Country Population Setting	Comparison (total daily dose in mcg)	Quality Rating
Jarjour et al. 2006[221]	RCT, DB 88 24 weeks Note: the subjects in this study were a subset of the subjects in Busse et al. 2003[212] and thus were not included in meta-analyses to avoid double-counting.	Multinational (US, Canada, UK) Age≥18, well controlled during final run-in on FP (500), excluded smokers with > 10 pack-year history Multicenter	FP/SM DPI (200/100) compared with FP DPI (500)	Fair
Lemanske et al. 2010[229]	RCT 182 48 wks (3 cross-over periods of 16 wks each)	US Age 6-17 years, mild-to-moderate asthma uncontrolled on low-dose ICS Childhood Asthma Research and Education Network Centers	FP DPI (500) FP/SM DPI (200/100) FP (200) DPI + ML (5-10 mg)	Fair
Peters et al. 2007[139]	RCT, DB 500 16 weeks	US Age ≥6, controlled on FP (200), severity NR, 10-18% were former smokers Multicenter	FP/SM (100/50) QID vs. FP (200) vs. ML (5-10 mg) All delivery devices=DPIs	Fair
Schermer et al. 2007[237]	RCT, DB 177 (137 with asthma and 40 with COPD, results presented separately) 12 weeks	Netherlands Age ≥12, on ICS for at least 3 months, NR whether controlled or not, severity NR, enrolled smokers (17% compared with 37%) Multi-site, patients recruited by 41 Family Practice physicians	FP/SM (200 or 500/100) compared with FP (500 or 1000) All delivery devices - DPI	Fair

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Table 18. Characteristics of head-to-head studies comparing inhaled corticosteroid and long-acting beta-2 agonist (in one or separate inhalers) with higher-dose inhaled corticosteroid

Study	Study Design N Duration	Country Population Setting	Comparison (total daily dose in mcg)	Quality Rating
Vaessen-Verne, 2010[238]	RCT, DB 158 26 weeks	Netherlands Age 6-16, children still symptomatic on conventional dose of inhaled corticosteroids Multi-center	FP/SM (100/50) diskus twice daily compared with FP (200) diskus twice daily	Fair
van Noord et al. 1999[239]	RCT, DB 274 12 weeks	Netherlands Age ≥18, mild or moderate persistent, uncontrolled on ICS, smoking status NR Multi-center (27)	Addition of SM compared with doubling ICS dose FP (200) + SM (100) vs FP (400) FP (500) + SM (100) vs FP (1000) All delivery devices - DPI	Fair
Budesonide + formoterol compared with budesonide				
Bisgaard et al. 2006[210]	RCT, DB 341 12 months	Multinational (12) Age 4-11, mild-moderate persistent asthma, not controlled on ICS, smoking status NR Multicenter (41)	SMART [BUD/FM (80/4.5) +BUD/FM as needed] vs BUD/FM (80/4.5) compared with BUD (320) All given via DPI,	Fair
Kips et al. 2000[227]	RCT, DB 60 1 year	Multinational (Canada, UK and Belgium) Age 18-70, on ICS, controlled for at least 10 days out of the 1 month run-in, moderate, smoking status NR Multicenter (3 University clinics)	BUD/FM DPI (200/24)[a] compared with BUD DPI (800)	Fair

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Table 18. Characteristics of head-to-head studies comparing inhaled corticosteroid and long-acting beta-2 agonist (in one or separate inhalers) with higher-dose inhaled corticosteroid

Study	Study Design N Duration	Country Population Setting	Comparison (total daily dose in mcg)	Quality Rating
Lalloo et al. 2003[228]	RCT, DB 467 12 weeks	Multinational (Czech Republic, Hungary, Norway, Poland, South Africa, Sweden, United Kingdom) Age ≥ 18, mild to moderate, uncontrolled on ICS, smokers excluded Multicenter (51) University Centers	BUD/FM DPI (160/9) compared with BUD DPI (400)	Fair
O'Byrne et al. 2001[232] OPTIMA trial	RCT, DB 1970 (698 in Group A, 1272 Group B) 1 year	Multinational Age ≥ 12, uncontrolled, mild persistent asthma, smoking status NR multicenter (198)	**Group A** (used no ICS for ≥ 3 months): Placebo compared with BUD (200) compared with BUD+FM (200+9) **Group B** (taking ICS for ≥ 3 months): BUD (200) vs. BUD(200) +FM (9) vs. BUD (400) vs. FM + BUD (9/400) All delivery devices=DPIs	Fair
O'Byrne et al. 2005[233]	RCT, DB 2760 1 year	Multinational (22 countries) Age 4-80, uncontrolled on ICS, moderate persistent asthma, smoking status NR Multicenter (246 centers)	BUD/FM (160/9) (+ SABA for relief) compared with BUD/FM (160/9) (maintenance & relief) compared with BUD (640) Drug 1: 925 Drug 2: 909 Drug 3: 926 All delivery devices=DPIs	Fair

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Table 18. Characteristics of head-to-head studies comparing inhaled corticosteroid and long-acting beta-2 agonist (in one or separate inhalers) with higher-dose inhaled corticosteroid

Study	Study Design N Duration	Country Population Setting	Comparison (total daily dose in mcg)	Quality Rating
Peters et al. 2008[236]	RCT 708 52 weeks	US ≥ 12 years with a documented clinical diagnosis of moderate to severe asthma Multicenter	BUD (640) + FM (18) BID (160/4.5 x 4 inhalations) vs. BUD (320) + FM (9) BID (160/4.5 x 2 inhalations) vs. BUD (640) BID All delivery devices - pMDI	Fair
Pauwels, et al. 1997[235] AND Juniper, et al. 1999[225] FACET (Formoterol And Corticosteroids Establishing Therapy) International study group O'Byrne et al. 2008[234]	RCT, DB, DD 852 (470 in quality of life evaluation) 12 months	Multinational (9: Belgium, Canada, Netherlands, Israel, Italy, Luxembourg, Norway, Spain, and UK) Age 18-70, uncontrolled on ICS, severity NR, smoking status NR Multicenter (71)	BUD (200) compared with BUD (200)+ FM (24) compared with BUD (800) compared with BUD (800)+ FM (24) All delivery devices - DPI	Fair
Beclomethasone + salmeterol compared with beclomethasone				
Greening et al. 1994[217] AND Hyland, 1995[219]	RCT, DB, DD 429 21 weeks	UK Age ≥ 18 with uncontrolled asthma on low-dose ICS, severity NR, enrolled 26-27% smokers in each group General practice Centers (99)	BDP MDI (400) + SM DPI (100) compared with BDP MDI (1000)	Fair
Kelsen et al. 1999[226]	RCT, DB, DD 483 24 weeks	US Age ≥18 with uncontrolled on ICS, severity NR, smokers excluded 34 outpatient clinical sites	BDP MDI (336) + SM (84) MDI compared with BDP MDI (672)	Fair

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Table 18. Characteristics of head-to-head studies comparing inhaled corticosteroid and long-acting beta-2 agonist (in one or separate inhalers) with higher-dose inhaled corticosteroid

Study	Study Design N Duration	Country Population Setting	Comparison (total daily dose in mcg)	Quality Rating
Murray et al. 1999[231]	RCT, DB, DD 514 24 weeks	US Age ≥18, uncontrolled on ICS, severity NR, smoking status NR Multicenter (35)	BDP MDI (336) + SM MDI (84) compared with BDP MDI (672)	Fair
Verberne et al. 1998[240]	RCT, DB 177 1 year	Multinational (Netherlands, UK) Children and adolescents age 4-18, mild to moderate asthma, on ICS ≥3 months, stable asthma for ≥1 month prior to run-in, smoking status NR Multicenter (outpatient clinics of 9 hospitals, 6 university hospitals, and 3 general hospitals)	BDP (400) + SM (100) vs. BDP (800) vs. BDP (400) All given by DPI	Fair
Vermetten et al. 1999[104]	RCT, DB 233 12 weeks	Netherlands Age 18-66, on ICS for ≥ 6 weeks, mild persistent asthma, enrolled 33% smokers Primary care	BDP (400)+ SM (100) compared with BDP (800) All given by DPI	Fair
Woolcock et al. 1996[242]	RCT, DB 738 24 weeks	Multinational (14 countries) Age ≥ 17, uncontrolled on ICS, severity NR, 13-19% smokers in each group Multicenter (72)	BDP (1000) + SM (100) vs. BDP (1000) + SM (200) vs. BDP (2000) All given by MDI	Fair
Beclomethasone + formoterol compared with beclomethasone				
Bouros et al. 1999[211]	RCT, open 134 3 months	Greece Age ≥ 18, poorly controlled on ICS, severity NR, smoking status NR Multicenter (11)	BDP/FM pMDI (500/24) compared with BDP pMDI (1000)	Fair

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Table 18. Characteristics of head-to-head studies comparing inhaled corticosteroid and long-acting beta-2 agonist (in one or separate inhalers) with higher-dose inhaled corticosteroid

Study	Study Design N Duration	Country Population Setting	Comparison (total daily dose in mcg)	Quality Rating
Huchon et al. 2009[218]	RCT 645 24 weeks	Russia, France, Poland, Romania, Hungary, Belgium Men and non-pregnant women (18-70 years), moderate to severe persistent asthma Multicenter	BDP/FM pMDI (400/24 Vs. BDP pMDI (1000) + FM DPI (24) Vs. BDP pMDI (1000)	Good
Mitchell et al. 2003[230]	RCT, DB, DD 203 12 weeks	Australia Age ≥ 18, moderate to severe, uncontrolled on ICS, 8-10% smokers in each group Multicenter (16), outpatients	BDP MDI (1000) + FM DPI (24) compared with BDP MDI (2000)	Fair
Fluticasone propionate + salmeterol compared with budesonide				
Jenkins et al. 2000[222] AND Juniper et al. 2002[224]	RCT, DB, DD 353 (subanalysis 113 for AQLQ) 24 weeks	Multinational (Australia, Finland, Sweden) Age ≥12, moderate to severe persistent asthma, uncontrolled on ICS, excluded smokers with > 10 pack-year smoking history Multicenter (44)	FP/SM DPI (500/100) compared with BUD DPI (1600)	Fair
Johansson et al. 2001[223]	RCT, DB, DD 349 12 weeks	Multinational (6: Canada, Greece, Israel, Italy, S Africa, and Sweden) Age ≥ 12, mild to moderate persistent asthma, uncontrolled on previous therapy (~80% ICS), excluded smokers or those with > 10 pack-year smoking history Multicenter	FP/SM DPI (200/100) compared with BUD DPI (800)	Good

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Table 18. Characteristics of head-to-head studies comparing inhaled corticosteroid and long-acting beta-2 agonist (in one or separate inhalers) with higher-dose inhaled corticosteroid

Study	Study Design N Duration	Country Population Setting	Comparison (total daily dose in mcg)	Quality Rating
Budesonide + formoterol compared with fluticasone propionate				
Bateman et al. 2003[207]	RCT, DB, DD 344 12 weeks	Multinational (6: Germany, Greece, Israel, Netherlands, Portugal, S. Africa) Age ≥ 18; moderate persistent asthma, previous use of constant dose of ICS > 30 days at a constant daily dose of 200-1000mcg, 5-7% smokers in each group Multicenter (37)	BUD/FM DPI (320/9) compared with FP DPI (500)	Fair
Fluticasone propionate + salmeterol compared with triamcinolone acetonide				
Baraniuk et al. 1999[64] This study is also listed above under FP+SM compared with FP section	RCT, DB, triple-dummy 680 12 weeks	US Age ≥ 12, uncontrolled with low-dose ICS, severity NR, smokers excluded Pulmonary/allergy medicine clinics (50)	FP MDI (196) + SM (84) vs. FP MDI (440) vs. TAA MDI (1200)	Fair
Mometasone furoate + formoterol compared with mometasone furoate				
Weinstein, 2010[241]	RCT, DB 473 12 weeks	North America, Latin America, Russia, Ukraine, and Europe ≥12 years; history of asthma deteriorations in preceding 2-12 months requiring treatment with glucocorticoid steroids	MF/FM (400/20) vs MF (800)	Fair

Abbreviations: AQLQ = Asthma Quality of Life Questionnaire; BDP = beclomethasone dipropionate; BID – twice per day; BUD = Budesonide; CI = confidence interval; FP = Fluticasone Propionate; ICS = Inhaled Corticosteroids; LABAs = Long-Acting Beta-2 Agonists; MA=meta-analysis; OCS = oral corticosteroids; QID = once per day; QOL = quality of life; RCT= randomized controlled trial; RR = relative risk; SM = Salmeterol; SMD = standard mean difference; SR=systematic review; TAA = Triamcinolone Acetonide; WMD = weighted mean difference.

Symbol use: Drug X > Drug Y = statistically significant difference in outcomes favoring Drug X; Drug X > Drug Y trend = point estimate favors Drug X, but the difference is not statistically significant or tests of statistical significance were NR; No difference = no statistically significant difference or tests of statistical significance were not reported and outcomes are similar.

[a] The dose of BUD/FM (200 mcg BUD/6 mcg FM) used in this study is only available Canada.

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3. Inhaled corticosteroid (ICS) and long-acting beta-2 agonist (LABA) compared with long-acting muscarinic antagonist (LAMA)

For the comparison of TIB and SM/FP, we included a good-quality Cochrane review[250] of 2 eligible RCTs in patients with COPD.[251,252] For the comparison of TIB versus FF/VI, we included 2 fair-quality, unpublished, 12-week RCTs (N=880).[50,53] There is low-strength evidence that, compared with TIB, FP/SM was associated with lower risk of mortality, higher risk of hospitalization and a higher proportion of patients with a clinically significant improvement in quality of life and no difference in effects on exacerbations. There is low-strength evidence that TIB and FF/VI do not differ in their effects on mortality and insufficient evidence to draw conclusions about how TIB and FF/VI compare for hospitalizations, exacerbations and quality of life. For the comparison of umeclidimium bromide/VI 62.5/25 mcg versus TIB 18 mcg, 3 unpublished, 24-week RCTs of 1759 patients with COPD provided low-strength evidence of no statistically significant difference in risk of mortality or quality of life, but no data on exacerbations or hospitalizations were provided.[54,55,253] We found no evidence of this comparison in patients with asthma.

Tiotropium (TIB) compared with fluticasone propionate (FP)/salmeterol (SM)
We included a good-quality Cochrane review[250] that included 3 RCTs[251,252,254] that compared TIB to SM/FP in 1528 participants with COPD. Two of these RCTs met our inclusion criteria.[251,252] The third trial did not meet our criteria because it was published in a non-English language; consequently, we do not discuss its results here.[254] The end date of the Cochrane review search was November 2012 and we did not identify any new trials published since that time.

Both eligible trials compared TIB 18 mcg/d to FP/SM 500/50 mcg/d. The INSPIRE RCT (Investigating New Standards for Prophylaxis in Reduction of Exacerbations) randomized 1323 participants and had a 2-year follow-up.[251] The unpublished RCT randomized 125 participants and had a 12-week follow-up.[252] Because of the variation in follow-up duration, the Cochrane review authors did not pool data from these RCTs. The Cochrane review authors also noted that both RCTs had a high risk of attrition bias: they suffered from high and imbalanced rates of withdrawal and they did not collect data on patients who withdrew.

INSPIRE provided low-strength evidence that SM/FP was associated with a lower risk of mortality (OR 0.55; 95% CI, 0.33 to 0.93) and more patients achieved a clinically important improvement in quality of life (increase of 4 or more units on the St. Georges Respiratory Questionnaire; OR 1.29 ; 95% CI 1.04 to 1.60), but there was a higher risk of hospitalization (OR 1.32; 95% CI, 1.04 to 1.67) with SM/FP. There was no statistically significant difference between SM/fluticasone and TIB in exacerbations (OR 1.13; 95% CI 0.91 to 1.41). Data from the unpublished 12-week study did not add any additional evidence.

Tiotropium (TIB) compared with vilanterol (VI)/fluticasone furoate (FF)
We included 2 fair-quality, unpublished, 12-week RCTs (N=880) that compared TIB 18 mcg/d to FF/VI 100/25 mcg/d in patients with COPD who had or were at risk for comorbid cardiovascular disease.[50,53] These RCTs provide low-strength evidence of no statistically significant difference between TIB and FF/VI in mortality (0.9% vs 0%; OR, 4.97; 95% CI, 0.58 to 42.77). The unpublished reports of these RCTs did not provide any data on any additional effectiveness/efficacy outcomes of interest.

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Tiotropium (TIB) compared with umeclidinium bromide (UMB)/vilanterol (VI)
We included 3 fair-quality, unpublished, 24-week RCTs (N=1759) that compared umeclidinium bromide (UMB)/VI 62.5/25 mcg to TIB 18 mcg/d in patients with COPD (ZEP117115, DB2113374, DB2113360).[54,55,253] Data on deaths were available from the Result Summaries from the GSK Clinical Study Register. Deaths were rare, with only 0.3% in the umeclidinium/bromide group and 0.2% in the TIB group (OR 1.28; 95% CI, 0.24 to 6.7), which provided low-strength evidence of no statistically significant difference between the 2 drugs.

During public comment, a GSK representative provided additional unpublished data from studies DB2113374 and DB2113360 (N=1694) on scores on the COPD Assessment Test (CAT), St. George's Respiratory Questionnaire (SGRQ), Transition Dyspnea Index (TDI) and Shortness of Breath with Daily Activities Questionnaire (SOBDA) and rescue albuterol use.[255] Data from these 2 trials provided low-strength evidence of no statistically significant differences between UMB/VI 125 mcg/25 mcg, 62.5 mcg/25 mcg or TIB in least squares mean change on the SGRQ Total Score (DB2113360: -9.03 vs -6.87 vs -7.62; P=0.346 and P=0.607; DB2113374: -10.52 vs -9.95 vs -9.78; P=0.588 and P=0.904). There were no consistent differences between UMB/VI 125 mcg/25 mcg, 62.5 mcg/25 mcg or TIB on TDI or SOBDA scores. Evaluation of differences between UMB/VI 125 mcg/25 mcg, 62.5 mcg/25 mcg or TIB on CAT scores was not reported. Reductions in number of puffs per day for rescue albuterol use were statistically significant greater for UMB/VI 125 mcg/25 mcg compared with TIB (DB2113374: -3.2 compared with -2.1, P<0.001; DB2113360: -2.0 compared with -1.4; P=0.031).

4. Inhaled corticosteroid (ICS) and leukotriene receptor antagonist (LTRA) compared with inhaled corticosteroid

We found 1 systematic reviews with meta-analyses[256,257] and 3 RCTs[150,229,258-261] meeting our inclusion/exclusion criteria in patients with asthma (Table 19). Most studies were conducted in adolescent and adult populations; 1 study enrolled a pediatric population ages 6 to 14[261] and 1 enrolled children and adolescents (ages 6 to 17 years).[229]

Overall, there is no apparent difference in symptoms, exacerbations, or rescue medicine use between those treated with ICSs plus LTRAs compared to those treated with increasing the dose of ICSs. (Appendix E, Table E-8). There were some conflicting results and further research may alter the results.

We identified no reviews or head-to-head studies comparing ICS/LTRA with ICS in patients with COPD.

Description of studies
We found 2 systematic reviews with meta-analyses[256] and 3 RCTs[229,258,259,261] meeting our inclusion/exclusion criteria (Table 19). An additional systematic review[262] reported additional data for 1 of the 3 included RCTs.[229] Two trials[261 258,259] compared budesonide plus ML with budesonide alone; 1 study[229] compared the combination of fluticasone and ML with an increased dose of fluticasone.

Study populations
The 3 RCTs included a total of 1142 patients. One study was conducted in adolescent and adult populations;[258,259] 1 study enrolled a pediatric population ages 6 to 14[261] and 1 enrolled children and adolescents (6 to 17 years of age).[229] One was conducted in the United States, 1 in India, and 1 was multinational. Asthma severity ranged from mild persistent to severe persistent. One

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enrolled patients with mild to moderate persistent asthma; 1 enrolled patients with mild to severe persistent asthma; 1 enrolled patients with moderate persistent asthma.

Methodologic quality

The e included RCTs were fair-quality studies. The method of randomization and allocation concealment was rarely reported.

Head-to-head comparisons

Inhaled corticosteroid (ICS)/leukotriene receptor antagonist (LTRA) compared with increased inhaled corticosteroid

For ICS plus LTRA compared with increased doses of ICS, only 3 of the trials included in the systematic review compared licensed doses of LTRAs with increasing the dose of ICSs in patients with asthma. The meta-analyses found no significant difference in any outcomes including the following: change from baseline in symptoms score with licensed (WMD 0.01, 95% CI: -0.09, 0.10) or higher than licensed doses of LTRA (WMD -0.06, 95% CI: -0.16, 0.03); risk of experiencing an asthma exacerbation requiring systemic steroids with licensed doses (RR 0.92, 95% CI: 0.56, 1.51) or higher than licensed doses of LTRA (RR 1.05 95% CI: 0.55, 2.00); withdrawals due to poor asthma control with licensed (RR 0.49, 95% CI: 0.15, 1.63) or higher than licensed doses of LTRA (RR 0.72 95% CI: 0.29, 1.76); and change from baseline in use of rescue beta-agonists with licensed (WMD -0.03 95% CI: -0.24, 0.18) nor higher than licensed doses of LTRA (WMD 0.00 95% CI: -0.37, 0.37). We did not find any studies comparing ICS/LTRA with an increased dose of the same ICS in patients with COPD.

Budesonide (BUD)/montelukast (ML) compared with budesonide increased dose

We found 2 fair RCTs[258,259,261] comparing the combination of BUD/ML with an increased dose of BUD (Table 20). One fair multinational trial (N = 889) compared medium dose BUD (800 mcg/day) plus ML (10 mg/day) (N = 448) with high dose BUD (1600 mcg/day) (N = 441) for 16 weeks.[258,259] The trial enrolled subjects age 15 to 75 with uncontrolled asthma treated with medium dose ICS. At endpoint, there were no statistically significant differences between those treated with BUD/ML and those treated with BUD for percentage of asthma free days, daytime symptom score, percentage of nights with awakenings, percentage of days with an exacerbation, percentage of patients requiring oral steroids or hospitalization, rescue medicine use, or quality of life. Adherence was high for both the tablets and inhalers, with over 95% of days fully compliant.

The other trial[261](N = 71) compared low dose BUD (400 mcg/day) (N = 33) with low dose BUD (200 mcg/day) plus ML (5 mg/day) (N = 30) for 12 weeks. Subjects with moderate persistent asthma age 6 to 14 were enrolled from a Pediatric Asthma Clinic in India. At endpoint, those treated with increased dose of BUD had fewer exacerbations compared to BUD/ML (9.1% compared with 33.3%; $P < 0.01$). Adherence was high in both groups with only 1 patient declaring non-adherence.

Fluticasone propionate (FP)/montelukast (ML) compared with fluticasone propionate increased dose

We found 1 fair-quality RCT[229] (N = 182) comparing the combination of FP/ML with an increased dose of FP in children and adolescents (6 to 17 years of age). The trial used a triple cross-over design. Subjects with uncontrolled asthma while receiving FP (100 twice daily) were

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randomized to FP (250 twice daily), FP (100 twice daily) plus SM, or FP (100 twice daily) plus ML. The primary outcome was a composite of exacerbations, number of asthma control days, and FEV_1. One hospitalization for asthma-related symptoms occurred in each of the 3 treatment groups. A total of 120 prednisone bursts were prescribed for exacerbations (47 during treatment with FP compared with 43 during treatment with FP/ML, *P* = NR). A 2013 Cochrane systematic review[262] of combination therapy with LMs and ICSs identified the same single trial[229] comparing ICS/LM with higher-dose ICS. The review authors calculated a relative risk not reported in the original trial publication; it suggested slightly lower exacerbation risk for FP/ML compared with higher-dose FP, but the difference was not statistically significant (RR 0.82, 95% CI: 0.54 to 1.25).

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Table 19. Characteristics of head-to-head studies comparing Inhaled corticosteroid and leukotriene receptor antagonist with inhaled corticosteroid

Study	Study design N Duration	Country Study population Setting	Comparison (total daily dose)	Quality rating
Inhaled corticosteroid and leukotriene receptor antagonist compared with inhaled corticosteroid increased dose				
Ducharme et al. 2004[256]	Systematic Review with meta-analysis 27 studies (5871 subjects)	2 trials in children; 25 in adults	LTRA plus ICS vs. ICS same dose, ICS same dose tapering, or ICS increased dose.	Good
Budesonide and montelukast compared with budesonide increased dose				
Jat et al. 2006[217]	RCT 71 12 weeks	India Age 6-14 Pediatric Asthma Clinic	BUD (400) vs. BUD (200) + ML (5) Low dose ICS	Fair
Price et al. 2003[258,259] COMPACT	RCT 889 16 weeks	Multinational Age 15 – 75 Multicenter	ML (10) + BUD (800) vs. BUD (1600) Medium to High dose ICS	Fair
Fluticasone propionate and montelukast compared with fluticasone propionate increased dose				
Lemanske et al. 2010[229] BADGER	RCT 182 48 wks (3 cross-over periods of 16 wks each)	United States Age 6-17 Multicenter	FP (500) vs. FP/SM (200/100) vs. FP (200) + ML (5-10) High vs. low vs. low dose ICS	Fair

Abbreviations: AQLQ = Asthma Quality of Life Questionnaire; BUD = Budesonide; CI = confidence interval;; FM = Formoterol; FP = Fluticasone Propionate; ICS = Inhaled Corticosteroids; LABAs = Long-Acting Beta-2 Agonists; LTRAs = Leukotriene receptor antagonists; MA=meta-analysis; ML = Montelukast; NR = not reported; NS = not statistically significant; OR = odds ratio; QOL = quality of life; RCT= randomized controlled trial; SM = Salmeterol; SMD = standard mean difference; SR = systematic review; WMD = weighted mean difference.

Symbol use: Drug X > Drug Y = statistically significant difference in outcomes favoring Drug X; Drug X > Drug Y trend = point estimate favors Drug X, but the difference is not statistically significant or tests of statistical significance were NR; No difference = no statistically significant difference or tests of statistical significance were not reported and outcomes are similar.

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5. Combination products (inhaled corticosteroids [ICS]/long-acting beta-agonists [LABAs]) compared with leukotriene modifiers (LMs)

We found 5 RCTs[139,157,263-265] meeting our inclusion/exclusion criteria for this comparison (Table 20). All 5 compared low dose FP plus SM with ML. [139,157,264] Overall, our meta-analysis and results from the 5 RCTs found the combination of FP plus SM to be more efficacious than ML for preventing exacerbations in persistent asthma (Appendix F and Appendix E, Table E-9). Leukotriene modifiers are approved for asthma only, and we did not identify any review or head-to-head studies comparing ICS/LABA with LM in patients with COPD.

Study populations

The 5 RCTs[139,157,263-265] included a total of 2,188 patients. Two of the RCTs were in adolescents and adults, 1 enrolled subjects over the age of 6[139] (~15% of subjects < 12 years of age), and 2 enrolled children ages 6-14.[157,264] Four studies were conducted in the United States and 1 study[264] was conducted at sites in both Latin America and Turkey. Asthma severity ranged from mild persistent to severe persistent: 2 studies enrolled subjects with mild to moderate persistent asthma, and 3 studies enrolled subjects with any severity of persistent asthma.

Methodologic quality

Four trials were rated fair quality and 1[265] was rated good quality.

Sponsorship

Of the 5 RCTs, 3 were funded by pharmaceutical companies; only 1 was funded primarily by sources other than pharmaceutical companies. One trial did not report the source of funding, but a significant portion of the study design was dictated by a pharmaceutical company and several authors reported a primary affiliation with the company.[264]

Head-to-head comparisons

Fluticasone propionate (FP)/salmeterol (SM) compared with montelukast (ML)

The 5 included studies are described below. We conducted a meta-analysis for exacerbations, and found a statistically significant difference favoring those treated with FP/SM (SMD 0.26, 95% CI: 0.16, 0.35) (Appendix F). Those treated with FP/SM also had greater improvement in the percentages of symptom-free days and rescue medicine-free days than those taking ML.

The 5 studies included 1 good-quality RCT[265] and 4 fair-quality RCTs (Table 20).[139,157,263,264] The good-quality RCT (N = 432) compared low dose FP/SM (200 mcg/100 mcg daily) (N = 216) with ML (10 mg/day) (N = 216) as monotherapy for 12 weeks.[265] Subjects with uncontrolled asthma treated with oral or inhaled short-acting beta-agonists age 15 and older were enrolled from 51 centers in the United States. At endpoint, those treated with FP/SM showed a greater improvement in all outcomes compared to ML, including a decrease in the combined asthma symptom score (-1 compared with -0.7; $P \leq 0.001$), increase from baseline in % symptom free days (+40.3% compared with +27%; $P \leq 0.001$), increase from baseline in % of awakening free nights (+29.8% compared with +19.6%; $P = 0.011$), decrease from baseline in nights/week with awakenings (-2.2 compared with -1.6; $P \leq 0.001$), decrease in puffs/day (-3.6 compared with -2.2; $P \leq 0.001$), increase in % of rescue free days (53.4% compared with 26.7%; $P \leq 0.001$), and increase in quality of life (AQLQ overall score, increase: 1.7 compared with 1.2; $P <$

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0.001). Exacerbations occurred less frequently in the FP/SM group (3% compared with 6%; *P* = NR). Compliance was approximately 99% in both groups.

The first fair-quality RCT (N = 423) also compared low dose FP/SM (200 mcg/100 mcg daily) (N = 211) with ML (10 mg/day) (N = 212) for 12 weeks.[263] Subjects with uncontrolled asthma treated with oral or inhaled short-acting beta-agonists age 15 or older were enrolled from multiple centers in the United States. At endpoint, results were similar to those in the good-quality RCT described above,[265] with significant differences for all outcomes favoring FP/SM over ML, including decreased symptoms, rescue medicine use, and exacerbations (0%, 5%; *P* < 0.001) (Table 20).

The remaining 3 RCTs showed mixed results, with some outcomes favoring FP/SM and others showing no difference between the 2 regimens. One trial (N = 500) compared low-dose FP (200 mcg/day) (N = 169) with low-dose FP (100 mcg/day) plus SM (50 mcg/day) (delivered once daily at night) (N = 165) and also with ML (5-10 mg/day) (N = 166) for 16 weeks.[139] Subjects were age 6 and older, had mild to moderate asthma controlled on ICS, and were enrolled from multiple American Lung Association Asthma Clinical Research Centers in the United States. At endpoint, there were no significant differences between FP plus SM and ML in symptom-free days or rescue medicine use. However, there were significant differences in the percentage of patients with treatment failure (20.4% compared with 30.3%; *P* = 0.03) and asthma control (ACQ: 0.71 compared with 0.82; *P* = 0.004) favoring FP plus SM. Adherence was good for all groups (FP/SM 93.3% compared with ML 90.5%).

Another fair-quality RCT (N = 285), the Pediatric Asthma Controller Trial (PACT), compared low dose FP 200 mcg/day via DPI (N = 96) with ML 5 mg/day (N = 95) and with the "PACT combination" of low dose FP plus SM (each 100 mcg/day) via DPI, given as FP 100 mcg plus SM 50 mcg in the morning plus SM 50 mcg in the evening for 48 weeks (N = 94).[157] Of note, the dose of FP/SM used was outside of the product label recommendation. Subjects with mild to moderate asthma age 6 to 14 were enrolled from Childhood Asthma Research and Education Centers in the United States. The trial found favorable results for FP/SM in the change in the percentage of asthma control days from baseline (33.3% compared with 22.3%; *P* = 0.011). Nocturnal asthma symptoms requiring albuterol (NASRA) were less for the PACT combination (median 3.0 NASRA per year) than for ML (6.5), but the difference was not statistically significant (p=0.16).[165] At endpoint, the trial found no significant difference in the overall percentage of asthma control days (52.5% compared with 59.6%; *P* = 0.08). There was no significant difference in asthma control as measured by change in ACQ score from baseline (-0.45 compared with 0.55; *P* = 0.42). Adherence was similar between groups (86% compared with 90%; *P* = NR).

A final RCT showing mixed results, the Pediatric Asthma Control Evaluation (PEACE) study, enrolled children ages 6 to 14 with mild to moderate persistent asthma from outpatient centers at 4 sites in Turkey and 23 in Latin America.[264] Using a double-blind, double-dummy design, 281 children treated with FP/SM 100 mcg/50 mcg twice daily were compared to 267 patients treated with ML 5 mg daily. The results showed significant improvement in the percentage of symptom free days (OR 1.74, 95% CI 1.07 – 2.82) and asthma-controlled weeks (16.7% more in FP/SM group, 95% CI 8.3 – 16.7). The risk of not achieving well-controlled asthma was 3 times greater for patients taking ML compared to those taking FP/SM (OR 2.94, 95% CI 1.97-4.37, controlling for age and sex).[266] The trial found no difference between groups in the percentage of nights without awakenings due to nocturnal symptoms (OR 2.33, 95% CI 0.73 – 7.47). The mean exacerbation rate and time was significantly reduced with FP/SM therapy

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(0.12 vs. 0.3, OR 0.4, 95% CI 0.29 – 0.57) and the number of patients exacerbation-free at 84 days was 89.6% in FP/SM patients compared with 74.8% in the ML group (treatment difference, 15%; 95% CI: 8-22, P < 0.001)). In addition, the percentage of rescue free days increased significantly with FP/SM treatment (OR 3.24, 95% CI 2.09– 5.02). Quality of life measures, however, demonstrated mixed results. While *PACQLQ* scores were higher in the FP/SM group (mean treatment difference 0.54, 95% CI 0.06 – 1.02), no difference was noted between groups with respect to *PAQLQ* score (mean treatment difference 0.09, 95% CI -0.12 – 0.30). Finally, while 7.5% of FP/SM treated patients required some form of unscheduled health care contact during the study period, substantially more patients on ML therapy required medical attention (*P* = NR). Adherence was similar between groups (87% compared with 84%; *P* = NR).

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Table 20. Characteristics of head-to-head studies comparing inhaled corticosteroids and long-acting beta-2 agonists with leukotriene modifiers in patients with asthma

Study	Study design N Duration	Country Study population Setting	Comparison (total daily dose)	Quality rating
Montelukast compared with fluticasone propionate plus salmeterol				
Pearlman et al. 2002[265]	RCT 432 12 weeks	United States Age 15 and older, mild to severe persistent asthma, smoking status NR Multicenter (51)	FP/SM (200 mcg/100 mcg) vs. ML (10 mg) Low dose ICS	Good
Calhoun et al. 2001[263]	RCT 423 12 weeks	United States Age 15 and older, mild to severe persistent asthma, smoking status NR Multicenter	FP/SM (200 mcg/100 mcg) vs. ML (10 mg) Low dose ICS	Fair
Maspero et al. 2008[264,266] Pediatric Asthma Control Evaluation (PEACE) study	RCT DB, double dummy 548 12 weeks	Latin America & Turkey Children 6-14, mild to moderate persistent asthma Multicenter (23 Latin America, 4 Turkey) Outpatient setting	FP (200 mcg)/SM (100 mcg) vs. ML (5 mg) Low dose ICS	Fair
Peters et al. 2007[139]	RCT 500 16 weeks	United States Age 6 and older, mild to moderate asthma, smoking status NR Multicenter	FP (200 mcg) vs. FP/SM (100 mcg/50 mcg) vs. ML (5 – 10 mg) Low dose ICS	Fair

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Table 20. Characteristics of head-to-head studies comparing inhaled corticosteroids and long-acting beta-2 agonists with leukotriene modifiers in patients with asthma

Study	Study design N Duration	Country Study population Setting	Comparison (total daily dose)	Quality rating
Montelukast compared with fluticasone propionate plus salmeterol				
Sorkness et al. 2007[157,165] Pediatric Asthma Controller Trial (PACT)	RCT 285 48 weeks	United States Children age 6-14, mild to moderate persistent asthma, excluded current smokers within the past year Childhood Asthma Research and Education Centers	FP (200 mcg) vs. FP/SM (100 mcg/50 mcg) in the morning + SM (50 mcg) in the evening vs. ML (5 mg) Low dose ICS	Fair

Abbreviations: AQLQ = Asthma Quality of Life Questionaire; BUD = Budesonide; CI = confidence interval;; FM = Formoterol; FP = Fluticasone Propionate; ICS = Inhaled Corticosteroids; LABAs = Long-Acting Beta-2 Agonists; LTRAs = Leukotriene receptor antagonists; MA=meta-analysis; ML = Montelukast; NR = not reported; NS = not statistically significant; OR= odds ratio; QOL = quality of life; RCT= randomized controlled trial; SM = Salmeterol; SR=systematic review.
Symbol use: Drug X > Drug Y = statistically significant difference in outcomes favoring Drug X; Drug X > Drug Y trend = point estimate favors Drug X, but the difference is not statistically significant or tests of statistical significance were NR; No difference = no statistically significant difference or tests of statistical significance were not reported and outcomes are similar.

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6. Long-acting beta agonist (LABA) and inhaled corticosteroid (ICS) compared with leukotriene receptor antagonist (LTRA) and inhaled corticosteroid (addition of LABAs compared with LTRAs as add-on therapy to ICSs)

We found 1 systematic review with meta-analysis, first published in 2006[267] and updated in 2011,[268] and 8 RCTs[229,269-275] that met our inclusion/exclusion criteria and that compared the addition of a LABA with the addition of an LTRA for patients with asthma poorly controlled on ICS therapy. Risk of bias in included studies was generally low. We found no evidence comparing LABAs with LTRAs as add-on therapy to ICSs in patients with COPD.

All 8 of the RCTs that met our inclusion criteria were also included in the 2011 systematic review, so we focus here on the results of the review rather than the individual trials. The review included 15 full-text reports; only 1 of these included children less than 12 years of age (the age range in this study was 6 to 17 years), [229] and this trial did not provide sufficient data for analysis. Eleven of the review's trials contributed data to their meta-analyses of the 6 critical outcomes identified for this update. These 11 trials included a total of 6,292 patients.

Overall, results from this good-quality systematic review with meta-analyses provide high-strength evidence (Appendix E, Table E-21) that the addition of a LABA to ICS therapy prevents exacerbations in more patients than does the addition of an LTRA to ICS therapy for adolescents and adults with persistent asthma. This difference held for patients adding SM to ICS therapy compared to those adding ML. Strength of evidence was also high that the choice of a LABA versus an LTRA did not affect quality of life. Quality of life was also the same for those adding SM vs ML (moderate-strength evidence) and those adding SM versus ZAF (low-strength evidence).

Study interventions

The systematic review included RCTs conducted in patients with persistent asthma where a LABA or LTRA was added to ICS for 4 to 48 weeks (weighted mean 26 weeks). Inhaled short-acting beta-2 agonists and short courses of oral steroids were permitted as rescue medications. Subjects had to be on a stable dose of ICS throughout the trials. Of the 11 studies we assessed in the updated systematic review,[268] 9 compared 100 mcg/day of SM plus ICS with 10 mg/day of ML plus ICS. The other 2 trials compared either SM or FM with ZAF (40 mg/day) as add-on therapy to ICSs. Most trials (N=7) used low-dose FP as the ICS in both treatment arms. Of the remaining 4 trials, 1 used low-dose BUD in both arms; 1 combined high-dose BDP with ML, and medium to high dose FP with SM; and the last 2 trials had varying ICS drugs and doses.

Study populations

All of the 11 trials we assessed were conducted in adult populations. Two studies were conducted in the United States, 1 in the United States and Puerto Rico, 1 in France, and 1 in the UK. Three were multinational trials including 6, 19, and 37 countries, and for the remaining 3 trials the study and/or review did not report the country or countries where the trials took place. For most studies the study or review did not report asthma severity; for the 4 where severity was reported, it was either mild to moderate (one study), moderate (2 studies) or moderate to severe (one study).

Sponsorship

All 11 RCTs were funded by pharmaceutical companies.

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Head-to-head comparisons

One good-quality systematic review with meta-analysis compared LABAs with LTRAs as add-on therapy to ICSs in patients with asthma.[267,268] Eleven of the review's trials, including 6,292 patients, contributed data to meta-analyses we report here. Six of these eleven trials met our inclusion criteria,[269-274] and 5 did not.

The systematic review provided high-strength evidence that LABA plus ICS was significantly better than LTRA plus ICS for preventing exacerbations (Appendix E, Table E-21).[268] Six trials contributed to the primary outcome showing a significant decrease in risk of exacerbation requiring systemic steroids for those treated with LABAs (RR 0.83; 95% CI, 0.71 to 0.97). The reported number of patients who must be treated with the combination of LABA and ICS instead of LTRA and ICS to prevent 1 exacerbation over 48 weeks was 38 (95% CI, 22 to 244).

Quality of life was also slightly better for patients treated with LABA/ICS. The change in Asthma Quality of Life Questionnaire score from baseline, measured on a 7-point scale, was 0.11 points higher for patients using LABAs as add-on to ICSs, compared to those adding LTRAs (95% CI, 0.05 to 0.17). However, the minimal important difference established for the AQLQ is 0.5 points.[276] The systematic review thus provides high-strength evidence that there is no clinically important difference in quality of life between patients adding LABAs to ICS therapy for asthma and those adding LTRAs (Appendix E, Table E-21). However, reported symptoms and rescue medicine use all favored LABAs: compared to patients using LTRAs as add-on therapy, those adding LABAs had fewer symptoms, more symptom-free days, more days when they did not require rescue medicine use, and fewer nighttime awakenings (all differences statistically significant in meta-analyses). There was no significant heterogeneity in any of the meta-analyses we discuss here.

Salmeterol (SM) and inhaled corticosteroid (ICS) compared with montelukast (ML) and inhaled corticosteroid

The systematic review included sub-analyses grouping trials by specific LABA and LTRA comparisons in patients with asthma. It provided high-strength evidence from 9 trials that patients adding SM to ICS had a lower risk of exacerbations than those adding ML. Two trials provided moderate-strength evidence that there were no clinically important differences in quality of life for SM compared with ML as add-on therapy (Appendix E, Table E-21). These results for exacerbations and quality of life were similar to those for the overall drug classes, since most of the trials in the review compared SM and ML. Four included trials provided data on hospitalizations due to exacerbations, and 1 on mortality, all 5 trials comparing SM with ML; however, evidence from these trials was insufficient to compare SM and ML for these outcomes.

Salmeterol (SM) and inhaled corticosteroid (ICS) compared with zafirlukast (ZAF) and inhaled corticosteroid

For this comparison as well, there were no clinically important differences in quality of life between intervention arms, though strength of evidence was low from the 1 trial reporting this outcome for SM compared with ZAF, a trial which was included in the systematic review but did not meet our inclusion criteria.[277] The same single trial reported exacerbations, but evidence was insufficient to compare this outcome between patients taking SM versus ZAF (Appendix E, Table E-21).

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7. Leukotriene receptor antagonist (LRA) and long-acting beta-2 agonist (LABA) compared with inhaled corticosteroid (CS) and long-acting beta-2 agonist

We found 1 fair-quality RCT comparing LTRA plus LABA with ICS plus LABA (Appendix E, Table E-16 and Table 21).[278] This fair-rated, placebo-controlled, multi-center RCT (N = 192, 110 eligible for primary analysis) compared ML (10 mg/day) plus SM (100 mcg/day) plus placebo ICS (N = 98) with low-dose BDP (160 mcg/day) plus SM (100 mcg/day) plus placebo LTRA (N = 92) for 14 weeks, washout for 4 weeks, then crossover for another 14 weeks.[278] Subjects age 12 to 65 with moderate asthma were enrolled from multiple sites in the United States. There was a 4-week run-in period that involved a single-blind treatment with both BDP (160 mcg/day) and ML (10 mg/day). The primary objective of the study was to assess time until treatment failure. For each subject, a treatment regimen was considered superior if time to treatment failure was longer while the patient took that regimen than it was when he or she took the other regimen. The trial was terminated early because the Data and Safety Monitoring Board determined that the primary research question had been answered. For 29 subjects, ICS/LABA was superior (longer time to treatment failure), and for 8 subjects LTRA/LABA was superior (P = 0.0008). The remaining 73 subjects did not experience treatment failure during the trial's 14 weeks of treatment.

Table 21. Characteristics of head-to-head studies comparing leukotriene receptor antagonist and long-acting beta-2 agonist with inhaled corticosteroid and long-acting beta-2 agonist

Study	Study design N Duration	Country Study population Setting	Comparison (total daily dose)	Quality rating
Montelukast plus salmeterol compared with beclomethasone plus salmeterol				
Deykin et al. 2007[278]	RCT 192 14 weeks, washout for 4 weeks, then crossover for 14 weeks	United States Age 12 to 65 Multicenter	ML (10 mg) + SM (100 mcg) plus placebo ICS vs. BDP (160 mcg) + SM (100 mcg) plus placebo LTRA Low dose ICS	Fair

Abbreviations: BDP = Beclomethasone dipropionate; ICS = Inhaled Corticosteroids; LABAs = Long-Acting Beta-2 Agonists; LTRAs = Leukotriene receptor antagonists; ML = Montelukast; RCT= randomized controlled trial; SM = Salmeterol.
Symbol use: Drug X > Drug Y = statistically significant difference in outcomes favoring Drug X; Drug X > Drug Y trend = point estimate favors Drug X, but the difference is not statistically significant or tests of statistical significance were NR; No difference = no statistically significant difference or tests of statistical significance were not reported and outcomes are similar.

8. Inhaled corticosteroids (ICS) and long-acting muscarinic agonist (LAMA) compared with higher-dose inhaled corticosteroid

We included 1 RCT that compared co-therapy with TIB 18 mcg/day plus BDP 80 mcg/day compared with double-dose BDP (160 mcg/day) in patients whose asthma was not controlled by BDP 80 mcg/d alone.[192] That RCT provided low-strength evidence that co-therapy with TIB and BDP did not differ from double-dose BDP in their effects on exacerbations and quality of life and insufficient evidence to draw conclusions about mortality and hospitalizations. Leukotriene

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modifiers are approved in asthma only, and we found no evidence of this comparison in patients with COPD.

Tiotropium (TIB) added to beclomethasone (BDP) compared with double-dose beclomethasone

The TALC RCT (described above)[192] also compared TIB 18 mcg/d added to BDP 80 mcg/d to double-dose BDP (160 mcg/) in patients whose asthma was not controlled by BDP 80 mcg/d alone. The TALC RCT provides low-strength evidence that TIB and double-dose BDP have similar effects on exacerbations (4.3% compared with 7.6%; *P*=NR) and Asthma Quality-of-Life Questionnaire score (mean difference, 0.10; 95% CI, -0.07 to 0.27). There was only 1 hospitalization in each group and no deaths, but due to unknown consistency and imprecision, we did not draw conclusions about these outcomes. Tiotropium was superior to double-dose BDP in proportion of asthma-control days (difference of 0.79 days; 95% CI, 0.019 to 0.140), score for daily symptoms (difference of -0.11 points; 95% CI, -0.16 to -0.06) and score on the Asthma Control Questionnaire (difference of -0.18 points; 95% CI, -0.34 to -0.03).

Key Question 2. Adverse Events

What is the comparative tolerability and frequency of adverse events for controller medications used to treat outpatients with persistent asthma or COPD?

I. Intra-class Evidence (within a class)

A. Inhaled Corticosteroids (ICS)

Summary of findings

Asthma

Overall adverse events, tolerability, and common adverse events
Few RCTs were designed to assess adverse events as primary outcomes. The overall incidence of adverse events and withdrawals due to adverse events are similar for equipotent doses of ICSs in patients with asthma; results from head-to-head RCTs suggest no significant differences between ICSs (moderate-strength evidence). Overall summaries for specific adverse events are described below. There were no head-to-head trials comparing different ICSs in patients with COPD.

Osteoporosis/fractures/bone density
Two RCTs compared 1 ICS with another ICS in adult subjects with asthma.[279,280] No difference were seen between BDP and BUD in bone mineral density (BMD) and vertebral fractures in 374 adults.[279] A smaller trial reporting BMD randomized 69 asthmatic patients to medium and high doses of BDP or FP.[280] At 1 year, no significant differences in bone mass or metabolism were noted between the 2 treatment groups.

Growth retardation
Three head-to-head trials provide moderate-strength evidence that short-term (20 weeks to 1 year) growth velocity is reduced less with FP than with BDP[79] or BUD in patients with asthma.[82,281] A forth head-to-head trial found that CIC-treated subjects had a greater mean body

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height increase than BUD-treated subjects over 12 weeks.[106] Insufficient evidence exists to determine if long-term treatment with ICSs lead to a reduction in final adult height.

Acute adrenal crisis

Evidence from randomized trials and observational studies is insufficient to draw conclusions regarding the risk of rare but potentially fatal adverse events such as acute adrenal crisis. Nonetheless, multiple case reports have indicated that high-dose ICS treatment is associated with acute adrenal crisis, especially in children.[282-284] Evidence from intermediate outcomes cannot be extrapolated reliably to form conclusions about the comparative frequency of acute adrenal crisis for ICSs.

Cataracts

The single head-to-head RCT[285] evaluating eye lens opacity found CIC to be non-inferior to BDP (both delivered at high doses), with both treatments having minimal impact on the development and/or progression of lenticular opacities. No study compared the risk of developing posterior subcapsular opacity, per se, between 1 ICS and another. No study evaluated the link between childhood ICS use and risk of cataracts in older age.

Ocular hypertension and open-angle glaucoma

No study compared the risk of ocular hypertension or open-angle glaucoma between 1 ICS and another.

COPD

We identified no comparative trials in children or in patients with COPD.

Detailed assessment

Description of studies

Most studies that examined the efficacy of 1 ICS relative to another in patients with asthma (described in Key Question 1) also reported tolerability and adverse events. Six head-to-head RCTs and 1 observational study met our inclusion/exclusion criteria for tolerability or adverse events.[279-281,285-287] Seven of the head-to-head RCTs included children < 12.[79,82,88,99,100,106,281]

Methods of adverse events assessment differed greatly. Few studies used objective scales such as the adverse reaction terminology from the World Health Organization. Most studies combined patient-reported adverse events with a regular clinical examination by an investigator. Often it was hard to determine if assessment methods were unbiased and adequate; many trials reported only those adverse events considered to be related to treatment. Rarely were adverse events prespecified and defined. Short study durations and small sample sizes limited the validity of adverse events assessment in many trials. Many studies excluded eligible participants that did not tolerate treatment during the run-in period, limiting the generalizability of adverse event assessment. Few RCTs were designed to assess adverse events as primary outcomes; some studies were post hoc analyses or retrospective reviews of databases.

Overall adverse events, tolerability, and common adverse events

Of the 47 head-to-head studies reviewed for this section (all conducted in patients with asthma), most reported frequency of adverse events without tests of statistical significance (Appendix J, Asthma update 1 report). The vast majority of studies reported similar results for equipotent ICS

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doses. Only 5 studies reported a difference of greater than 5% in overall adverse events for equipotent doses.[67,96,99,101,112] Only 1 study reported a statistically significant difference in overall adverse events between 2 ICSs (overall AEs (%): 20 compared with 5, $P < 0.001$ for FP compared with TAA, but the study did not compare equipotent doses.[83] Four studies reported a difference of greater than 5% in withdrawals due to AEs for equipotent doses.[69,73,99,280]

Most head-to-head trials reported specific adverse events. Oral candidiasis, rhinitis, cough, sore throat, hoarseness, headache, and upper respiratory infection were among the most commonly reported adverse events. In most head-to-head trials oral candidiasis, rhinitis, cough, sore throat, hoarseness, and bronchitis were reported in fewer than 10% of ICS-treated patients. Upper respiratory tract infections were reported by 3 to 32% of study participants. For common specific adverse events, just 3 trials reported a statistically significant difference between equipotent doses of different ICSs.[70,73,91] One reported a greater incidence of headache in those treated with BDP than those treated with FP (7% compared with < 1%, $P = 0.03$);[91] 1 reported a greater incidence of upper respiratory tract infection with TAA than with BDP (10.4% compared with 2.7%, $P = 0.027$);[73] 1 reported a greater incidence of oral candidiasis with FP than with CIC (3.8% vs. 0%, $P = 0.002$);[70] and 1 reported that a greater proportion of patients experienced local oropharyngeal adverse effects (candidiasis and dysphonia) with FP than with CIC (p = 0.0023).[66] Meta-analysis of trials reporting "oral candidiasis-thrush" that compared equipotent doses of CIC with FP revealed lower odds of oral candidiasis-thrush for those treated with CIC (OR 0.33, 95% CI 0.17, 0.64, Appendix F).

Specific adverse events

Bone density/osteoporosis

Two fair-quality RCTs compared an ICS to another in asthma patients.[279,280] One 24-month open-label trial measuring BMD and vertebral fractures randomized 374 adult patients with asthma to BDP or BUD.[279] Patients were titrated to the minimal effective dose following a pre-specified management plan; subjects who required more than 3 courses of oral corticosteroids were withdrawn. At 2 years, no significant differences in BMD were reported between the 2 treatment groups. A smaller trial reporting BMD randomized 69 asthmatic patients to medium and high doses of BDP or FP.[280] At 1 year, no significant differences in bone mass or metabolism were noted between the 2 treatment groups (Table 22).

Table 22. Summary of studies on bone density or fractures in patients with asthma

Author Year	N	Design	Population	Results	Quality rating
Adult populations					
Medici et al. 2000[280]	69	RCT	Asthma (adult)	No difference in BMD between BDP- and FP-treated patients over 1 year	Fair
Tattersfield et al. 2001[279]	374	RCT (open label)	Asthma (adult)	No difference in BMD/fractures between BDP or BUD over 2 years	Fair

Abbreviations: BDP = beclomethasone dipropionate; BUD = Budesonide; RCT= randomized controlled trial

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Growth

Four head-to-head RCTs comparing FP to BDP,[79] FP to BUD,[82,281] or CIC to BUD[106] assessed differences in growth in asthma patients (Table 23). A fair-quality, 1-year, multinational head-to-head trial determined differences in growth velocity comparing a medium dose of FP (400 mcg/day) to a medium dose of BDP (400 mcg/day) in 343 pre-pubertal children with asthma.[79] ITT analysis revealed that adjusted mean growth velocity was significantly greater in fluticasone than in BDP-treated patients (+0.70 cm/year; 95% CI: 0.13 to 1.26; $P < 0.02$). Another fair-quality RCT compared growth velocity in 60 children treated with either a low dose of FP (200 mcg/day) or a low dose of BUD (400 mcg/day) over 1 year.[281] Fluticasone propionate-treated children had less reduction in growth velocity than the BUD-treated group (height standard deviation score: 0.03 compared with 0.23; $P < 0.05$); the authors did not provide absolute numbers in centimeters of differences in growth. The third RCT compared differences in growth velocity in 333 children treated with a medium dose of FP (400 mcg/day) or a medium dose of BUD (800 mcg/day) over 20 weeks.[82] Linear growth velocity was greater for fluticasone-treated children compared to those treated with BUD (adjusted mean increase in height: 2.51 cm compared with 1.89; difference 6.2 mm (95% CI: 2.9-9.6, $P = 0.0003$). The forth RCT compared growth in 621 children (age 6-11) treated with either a low dose of CIC (160 mcg/day) or a low dose of BUD (400 mcg/day) over 12 weeks. Ciclesonide-treated subjects had a greater mean body height increase (1.18 cm vs. 0.70 cm, P=0.0025). One fair-quality retrospective observational study in Croatia using anonymous patient data from Children's Hospital Srebrnjak Database studied linear growth velocity in prepubertal children aged 4 to 9.5 years with persistent asthma for a period of 23 weeks.[288] Results for growth in this observational study were difficult to compare for FP versus BUD because local indications for BUD specified age greater than 6 years, versus 1 year for fluticasone, the mean age of patients given BUD was substantially higher than that of FP patients (7.16 vs. 6.53 years). Additionally, fewer patients were treated with BUD than FP (43 vs. 502).

Table 23. Summary of studies on growth retardation

Author Year	N	Design	Population	Duration	Results	Quality rating
Head-to-head comparisons of ICS compared with ICS						
De Benedictis et al. 2001[79]	343	RCT	Pre-pubertal children with asthma	1 year	Greater growth velocity in FP than in BDP group	Fair
Ferguson et al, 1999[82]	333	RCT	Children with asthma	20 weeks	Greater growth velocity in FP than in BUD group	Fair
Kannisto et al. 2000[281]	75	RCT	Children with asthma	1 year	Greater growth velocity in FP than in BUD group	Fair
von Berg et al. 2007[106]	621	RCT	Children with asthma	12 weeks	Greater increase in growth in CIC than in BUD group	Fair

Abbreviations: BDP = beclomethasone dipropionate; BUD = budesonide; CIC = ciclesonide; FP = fluticasone propionate; RCT = randomized controlled trial.

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Acute adrenal crisis
The use of ICSs includes the risk of altered hypothalamic-pituitary axis (HPA axis) functioning and the rare possibility of resultant adrenal suppression. We did not find any studies meeting our inclusion/exclusion criteria reporting on the comparative frequency of clinical adrenal insufficiency in patients treated with ICSs. However, multiple studies report on adrenal suppression during ICS therapy using urinary or serum cortisol levels and results of stimulation tests as intermediate outcomes. It is unclear to what extent results from such studies of HPA axis suppression can be extrapolated to assess differences in risks for clinically significant adrenal suppression.

Cataracts
Systemic corticosteroid-induced cataracts typically are located on the posterior side of the lens and are referred to as posterior subcapsular cataracts (PSC). No study compared the risk of developing PSC between an ICS and another. One head-to-head RCT evaluated the effect of CIC and BDP on eye lens opacity in adult patients with asthma and found CIC to be non-inferior to BDP (both delivered at high doses) (Table 24).[285] Both treatments were found to have minimal impact on lenticular opacity development and/or progression.

Table 24. Summary of studies on posterior subcapsular cataracts

Author Year	N	Design	Population	Results	Quality rating
Chylack et al. 2008[285]	1,568	RCT	Adults (age ≥ 18)	Mean changes in nuclear opalescence and cortical and posterior subcapsular opacification were small and similar between ciclesonide and BDP	Fair

Ocular hypertension and open-angle glaucoma
No study compared 1 ICS to another for the risk of ocular hypertension or open-angle glaucoma.

B. Leukotriene Modifiers (LMs)

Summary of findings
There is insufficient head-to-head data (2 trials in asthma patients) to determine differences in tolerability or overall adverse events between any of the LMs using direct evidence. We identified no comparative trials in children or in patients with COPD.

Detailed assessment

Overall adverse events
We found 2 fair-quality head-to-head trials comparing 1 LM with another that met inclusion/exclusion criteria for our review.[113,114] One trial compared quality of life outcomes between ML and ZAF at recommended doses in adults with mild persistent asthma, but did not report whether adverse events occurred in either group. The second trial compared ZIL and ML

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in patients in India with mild to moderate asthma.[114] No patient in either drug arm reported serious adverse events or withdrew due to adverse events.

Liver toxicity

In 1 head-to-head trial comparing ML with ZIL in patients with asthma,[114] 2 patients (2%) taking ZIL developed altered liver function tests (LFT), 1 with alanine aminotransferase (ALT) elevation and 1 with total bilirubin elevation. None of the patients taking ML showed such changes. However, the difference between groups was not statistically significant (risk difference calculated for this review: 0.02, 95% CI -0.02 to 0.06, i.e. the incidence of LFT abnormalities in patients taking ZIL increased by 2 per 100 subjects compared to patients taking ML, but the 95% CI included no difference.) In addition, no patient in either group had clinical symptoms or signs of liver toxicity.

C. Long-Acting Beta-2 Agonists (LABAs)

Arformoterol, FM, IC, and SM, the 4 LABAs currently available in the United States for the treatment of asthma and COPD, are all selective beta-2 adrenergic receptor agonists.

Of greater concern are reports that regular use of LABAs increases the risk of asthma-related death.[9,289-292] Subgroup analysis from 1 study[289] has suggested this risk may be significantly higher in African Americans (see Key Question 3). These concerns have resulted in an FDA boxed warning for products that contain any LABA. Experts recommend strongly against using LABAs as monotherapy for long-term control of persistent asthma.[1] LABAs are contraindicated for use as monotherapy in patients with persistent asthma.[9,290-292] In June 2010, the FDA announced it was requiring manufacturers to revise their drug labels.[293] The new recommendations in the updated labels state the following:[293]

- Use of a LABA alone without use of a long-term asthma control medication, such as an inhaled corticosteroid, is *contraindicated* (absolutely advised against) in the treatment of asthma.
- LABAs should not be used in patients whose asthma is adequately controlled on low or medium dose inhaled corticosteroids.
- LABAs should only be used as additional therapy for patients with asthma who are currently taking but are not adequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid.
- Once asthma control is achieved and maintained, patients should be assessed at regular intervals and step down therapy should begin (e.g., discontinue LABA), if possible without loss of asthma control, and the patient should continue to be treated with a long-term asthma control medication, such as an inhaled corticosteroid.
- Pediatric and adolescent patients who require the addition of a LABA to an inhaled corticosteroid should use a combination product containing both an inhaled corticosteroid and a LABA, to ensure adherence with both medications.

The FDA believes that when LABAs are used according to the recommendations outlined above and in the approved drug labels, the benefits of LABAs in improving asthma symptoms outweigh their risks of increasing severe asthma exacerbations and deaths from asthma.[293]

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For this review, we sought evidence of comparative safety of LABAs with respect to severe adverse events. Additional information on all-cause mortality is provided in Key Question 1.

Summary of findings

We identified 4 RCTs in patients with asthma that met our inclusion criteria and provided direct evidence regarding the relative safety of FM (or the equivalent drug eFM) and SM (described in Evidence Tables). We rated 3 studies[115,117,118,126] as fair quality for assessment of adverse events. The fourth[116] was rated as poor quality for assessment of adverse events. However, since it was the only head-to-head trial performed specifically in children, we describe it in this section. In general, these trials were of relatively short duration, with none lasting more than 24 weeks. All were designed primarily to assess efficacy. Adverse events were typically collected via spontaneous reports from patients or "general questioning" by the investigators, though study withdrawals and reasons for withdrawals were reported. In these trials, all patients were taking ICS at the time of enrollment, and severe adverse events were rare. We also identified 2 systematic reviews with meta-analyses that compared subjects treated with FM and subjects treated with SM.[294,295] Overall, limited evidence from head-to-head trials and from systematic reviews provides no evidence of a difference in tolerability or adverse events between FM and SM in patients with asthma, regardless of whether or not corticosteroids are used concurrently.

For this update we identified 6 new, fair-quality trials comparing LABAs in patients with COPD.[119,120,122-125] All are described in detail in Key Question 1. Three trials[122-124] compared IC with SM, and another compared IC with FM.[119] One trial[125] compared ARF with FM, and the final trial compared FM delivered with a nebulizer to FM via dry powder inhaler.[120] The trials provided low-strength evidence that rates of serious adverse events and withdrawals due to adverse events did not differ between patients taking ARF and those taking FM. Patients taking IC were less likely to withdraw due to adverse events than those taking FM; the difference was statistically significant for the higher IC dose, though not for the lower IC dose. Patients taking IC were more likely than those taking SM to experience severe harms or withdraw due to harms, but neither difference was statistically significant (Appendix E, Table E-24). Evidence was insufficient to compare harms in patients taking FM via nebulizer versus FM via DPI (Appendix E, Table E-21).

Detailed assessment

Arformoterol (ARF) compared with formoterol (FM)

Asthma. We did not identify any good- or fair-quality systematic reviews or head-to-head trials that compared ARF with FM in subjects with asthma.

COPD. One fair-quality trial[125] included 444 patients with asthma from 62 centers in the United States. Patients received 6 months of treatment with either 30 or 50 mcg ARF daily via nebulizer, or 24 mcg/day FM via DPI. Withdrawals due to harms appeared similar across treatment arms, with 10.1% of patients taking 30 mcg ARF withdrawing, 10.9% of those taking 50 mcg ARF, and 8.2% of those taking FM, though the study did not report a statistical comparison. Serious adverse events also appeared similar between ARF and FM, though results differed for the 2 doses of ARF. We calculated RR 1.41 (95% CI, 0.75 to 2.66) for patients taking ARF 30 compared to those taking FM, and RR 0.71 (95% CI, 0.33 to 1.52) for those taking 50 mcg of ARF versus FM; though RRs appeared inconsistent, both 95% CIs included 1.0 (no effect). The

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study thus provides low-strength evidence that serious harms and withdrawals due to harms do not differ between ARF and FM.

Arformoterol (ARF) compared with salmeterol (SM)
We did not identify any good- or fair-quality systematic reviews or head-to-head trials that compared ARF with SM in subjects with asthma or COPD.

Formoterol (FM) (nebulized) compared with formoterol (FM) dry powder inhaler (DPI)

Asthma. We did not identify any good- or fair-quality systematic reviews or head-to-head trials that compared nebulized FM with FM via DPI in subjects with asthma.

COPD. A fair-quality trial[120] compared 2 formulations of FM, 1 delivered via nebulizer and the other via DPI. The trial enrolled 237 patients with COPD from 38 centers in the United States for 12 weeks of treatment with FM 40 mcg via nebulizer or 24 mcg via DPI. Few patients experienced serious adverse events (N=4 overall) or withdrew due to adverse events (N=8), and evidence was insufficient to compare these outcomes for the 2 FM formulations.

Formoterol (FM) compared with indacaterol (IC)

Asthma. We did not identify any good- or fair-quality systematic reviews or head-to-head trials that compared FM with IC in subjects with asthma.
COPD. The INVOLVE Study of 1,300 patients in 25 countries outside the United States compared the newest LABA, IC, with FM. Over 52 weeks of treatment subjects received 300 mcg/day of IC, 600 mcg/day of IC, or 24 mcg/day of FM, all via DPI. The study did not report serious adverse events, but for both doses of IC fewer patients withdrew due to adverse events than did patients taking FM. However, the differences did not reach statistical significance: we calculated RR 0.85 (95% CI 0.56 to 1.30) for withdrawals in patients taking 300 mcg IC and RR 0.58 (95% CI 0.36 to 0.94) for 600 mcg IC, each compared with patients taking FM.

Formoterol (FM) or eformoterol (eFM) compared with salmeterol (SM)

Asthma. Of the 4 included head-to-head trials, 2 were conducted only in adults,[118,126] 1 enrolled adults and adolescents[115] and 1 enrolled only children and adolescents between 6-17 years old.[116] All 4 trials compared FM (12 mcg twice daily) with SM (50 mcg twice daily). Only 1[115] of the 4 trials was blinded. Detailed descriptions of these RCTs are provided in the Key Question 1 section of this report with the exception of 1 study that was included for this section but not for efficacy outcomes,[126] which is described in the Evidence Tables.

One open-label RCT conducted in the United States[126] compared FM (24 mcg/day) to SM (50 mcg/day) in 528 adult asthmatics who were already taking low dose ICSs. The duration of the study was 24 weeks and the investigator found similar numbers of total withdrawals (14.5% compared with 11.3%) and withdrawals due to adverse events (5.7% compared with 3.4%).

One trial[115,296] randomized 469 patients to blinded eFM via DPI, SM via DPI, or SM via MDI. They found similar rates of hospital admission and ED visits and total study withdrawals. Another trial[117] compared FM administered via DPI with SM given via DPI in 482 adult asthmatics. The trial found comparable rates of hospitalizations, study withdrawals, withdrawals due to adverse events, and drug-related adverse events. The only trial enrolling children and

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adolescents[116] randomized subject (N = 156) to FM or SM and also found similar rates of study withdrawals and withdrawals due to adverse events.

Two systematic reviews compared SM and FM directly. The first review[295] compared the risk of adverse events in patients with chronic asthma who received FM *and corticosteroid* versus SM *and corticosteroid* for chronic asthma. One trial compared FM and BDP to SM and FP, and the other 7 trials compared FM and BUD to SM and FP. The reviewers found no significant differences in any serious adverse events, including all-cause mortality (OR 1.03, 95%: CI 0.06 to 16.44), all-cause non-fatal serious adverse events (OR 1.14, 95% CI: 0.82 to 1.59), and asthma-related serious adverse events (OR 0.69, 95% CI: 0.37 to 1.26). The study using BDP instead of BUD was relatively small (N=228 participants) and reported no deaths or hospital admissions.

The second systematic review[294] compared the risk of adverse events in patients with chronic asthma who received FM versus SM, without the addition of ICS. This review was first published in 2009[294] and updated in 2013 with searches through January 2012;[297] however, the update found no new studies to include, and we therefore excluded the 2013 publication from this report. The 2009 review found no statistically significant differences in any serious adverse events, including all-cause mortality (one total death in the SM group, not attributable to asthma), all-cause serious adverse events in adults (OR 0.77, 95% CI: 0.46 to 1.28), all-cause serious events in children (OR 0.95, 95% CI: 0.06 to 15.33), and asthma-related serious adverse events in adults (OR 0.86, 95% CI: 0.29 to 2.57) and children (no events in either group).

COPD. We did not identify any good- or fair-quality systematic reviews or head-to-head trials that compared FM with SM in subjects with COPD.

Indacaterol (IC) compared with salmeterol (SM)

Asthma. We did not identify any good- or fair-quality systematic reviews or head-to-head trials that compared IC with SM in subjects with COPD.

COPD. Two fair-quality RCTs[122,123] compared treatment with 150 mcg daily of IC with 100 mcg of SM in COPD patients, and a third small trial compared 300 mcg daily of IC to 100 mcg of SM.[124] One trial[122] recruited 1,123 patients from 8 countries including the United States for 12 weeks' treatment; another[123] treated 667 patients from 15 non-US countries for 26 weeks; and 1 included 186 patients in a 52-week trial in Japan[124] Both serious harms and withdrawals due to harms appeared to favor SM, though differences were not statistically significant. Our meta-analyses comparing IC with SM calculated OR 1.19 (95% CI 0.74 to 1.90) for withdrawals due to harms, and OR 1.51 (95% CI 0.99 to 2.28) for serious harms.

D. Combination Products: Inhaled Corticosteroid (ICS) plus Long-acting Beta-2 Agonist (LABA) compared with Inhaled Corticosteroid plus Long-acting Beta-2 Agonist

Summary of findings

Asthma. We found 7 RCTs with 11 publications[47,48,57,127-134] that compared the combination of an ICS plus a LABA with another ICS/LABA combination for controller therapy treatment of asthma. Four trials compared fixed- dose combination inhalers containing BUD/FM to fixed-dose combination inhalers of FP/SM.[127,129,130,132] Two compared fixed-dose combination inhalers containing FP/SM to fixed-dose combination inhalers of MF/FM.[47,133] A single study compared

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fixed-dose combination inhalers containing FP/SM to fixed-dose combination inhalers of FF/VI.[48]

Overall, results from these 4 large trials up to 6 months in duration provide moderate-strength evidence that there is no significant difference in the risk of withdrawal due to an adverse event between fixed-dose combination treatment with BUD/FM and FP/SM. The results of our meta-analysis indicated a relative risk of 1.02 (95% CI 0.68, 1.54). The risk of experiencing a serious adverse event was also not statistically significantly different between the combination products (pooled RR 1.30, 95% CI 0.88 to 1.90).

Moderate-strength evidence indicates no statistically significant differences in withdrawal due to adverse events or risk of serious adverse events between groups assigned to fixed-dose combination inhalers of MF/FM compared with those assigned to FP/SM. Low-strength evidence suggests no difference in risk of withdrawal due to adverse events or incidence of serious adverse events between MF/FM and FP/SM, although numerically higher rates were reported with MF/FM than with FP/SM.

Low-strength evidence from a single study of fixed-dose combination inhalers of FF/VI compared with FP/SM suggests no difference in rates of withdrawal due to adverse events or serious adverse events between drugs.

COPD. We found 4 RCTs and 1 observational study comparing adverse event rates in patients with COPD treated with fixed-dose combination products of an ICS/LABA. Low-strength evidence from a single fair-quality observational study indicates that patients using FP/SM had an increased risk of pneumonia and pneumonia-related mortality compared with BUD/FM. The risk of pneumonia was significantly higher with FP/SM compared with BUD/FM; RR 1.73 (95% CI 1.57 to 1.90) with a calculated number needed to treat of 23 (95% CI 18 to 37). Mortality related to pneumonia was also increased with FP/SM compared with BUD/FM; RR 1.76 (95% CI 1.22 to 2.53).

Based on three 12-week trials, although rates were low in both groups, evidence is insufficient to determine whether withdrawals due to adverse events, serious adverse events or mortality differ between FF/VI and FP/SM. A single good-quality trial provided low-strength evidence of no differences in adverse events between BPD/FM and BUD/FM over a 48-week period.

Detailed assessment

Description of studies

Asthma. In patients with asthma, 4 RCTs compared BUD/FM with FP/SM, 2 compared FP/SM with MF/FM and 1 compared FP/SM with FF/VI. Study duration ranged from 12 to 52 weeks.[133]

Within-trial equipotency of daily ICS dose varied for the trials of BUD/FM compared with FP/SM. All 4 trials administered the same total daily dose of FP/SM (500/100), which is considered a medium daily dose of ICS when delivered via DPI and a high daily dose when delivered via pMDI. In 2 trials, 500 mcg of FP was compared with an equipotent daily dose of BUD,[127,128,130] while 2 studies medium daily doses of BUD were compared with a high dose of FP.[129,131,132,134]

A 52-week trial of MF/FM and FP/SM randomized patients to moderate (200 mcg MF per day, 250 mcg FP via MDI) or high (400 mcg MF per day, 500 mcg FP via MDI based on their prior dosing of ICS,[133] while a 12-week trial randomized to medium doses of MF/FM using

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a MDI and medium doses of FP/SM using a DPI.[47] The 52-week trial was designed specifically to assess long-term harms, and measured only minimal benefits outcomes.

Lastly, FF/VI 100/25 mcg once daily using a DPI was compared with FP/SM 150/50 mcg twice daily using a MDI.[48]

COPD. We found 1 good-quality 48-week RCT, 3 unpublished 12-week RCTs with results posted on the ClinicalTrials.gov website, comparing 2 fixed-dose combination products for treatment of COPD and 1 retrospective cohort study reporting pneumonia-related adverse events with fixed-dose combination products in patients with COPD.[49,51,52] The 48-week, multi-country RCT compared BDP/FM 200mg/12mg pMDI, BUD/FM 400mg/12mg DPI, or FM 12 mg DPI alone (all BID) in patients with severe COPD.[135] All 3 unpublished trials compared FF/VI with FP/SM. The cohort study compared FP/SM to BUD/FM.

Study populations

Asthma. The 4 head-to-head RCTs of BUD/FM compared with FP/SM included a total of 5,818 subjects. All studies were conducted in adolescent and/or adult populations. None included children < 12 years of age. All trials were multinational. All enrolled subjects that were not adequately controlled on current therapy. Three were conducted in subjects with moderate to severe persistent asthma; 1 did not report the severity classification.[132,134] Three trials (75%) excluded smokers with at least a 10 pack-year history; 1 (25%) allowed some smokers and reported that 5% to 7% of subjects in each group were current smokers.

The 2 trials of MF/FM and FP/SM included a total of 1,126 patients ≥ 12 years old, 1 conducted at sites in North America and the other at sites in South America. The 52-week study included stable patients using moderate to high doses of ICS, while the 12 week study included patients on a stable regimen with moderate dose ICS, but with ≥2 exacerbations in the last year. Both studies excluded current and ex-smokers.

The trial of FF/VI compared with FP/SM enrolled 806 patients (> 12 years old) with stable asthma, taking medium doses of an ICS, and with FEV1 reversibility of > 12% and > 200 mL after albuterol administration. The study excluded current and ex-smokers, and was conducted in multiple countries worldwide.

COPD. The 48-week good-quality, multi-country RCT enrolled 718 patients with severe COPD according to the GOLD guidelines, including at least 1 serious exacerbation in the last year. [135] The study population had 37% current smokers, and a mean of 38 pack-years of smoking for all patients enrolled. The mean percent predicted normal FEV1 pre-bronchodilator was 42%. The 3 fair-quality trials were multinational, with 1 including sites in the United States. In these trials, patients were current or former smokers (≥ 10 pack years) 40 years old or greater and with a post-albuterol FEV_1 to Forced Vital Capacity ratio of ≤ 0.7 and a post-albuterol FEV_1 of ≤ 70% of predicted normal values. The percent of females ranged from 18% to 36%, and the mean age was 62 years.

In a fair-quality cohort study, conducted in Sweden, the percent female was 53%, and the mean post-bronchodilator FEV_1 was 50% of predicted normal and 48% were current smokers.

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Sponsorship

Asthma. Of the 7 trials, 6 (86%) were funded by pharmaceutical companies; 1 trial did not report the source of funding but at least 1 author had a primary affiliation with a pharmaceutical company. No trials were funded primarily by a source other than a pharmaceutical company.

COPD. All of the unpublished RCTs were funded by GlaxoSmithKline, the manufacturer of the FF/VI fixed-dose combination product, the published RCT was funded by a French pharmaceutical company and the cohort study was funded by the manufacturer of the BUD/FM fixed-dose product, AstraZeneca.

Head-to-head comparisons

Budesonide (BUD)/formoterol (FM) compared with beclomethasone (BDP)/formoterol (FM)

In the trial of 718 patients with severe COPD, differences in rates of serious adverse events, any adverse events, withdrawals due to adverse events and pneumonia were not different between the groups.[135] Rates for withdrawing due to adverse events were 3.8% with BPD/FM and 2.5% with BUD/FM, rates of pneumonia were 2.1% versus 2.9%, respectively. While 2 patients died in the BPD/FM group and 4 in the BUD/FM group none were reported to be related to drug treatment.

Budesonide (BUD)/formoterol (FM) compared with fluticasone propionate (FP)/salmeterol (SM)

Asthma: Based on meta-analysis, 4 trials provided moderate-strength evidence of no statistically significant difference between BUD/FM and FP/SM in the number of patients withdrawing from the study due to an adverse event; RR 1.02 (95% CI 0.68, 1.54) (Appendix F, Evidence Tables A and B).[127,129,130,132] The risk of experiencing a serious adverse event was also not statistically significantly different between the combination products (pooled RR 1.30, 95% CI 0.88 to 1.90). Post hoc subgroup analyses of data in patients 16 years old or greater in 2 studies indicated similar findings.[128,131]

COPD. A fair-quality retrospective cohort study, based on Swedish primary care medical records and linked databases, was conducted to assess the risk of pneumonia in patients with COPD using BUD/FM or FP/SM provides low-strength evidence of an increased risk of pneumonia and pneumonia-related mortality in patients using FP/SM compared with BUD/FM.[298] The study used propensity score matching to reduce confounding by indication, using age, sex, exposure to various drugs, diagnosis of chronic diseases and number of hospital admissions in the past 2 years. The follow-up period was up to 10 years, or the end of use of the fixed-dose combination product, emigration or death. The risk of pneumonia was significantly higher with FP/SM compared with BUD/FM; RR 1.73 (95% CI 1.57 to 1.90) with a calculated number needed to treat of 23 (95% CI 18 to 37). Similar results were found for pneumonia requiring hospitalization (RR 1.74. 95% CI 1.56 to 1.94). Analysis of baseline risk factors indicated that those with greater disease burden had higher rates with FP/SM than with BUD/FM. Mortality related to pneumonia was also increased with FP/SM compared with BUD/FM; RR 1.76 (95% CI 1.22 to 2.53). The study did not report the rate of discontinuations due to adverse events or the rate of serious adverse events.

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Fluticasone propionate (FP)/salmeterol (SM) compared with mometasone furoate (MF)/ formoterol (FM)

Asthma: Based on 2 studies, moderate-strength evidence suggests no difference in the rate of withdrawal due to adverse events or incidence of serious adverse events between MF/FM and FP/SM at medium doses. (Appendix F, Evidence Tables A and B).[47,133] The 2 studies differed in duration by 40 weeks, so data were not pooled. We calculated the individual relative risks as shown in Table 25 below. The high dose arm of the Maspero study indicates a potential for greater risk for both study withdrawal and serious adverse events with high dose MF/FM compared with FP/SM, although confidence intervals are not statistically significant. Evidence for the higher doses was rated low strength.

Table 25. Risk of adverse event outcomes: MF/FM compared with FP/SM

Study, dose	Dose	Relative Risk (95% CI)
Serious Adverse Events		
Bernstein 2011	Medium	0.95 (0.29 – 3.03)
Maspero 2010	Medium	0.84 (0.27 – 2.64)
Maspero 2010	High	2.0 (0.50 – 8.21)
Withdrawal due to Adverse Events		
Bernstein 2011	Medium	0.95 (0.35 – 2.56)
Maspero 2010	Medium	1.21 (0.28 – 5.32)
Maspero 2010	High	6.54 (0.81 – infinity)[a]

[a] Zero events in FP/SM group, 0.5 continuity factor used.

COPD. No studies comparing these 2 products in patients with COPD were found.

Fluticasone propionate (FP)/salmeterol (SM) compared with fluticasone furoate (FF)/ vilanterol (VI)

Asthma. In a single good-quality trial (N = 806), after 24 weeks of treatment, there were no differences found between FP/SM and FF/VI in withdrawal due to adverse events or incidence of serious adverse events.[48] Asthma exacerbation was included as a serious adverse event and occurred in 1 patient; however the group this patient was assigned was not reported. This evidence is low strength due to imprecision and lack of a corroborating study.

COPD. Three RCTs with results reported on the ClinicalTrials.gov trial registry provide insufficient-strength evidence on comparative harms for FF/VI and FP/SM used for 12 weeks in patients with COPD.[49,51,52] For withdrawals due to adverse events, combining all 3 trials together results in a relative risk of 1.38 (95% CI 0.39 to 4.93) with an I-squared of 53%. Removing 1 trial that used a high dose of FP/SM (500 mcg/50 mcg twice daily versus 250 mcg/50 mcg in the other 2 trials) results in a relative risk of 0.09 (95% CI 0.39 to 2.48) and a chi square P of 0.07 (I-squared inestimable). Serious adverse events and mortality rates were low in the trials, and pooled analyses are similarly inconclusive and difficult to interpret due to heterogeneity and imprecise estimates. Using all 3 trials, the risk of serious adverse events was relative risk of 1.03 (95% CI 0.40 to 2.53, I-squared 23%), and with removal of the higher dose study became relative risk of 0.69 (95% CI 0.26 to 1.80). Across the 3 trials (N = 1558 total), 2 patients died in the FF/VI groups and 1 died in the FM/SM groups.

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E. Long-Acting Muscarinic Antagonists (LAMAs)

There were no reviews or head-to-head studies comparing a LAMA with another in patients with asthma or COPD.

II. Inter-class Comparisons (between classes)

A. Monotherapy

1. Inhaled corticosteroids (ICSs) compared with leukotriene modifiers (LMs)

Summary of findings

Asthma. We found 2 systematic reviews with meta-analyses[136,137] and 16 RCTs[139-145,147,149,152-156,159,162-164] that compared ICSs and LMs (described in Evidence Tables and in the Key Question 1 section of this report). For this update we also identified 1 observational study comparing ML and inhaled corticosteroids in children that met our inclusion criteria.[288]

Overall, data from 2 good-quality systematic reviews, numerous fair-rated head-to-head RCTs and 1 observational study provide no evidence of a difference in adverse events between ICSs and LMs. Of note, trials were generally not designed to compare tolerability and adverse events.

COPD. We did not identify any good- or fair-quality systematic reviews or head-to-head trials that compared inhaled corticosteroids with LMs in subjects with COPD.

Detailed assessment

One good-quality systematic review with meta-analysis[137,299] provides the best evidence for adverse events and tolerability in patients with asthma. The meta-analysis found the same risk of experiencing any adverse effects in patients taking LMs compared to those taking ICSs (N = 22 trials, 3 in children, RR 1.00, 95% CI: 0.95 to 1.05). Serious adverse events were not assessed. Patients in the LM arm appeared somewhat more likely than those in the ICS arm to withdraw due to adverse events; however, despite the large body of evidence available the difference was not statistically significant (N = 25 trials, 8 in children, 8,518 patients; RR 1.24, 95% CI 0.95 to 1.63). For both overall adverse events and withdrawals due to adverse events, results were similar in subanalyses of adult versus pediatric patients. The review also assessed liver enzyme elevation, which was reported in 7 trials, 6 of them in adults. LFT abnormalities appeared slightly more likely in patients taking LMs, though the difference was not statistically significant (RR 1.13, 95% CI, 0.58 to 2.19).

A second systematic review with meta-analysis[136] included 18 studies (N = 3,757) enrolling children and adolescents less than 18 years of age, 13 of which compared ICS therapy to that of ML. Six of the included trials also met our inclusion criteria;[147,154,158-160,166] 7 did not. Duration of studies varied but ranged from 4-12 weeks, 24-28 weeks, and 48-56 weeks, with 1 study being 112 weeks long. While most of the studies included patients age 6-18, 1 study included children younger than 6 (2-8 years) for which a nebulizer was used for ICS administration. Intervention drugs included oral ML (4 to 10 mg) compared to either inhaled BDP 200-400 mcg/day (0.5 mg nebulized), FP 200 mcg/day, BUD 200-800 mcg/day or TAA

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400 mcg/day. Data related to adverse effects were available in 5 of the 18 trials. Overall, the meta-analysis reported no difference between ICS- and ML-treated patients with respect to incidence of adverse effects (N = 1,767, RR 0.98, 95% CI 0.86 – 1.11, P = 0.73).

Most trials that examined the efficacy of ICSs compared to LMs (described in Key Question 1) also reported tolerability and adverse events. Study duration ranged from 6 weeks to 56 weeks. Methods of adverse events assessment differed greatly. Few studies used objective scales such as the adverse reaction terminology from the World Health Organization. Most studies combined patient-reported adverse events with a regular clinical examination by an investigator. Often it was difficult to determine if assessment methods were unbiased and adequate; many trials reported only those adverse events considered to be related to treatment. Rarely were adverse events prespecified and defined.

Overall tolerability and adverse events from individual head-to-head trials are summarized in the Evidence Tables. Most studies did not find a significant difference between ICSs and LMs for overall tolerability and adverse events, including 1 trial comparing FP with ML identified for this update.[155] Specific adverse events reported with ICSs (see Key Question 2 section on ICSs above), such as cataracts and decreased growth velocity, were not found among patients taking LTRAs. One fair-quality head-to-head RCT (N = 360) compared linear growth rates in prepubertal children treated with ML, BDP, or placebo.[141] The mean growth rate of subjects treated with BDP was 0.81 cm less than that of subjects treated with ML over the study's 56-week duration. In contrast, a retrospective cohort study of 844 children ages 4 to 9.5 years taking ML (N=245), FP (N=502) or BUD (N=43) found no significant difference in linear growth velocity between those taking ML (0.180 mm/day, SE 0.0055) and those taking 1 of the inhaled corticosteroids (0.187 mm/day, SE 0.0044).[288]

2. Inhaled corticosteroids (ICSs) compared with long-acting beta-2 agonists (LABAs)

Summary of findings

Although evidence from 15[167-171,173-175,177,179-182,184,185] head-to-head trials (4773 subjects) provides no evidence of a difference in overall adverse events between ICSs and LABAs in adults and adolescents with asthma, LABAs are not recommended nor approved for use as monotherapy for persistent asthma because they may increase the risk of asthma-related death.[1] Overall tolerability and adverse events from individual head-to-head trials are summarized in (Evidence Tables A and B). Rates of overall adverse events and withdrawals due to adverse events were similar for those treated with ICSs and those treated with LABAs.

We identified 1 good-quality systematic review of ICS versus LABA in patients with COPD.[186] The review included 7 RCTs (combined N=5997) and all met inclusion criteria for this report. All studies were rated unclear to low risk of bias on randomization, allocation concealment, blinding, completeness of data and selective reporting. All studies were multicenter, double-blind RCTs with durations of 6 months to 3 years. The mean age of participants was 64 years with 62% to 78% males. Four studies compared FP with SM. Three studies compared BUD with FM. There was no difference in risk of any adverse event between ICS and LABA (OR 1.12, 95% CI 0.96 to 1.30, 5 studies). However, serious pneumonia adverse events were increased with ICS versus LABA (OR 1.48, 95% CI 1.13 to 1.94, 5 studies) although this was not the case in the sole RCT of BUD versus FM reporting serious pneumonia (OR 2.82, 95% CI 0.40 to 20.16).

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Two multicenter, double-blind RCTs published since this review compared MF with FM in 26 week trials with 26 week extension.[187,300] There was no difference between MF and FM in study withdrawals due to adverse events, risk of experiencing an adverse event, and risk of experiencing a serious adverse event.

Detailed assessment

Fluticasone propionate (FP) compared with salmeterol (SM)

Asthma. Evidence from several systematic reviews suggests that LABAs may increase the risk of asthma-related death (see Key Question 2, Long-Acting Beta-Agonists section).

COPD. We identified 1 good-quality systematic review of ICS versus LABA in patients with COPD.[186] The review included 4 RCTs (combined n=4527) that compared FP with SM. The daily SM dose for all studies was 100 mcg; for 3 studies, including the largest study, the daily fluticasone dose was 1000 mcg, with a daily dose of 500 mcg in the fourth study. All studies were multicenter, double-blind RCTs from 6 months to 3 years duration. The mean age of participants was 64 years with 62% to 76% males. The risk of any adverse event of any non-fatal serious adverse event were not different in the fluticasone groups versus the SM groups (OR 1.14, 95% CI 0.96 to 1.35, 4 studies; OR 1.17, 95% CI 0.60 to 2.28, 3 studies, respectively). However serious pneumonia adverse events were increased with FP (OR 1.46, 95% CI 1.12 to 1.92, 4 studies).

Beclomethasone (BDP) compared with salmeterol (SM)
There were no reviews or head-to-head studies comparing BDP with SM in patients with asthma or COPD.

Budesonide (BUD) compared with formoterol (FM)

Asthma. There were no reviews or head-to-head studies comparing BUD with FM in patients with asthma.

COPD. We identified 1 good-quality systematic review of ICS versus LABA in patients with COPD. The review included 3 RCTs (combined n=1470) that compared BUD with FM. The daily FM dose for all studies was 18 mcg; for 2 studies the daily BUD dose was 800 mcg, with a daily dose of 640 mcg in the third study. All studies were multicenter, double-blind RCTs with durations from 6 months to 1 year. The mean age of participants was 64 years with 67% to 78% males. One study provided data for risk of experiencing any adverse event (n=559) and found when treated with BUD versus FM (OR 1.03, 95% CI 0.74 to 1.44). Results were similar for serious, non-fatal adverse events based on a pooled analysis of 3 studies (OR 1.01, 95% CI 0.77 to 1.31). One study reported risk of serious pneumonia. While the point estimate favored FM, the confidence interval was wide (OR 2.82, 95% CI 0.40 to 20.16).

Mometasone furoate (MF) compared with formoterol (FM)

Asthma. Two fair-quality RCTs of 26 weeks duration compared MF 200 mcg[185] or MF 100 mcg[184] with FM 10 mcg in patients with asthma. The most frequent adverse event in both trials was upper respiratory infections but did not differ between groups in either trial (p-values not

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reported). Severe or serious adverse events were also similar between groups in both RCTs (p-values not reported).

COPD. One good-quality[300] and 1 fair-quality RCT[187] of 26 weeks duration compared MF 400 mcg with FM 10 mcg (combined n=915). Combined, the mean age of subjects was 60 years and 77% were male. Approximately 48% were current smokers. There was no difference between MF and FM in withdrawals due to adverse events (RR 0.77, 95% CI 0.29 to 2.08, p=0.60, I^2=53%), risk of any adverse event (RR 0.94, 95% CI 0.78 to 1.12, p=0.46, I^2=0%), and risk of a serious adverse event (RR 0.98, 95% CI 0.63 to 1.52, p=0.92, I^2=0%). Results were similar with the additional data from the 26-week extensions.

Fluticasone propionate (FP) compared with formoterol (FM)

Asthma. We identified 1 good-quality 12-week RCT (n=239) comparing FP 100 mcg with FM 10 mcg in patients with mild to moderate asthma.[183] Patients were ≥ 12 years with a mean age of 39 and equally spit between males and females. Current smokers were excluded, as well as those with a smoking history of at least 10 pack-years. There was no difference between treatment with fluticasone and FM in study withdrawals due to adverse events (RR 0.56, 95% CI 0.19 to 1.62, p=0.29), risk of experiencing any adverse event (RR 1.08, 95% CI 0.78 to 1.49, p=0.65), or severe adverse event (RR 0.55, 95% CI 0.21 to 1.44, p=0.22).

COPD. We identified no reviews or head-to-head studies comparing FP with FM in patients with COPD.

3. Leukotriene modifiers (LMs) compared with long-acting beta-2 agonists (LABAs)

Summary of findings

Overall, 2 small head-to-head trials do not provide sufficient evidence to draw conclusions about the comparative tolerability and adverse events of LMs and LABAs for use as monotherapy for persistent asthma. Of note, LABAs are not recommended or approved for use as monotherapy for persistent asthma because they may increase the risk of asthma-related death.[1] We identified no reviews or head-to-head studies comparing LM with LABA in patients with COPD.

Detailed assessment

We found 2 fair-quality RCTs[189,190] that included head-to-head comparisons of 1 LM with 1 LABA. In both trials, overall adverse events and/or withdrawals due to adverse events were similar between those treated with LMs and those treated with LABAs (Evidence Tables).

4. Long-acting muscarinic antagonists (LAMAs) compared with long-acting beta-2 agonists (LABAs)

Summary of findings

Asthma. In patients whose asthma was not controlled by inhaled corticosteroids alone, there is low-strength evidence of no significant difference between step-up therapy with either TIB or SM in withdrawals due to adverse events or the proportion of patient with serious harms.

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COPD. Compared to SM, there is moderate-strength evidence that TIB is associated with fewer COPD patients experiencing a nonfatal serious adverse event and low-strength evidence that TIB is associated with a lower proportion of patients who withdraw due to adverse events. There is low-strength evidence that TIB does not differ from IC or FM in the proportion of patients with nonfatal serious harms or who withdrew due to harms.

Detailed assessment

Tiotropium (TIB) compared with long-acting beta-2 agonists (LABAs)

Tiotropium (TIB) compared with salmeterol (SM)

Asthma. Two fair-quality RCTs provide low-strength evidence of no statistically significant differences in withdrawals due to harms between TIB and SM add-on treatment in patients whose asthma was not controlled by inhaled corticosteroids alone (pooled OR 3.13; 95% CI, 0.49 to 20.04; 1% versus 0.3%).[191,192] For patients with the B16-Arg/Arg genotype, there is low-strength evidence of no statistically significant differences between TIB and SM in rate of serious adverse events (1.6% compared with 5.2%; OR 0.29; 95% CI, 0.03 to 1.56).[191] Tiotropium and SM were comparable on all other harms. The Key Question 1 section of this report describes these RCTs in more detail and results are provided in the Evidence Tables.

COPD. Four RCTs in 3 publications with 8936 participants) provided data on harms.[194-196] Compared with SM, TIB was associated with significant lower proportions of patients with nonfatal serious harms (11.8% compared with 13.6%; OR 0.85; 95% CI, 0.75 to 0.96; moderate-strength evidence) and withdrawals due to harms (7.1% compared with 8.6%; OR 0.81; 95% CI, 0.69 to 0.95; low-strength evidence).

Tiotropium (TIB) compared with indacaterol (IC)

Asthma. We found no reviews or head-to-head studies comparing TIB with IC in patients with asthma.

COPD. Two RCTs with 2856 participants with moderate to severe COPD provided low-strength evidence of no statistically significant differences between TIB and IC in proportions of patients with nonfatal serious harms (6.0% compared with 5.4%; OR 1.10; 95% CI, 0.78 to 1.55) and withdrawals due to harms (3.6% compared with 5.3%; OR 0.72; 95% CI, 0.49 to 1.05) after 12 to 26 weeks.[198,199] One RCT with 3444 participants with severe COPD also provided low-strength evidence that TIB and IC had similar rates of adverse event-related withdrawals (5.6% compared with 5.9%) and rates of any serious adverse event (15% in both groups).[200]

Tiotropium (TIB) compared with formoterol (FM)

Asthma. We found no reviews or head-to-head studies comparing TIB with FM in patients with asthma.

COPD. One RCT with 431 participants provided data on harms for the comparison of TIB and FM.[197] This RCT provided low-strength evidence of no statistically significant differences between TIB and FM in proportions of patients with nonfatal serious harms (5.9% compared

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with 2.9%; OR 2.13; 95% CI, 0.74 to 6.94; from good-quality Cochrane review)[193] and withdrawals due to harms (4.5% compared with 3.8%; OR 1.20; 95% CI, 0.46 to 3.09).

5. Inhaled corticosteroids (ICSs) compared with phosphodiesterase-4 (PDE-4) inhibitors

Summary of evidence

As described in Key Question 1, we found 1 trial[202] that compared an ICS to a PDE-4 inhibitor in patients with asthma. This fair-quality trial provided insufficient evidence to compare serious adverse events between the treatment arms, but did suggest more withdrawals due to adverse effects in patients taking RF.

Detailed assessment

The single included trial comparing an ICS to a PDE-4 inhibitor enrolled 499 adolescents and adults with asthma from centers in the UK and Europe, and administered either 400 mcg/day BDP dipropionate or 500 mcg/day RF over 12 weeks. Few patients experienced serious harms, only 3 of those taking RF and 2 taking BDP (1% of patients in each arm), providing insufficient evidence to compare this outcome between the 2 drugs. However, 9 patients in the RF arm withdrew due to adverse events, compared to just 1 in the BDP arm. We calculated a RR of 8.75 (95% CI, 1.45 to 53.25) for withdrawals due to adverse events; though the confidence interval was very wide, it did exclude no difference between the drugs (Appendix E, Table E-32). We did not identify any reviews or head-to-head studies comparing ICS with PDE-4 inhibitors in patients with COPD.

B. Combination Therapy

1. Inhaled corticosteroid (ICS) and long-acting beta-2 agonist (LABA) compared with higher-dose inhaled corticosteroid
(addition of LABA to ICS compared with increasing the dose of ICS)

Summary of findings

We found 4 systematic reviews with meta-analysis[203-206] and 35 RCTs (39 publications)[64,104,139,207-242] that included head-to-head comparisons between an ICS/LABA with a higher-dose ICS meeting our inclusion/exclusion criteria in patients with asthma. Nine trials[139,210,215,216,229,233,238,240,241] included children, and 2 enrolled an exclusively pediatric population under 12 years of age.[210,215]

Overall, results from a good-quality systematic review with meta-analysis[205] and numerous RCTs found no difference in overall adverse events or withdrawals between subjects treated with ICSs plus LABAs and subjects treated with an increased dose of ICSs. Those treated with ICSs plus LABAs had an increased rate of tremor (N = 10, RR 2.96, 95% CI: 1.60, 5.45). Just 1 of the RCTs enrolled an exclusively pediatric population < 12 years of age (4 included some subjects < 12) and results are not necessarily applicable to pediatric populations.

We found no reviews or head-to-head studies comparing ICS/LABA with a higher-dose ICS in patients with COPD.

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Detailed assessment

We found 4 systematic reviews with meta-analysis[203-206] and 35 RCTs[64,104,139,207-242] that included head-to-head comparisons between an ICS/LABA with a higher-dose ICS in patients with asthma meeting our inclusion/exclusion criteria. These trials compared the addition of a LABA to an ICS with increasing the dose of the ICS. Although 8 trials[139,210,216,229,233,238,240,241] included children, just 1 enrolled an exclusively pediatric population under 12 years of age.[210] The trials are described in the Key Question 1 section of the report.

The largest systematic review, in patients with asthma, reported no difference in overall withdrawals (all reasons) (N = 39, RR 0.92, 95% CI: 0.84 to 1.00), overall side events (N = 30, RR 0.99, 95% CI: 0.95 to 1.03), or specific side effects, with the exception of an increase rate of tremor in the LABA group (N = 11, RR 1.84, 95% CI: 1.20 to 2.82), however this result became insignificant when a single study using a higher dose of LABA was removed from the analysis. The rate of withdrawals due to poor asthma control favored the combination of LABA and ICS (N = 29, RR 0.71, 95% CI: 0.56 to 0.91). The overall adverse events, withdrawals due to adverse events, and specific adverse events for the included RCTs appear consistent with these findings (Evidence Tables A and B).

2. Inhaled corticosteroid (ICS) and long-acting beta-2 agonist (LABA) compared with inhaled corticosteroid (different drug)

We identified 3 RCTs that compared an ICS plus a LABA with a different inhaled corticosteroid in patients with asthma. One trial compared FP/SM with CIC and 2 compared FF/VI with FP. We found no reviews or head-to-head studies comparing ICS/LABA with a different ICS in patients with COPD.

Fluticasone propionate (FP)/salmeterol (SM) compared with ciclesonide (CIC)

We identified 1 fair-quality RCT (n=432) in patients with mild persistent asthma who were randomized to CIC 160 mcg once daily or FP/SM 200/100 twice daily.[247] Patients were ≥ 12 years of age (mean age 30), 43% male, non- or ex-smokers with a smoking history of < 10 pack years. Ciclesonide increased the risk of experiencing any adverse event versus FM/SM (RR 1.15, 95% CI 1.01 to 1.30, p=0.04), although most events were considered mild to moderate.

Fluticasone furoate (FF)/vilanterol (VI) compared with fluticasone propionate (FP)

We identified 1 good-quality[248] and 1 fair-quality, unpublished RCT[56] that compared FF/VI with FP via DPI. The good-quality study (n=503, mean age = 39, 37% male, duration=52 weeks) primarily evaluated safety. Patients were randomized to FF/VI (200/25 mcg or 100/25 mcg once daily) or FP (500 mcg) twice daily. There were few study withdrawals due to adverse events (8/403 treated with FF/VI and 6/100 treated with FP; RR 0.66, 95% CI 0.18 to 2.45, p=0.54). The risk of experiencing any adverse event was also similar (RR 0.93, 95% CI 0.81 to 1.06, p=0.29), although the risk of any serious adverse event was reduced with FF/VI (RR 0.14, 95% CI 0.04 to 0.48, p=0.002).

The fair-quality, unpublished study (n=392, mean age 47, 41% male, duration=24 weeks) randomized patients to FF/VI 200/25 mcg once daily or FP 500 mcg twice daily via DPI. As in the published study, there were few withdrawals due to adverse events (7/197 treated with FF/VI and 2/195 treated with FP, RR 3.46, 95% CI 0.73 to 16.47, p=0.12). The risk of experiencing a non-serious adverse event similar between the FF/VI and FP groups (RR 0.84, 95% CI 0.64 to

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1.11, p=0.22), as was the risk of any serious adverse event (RR 2.97, 95% CI 0.61 to 14.53, p=0.18).

3. Inhaled corticosteroid (ICS) and long-acting beta-2 agonist (LABA) compared with long-acting muscarinic agonist (LAMA)

Summary of findings

When compared with FP/SM in patients with COPD, there is low-strength evidence that TIB is associated with a significantly lower proportion of patients with serious harms, but the drugs do not differ in the proportion of patients who withdraw due to adverse events. Compared with FF/VI, there is low-strength evidence that TIB does not differ in the proportion of COPD patients with serious adverse events, but insufficient evidence to draw conclusions about the comparative effect on withdrawals due to adverse events. Compared with UMB/VI, there is low-strength evidence that TIB does not differ in its risk of withdrawal due to adverse events, but insufficient evidence to draw conclusions about the comparative effect on serious harms.

We identified no reviews or head-to-head studies comparing ICS/LABA with LAMA in patients with asthma.

Detailed assessment

Tiotropium (TIB) compared with fluticasone propionate (FP)/salmeterol (SM)

According to a good-quality Cochrane review[250] that included 2 eligible RCTs that compared FP/SM 500/50 to TIB 18 mcg/d,[251,252] findings from the 2-year INSPIRE trial provided low-strength evidence that SM/fluticasone had a higher risk of serious harms (OR 1.55; 95% CI 1.21 to 1.98), but similar rates of withdrawals due to adverse events (OR 1.03; 95% CI, 0.72 to 1.47) in patients with COPD.[251] Also in INSPIRE, proportions of patients with pneumonia was statistically significantly greater with fluticasone/SM (OR 2.13; 95% CI, 1.33 to 3.40).[250] The unpublished 12-week study provided low-strength evidence that TIB and fluticasone/SM had similar shorter-term rates of withdrawals due to adverse events (3% compared with 0%) and serious adverse events (3% compared with 2%).

Tiotropium (TIB) compared with vilanterol (VI)/fluticasone furoate (FF)

The 2 fair-quality, unpublished, 12-week RCTs (N=880) described above provided low-strength evidence of no statistically significant difference between TIB 18 mcg/d and FF/VI 100/25 mcg/d in proportions of COPD patients with serious harms (4.3% compared with 3.9%; OR 1.11, 95% CI, 0.57 to 2.16). The proportion of patients who withdrew due to harms was 5% for TIB and 6% for FF/VI in GSK study HZC115247 (OR 0.83; 95% CI, 0.22 to 2.98) and 4% and 2%, respectively in GSK study HZC115805 (OR 2.02; 95% CI, 0.69 to 6.64), but unacceptable inconsistency and imprecision across these findings precluded a conclusion about the pooled estimate of effect for this outcome (OR 1.38; 95% CI, 0.67 to 2.85). The proportion of patients with any adverse event, pneumonia and other specific adverse events were similar for TIB and FF/VI.

Tiotropium (TIB) compared with umeclidinium bromide/vilanterol (VI)

We included 3 fair-quality, unpublished, 24-week RCTs (N=1759) that compared UMB/VI 62.5/25 mcg to TIB 18 mcg/day in patients with COPD and provided low-strength evidence of

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no statistically significant difference in withdrawals due to adverse events (5.4% compared with 3.9%; OR 1.42; 95% CI, 0.90 to 2.23).[54,55,253] The proportion of patients with a serious adverse event was 5.1% for UMB/VI and 4.5% for TIB (OR 1.09; 95% CI, 0.46 to 2.62), but unacceptable inconsistency and imprecision precluded a conclusion about this outcome.

4. Inhaled corticosteroid (ICS) and leukotriene receptor agonist (LTRA) compared with higher-dose inhaled corticosteroid

Summary of findings

We found 1 good-quality systematic review with meta-analysis[256] and 2 RCTs[258-260] meeting our inclusion/exclusion criteria in patients with asthma. Both RCTs were in adolescents and adults ≥ 12 years of age.

Overall, the addition of LTRAs to ICSs compared to continuing the same dose of ICSs or to increasing the dose of ICSs resulted in no significant differences in overall adverse events or withdrawals due to adverse events. Trials were generally not designed to compare tolerability and adverse events and many used higher than licensed doses of LTRAs. Evidence in children younger than 12 years of age is limited. Just 2 of the 27 trials in the systematic review enrolled children.

We identified no reviews or head-to-head studies comparing LM/ICS with higher-dose ICS in patients with COPD.

Detailed assessment

We found 1 good systematic review with meta-analysis[256] and 2 RCTs[258-260] meeting our inclusion/exclusion criteria (Evidence Tables). These are described in the Key Question 1 section of the report. The systematic review included 27 studies (5871 subjects); 2 of the studies were in children and 25 were in adults.

Inhaled corticosteroid (ICS) and leukotriene receptor agonist (LTRA) compared with increased inhaled corticosteroid

For ICS plus LTRA compared with increased doses of ICS, the systematic review reported no significant differences in overall adverse events (2 trials, RR 0.95, 95% CI: 0.84 to 1.06), risk of elevated liver enzymes (2 trials, RR 0.8 95% CI: 0.34 to 1.92), or withdrawals due to adverse events (2 trials, RR 1.14, 95% CI: 0.55 to 2.37) among trials using licensed doses of LTRAs. The trials that used 2 to 4-fold higher than licensed doses of LTRA had a 5-fold increased risk of liver enzyme elevation (3 trials, RR 4.97 95% CI: 1.45 to 17).

One fair-quality 16 week trial[258,259] (N = 889) reported similar rates of overall adverse events (37.1% compared with 41.3%; P = NR) between groups.

7. Combination products (inhaled corticosteroid [ICS] and long-acting beta-2 agonist [LABA]) compared with leukotriene modifiers (LMs)

Summary of findings

We identified 4 RCTs[139,263-265] meeting our inclusion/exclusion criteria for this comparison. All 3 compared low dose FP plus SM with ML. Overall, ICS/LABA combinations and LMs have similar rates of overall adverse events and withdrawals due to adverse events based on limited direct evidence from 4 short-term trials.

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Detailed assessment

We found 4 RCTs[139,263-265] comparing low dose FP plus SM with ML in patients with asthma. Two of the RCTs were in adolescents and adults, 1 enrolled subjects over the age of 6[139] (~15% of subjects were < 12 years of age) and 1 enrolled only children age 6-14 years.[264]

The trials are described in more detail in the Key Question 1 section of the report. The 4 trials reporting withdrawals due to adverse events reported similar rates for those treated with ML (range 0.6% to 4%) and those treated with FP/SM (range 0% to 3%); in each case the withdrawal rates in the 2 groups were within 1% of each other. The 3 trials reporting serious adverse events also reported similar, low rates between groups, less than 3% in any intervention group and with differences between FP/SM and ML groups ranging from 0% to 0.5% (Evidence Tables).

We did not identify any reviews or head-to-head trials that compared combined therapy with inhaled corticosteroids and LABAs with LMs in patients with COPD.

8. Inhaled corticosteroid (ICS) and long-acting beta-2 agonist (LABA) compared with inhaled corticosteroid and leukotriene receptor antagonist (LTRA) (addition of LABA compared with LTRA to ongoing ICS therapy)

Summary of findings

We found 1 systematic review with meta-analysis, first published in 2006[267] and updated in 2011[268] and 6 RCTs[269-274] that compared the addition of a LABA with the addition of an LTRA for asthma patients poorly controlled on ICS therapy. All 6 of the RCTs meeting our inclusion criteria were also included in the systematic review, and we focus here on the results of the systematic review (described in detail in Key Question 1) Eleven of the trials included in the review (N=6,292) contributed data to meta-analyses we report here.

Overall, results from a good-quality systematic review with meta-analysis provide high-strength evidence that there is no difference in withdrawals due to adverse events between subjects treated with ICS plus LABA therapy and subjects treated with ICS plus LTRA therapy. The review provided moderate evidence that more patients adding LABAs to ICS therapy had serious harms than did patients adding LTRAs. These results held for trials comparing the specific drugs SM and ML, both added to ICSs. There was insufficient evidence to assess adverse events for the LTRA ZAF compared with either SM or FM. We found no RCTs enrolling children < 12 years of age; the systematic review included just 1 trial in children, but this trial did not contribute data to the meta-analyses. Thus, there is insufficient evidence to draw conclusions in children < 12 years of age.

We did not identify any fair- or good-quality systematic reviews or head-to-head studies of ICS/LABA compared with ICS/LTRA in patients with COPD.

Detailed assessment

The systematic review reported no difference in withdrawals due to adverse events in patients with asthma (11 studies, RR 1.01, 95% CI 0.79 to 1.29 comparing drug classes LABA/ICS to LTRA/ICS; similar results for SM/ICS versus ML/ICS). For serious adverse events, the relative risk comparing LABAs with LTRAs as add-on therapy was 1.35 (95% CI 1.00 to 1.82), with again results very similar for SM versus ML as add-on therapy. There was also no significant difference in rates of elevated liver enzymes between patients treated with SM and ML (1 study,

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RR 1.13, 95% CI 0.66 to 1.94 comparing LABA/ICS to LM/ICS). The review included 1 study each comparing SM with ZAF and FM with ZAF, and evidence was insufficient to compare harms for these specific drugs (Appendix E, Table E-35).

COPD. We did not identify any good- or fair-quality systematic reviews or head-to-head trials that compared LABAs and LTRAs as add-on therapy to ICSs in subjects with COPD.

9. Leukotriene receptor antagonist (LTRA) and long-acting beta-2 agonist (LABA) compared with inhaled corticosteroid (ICS) and long-acting beta-2 agonist

We did not identify any fair- or good-quality systematic reviews or head-to-head studies comparing LTRA/LABA with ICS/LABA in patients with asthma or COPD which reported adverse events.

10. Inhaled corticosteroid (ICS) and long-acting muscarinic agonist (LAMA) compared with higher-dose inhaled corticosteroid

Summary of findings

Compared with double-dose BDP, in patients with asthma, there is low-strength evidence that co-therapy with TIB and BDP did not differ from in the proportion of patients who withdrew due to harms and insufficient evidence to draw conclusions about effects on serious adverse events. We did not identify any fair- or good-quality systematic review or head-to-head studies comparing ICS/LAMA with higher-dose ICS in patients with COPD.

Detailed assessment

Tiotropium (TIB) added to beclomethasone (BDP) compared with double-dose beclomethasone

The TALC RCT (described above)[192] provided low-strength evidence that TIB 18 mcg/d added to BDP 80 mcg/d and double-dose BDP (160 mcg/) have similar risk of withdrawals due to harms (0.5% compared with 0.5%) in patients with asthma.

Key Question 3.

Are there subgroups of patients based on demographics (age, racial groups, gender), asthma or COPD severity, comorbidities (drug-disease interactions, including obesity), other medications (drug-drug interactions), smoking status, genetics, or pregnancy for which asthma or COPD controller medications differ in efficacy, effectiveness, or frequency of adverse events?

Summary of Findings

We did not find any studies that directly compared the efficacy or adverse events of our included drugs between subgroups and the general population in patients with asthma or COPD. In head-to-head comparisons, few subgroups based on age, racial groups, sex, other medications, or comorbidities were evaluated. We did not find any studies meeting our inclusion/exclusion

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criteria that directly compared our included medications and found a difference in the comparative efficacy, tolerability, or adverse events.

Detailed Assessment

I. Demographics

Age

Asthma. Differences in efficacy, tolerability, and adverse events between children < 12 years of age and adolescents or adults ≥ 12 are described in the body of the report (Key Questions 1 and 2) in the appropriate sections. These differences are also noted in the overall summary table. Therefore, they are not discussed here.

Only a few trials have studied the efficacy and safety of asthma medications in very young children (less than 3 years). Budesonide inhalation suspension is the only ICS that is approved for use in children down to 12 months of age. Montelukast is also approved for use in patients 1 year or older (see Introduction, Table 2). We found no head-to-head studies comparing the efficacy or safety of our included drugs in very young children with efficacy or safety in older children, adolescents, or adults. We did find 1 trial comparing BUD with ML in children ages 2-8 with mild persistent asthma.[159] A subgroup analysis of patients ages 2-4[58] (Table 26) shows that those taking BUD had 1.35 exacerbations (mild or severe) per patient per year, while those taking ML had 2.30 (p=0.003). The difference between treatment groups was greater for children 2 to 4 than in the full population ages 2 to 8, "possibly suggesting that ML is less effective at controlling asthma in the younger subpopulation of patients". Quality of life was similar between the 2 treatment groups in both age groups, though a measure of the child's emotional health in the Children's Health Survey for Asthma favored ML in children age 2 to 4. Serious adverse events occurred in 2% of BUD patients age 2 to 4 compared with 6% of ML patients; the difference again was greater than for patients age 2 to 8, though the investigators did not comment on differences in adverse effects between the age groups.

COPD. In a case control study of elderly patients with COPD, mean age 78 years, the subjects were identified using the Quebec health insurance database and followed-up for 5.4 years to identify rates of serious pneumonia.[301] Serious pneumonia was higher with current users (defined as subjects with last prescription was dispensed within 60 days of the index date) of fluticasone and BUD compared to their control groups. Fluticasone is associated with 2-fold (100%) increase in serious pneumonia (RR 2.01; 95% CI 1.93 to 2.10), with higher dose indicating greater incidences of pneumonia. Budesonide is associated with 17% increase in rates of serious pneumonia (RR 1.17; 95% CI 1.09 to 1.26) without a dose-response effect.

Racial groups

We did not find any studies that directly compared the efficacy and tolerability of included drugs within 1 racial or ethnic group to efficacy and tolerability in another such group. Two studies performed subgroup analyses in patients with asthma; results may provide indirect evidence of differences between racial groups (Table 26).

A good systematic review examined both efficacy and safety outcomes of studies comparing LABAs to placebo in "real world" asthmatic populations in which only some patients were using regular ICSs at baseline.[302] This study is described in detail in the Key Question 2 section of this report. A post-hoc subgroup analysis indicated that African Americans may be

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more likely to experience respiratory-related death and life threatening adverse events than Caucasians (Relative Risk Increase 3.9; 95% CI: 1.29, 11.84). There was, however, no significant difference found in asthma-related deaths between African Americans and Caucasians; results from life table analyses were not significantly different between African Americans (7 compared with 1; RR 7.26; 95% CI: 0.89, 58.94), and Caucasians (6 compared with 1; RR 5.82; 95% CI: 0.70, 48.37).

The Salmeterol Multicenter Asthma Research Trial (SMART),[289] a large 28-week randomized, double-blind study assessed the safety of salmeterol MDI (42 mcg twice/day) compared with placebo in asthma patients. We excluded placebo-controlled trials from this updated review, and so do not discuss this trial in detail. However, the trial reported statistically significant increases in respiratory-related deaths, asthma-related deaths, and in combined asthma-related deaths or life-threatening experiences for subjects receiving SM compared to those receiving placebo. The increased risk was thought to be largely attributable to the African-American subpopulation. The FDA released a safety alert based on the results of the trial, reporting that there were no significant differences in asthma-related events between SM and placebo in Caucasian patients; however, in African Americans, there was a statistically significantly greater number of asthma-related events, including deaths, in SM- compared with placebo-treated patients.[303]

A head-to-head trial identified for this 2014 update[125] compared 2 LABAs in COPD patients, and analyzed harms for racial subgroups (Table 26). The trial enrolled 444 patients from 62 US centers; 63 patients were African American and 375 Caucasian. Patients received 6 months' treatment with 24 mcg/day FM via DPI or 1 of 2 doses of ARF (30 mcg or 50 mcg daily). The trial found little difference between drug arms in withdrawals due to adverse events in Caucasians (range 7.9 to 9.5% across treatment arms). For African Americans, though very few withdrawals occurred, it appeared that more patients withdrew due to adverse effects with ARF than with FM; withdrawals were slightly higher for ARF 30 mcg (14.3%) than for FM (10.5%), and higher still for the higher ARF dose (21.7%, suggesting a positive dose-response relationship). Consistent with the SMART trial showing higher risks of LABA use in African Americans, rates of withdrawal due to adverse events were higher in each drug arm for African Americans than they were for Caucasians. For serious adverse events, the comparison of ARF and FM was difficult to interpret for Caucasians, with more patients taking ARF 30 experiencing SAEs (13.5%) than patients taking FM (8.7%), but fewer patients taking ARF 50 experiencing SAEs (3.3%, i.e. there was no dose-response relationship for ARF versus FM). For African Americans, SAE rates for FM and ARF 30 were about the same (15.8% versus 14.3%), but the rate of SAEs in patients taking ARF 50 was higher (26.1%). Again, the African American subgroup in this trial was small and few adverse events occurred overall, so these results should be interpreted with caution.

One fair-quality multicenter trial in patients with asthma compared ML (10 mg/d plus SM (100 mcg/d plus placebo ICS) with low dose BDP (160 mcg/d plus SM 100 mcg/day plus placebo LTRA) for 14 weeks, washout for 4 weeks, then crossover for another 14 weeks.[278] This study is described in detail in Key Question 1. The LTRA plus LABA combination led to significantly more subjects having a shorter time to treatment failure compared to ICS plus LABA (29 compared with 8; $P = 0.0008$). Subgroup analysis found no difference between races. The proportion of Caucasian subjects with preferential protection against treatment failure while using an ICS/LABA (relative to an LTRA/LABA) was not significantly different from the proportion of African-American subjects ($P = 1.0$).

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Gender

We found 1 observational study that assessed ICS harms in premenopausal women with asthma, and another that directly compared the efficacy and tolerability of ICSs and LMs between boys and girls age 4 to 9.5 years.

One prospective cohort study (described in detail in Key Question 2) evaluated the risk of osteoporosis in premenopausal women using TAA and found a dose-related decline in BMD. Although several other studies conducted in mixed populations of men and women found no relationship between ICS use and BMD, evidence is insufficient to support a differential decline in BMD between male and female patients treated with ICSs.

A retrospective cohort study of 844 children with asthma in Croatia[288] compared linear growth velocity between girls and boys taking either ML or the ICSs FP or BUD (Table 26). The study found no significant differences according to sex or age between treatment groups including ICS and non-ICS (ML) groups (ANOVA, $p>0.05$ for all comparisons). The study actually showed slightly higher mean growth velocity in patients taking ICSs compared to those taking ML, in contrast to negative effects of ICSs on growth more typically reported. This was especially true for BUD among girls; however, because of prescribing practices in Croatia the mean age of patients taking BUD was also higher, which may explain differences in growth rates in this group. The BUD group also represented just 5% of the total cohort, and standard errors were higher in this group.

We identified no evidence for subgroup differences based on gender in patients with COPD.

II. Comorbidities

We did not find any study that directly compared the efficacy, effectiveness, or tolerability of our included drugs in populations with specific comorbidities. Because mixed evidence supports an increased risk of osteoporotic fractures, cataracts, and glaucoma in ICS-treated asthma patients (especially at high doses), ICSs should be used with care in populations at increased risk for these conditions. No evidence reflects different risks between 1 ICS and another. We identified no evidence for subgroup differences based on comorbidities in patients with COPD.

III. Other medications

A good-quality Cochrane review[193] reported that 2 RCTs of patients with COPD[195,196] found no statistically significant difference among subgroups that were, or were not, taking inhaled corticosteroids, in the comparison between TIB and SM in the proportion of patients with 1 or more exacerbations. We did not find any evidence for subgroup differences based on additional medications taken in patients with asthma.

IV. Smoking status

We found 1 cross-over study comparing asthmatic smokers and nonsmokers.[305] In this study, 44 nonsmokers (total lifetime smoking history of less than 2 pack-years and no smoking for at least 1 year) and 39 “light” smokers (currently smoking 10-40 cigarettes/day and a 2-15 pack-year history) were randomized to BDP (320 mcg/d) or ML (10 mg/d) for 8 weeks of active treatment, an 8-week washout, and then 8 weeks of active treatment with the other medication. Both smokers and non-smokers showed some improvement in change in average quality of life scores.

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However, the change from baseline was only statistically significant in ML-treated non-smokers. Average change was greater in ML-treated non-smokers compared with smokers than it was in BDP-treated non-smokers compared with smokers. The difference was not based on a direct statistical comparison between the ML and BDP groups and further studies are needed to determine if there are differences in the response to ML and/or BDP based on smoking status.

A randomized trial in 683 current smokers in the UK[155] compared 500 mcg/day of FP to 10 mg/day of ML in patients with asthma. The study did not include a comparison group of non-smokers. Exacerbation rates were lower for fluticasone than ML (OR 0.75, 95% CI 0.43 to 1.31). Though the risk reduction was not statistically significant, it was similar in magnitude to that seen for studies overall (0.70, 95% CI 0.57 to 0.86, Key Question 1; includes this trial in smokers and 4 others in other populations.) Adverse events did not differ between FP and ML in this study in smokers, similar to results found overall for ICSs compared to LMs (Key Question 2).

We found no evidence for subgroups differences based on smoking status in patients with COPD.

V. Pregnancy

Maintaining adequate control of asthma during pregnancy is important for the health and well-being of both the mother and her baby. Inadequate control of asthma during pregnancy has been associated with higher rates of premature birth, intrauterine growth retardation, lower birth weight, perinatal death, and preeclampsia.[1,306,307] Expert opinion recommends ICSs as the preferred treatment for long-term control of asthma symptoms in pregnancy.[1] This preference is based on favorable efficacy data in both non-pregnant and pregnant women and also on safety data in pregnant women; results do not show an increased risk of adverse perinatal outcomes.[1]

FDA-approved labeling classifies medications by the potential for risk during pregnancy. Budesonide is the only ICS labeled as a pregnancy category B – i.e., no well-controlled studies have been conducted in women but animal studies have found little to no risk. Other ICS products are pregnancy category C – i.e., no well-controlled studies have been conducted in women but animal studies have shown harmful effects on the fetus. Currently, ICS product labeling recommends the use of an ICS in pregnancy only when anticipated benefits outweigh potential risk.[308]

In general, BUD is the preferred ICS because more data are available on its use during pregnancy than other ICSs. Minimal published data are available on the efficacy and safety of LTRAs or LABAs during pregnancy, but there is theoretical justification for expecting the safety profile of LABAs to resemble that of albuterol, for which there are data related to safety during pregnancy.[1]

We found 1 systematic review and 2 observational studies focusing on ICS use in pregnant asthmatics. We did not identify any studies assessing the efficacy or safety of LABAs, LTSIs, or anti-IgE therapy during pregnancy. One systematic review with meta-analysis showed that ICSs did not increase the rates of any adverse obstetrical outcomes.[309] Studies were eligible for inclusion in this analysis if the included women were exposed to any therapeutic dosage of any fluticasone, BDP, BUD, TAA or FLUN during pregnancy. Studies were excluded if either did not have a control group or had a control group comprised of non-asthmatic women. Four studies met inclusion criteria. The summary OR for major malformations in 2 studies was 0.96 (95% CI: 0.51, 1.83; P = 0.9582). The summary OR for preterm delivery in 3 studies was 0.99 (95% CI: 0.8, 1.22; P = 0.9687). The summary OR for low birth weight delivery in 2 studies was 0.89 (95% CI: 0.7, 1.14; P = 0.4013). The summary OR for pregnancy-induced hypertension in

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3 studies was 0.97 (95% CI: 0.84, 1.2; P = 0.9932). Tests for heterogeneity (P = 0.9249, P = 0.2521, P = 0 .6146 and P = 0.0013, respectively) indicated that the studies for major malformation, preterm delivery and low birth weight were not significantly heterogeneous and could be combined. ICSs do not increase the risk of major malformations, preterm delivery, low birth weight and pregnancy-induced hypertension.

A second observational study[310] aimed to investigate the association between doses of ICSs during the first trimester of pregnancy and the risk of congenital malformations among women with asthma. The study found that women using low to moderate doses of ICSs (>0 to 1000 mcg/d equivalent BDP) were not at increased risk of having a baby with a malformation than women who did not use ICSs during the first trimester. Women using high doses of ICSs (>1000 mcg/d) were more likely to have a baby with a malformation than women who used low to moderate doses (adjusted RR, 1.63; 95% CI, 1.02 to 2.60). However, these results should be interpreted with caution as confounding by severity of asthma cannot be ruled out as the cause of these findings.

We also identified 1 observational study of 6199 women with asthma giving birth between 1998 and 2008 in Canada (7376 pregnancies).[311] Women were exposed to ICS (n=4198 pregnancies), LABA (650 pregnancies), or neither (3178 pregnancies). Fluticasone propionate alone was the most commonly used ICS (76%) followed by BUD alone (14.5%). Salmeterol was the most commonly prescribed LABA (69.7%), followed by FM (29.2%). All women treated with LABA were also prescribed ICS. Women exposed to LABA and higher-dose ICS were more likely to have diabetes and moderate or severe asthma prior to pregnancy. Exposure during pregnancy to LABA did not significantly affect the odds of low birth weight babies, preterm birth, or babies small for gestational age. The effect of exposure to ICS differed by ICS dose. There was no effect of ICS at lower doses but at the equivalent of 500 mcg/day of fluticasone the odds of having a low birth weight baby was 1.66, 95% CI 1.01 to 2.73) and the odds of having a small for gestational age baby was 1.80, 95% CI 1.19 to 2.71). Exposure to inhaled corticosteroids during pregnancy did not affect the odds of preterm birth even at the highest steroid dose (OR, 1.13, 95% CI 0.65 to 1.97).

Insufficient data exists to determine if risks associated with ICSs differ among ICSs. Additionally we identified no evidence for subgroup differences related to pregnancy in patients with COPD.

VI. Genetics

Several genes (coding for LTRA, ICS, or beta-agonist receptors), have been associated with response to medications used in the treatment of asthma.[1,312-316] To date, there is not sufficient evidence to draw conclusions about whether testing for variants in these genes has any clinical utility (insufficient-strength evidence). Multiple studies have investigated the impact of polymorphisms of the beta-2 adrenoreceptor gene (ADRB2) on response to beta-agonist therapy, but none have demonstrated clinical validity or clinical utility of testing for ADRB2 polymorphisms.[1,312,313,316,317]

Two studies have prospectively evaluated the effects of drugs to treat asthma in patients with ADRB2 polymorphisms. One RCT (N=544) evaluated therapy with a LABA alone and in combination with an ICS and found no evidence of a pharmacogenetic effect of β-receptor variation on SM response.[317] It reported no difference over 16 weeks in response to SM for various ADRB2 genotype (Arg/Arg vs. Gly/Gly vs. Arg/Gly). The second RCT compared 16 weeks of treatment with TIB 5 mcg/d and SM 50 mcg/d when added to 400 to 1000 mcg/d of

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BUD or equivalent in 388 patients with asthma with the B16-Arg/Arg genotype.[191] There were no statistically significant differences between TIB and SM in exacerbations, quality of life, withdrawals due to adverse events, or serious adverse event outcomes and these findings were comparable to those of another RCT that compared TIB and SM in a broader patient population.[192]

We identified no evidence for subgroup differences based on genetics in patients with COPD.

VII. Disease Severity

The 6-month trial in patients with mild to severe asthma comparing equipotent doses of FP 125 mcg/day, BDP 200 mcg/day or BUD 200 mcg /day according to disease severity found significant improvements in SGRQ total score in favor of FP at 6 months compared to BUD or BDP in mild persistent asthma. For patients with moderate persistent asthma, FP was considered better than BDP and comparable to BUD at 6 months. In patients with severe asthma, there were no statistically significant difference between the 3 groups.[110]

The 1-year Prevention of Exacerbations with Tiotropium in COPD (POET-COPD) trial randomized 7376 patients with moderate to very severe COPD and found that, compared with SM 50 mcg twice daily in the overall study population, TIB 18 mcg once daily significantly increased time to first exacerbation and time to first severe exacerbation, reduced annual rates of moderate-to-severe and severe exacerbations, and had similar rates of mortality, withdrawals due to adverse events and proportions of patients with serious adverse events.[196] Other findings for the overall study population are described in more detail in Key Questions 1 and 2. Preplanned subgroup analyses of the POET-COPD trial based on disease severity found that, compared to SM, TIB also significantly prolonged time to first exacerbation in patients with less severe disease (Global Initiative for Chronic Obstructive Lung Disease [GOLD] Stage II (HR 0.88; 95% CI, 0.79-0.99) and in patients who were naïve to prior maintenance therapy (HR 0.79; 95% CI, 0.65-0.97).[318] In the GOLD Stage II subgroup, TIB also significantly prolonged time to first hospitalized exacerbation (HR 0.66; 95% CI, 0.48-0.91) and significantly reduced the annual rates of hospitalized exacerbations (RR 0.70; 95% CI, 0.57-0.85), but did not significantly reduce the annual rate of overall exacerbations (RR 0.91; 95% CI, 0.81-1.01). In the subgroup of maintenance naïve patients, TIB also significantly reduced annual rates of overall exacerbations (RR 0.77; 95% CI, 0.63-0.94), but did not significantly reduce annual rates of hospitalized exacerbations or significantly prolong time to first hospitalized exacerbation (effect estimates not reported). As with the overall study population, number of deaths were similar for TIB and SM in both the GOLD stage II and maintenance naïve subgroup (data not reported). Likewise, there was no statistically significant difference between TIB and SM in incidence of serious adverse events in the GOLD stage II (RR 0.93; 95% CI, 0.77-1.13) and the maintenance naïve subgroups (RR 0.87; 95% CI, 0.63-1.18).

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Table 26. Summary of studies evaluating subgroups of patients for whom controller medications may differ in efficacy or frequency of adverse events

Study	Study design N Duration	Country Population Setting	Comparison (total daily dose)	Results	Quality rating
Age (less than 3 years)					
Szefler et al. 2007[159]	RCT, open label 395 52 weeks	United States Children 2-8, mild persistent asthma, smoking status NR Multicenter	BUD inhalation suspension (BIS) (0.5 mg) vs. ML (4 or 5 mg) Low dose ICS	Exacerbations: BIS 1.23/patient/year, ML 1.63 (p=0.034) QOL: CHQ-P50 and CHSA similar between groups SAEs: BIS 4 patients (2%), ML 8 (4%)	Fair
Szefler et al. 2013[58]	203	Subgroup analysis: Children ages 2-4		Exacerbations: BIS1.35/ patient/ year, ML 2.30 (p=0.003) QOL: no significant differences in CHQ-PF50 or CHSA, except for the CHSA's patient emotional health subscale which favored ML SAEs: BIS 2 (2%), ML 6 (6%)	
Suissa, 2013[301]	Case control 218049	Canada Older adults, 78 years with COPD		Serious pneumonia (vs control) Current users Fluticasone : RR 2.01, (95% CI 1.93 to 2.10) Current users Budesonide: RR 1.17; (95% CI 1.09 to 1.26)	Fair
Racial groups					
Walters et al. 2007[302]	Systematic review with meta-analysis 67 RCTs (N = 42,333 Duration: ≥ 4 weeks	Multinational Adults and children with asthma who were not uniformly on ICS. (Studies in which all subjects uniformly taking ICS were excluded from this review.)	Regular inhaled LABA (either SM or FM) administered twice daily vs. placebo.	Composite endpoint of respiratory-related death and life threatening adverse events (intubation and mechanical ventilation): Greater in African-Americans than Caucasians (Relative Risk Increase 3.9; 95% CI: 1.29, 11.84).	Good

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Study	Study design N Duration	Country Population Setting	Comparison (total daily dose)	Results	Quality rating
Hanania et al. 2010[125]	RCT 444 6 months	US COPD Age ≥ 35, 45% current smokers Multicenter (62), setting NR	ARF NEB (30) vs. ARF NEB (50) vs. FM DPI (24)	WAEs: Caucasian: FM N=10 (7.9%), ARF 30 N=12 (9.5%), ARF 50 N=11 (9.0%) Black: FM N=2 (10.5%), ARF 30 N=3 (14.3%), ARF 50 N=5 (21.7%) SAEs: Caucasian: FM N=11 (8.7%), ARF 30 N=17 (13.5%), ARF 50 N=4 (3.3%) Black: FM N=3 (15.8%), ARF 30 N=3 (14.3%), ARF 50 N=6 (26.1%)	Fair
Deykin et al. 2007[278]	RCT 192 14 weeks, washout for 4 weeks, then crossover for 14 weeks	US Ages 12-65 asthmatics No current smokers Multicenter	ML (10 mg/d) + SM (100 mcg/d) + placebo ICS vs. BDP (160 mcg/d) + SM (100 mcg/d) + placebo LTRA Low dose ICS	No difference in proportion of Caucasian subjects with preferential[a] protection against treatment failure while using ICS + LABA (relative to an LTRA/LABA) as vs. that in the African-American subjects (*P* = 1.0)	Fair
Gender					
Erceg et al. 2012[288]	Retrospective cohort 844 Follow-up NR; 2y, 3mo of data assessed	Croatia Persistent asthma Age 4 to 9.5 Children's Hospital Srebrnjak	Doses NR FP (N=502) vs. BUD (N=43) vs. ML (N=245) Mean ages(y): FP: 6.53 BUD: 7.16 ML: 6.87	Linear Growth Velocity (mm/day, mean±SE): Boys: FP: 0.186±0.0058 BUD:0.167±0.0141 ICS: 0.184±0.0055 ML:0.180±0.0066 Girls: FP:0.189±0.0072 BUD:0.236±0.0283 ICS: 0.194±0.0071 ML: 0.181±0.0098	Fair
Smoking status					
Lazarus et al. 2007[305] SMOG study	RCT, DB, DD crossover 83 24 weeks (16 weeks with 8 week washout between)	US Age 18-50 asthmatics Multicenter	Smokers vs. non-smokers	Change in AQOL average score: ML /Non-smoker 0.23 (0.04, 0.42 ; *P* = 0.02) ML smoker 0.07 (-0.19, 0.32; *P* = NS) BDP Non-smoker 0.13 (-0.06, 0.32; *P* = NS) BDP Smoker 0.12 (-0.13, 0.37; *P* = NS)	Fair

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Table 26. Summary of studies evaluating subgroups of patients for whom controller medications may differ in efficacy or frequency of adverse events

Study	Study design N Duration	Country Population Setting	Comparison (total daily dose)	Results	Quality rating
Price et al. 2013[155]	RCT 683 6 months	UK Age 18 to 55, chronic asthma, all subjects active cigarette smokers Multicenter (131)	FP (500 mcg) vs. ML (10 mg)	Exacerbations (FP vs ML): 5 studies including Price: OR 0.70, 95% CI 0.57 to 0.86 Price (smokers): OR 0.75, 95% CI 0.43 to 1.31 Adverse events: no evidence of a difference in adverse events between ICSs and LMs overall (KQ2) or for smokers (Price)	Fair
Pregnancy					
Blais et al. 2009[310]	Cohort 13,280 pregnancies	Pregnant women with asthma Canada	no ICS use (8, 734 pregnancies) vs. >0-1000 mcg/d (4,392 pregnancies) vs. >1,000 mcg/d (154 pregnancies)	Adjusted RRs, all malformations: G1: 1.08 (0.94-1.24) G2: Reference G3: 1.66 (1.02-2.68) Adjusted RRs, major malformations: G1: 1.06 (0.89-1.26) G2: Reference G3: 1.67 (0.91-3.06)	Fair
Norjavaara & Gerhardsson de Verdier, 2003[319]	Database review 293,948	Pregnant asthmatic women (Swedish)	BUD vs. control (no BUD exposure during pregnancy)	No difference in gestational age, birth weight, length, rate of stillbirths, or multiple births for children born to BUD-treated mothers. Rate of caesarean birth was higher in women taking BUD early in pregnancy ($P < 0.05$)	Fair
Cossette, 2013[311]	Cohort 7376 pregnancies	Pregnant woman with asthma	ICS vs LABA/ICS vs no treatment	LABA use not associated with low birth weight, small for gestational age, or preterm birth; ICS exposure at higher-doses associated with low birth weight and small for gestational age but not preterm birth	Fair

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Table 26. Summary of studies evaluating subgroups of patients for whom controller medications may differ in efficacy or frequency of adverse events

Study	Study design N Duration	Country Population Setting	Comparison (total daily dose)	Results	Quality rating
Rahimi et al. 2006[309]	Systematic review with meta-analysis (SR)	Pregnant asthmatic women	Any therapeutic dosage of any ICS (FP, BDP, BUD, TAA, flunisolide) vs. no ICS exposure	ICSs did not increase the rates of any obstetrical outcomes. Major malformations: Summary (2 studies) OR=0.96 (95% CI: 0.51, 1.83); *P* = 0.9582 Preterm delivery: Summary (3 studies) OR = 0.99 (95% CI: 0.8, 1.22); *P* = 0.9687 Low birth weight delivery: Summary (2 studies) OR = 0.89 (95% CI: 0.7, 1.14); *P* = 0.4013 Pregnancy-induced hypertension: Summary (3 studies) OR = 0.97 (95% CI: 0.84, 1.2); *P* = 0.9932	Fair

Abbreviations: AQOL = average quality of life; BUD = Budesonide; CI = confidence interval; DPI= Dry Powder Inhaler; FM = Formoterol; FP = Fluticasone Propionate; ICS = Inhaled Corticosteroids; LABAs = Long-Acting Beta-2 Agonists; LTRAs = Leukotriene receptor antagonists; MA=meta-analysis; ML = Montelukast; NR = not reported; NS = not statistically significant; OR= odds ratio; QOL = quality of life; RCT= randomized controlled trial; RR = relative risk; SM = Salmeterol;; SR=systematic review.

[a] Treatment failure defined as increased as-needed albuterol, persistent asthma symptoms or drop in PEF despite rescue use, use of oral, parenteral, or non-study related ICS, emergency department therapy with steroids, drop in FEV1 or PEF, or physician clinical judgment for safety.

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SUMMARY

Strength of Evidence

The main results of this review are summarized in Table 27. Summaries of the-strength evidence for each comparison are presented in Appendix E. Efficacy studies provide moderate-strength evidence that equipotent doses of inhaled corticosteroids (ICSs) administered through comparable delivery devices do not differ in their ability to control asthma symptoms, prevent asthma exacerbations, reduce the need for additional rescue medication, or in the overall incidence of adverse events or withdrawals due to adverse events in patients with asthma. There was no evidence comparing different ICS in patients with chronic obstructive pulmonary disease (COPD) except in subgroups.

There was moderate-strength evidence that long-acting beta-2 agonists (LABAs) do not differ in ability to prevent exacerbations or hospitalizations or emergency visits or improve quality of life in patients with persistent asthma not controlled on ICS alone. There was also no difference in tolerability or adverse events between formoterol and salmeterol. In patients with COPD, there was low-strength evidence that arformoterol and formoterol are associated with similar exacerbation rates and improvements in quality of life, that formoterol and indacaterol have similar impacts on exacerbations and quality of life, and that indacaterol has a small transient advantage over salmeterol in its effects on quality of life, but differences disappear over time.

Evidence also did not support a difference between montelukast and zafirlukast in their ability to improve quality of life in patients with asthma (low-strength evidence). There was no evidence comparing leukotriene modifiers (LMs) in patients with COPD.

There was moderate-strength evidence of no difference between combination products fluticasone propionate/salmeterol and either budesonide/formoterol or mometasone furoate/formoterol in quality of life, exacerbations or asthma deteriorations, withdrawals due to adverse events, or serious adverse events in patients with asthma (when high doses of mometasone furoate combined with formoterol and fluticasone propionate combined with salmeterol were used, strength of evidence was low). Low-strength evidence did not support a difference between fluticasone propionate/salmeterol and fluticasone furoate/vilanterol in quality of life in treating asthma. There were no prospective, randomized, head-to-head clinical trials of ICS/LABA combination products available in the United States in patients with COPD.

Efficacy studies up to 56 weeks in duration provide consistent evidence of greater benefit for asthma patients treated with ICS monotherapy compared with those treated with LM monotherapy (high-strength evidence). Direct evidence suggested no difference in tolerability or overall adverse events between ICSs and LMs when used to treat asthma (moderate-strength evidence). Specific adverse events reported with ICSs, such as cataracts and decreased growth velocity, were not found among patients taking LMs. Evidence is insufficient to determine if long-term treatment with ICSs leads to a reduction in final adult height. There were no head-to-head studies of ICS versus LM in patients with COPD.

Overall evidence indicated that ICSs and leukotriene receptor antagonists (LTRAs) are safer than LABAs for use as monotherapy (high-strength evidence). LABAs were not recommended nor approved for use as monotherapy for persistent asthma because they may increase the risk of asthma-related deaths (high-strength evidence). In a pooled analysis of 7 studies, asthmatics treated with LABAs had an increased occurrence of exacerbations compared

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to those treated with ICS. However, in patients with COPD there was moderate-strength evidence of no difference between ICS and LABAs in exacerbations or hospitalizations due to exacerbations and low-strength evidence of no difference between treatments in mortality. Although there was low-strength evidence of no difference in risk of having any adverse event between ICS and LABAs, serious pneumonia was more frequent with ICS.

Low-strength evidence does not support a difference in patients with asthma between tiotropium and salmeterol in exacerbations, quality of life, withdrawals due to adverse events, or proportion of patients with serious harms. In patients with COPD, there was moderate-strength evidence that fewer patients experience an exacerbation or a nonfatal serious adverse event with tiotropium versus salmeterol and low-strength evidence of no difference between tiotropium and salmeterol in hospitalizations, proportions of patients with clinically significant improvement in quality of life, or proportion of patients who withdraw due to adverse events. For the comparison of IC and tiotropium, there is low-strength evidence that in patients with *severe* COPD, indacaterol provided less protection from exacerbations, but similar mortality and improved quality of life; and in a broader patient population of *moderate to severe* COPD, tiotropium was associated with significantly lower proportions of patients with clinically significant improvement in quality of life, but the 2 drugs did not differ in hospitalizations or exacerbations. Tiotropium and formoterol had similar effects on exacerbations. Additionally, there was no difference between tiotropium and salmeterol, indacaterol, or formoterol in withdrawals due to adverse events and no difference between tiotropium and indacaterol or formoterol in proportion of patients with nonfatal serious harms (low-strength evidence).

Low-strength evidence from 1 trial suggested that more asthma patients taking RF than BDP experience exacerbations and withdraw from the study due to adverse events. There were no trials comparing ICS with phosphodiesterase-4 inhibitors in patients with COPD.

Results from large trials up to 12 months in duration in patients with persistent asthma provided moderate-strength evidence of greater efficacy with the addition of a LABA to an ICS than with a higher-dose ICS (high-strength evidence for ≥12, low-strength for <12) with no difference in overall adverse events (with the exception of tremor which was increased in those taking ICS/LABA versus higher-dose ICS). There were no head-to-head studies comparing ICS/LABA versus a higher-dose ICS in patients with COPD.

When comparing an ICS/LABA with a different ICS in patients with asthma, low-strength evidence suggested no difference in exacerbations, adverse events, or withdrawals due to adverse events between fluticasone furoate/vilanterol and fluticasone propionate. There was also low-strength evidence that risk of experiencing any adverse events is greater with CIC versus fluticasone propionate plus salmeterol. No trials of ICS/LABA versus a different ICS were identified in patients with COPD.

There was no apparent difference in symptoms, exacerbations, rescue medicine use, overall adverse events, or withdrawals due to adverse events between asthma patients treated with ICSs plus LTRAs compared with those treated with increasing the dose of ICSs (moderate-strength evidence for ≥12, low-strength for <12). There were no similar head-to-head studies in COPD patients.

High-strength evidence from a meta-analysis of 5 RCTs indicated that fluticasone propionate plus salmeterol was more efficacious than montelukast for the treatment of persistent asthma in patients at least 12 years of age (moderate-strength evidence of greater efficacy with fluticasone propionate/salmeterol in children). There was low-strength evidence for similar rates

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of overall adverse events and withdrawals due to adverse events between treatments in patients with asthma. There were no trials of this comparison in patients with COPD.

Results provided high-strength evidence that the addition of a LABA to ICS therapy (ICS/LABA) is more efficacious than the addition of a LTRAs to ICS therapy (ICS/LTRA) in patients with persistent asthma (high-strength evidence for ≥12, low-strength for <12). We found no difference in overall adverse events or withdrawals due to adverse events between ICS/LABA and ICS/LTRAs (moderate-strength evidence for ≥12, insufficient for <12). There were no trials of ICS/LABA versus ICS/LTRA in COPD patients.

In patients with persistent asthma, low-strength evidence did not support a difference between tiotropium plus ICS versus a higher-dose ICS in exacerbations, improvements in quality of life or withdrawals due to harms. There were no head-to-head studies comparing tiotropium/ICS with a higher-dose of the same ICS in COPD patients.

In patients with COPD, treatment with fluticasone propionate plus salmeterol was associated with decreased mortality and better quality of life, but higher risk of hospitalization versus treatment with tiotropium (low-strength evidence). There was also low-strength evidence of no difference in mortality between tiotropium and fluticasone furoate/vilanterol or umeclidinium bromide/vilanterol. However, low-strength evidence supported reduced risk of serious harms with tiotropium compared with fluticasone propionate/salmeterol, although there was no difference in withdrawal due to adverse events. Tiotropium and fluticasone/vilanterol also did not differ in proportion of patients with serious adverse events and tiotropium and umeclidinium bromide/vilanterol did not differ in proportion of patients who withdraw due to harms (low-strength evidence). There were no trials of these comparisons in patients with asthma.

Limitations of this Report

As with other types of research, the limitations of this systematic review are important to recognize. These can be divided into 2 groups, those relating to applicability of the results (addressed below) and those relating to methodology within the scope of this review.

Methodological limitations of the review within the defined scope included the exclusion of studies published in languages other than English and lack of a specific search for unpublished studies. In addition, the data from RCTs included in this report have limited utility for assessing real-world adherence to medications. This is largely because they enrolled selected populations, often requiring a high degree of adherence to be included in the trial. For example, many of the trials had a run-in period during which adherence was assessed and then only included subjects that met a threshold for good adherence (e.g., adherence to 80% of recommended doses).

Unfortunately, for many drugs, there are few or no effectiveness studies and many efficacy studies. As a result, clinicians must make decisions about treatment for many patients who would not have been included in controlled trials and for whom the effectiveness and tolerability of the different drugs are uncertain. An evidence report indicates whether or not there is evidence that drugs differ in their effects in various subgroups of patients, but it does not attempt to set a standard for how results of controlled trials should be applied to patients who would not have been eligible for them. With or without an evidence report, these are decisions that must be informed by clinical judgment.

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Applicability

The applicability of the results are limited by the scope of the Key Questions and inclusion criteria and by the applicability of the studies included. Most studies included narrowly defined populations of patients who met strict criteria for case definition, had few comorbidities, and used few or no concomitant medications. Minorities, older patients, and the most seriously ill patients were often underrepresented.

Studies Currently Being Conducted

We identified no trials in progress that would meet inclusion criteria for this review that would potentially change conclusions.

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Table 27. Summary of the evidence by key question for controller medications for the treatment of persistent asthma or COPD in adolescents/adults ≥ 12 years of age and children < 12 years of age

Key Question 1. What is the comparative efficacy and effectiveness of controller medications used to treat outpatients with persistent asthma or COPD?

Strength of evidence	Conclusions
	Inhaled Corticosteroids (ICSs) compared with ICSs:
Moderate (≥ 12 years)	**Asthma** Efficacy studies provide moderate evidence that ICSs do not differ in their ability to control asthma symptoms, prevent exacerbations, and reduce the need for additional rescue medication at equipotent doses administered through comparable delivery devices. Relatively few studies reported exacerbations, healthcare utilization (hospitalizations, emergency visits), or quality of life outcomes. Long-term data beyond 12 weeks is lacking for most of the comparisons.
Moderate (< 12 years)	In children, the body of evidence supports the above conclusion, but data was only available for 5 comparisons (3 systematic reviews and 5 RCTs): beclomethasone compared with budesonide, beclomethasone compared with fluticasone propionate, budesonide compared with CIC, budesonide compared with fluticasone propionate, and CIC compared with fluticasone propionate.
	COPD We found no reviews or RCTs of ICS versus ICS in patients with COPD.
	Leukotriene Modifiers (LMs) compared with LMs:
	Asthma
Insufficient	Limited head-to-head evidence from 1 short-term study (12 weeks) in adults and adolescents ≥ 12 years of age does not support a difference between montelukast and zafirlukast in their ability to improve quality of life.
	Long-Acting Beta-2 Agonists (LABAs) compared with LABAs:
	Asthma[a]
Moderate	Results from 3 efficacy studies provide moderate evidence that LABAs do not differ in their ability to prevent exacerbations, improve quality of life, and prevent hospitalizations or emergency visits in patients ≥ 12 years with persistent asthma not controlled on ICSs alone. In children, direct evidence is limited to 1 fair-quality trial enrolling children and adolescents age 6-17. The trial reported no difference in exacerbations, quality of life, missed work, or missed school in subjects treated with eformoterol compared to those treated with salmeterol.
	COPD
Low	Arformoterol and formoterol are associated with similar exacerbation rates and improvements in quality of life. Nebulized formoterol is similar to formoterol via DPI in its effects on exacerbations and quality of life. Formoterol and indacaterol have similar impacts on exacerbations and quality of life. Indacaterol has a small transient advantage over salmeterol in its effects on quality of life, but differences disappear over time.

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Key Question 1. What is the comparative efficacy and effectiveness of controller medications used to treat outpatients with persistent asthma or COPD?	
Strength of evidence	**Conclusions**
	Combination Products: ICS+LABA compared with ICS+LABA **Asthma**
Moderate (≥ 12 years)	**Budesonide/Formoterol (BUD/FM) compared with Fluticasone propionate/Salmeterol (FP/SM):** Results from large trials up to 6 months in duration comparing equipotent steroid components support no significant difference in efficacy or quality of life between fixed-dose combination treatment with BUD/FM and with FP/SM. The results of our meta-analyses show no difference between those treated with BUD/FM and those treated with FP/SM in either exacerbations requiring oral steroids or exacerbations requiring emergency visit or hospital admission.
Moderate (≥ 12 years)	**Fluticasone propionate/Salmeterol (FP/SM) compared with Mometasone furoate/Formoterol (MF /FM)** Moderate-strength evidence from 2 trials (12 and 52 weeks) indicated no difference in asthma deteriorations between MF/FM and FP/SM at medium doses. Low-strength evidence from a single study was unable to differentiate MF/FM and FP/SM at high doses.
Low (≥ 12 years)	**Fluticasone propionate/salmeterol (FP/SM) compared with Fluticasone furoate/vilanterol (FF/VI)** Low-strength evidence suggests no difference in quality of life between the treatments.
Insufficient (< 12 years)	None of the trials included children < 12 years of age.
Low	COPD A single good-quality 48-week trial of patients with severe COPD found no difference in rates of exacerbations or improvement in quality of life between BPD/FM and BUD/FM.
	ICSs compared with Leukotriene Modifiers:
	Asthma
High	Efficacy studies up to 56 weeks in duration provide consistent evidence favoring ICSs over LTRAs for the treatment of asthma as monotherapy for both children and adults. Those treated with LTRAs had a significantly higher occurrence of exacerbations than those treated with ICSs (OR 0.70; 95% CI, 0.57 to 0.86 for fluticasone propionate vs montelukast). In addition, our meta-analyses found statistically significant differences in favor of ICSs over LTRAs for quality of life.
Low	An analysis of a subset of 154 children age 6 to 14 in 1 trial found that those treated with fluticasone propionate had significantly fewer emergency department visits and missed school days than those treated with montelukast.
	ICSs compared with LABAs for monotherapy:
High	**Asthma**[a] Efficacy studies up to 12 months in duration provide consistent evidence favoring ICSs over LABAs for the treatment of asthma as monotherapy for children and adults. Those treated with LABAs had a significantly higher occurrence of exacerbations than those treated with ICSs (OR 2.12, 95% CI 1.53 to 2.95, p<0.001, 7 studies).
Low	**COPD** No difference between ICS and LABA in mortality (OR 1.17, 95% CI 0.97 to 1.42; 1 SR of 7 RCTs)

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Key Question 1. What is the comparative efficacy and effectiveness of controller medications used to treat outpatients with persistent asthma or COPD?	
Strength of evidence	**Conclusions**
Moderate	No difference between ICA and LABA in exacerbations (OR 0.96, 95% CI 0.89 to 1.02, 1 SR of 4 RCTs), or in hospitalizations due to exacerbations (Risk Ratio 1.07, 95% CI 0.91 to 1.26, 1 study)
	Tiotropium compared with LABAs
	Asthma[a]
Low	Evidence does not support a difference between tiotropium and salmeterol in exacerbations or quality of life.
	COPD
Moderate	Tiotropium is associated with fewer patients experiencing 1 or more exacerbations than salmeterol.
Low	Tiotropium and salmeterol do not differ in hospitalizations and proportions of patients with clinically significant improvement in quality of life. For the comparison of indacaterol and tiotropium, in patients with *severe* COPD, indacaterol provided less protection from exacerbations, but similar mortality and improved quality of life; and in a broader patient population of *moderate to severe* COPD, indacaterol provided better quality of life, but the 2 drugs did not differ in hospitalizations or exacerbations.. Tiotropium and formoterol do not differ in exacerbations.
	ICS compared with PDE-4 inhibitors:
	Asthma
Low	More patients taking roflumilast experienced exacerbations than did those taking beclomethasone.
	ICS/LABA compared with ICS (increased dose) (addition of LABA to ICS compared with increasing the ICS dose):
High (≥ 12 years)	Results from large trials up to 12 months in duration support greater efficacy with the addition of a LABA to an ICS than with a higher-dose ICS for adults and adolescents with persistent asthma. Our meta-analysis shows statistically significantly greater improvement in symptom-free days, symptom scores, rescue-free days, and rescue medicine use for subjects treated with ICS/LABA. Despite a trend toward fewer subjects with exacerbations in the ICS/LABA group, the difference was not statistically significant in our analysis
Low (< 12 years)	Two trials exclusively enrolled children < 12 (7 trials included some subjects < 12) and results are not necessarily generalizable to pediatric populations. **COPD** We found no reviews or RCTs of ICS/LABA versus ICS same dose in patients with COPD.
	ICS/LABA compared with ICS (different drug):
Low	**Asthma** When comparing ICS/LABA with a different ICS in patients with asthma, there was no difference in exacerbations between fluticasone furoate plus vilanterol versus fluticasone propionate. **COPD** There was no evidence comparing ICS/LABA and a different ICS in patients with COPD.

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Key Question 1. What is the comparative efficacy and effectiveness of controller medications used to treat outpatients with persistent asthma or COPD?	
Strength of evidence	**Conclusions**
	ICS/LTRA compared with ICS (increased dose):
	Asthma
Moderate	There is no apparent difference in exacerbations between patients ≥ 12 years treated with ICSs plus LTRAs and those treated with an increased dose of ICSs. There were some conflicting results and further research may alter the results.
Low	Two trials enrolled children < 12 years of age; 1 reported fewer exacerbations in those treated with ICS/LTRA compared to increasing the dose of BUD, but the other reported no difference between groups for hospitalizations due to asthma and similar numbers of oral steroid courses.
	Combination products (ICS/LABA) compared with LTRAs:
	Asthma
High	Overall, our meta-analysis and results from 5 RCTs find the combination of fluticasone propionate plus salmeterol to be more efficacious than montelukast for preventing exacerbations in patients ≥ 12 years with persistent asthma.
Moderate	Two of the 5 trials showing greater efficacy for combination products enrolled children ages 6-14 and another included about 15% of subjects < 12 years of age.
	LABA/ICS compared with LTRA/ICS
	Asthma
High	For the drug classes overall, fewer patients taking LABA/ICS had exacerbations than those taking LTRA/ICS; similarly, fewer patients taking SM/ICS had exacerbations than those taking ML/ICS. There was no clinically important difference between LABA/ICS and LTRA/ICS in quality of life.
Moderate	There was no clinically important difference between SM/ICS and ML/ICS in quality of life.
Low	There was no clinically important difference between SM/ICS and ZAF/ICS in quality of life.
	LTRA/LABA compared with ICS/LABA:
	Asthma
Moderate	Results from one 32 week cross-over trial, which was terminated early, reported that patients ≥ 12 years treated with LTRA/LABA had significantly shorter time to treatment failure than those treated with ICS/LABA (*P* = 0.0008).
	Tiotropium/ICS compared with higher-dose ICS
	Asthma
Low	Co-therapy with tiotropium and beclomethasone did not differ from double-dose beclomethasone in their effects on exacerbations and quality of life.
	Tiotropium compared with fixed-dose combination products
	COPD

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Key Question 1. What is the comparative efficacy and effectiveness of controller medications used to treat outpatients with persistent asthma or COPD?	
Strength of evidence	**Conclusions**
Low	Compared with tiotropium, fluticasone propionate/salmeterol was associated with lower risk of mortality, better quality of life, but higher risk of hospitalization. Tiotropium and fluticasone propionate/salmeterol do not differ in their effects on exacerbations. Tiotropium does not differ in its effect on mortality as compared with either fluticasone furoate/vilanterol or umeclidinium bromide/vilanterol. Tiotropium and umeclidinium bromide/vilanterol do not differ in their effects on quality of life.

[a]LABA monotherapy contraindicated since 2010 in patients with asthma (see Key Question 2).

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Key Question 2. What is the comparative tolerability and frequency of adverse events for controller medications used to treat outpatients with persistent asthma or COPD?	
Strength of evidence	**Conclusions**
	Inhaled Corticosteroids (ICSs):
Moderate (≥ 12 years)	**Asthma** The overall incidence of adverse events, withdrawals due to adverse events, and specific adverse events (other than reduction in growth velocity and oral candidiasis) are similar for equipotent doses of ICSs.
Moderate (< 12 years)	**Asthma** Three fair head-to-head trials provide evidence that short-term (20 weeks to 1 year) growth velocity is reduced less with fluticasone propionate than with beclomethasone or budesonide. A fourth head-to-head trial found that CIC-treated subjects had a greater mean body height increase than budesonide-treated subjects over 12 weeks.
	COPD We found no reviews or RCTs comparing ICS to ICS in patients with COPD.
	Long-Acting Beta-2 Agonists (LABAs):
	Asthma[a]
Moderate	Limited direct evidence from head-to-head trials and from systematic reviews provides no evidence of a difference in tolerability or adverse events between formoterol and salmeterol in adults and children.
	COPD
Low	Patients taking arformoterol and formoterol have similar rates of serious adverse events and withdrawals due to adverse events. Compared with formoterol, patients taking indacaterol were less likely to withdraw due to harms than those taking indacaterol, though the difference was not statistically significant for the lower IC dose. There was a non-significant trend toward higher rates of serious adverse events and withdrawals due to adverse events with indacaterol compared with salmeterol.
	Combination Products: ICS/LABA versus ICS/LABA
Moderate (≥ 12 years)	**Asthma** **Budesonide/Formoterol (BUD/FM) compared with Fluticasone propionate/Salmeterol (FP/SM):** Data from 4 large head-to-head trials (5,818 subjects) provide no evidence of a difference in overall adverse events, serious adverse events or withdrawal due to adverse events between BUD/FM and FP/SM in adults and adolescents.

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Key Question 2. What is the comparative tolerability and frequency of adverse events for controller medications used to treat outpatients with persistent asthma or COPD?	
Strength of evidence	**Conclusions**
Moderate (≥ 12 years)	**Fluticasone propionate/Salmeterol (FP/SM) compared with Mometasone furoate/Formoterol (MF /FM)** Moderate-strength evidence indicates no difference in withdrawal due to adverse events or risk of serious adverse events between MF/FM and FP/SM at medium doses. Low-strength evidence suggests no difference in risk of withdrawal due to adverse events or incidence of serious adverse events between MF/FM and FP/SM, although numerically higher rates were reported with MF/FM than with FP/SM at high doses
Low (≥ 12 years)	**Fluticasone propionate/salmeterol (FP/SM) compared with Fluticasone furoate/vilanterol (FF/VI)** Low-strength evidence from a single study of fixed- dose combination inhalers of FP/VI compared with FP/SM suggests no difference in rates of withdrawal due to adverse events or serious adverse events between drugs.
Insufficient (< 12 years)	None of the trials included children < 12 years of age.
Low (≥ 12 years)	**COPD** **Budesonide/Formoterol (BUD/FM) compared with Beclomethasone/Formoterol (BPD/FM)** A single good-quality trial did not suggest differences in adverse events, withdrawals due to adverse events, pneumonia or mortality between BUD/FM and BPD/FM.
Low (≥ 12 years)	**Budesonide/Formoterol (BUD/FM) compared with Fluticasone propionate/Salmeterol (FP/SM):** Low-strength evidence from a single fair-quality observational study indicates that patients using FP/SM had an increased risk of pneumonia and pneumonia-related mortality compared with BUD/FM. The risk of pneumonia was significantly higher with FP/SM compared with BUD/FM; relative risk 1.73 (95% CI 1.57 to 1.90). The risk of mortality related to pneumonia with FP/SM compared with BUD/FM was also increased; relative risk 1.76 (95% CI 1.22 to 2.53).
Insufficient	**Fluticasone propionate/salmeterol (FP/SM) compared with Fluticasone furoate/vilanterol (FF/VI)** Based on three 12-week trials, although rates were low in both groups, evidence is insufficient to determine whether withdrawals due to adverse events, serious adverse events or mortality differ between FF/VI and FP/SM.
	COPD No head-to-head trials comparing 2 or more fixed-dose combination products of ICS/LABA in patients with COPD that reported harms outcomes were found
	ICSs compared with Leukotriene Modifiers:
	Asthma
Moderate	Data from 2 good-quality systematic reviews and numerous head-to-head RCTs provides no evidence of a difference in tolerability or overall adverse events (risk of withdrawal due to adverse effects: RR 1.24, 95% CI: 0.95 to 1.63, 25 trials) comparing leukotriene modifiers with ICSs in adults and children.
	ICSs compared with LABAs for monotherapy:
High (all ages)	**Asthma**[a] LABAs are not recommended nor approved for use as monotherapy for persistent asthma because they may increase the risk of asthma-related deaths. Overall evidence indicates that ICSs are safer than LABAs for use as monotherapy.

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Key Question 2. What is the comparative tolerability and frequency of adverse events for controller medications used to treat outpatients with persistent asthma or COPD?	
Strength of evidence	**Conclusions**
Low	**COPD** 1 good-quality systematic review of 4 studies found no difference between ICS and LABA in risk of having any adverse event (OR 1.12, 95% CI 0.96 to 1.30) Serious pneumonia AEs were more frequent with ICS than LABA based on a good-quality SR of 5 studies (OR 1.48, 95% CI 1.13 to 1.94
	Tiotropium compared with LABAs
	Asthma[a]
Low	Evidence does not support a difference between tiotropium and salmeterol in withdrawals due to adverse events or the proportion of patient with serious harms.
	COPD
Moderate	Compared to salmeterol, tiotropium is associated with fewer patients experiencing a nonfatal serious adverse event.
Low	Compared to salmeterol, tiotropium is associated with fewer patients withdrawing due to adverse events. Tiotropium does not differ from indacaterol or formoterol in the proportion of patients with nonfatal serious harms or who withdrew due to harms.
	ICSs compared with PDE-4 inhibitors
	Asthma
Low	Evidence from 1 trial suggests more patients taking roflumilast withdrew due to adverse events.
	ICS/LABA compared with ICS (increased dose) **(addition of LABA to ICS compared with increasing the ICS dose):**
Moderate (≥ 12 years)	**Asthma** Results from a good-quality systematic review with meta-analysis and numerous RCTs found no difference in overall adverse events or withdrawals between subjects treated with ICSs plus LABAs and subjects treated with an increased dose of ICSs. Those treated with ICSs plus LABAs had an increased rate of tremor (N = 11, RR 1.84, 95% CI: 1.20 to 2.82). Indirect evidence from a recent systematic review that included a post-hoc analysis of data from SMART suggests that the potential increased risk of asthma-related death for those taking LABAs may be confined to patients not taking ICSs at baseline.
Low (< 12 years)	Two of the RCTs enrolled an exclusively pediatric population < 12 years of age (7 included some subjects < 12) and results are not necessarily applicable to pediatric populations.
Insufficient	**COPD** We found no reviews or RCTs of ICS plus LABA versus higher-dose ICS in patients with COPD.
	ICS/LABA compared with ICS (different drug)
Low	**Asthma** When comparing and ICS/LABA with a different ICS there was no difference in adverse events or withdrawals due to adverse events between fluticasone furoate plus vilanterol and fluticasone propionate. There was also low-strength evidence that risk of experiencing any adverse events is greater with CIC versus fluticasone propionate plus salmeterol. **COPD** No trials of ICS/LABA versus a different ICS were identified in patients with COPD

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Key Question 2. What is the comparative tolerability and frequency of adverse events for controller medications used to treat outpatients with persistent asthma or COPD?	
Strength of evidence	**Conclusions**
	ICS/LTRA compared with ICS (increased dose)
	Asthma
Moderate	Evidence from 1 good-quality systematic review with meta-analysis (including 27 trials) found that the addition of LTRAs to ICSs compared to increasing the dose of ICSs resulted in no significant differences in overall adverse events or withdrawals due to adverse events in patients ≥ 12 years . Trials were generally not designed to compare tolerability and adverse events and many used higher than licensed doses of LTRAs.
Low	Evidence in children < 12 years of age is limited. Just 2 of the 27 trials in the systematic review enrolled children.
	Combination products (ICS/LABA) compared with LTRAs:
	Asthma
Low	ICS/LABA combinations and leukotriene modifiers have similar rates of overall adverse events and withdrawals due to adverse events based on direct evidence from 4 short-term trials. One of the 4 trials enrolled subjects at least 6 years of age (about 15% were <12 years old) and 1 enrolled only children ages 6 to 14.
	LABA/ICS compared with LTRA/ICS (addition of LABA compared with LTRA to ongoing ICS therapy)
	Asthma
High	Results from a good-quality systematic review with meta-analysis show no difference in withdrawals due to adverse events between drug classes LABA/ICS and LTRA/ICS, or between specific drugs salmeterol and montelukast as add-on therapy. Trials were generally not designed to compare tolerability and adverse events.
Moderate	Systematic review results suggest more patients taking LABAs as a class in addition to ICSs have serious adverse events than patients taking LTRAs as a class with ICSs. The same result holds for the specific drug comparison of salmeterol versus montelukast as add-on therapy.
	Tiotropium/ICS compared with higher-dose ICS
	Asthma
Low	Co-therapy with tiotropium and beclomethasone did not differ from double-dose beclomethasone in the proportion of patients who withdrew due to harms.
	Tiotropium compared with fixed-dose combination products
	COPD
Low	Compared with fluticasone propionate/salmeterol, tiotropium is associated with a significantly lower proportion of patients with serious harms, but the drugs do not differ in the proportion of patients who withdraw due to adverse events. Tiotropium and fluticasone furoate/vilanterol do not differ in the proportion of patients with serious adverse events. Tiotropium and umeclidinium bromide/vilanterol do not differ in the proportion of patients who withdraw due to adverse events.

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Key Question 3. Are there subgroups of these patients based on demographics (age, racial groups, gender), asthma severity, comorbidities (drug-disease interactions, including obesity), other medications (drug-drug interactions), smoking status, genetics, or pregnancy for which asthma controller medications differ in efficacy, effectiveness, or frequency of adverse events?	
Strength of evidence	**Conclusions**
	Age:
	Differences in the efficacy, tolerability, or adverse events between children <12 years of age and adolescents or adults ≥12 are described in the body of the report (Key Questions 1 and 2) and summaries above.
	Children ≤ 4 years of age
Low	We found no head-to-head studies comparing the efficacy or safety of our included drugs in this age group with older children, adolescents, or adults. One study of patients age 2 to 8 with asthma included a subgroup analysis of patients age 2 to 4. The subgroup analysis suggested more exacerbations per patient and more patients with serious adverse events for montelukast compared with budesonide, with risk differences greater among the younger patients.
	Elderly
Low	There was no head-to-head studies comparing the efficacy and safety of older adults treated with ICS. One case-control study on older adults found 2-fold increase in serious pneumonia with fluticasone propionate compared to controls with a dose-response relationship. Budesonide had 17% increase in serious pneumonia compared to controls without a dose-response effect.
	Racial groups:
Low	A trial including 63 African American and 375 Caucasian patients with COPD suggested higher risk of serious adverse events and withdrawals due to adverse events among African American patients taking arformoterol compared with formoterol, though there were few events in this small subgroup. These risk differences were not apparent among Caucasians.
	Gender:
Insufficient	We found 1 study reporting effects of ICSs on bone mineral density in premenopausal women with asthma, but evidence was insufficient to compare this outcome between women and men.
Low	One observational study suggested that the effects of montelukast compared with ICSs budesonide or fluticasone propionate on linear growth velocity do not differ between boys and girls.
	Comorbidities:
Insufficient	We did not find any studies meeting our inclusion/exclusion criteria that directly compared the efficacy, effectiveness, or tolerability of our included drugs in populations with specific comorbidities.
	Other medications (drug-drug interactions):
Insufficient	We did not find any studies meeting our inclusion/exclusion criteria that examined the impact of other medications on the comparative efficacy, tolerability, or adverse events of our included medications.
	Smoking status:
Low	One study comparing ML and BDP in smokers and non-smokers provides some information that there may be differential responses to treatment between smokers and non-smokers. Another study comparing ML and FP in smokers only showed similar results to studies in other populations for exacerbations and adverse events.
	Pregnancy:
Low	We did not find any studies that directly examined the comparative efficacy, tolerability, or adverse events of our included medications. Budesonide is the only ICS labeled pregnancy category B; the other ICSs are category C. LABA and lower dose ICS were not associated

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Key Question 3. Are there subgroups of these patients based on demographics (age, racial groups, gender), asthma severity, comorbidities (drug-disease interactions, including obesity), other medications (drug-drug interactions), smoking status, genetics, or pregnancy for which asthma controller medications differ in efficacy, effectiveness, or frequency of adverse events?	
Strength of evidence	**Conclusions**
	with low birth weight, preterm birth or small for gestational age babies. Higher dose ICS increased the risk of having a low birth weight or small for gestational age baby.
	Genetics:
Insufficient	To date, there is not sufficient evidence to determine whether genetic polymorphisms in general result in clinically important differences in responses to asthma medications. Multiple studies have investigated the impact of polymorphisms on response to various asthma treatments, but none have demonstrated clinical validity or clinical utility of testing for polymorphisms.
Low	One RCT provided low-strength evidence of no difference in response to salmeterol (with or without ICSs) for people with various ADRB2 (Beta-2 adrenoreceptor gene) genotypes (Arg/Arg vs. Gly/Gly vs. Arg/Gly)

CONCLUSIONS

Overall findings did not suggest that a single medication within any of the classes evaluated is significantly more effective or harmful than the other medications within the same class. Our results supported the general clinical practice of starting initial treatment for persistent asthma with an inhaled corticosteroid (ICS). For people with poorly-controlled persistent asthma taking an ICS, our findings suggested that the addition of a long-acting beta-2 agonist (LABA) is most likely to provide the greatest benefit as the next step in treatment. For patients with chronic obstructive pulmonary disease (COPD), our results indicated that monotherapy with ICS and LABAs are similarly effective and have similar risk of experiencing any adverse event. However, there was low-strength evidence that treatment with ICS increases the risk of serious pneumonia. In general the evidence for newer asthma and COPD medications is of insufficient or low strength for most benefit and harms outcomes.

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REFERENCES

1. National Heart Lung and Blood Institute (NHLBI), The National Asthma Education and Prevention Program (NAEPP) Guidelines for the Diagnosis and Management of Asthma (EPR-3/July 2007), available at: http://www.nhlbi.nih.gov/guidelines/asthma/index.htm; accessed July 15, 2008. 2007.
2. Global Initiative for Asthma (GINA), available at: http://www.ginasthma.com/Guidelineitem.asp??l1=2&l2=1&intId=37; accessed July 15, 2008.
3. American Lung Association Epidemiology & Statistics Unit Research and Program Services: Trends in Asthma Morbidity and Mortality, September 2012. http://www.lung.org/finding-cures/our-research/epidemiology-and-statistics-rpts.html. Accessed 3/21/2014.2012.
4. Centers for Disease Control National Center for Health Statistics, available at: http://www.cdc.gov/nchs/fastats/asthma.htm; accessed July 15, 2008.
5. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease (Updated 2014). Global Initiative for Chronic Obstructive Lung Disease (GOLD). 2014.
6. NIH National Heart Lung and Blood Institute. Morbidity and Mortality: 2012 Chartbook on cardiovascular, lung and blood diseases2012.
7. Qaseem A, Wilt TJ, Weinberger SE, et al. Diagnosis and management of stable chronic obstructive pulmonary disease: a clinical practice guideline update from the American College of Physicians, American College of Chest Physicians, American Thoracic Society, and European Respiratory Society. *Ann Intern Med.* Vol 155. 2011/08/04 ed2011:179-191.
8. Azmacort Product Label. http://www.accessdata.fda.gov/drugsatfda_docs/label/2008/018117s042lbl.pdf. Accessed December 5, 2013.
9. AstraZeneca. Symbicort Product Label. http://www1.astrazeneca-us.com/pi/symbicort.pdf. Accessed April 16, 2014.
10. AstraZeneca. Accolate Product Label. http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/020547s033lbl.pdf. Accessed December 5, 2013.
11. AstraZeneca. Pulmicort Flexhaler Product Label. http://www1.astrazeneca-us.com/pi/pulmicortfh.pdf. Accessed April 16, 2014.
12. AstraZeneca. Pulmicort Respules Product Label. http://www1.astrazeneca-us.com/pi/pulmicortrespules.pdf. Accessed April 16, 2014.
13. Boehringer I. Spiriva Product Label. http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021395s033lbl.pdf. Accessed December 5, 2013.
14. Zyflo Product Label. http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/020471s017lbl.pdf. Accessed December 5, 2013.
15. Zyflo CR Product Label. http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/022052s009lbl.pdf. Accessed December 5, 2013.

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16. Forest IL. Tudorza Pressair Product Label. http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/202450s000lbl.pdf. Accessed December 5, 2013.

17. Forest RII. Daliresp Product Label. http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/022522s003lbl.pdf. Accessed December 5, 2013.

18. GlaxoSmithKline. Serevent Product Label. http://www.accessdata.fda.gov/drugsatfda_docs/label/2004/20236s030,20692s026lbl.pdf. Accessed December 5, 2013.

19. GlaxoSmithKline. Flovent DISKUS Product Label. http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/020833s021lbl.pdf. Accessed December 5, 2013.

20. GlaxoSmithKline. Flovent HFA Product Label. http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021433s022lbl.pdf. Accessed December 5, 2013.

21. GlaxoSmithKline. Advair Diskus Product Label. http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021077s042lbl.pdf. Accessed December 5, 2013.

22. GlaxoSmithKline. Advair HFA Product Label. http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/021254s009lbl.pdf. Accessed December 5, 2013.

23. GlaxoSmithKline. Breo Ellipta Product Label. http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/204275s000lbl.pdf. Accessed December 5, 2013.

24. GlaxoSmithKline. Anoro Ellipta Product Label. http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/203975s000lbl.pdf. Accessed April 24, 2014.

25. Meda. Aerospan HFA Product Label. http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021247s008lbl.pdf. Accessed April 23, 2014.

26. Merck. Singulair Product Label. http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/020829s065,020830s066,021409s042lbl.pdf. Accessed December 5, 2013.

27. Merck. Foradil Aerolizer Product Label. http://www.merck.com/product/usa/pi_circulars/f/foradil/foradil_pi.pdf. Accessed December 5, 2013.

28. Merck SD. Dulera Product Label. http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/022518s013lbl.pdf. Accessed December 5, 2013.

29. Mylan. Perforomist Product Label. http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/022007s006lbl.pdf. Accessed April 23, 2014.

30. Novartis. Foradil Product Label. http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/020831s028lbl.pdf. Accessed December 5, 2013.

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31. Novartis. Arcapta Product Label. http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/022383s002lbl.pdf. Accessed December 5, 2013.

32. Roche P. Aerobid Product Label. http://www.drugs.com/pro/aerobid.html. Accessed December 5, 2013.

33. Schering. Asmanex Twisthaler Product Label. http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021067s013lbl.pdf. Accessed December 5, 2013.

34. Sunovion. Brovana Product Label. http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021912s006lbl.pdf. Accessed December 5, 2013.

35. Takeda G. Alvesco Product Label. http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/021658s006lbl.pdf. Accessed December 5, 2013.

36. Teva. QVAR Product Label. http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/020911s022lbl.pdf. Accessed December 5, 2013.

37. Global Strategy for Asthma Management and Prevention 2014, © Global Initiative for Asthma (GINA) all rights reserved. Available from http://www.ginasthma.org. .

38. Facts and Comparisons 4.0, available at: http://www.factsandcomparisons.com/; accessed July 15, 2008.

39. At-A-Glance Outpatient Management for Chronic Obstructive Pulmonary Disease (COPD). Global Initiative for Chronic Obstructive Lung Disease (GOLD)2013.

40. McDonagh MS, Jonas DE, Gartlehner G, et al. Methods for the drug effectiveness review project. *BMC Med Res Methodol.* Vol 12. 2012/09/14 ed2012:140.

41. Berkman ND, Lohr KN, Ansari M, et al. Grading the Strength of a Body of Evidence When Assessing Health Care Interventions for the Effective Health Care Program of the Agency for Healthcare Research and Quality: An Update. 2014/01/10 ed2008.

42. Owens DK, Lohr KN, Atkins D, et al. AHRQ series paper 5: grading the strength of a body of evidence when comparing medical interventions--agency for healthcare research and quality and the effective health-care program. *Journal of clinical epidemiology.* May 2010;63(5):513-523.

43. Sutton AJ, Duval SJ, Tweedie RL, Abrams KR, Jones DR. Empirical assessment of effect of publication bias on meta-analyses. *BMJ.* 2000;320(7249):1574-1577.

44. Lewis S, Clarke M. Forest plots: trying to see the wood and the trees. *BMJ.* 2001;322(7300):1479-1480.

45. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med.* 2002;21(11):1539-1558.

46. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ.* 2003;327(7414):557-560.

47. Bernstein DI, Cheema A, Cherrez-Ojeda I, et al. Efficacy and onset of action of MF/formoterol and fluticasone propionate/salmeterol combination treatment in subjects with persistent asthma. *Allergy Asthma Clin Immunol.* 2011/12/07/ 2011;7:21.

48. Woodcock A, Bleecker E, Lotvall J. Efficacy and Safety of Fluticasone Furoate/Vilanterol Compared With Fluticasone Propionate/Salmeterol Combination in Adult and Adolescent Patients With Persistent Asthma. *Chest.* 2013;144(4):1222-1229.

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Copyright Drug Effectiveness Review Project. All rights reserved.

49. GlaxoSmithKline. Study HZC113107 (ClinicalTrials.gov Identifier: NCT01342913). A 12-week study to evaluate the 24 hour pulmonary function of Fluticasone Furoate (FF)/Vilanterol Inhalation Powder (FF/VI Inhalation Powder) once daily compared with Salmeterol/Fluticasone Propionate (FP) Inhalation Powder twice daily in subjects with Chronic Obstructive Pulmonary Disease (COPD).2011.

50. GlaxoSmithKline. Study HZC115805 (ClinicalTrials.gov Identifier: NCT01627327). A 12-Week Study to Evaluate the 24-Hour Pulmonary Function Profile of Fluticasone Furoate /Vilanterol (FF/VI) Inhalation Powder 100/25mcg Once-Daily via a Novel Dry Powder Inhaler Compared with Tiotropium Bromide Inhalation Powder 18mcg Delivered Once-Daily via the HandiHaler in Subjects with Chronic Obstructive Pulmonary Disease (COPD) Who Have or Are at Risk for Co-morbid Cardiovascular Disease.2011.

51. GlaxoSmithKline. Study HZC112352 (ClinicalTrials.gov Identifier: NCT01323621). A 12-Week Study to Evaluate the 24-Hour Pulmonary Function Profile of Fluticasone Furoate (FF) /GW642444 (Vilanterol) (VI) Inhalation Powder 100/25mcg Once Daily Compared with Fluticasone Propionate/Salmeterol Inhalation Powder 250/50mcg Twice Daily in Subjects with Chronic Obstructive Pulmonary Disease (COPD).2012.

52. GlaxoSmithKline. Study HZC113109 (ClinicalTrials.gov Identifier: NCT 01323634). A 12-Week Study to Evaluate the 24-Hour Pulmonary Function Profile of Fluticasone Furoate (FF) /GW642444 (Vilanterol) (VI) Inhalation Powder 100/25mcg Once Daily Compared with Fluticasone Propionate/Salmeterol Inhalation Powder 250/50mcg Twice Daily in Subjects with Chronic Obstructive Pulmonary Disease.2012.

53. GlaxoSmithKline. Study HZC115247 (ClinicalTrials.gov Identifier: NCT01395888). A 12-week study to evaluate the effect of fluticasone furoate (FF, GW685698)/vilanterol (VI, GW642444) 100/25 mcg Inhalation Powder delivered once daily via a Novel Dry Powder Inhaler (NDPI) on arterial stiffness compared with Tiotropium bromide 18 mcg delivered once daily via a HandiHaler in subjects with chronic obstructive pulmonary disease (COPD).2012.

54. GlaxoSmithKline. A Multicenter trial comparing the efficacy and safety of GSK573719/GW642444 with GSK573719 and with tiotropium over 24 weeks in subjects wiht COPD. Study DB2113374 2012.

55. GlaxoSmithKline. A Multicenter trial comparing the efficacy and safety of GSK573719/GW642444 with GW642444 and with tiotropium over 24 weeks in subjects with COPD. Study DB21133602012.

56. GlaxoSmithKline. A randomised, double-blind, parallel group, multicentre study of Fluticasone Furoate/GW642444 Inhalation Powder, Fluticasone Furoate Inhalation Powder alone, and Fluticasone Propionate alone in the treatment of persistent asthma in adults and adolescents. Study HZA106829 (ClinicalTrials.gov Identifier: NCT01134042. *ClinicalTrials.gov.* 2010.

57. O'Connor RD, Patrick DL, Parasuraman B, Martin P, Goldman M. Comparison of Patient-Reported Outcomes During Treatment With Adjustable- and Fixed-Dose Budesonide/Formoterol Pressurized Metered-Dose Inhaler Versus Fixed-Dose Fluticasone Propionate/Salmeterol Dry Powder Inhaler in Patients With Asthma. *J Asthma.* 2010;47(2):217-223.

58. Szefler SJ, Carlsson L-G, Uryniak T, Baker JW. Budesonide Inhalation Suspension Versus Montelukast in Children Aged 2 to 4 Years with Mild Persistent Asthma. *J Allergy Clin Immunol Pract.* 2013;1(1):58-64.

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Copyright Drug Effectiveness Review Project. All rights reserved.

59. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *Journal of clinical epidemiology.* 2009;62(10):e1-34.

60. Adams N, Bestall JM, Jones PW. Inhaled beclomethasone versus budesonide for chronic asthma. *Cochrane Database of Systematic Reviews. 2000(1):CD003530.* 2000.

61. Adams N, Lasserson TJ, Cates CJ, Jones PW. Fluticasone versus beclomethasone or budesonide for chronic asthma in adults and children. *Cochrane Database Syst Rev.* 2007(4):CD002310.

62. Lasserson TJ, Cates CK, Jones AB, Steele EH, White J. Fluticasone versus HFA-beclomethasone dipropionate for chronic asthma in adults and children. *Cochrane Database Syst Rev.* 2006(2):CD005309.

63. Ayres JG, Bateman ED, Lundback B, Harris TA. High dose fluticasone propionate, 1 mg daily, versus fluticasone propionate, 2 mg daily, or budesonide, 1.6 mg daily, in patients with chronic severe asthma. International Study Group. *Eur Respir J.* Apr 1995;8(4):579-586.

64. Baraniuk J, Murray JJ, Nathan RA, et al. Fluticasone alone or in combination with salmeterol vs triamcinolone in asthma. *Chest.* Sep 1999;116(3):625-632.

65. Barnes NC, Marone G, Di Maria GU, Visser S, Utama I, Payne SL. A comparison of fluticasone propionate, 1 mg daily, with beclomethasone dipropionate, 2 mg daily, in the treatment of severe asthma. International Study Group. *Eur Respir J.* Jun 1993;6(6):877-885.

66. Bateman ED, Linnhof AE, Homik L, Freudensprung U, Smau L, Engelstatter R. Comparison of twice-daily inhaled ciclesonide and fluticasone propionate in patients with moderate-to-severe persistent asthma. *Pulm Pharmacol Ther.* 2008;21(2):264-275.

67. Berkowitz R, Rachelefsky G, Harris AG, Chen R. A comparison of triamcinolone acetonide MDI with a built-in tube extender and beclomethasone dipropionate MDI in adult asthmatics. *Chest.* Sep 1998;114(3):757-765.

68. Bernstein DI, Berkowitz RB, Chervinsky P, et al. Dose-ranging study of a new steroid for asthma: mometasone furoate dry powder inhaler. *Respir Med.* Sep 1999;93(9):603-612.

69. Boe J, Bakke P, Rodolen T, Skovlund E, Gulsvik A. High-dose inhaled steroids in asthmatics: moderate efficacy gain and suppression of the hypothalamic-pituitary-adrenal (HPA) axis. Research Council of the Norwegian Thoracic Society. *Eur Respir J.* Dec 1994;7(12):2179-2184.

70. Boulet LP, Bateman ED, Voves R, Muller T, Wolf S, Engelstatter R. A randomized study comparing ciclesonide and fluticasone propionate in patients with moderate persistent asthma. *Respir Med.* Aug 2007;101(8):1677-1686.

71. Boulet LP, Drollmann A, Magyar P, et al. Comparative efficacy of once-daily ciclesonide and budesonide in the treatment of persistent asthma. *Respir Med.* May 2006;100(5):785-794.

72. Bousquet J, D'Urzo A, Hebert J, et al. Comparison of the efficacy and safety of mometasone furoate dry powder inhaler to budesonide Turbuhaler. *Eur Respir J.* Nov 2000;16(5):808-816.

73. Bronsky E, Korenblat P, Harris AG, Chen R. Comparative clinical study of inhaled beclomethasone dipropionate and triamcinolone acetonide in persistent asthma. *Ann Allergy Asthma Immunol.* Apr 1998;80(4):295-302.

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Copyright Drug Effectiveness Review Project. All rights reserved.

74. Buhl R, Vinkler I, Magyar P, et al. Comparable efficacy of ciclesonide once daily versus fluticasone propionate twice daily in asthma. *Pulm Pharmacol Ther.* 2006;19(6):404-412.
75. Condemi JJ, Chervinsky P, Goldstein MF, et al. Fluticasone propionate powder administered through Diskhaler versus triamcinolone acetonide aerosol administered through metered-dose inhaler in patients with persistent asthma. *J Allergy Clin Immunol.* Oct 1997;100(4):467-474.
76. Connolly A. A comparison of fluticasone propionate 100 mcg twice daily with budesonide 200 mcg twice daily via their respective powder devices in the treatment of mild asthma. *European Journal of Clinical Research.* 1995:15-29.
77. Corren J, Berkowitz R, Murray JJ, Prenner B. Comparison of once-daily mometasone furoate versus once-daily budesonide in patients with moderate persistent asthma. *Int J Clin Pract.* Sep 2003;57(7):567-572.
78. Dahl R, Engelstatter R, Trebas-Pietras E, Kuna P. A 24-week comparison of low-dose ciclesonide and fluticasone propionate in mild to moderate asthma. *Respiratory Medicine.* August 2010;104 (8):1121-1130.
79. de Benedictis FM, Teper A, Green RJ, Boner AL, Williams L, Medley H. Effects of 2 inhaled corticosteroids on growth: results of a randomized controlled trial. *Arch Pediatr Adolesc Med.* Nov 2001;155(11):1248-1254.
80. Fabbri L, Burge PS, Croonenborgh L, et al. Comparison of fluticasone propionate with beclomethasone dipropionate in moderate to severe asthma treated for one year. International Study Group. *Thorax.* Aug 1993;48(8):817-823.
81. Fairfax A, Hall I, Spelman R. A randomized, double-blind comparison of beclomethasone dipropionate extrafine aerosol and fluticasone propionate. *Ann Allergy Asthma Immunol.* May 2001;86(5):575-582.
82. Ferguson AC, Spier S, Manjra A, Versteegh FG, Mark S, Zhang P. Efficacy and safety of high-dose inhaled steroids in children with asthma: a comparison of fluticasone propionate with budesonide. *J Pediatr.* Apr 1999;134(4):422-427.
83. Gross GN, Wolfe JD, Noonan MJ, et al. Differential effects of inhaled corticosteroids: Fluticasone propionate versus triamcinolone acetonide. *American Journal of Managed Care.* 1998;4(2):233-244.
84. Gustafsson P, Tsanakas J, Gold M, Primhak R, Radford M, Gillies E. Comparison of the efficacy and safety of inhaled fluticasone propionate 200 micrograms/day with inhaled beclomethasone dipropionate 400 micrograms/day in mild and moderate asthma. *Arch Dis Child.* Aug 1993;69(2):206-211.
85. Hansel TT, Benezet O, Kafe H, et al. A multinational, 12-week, randomized study comparing the efficacy and tolerability of ciclesonide and budesonide in patients with asthma. *Clin Ther.* Jun 2006;28(6):906-920.
86. Harnest U, Price D, Howes T, Sussman G. Comparison of mometasone furoate dry powder inhaler and fluticasone propionate dry powder inhaler in patients with moderate to severe persistent asthma requiring high-dose inhaled corticosteroid therapy: findings from a noninferiority trial. *J Asthma.* Apr 2008;45(3):215-220.
87. Heinig JH, Boulet LP, Croonenborghs L, Mollers MJ. The effect of high-dose fluticasone propionate and budesonide on lung function and asthma exacerbations in patients with severe asthma. *Respir Med.* Sep 1999;93(9):613-620.
88. Hoekx JC, Hedlin G, Pedersen W, Sorva R, Hollingworth K, Efthimiou J. Fluticasone propionate compared with budesonide: a double-blind trial in asthmatic children using

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powder devices at a dosage of 400 microg x day(-1). *Eur Respir J.* Nov 1996;9(11):2263-2272.

89. Knox A, Langan J, Martinot JB, Gruss C, Hafner D. Comparison of a step-down dose of once-daily ciclesonide with a continued dose of twice-daily fluticasone propionate in maintaining control of asthma. *Curr Med Res Opin.* Oct 2007;23(10):2387-2394.

90. Langdon C, Capsey L. Fluticasone propionate and budesonide in adult asthmatics: a comparison using dry powder inhaler devices. *British Journal of Clinical Research.* 1994:85-99.

91. Lorentzen KA, Van Helmond JL, Bauer K, Langaker KE, Bonifazi F, Harris TA. Fluticasone propionate 1 mg daily and beclomethasone dipropionate 2 mg daily: a comparison over 1 yr. *Respir Med.* Nov 1996;90(10):609-617.

92. Lundback B, Alexander M, Day J, et al. Evaluation of fluticasone propionate (500 micrograms day-1) administered either as dry powder via a Diskhaler inhaler or pressurized inhaler and compared with beclomethasone dipropionate (1000 micrograms day-1) administered by pressurized inhaler. *Respir Med.* Nov 1993;87(8):609-620.

93. Magnussen H, Hofman J, Staneta P, Lawo JP, Hellwig M, Engelstatter R. Similar efficacy of ciclesonide once daily versus fluticasone propionate twice daily in patients with persistent asthma. *J Asthma.* Sep 2007;44(7):555-563.

94. Molimard M, Martinat Y, Rogeaux Y, Moyse D, Pello JY, Giraud V. Improvement of asthma control with beclomethasone extrafine aerosol compared to fluticasone and budesonide. *Respir Med.* Jun 2005;99(6):770-778.

95. Nathan RA, Nayak AS, Graft DF, et al. Mometasone furoate: efficacy and safety in moderate asthma compared with beclomethasone dipropionate. *Ann Allergy Asthma Immunol.* Feb 2001;86(2):203-210.

96. Newhouse M, Knight A, Wang S, Newman K. Comparison of efficacy and safety between flunisolide/AeroChamber and budesonide/turbuhaler in patients with moderate asthma. AER-MD-04 Study Group. *Ann Allergy Asthma Immunol.* Mar 2000;84(3):313-319.

97. O'Connor B, Bonnaud G, Haahtela T, et al. Dose-ranging study of mometasone furoate dry powder inhaler in the treatment of moderate persistent asthma using fluticasone propionate as an active comparator. *Ann Allergy Asthma Immunol.* Apr 2001;86(4):397-404.

98. Ohbayashi H, Adachi M. Hydrofluoroalkane-beclomethasone dipropionate effectively improves airway eosinophilic inflammation including the distal airways of patients with mild to moderate persistent asthma as compared with fluticasone propionate in a randomized open double-cross study. *Allergol Int.* Sep 2008;57(3):231-239.

99. Pedersen S, Engelstatter R, Weber HJ, et al. Efficacy and safety of ciclesonide once daily and fluticasone propionate twice daily in children with asthma. *Pulm Pharmacol Ther.* Jun 2009;22(3):214-220.

100. Pedersen S, Garcia Garcia ML, Manjra A, Theron I, Engelstatter R. A comparative study of inhaled ciclesonide 160 microg/day and fluticasone propionate 176 microg/day in children with asthma. *Pediatr Pulmonol.* Oct 2006;41(10):954-961.

101. Raphael GD, Lanier RQ, Baker J, Edwards L, Rickard K, Lincourt WR. A comparison of multiple doses of fluticasone propionate and beclomethasone dipropionate in subjects with persistent asthma. *J Allergy Clin Immunol.* May 1999;103(5 Pt 1):796-803.

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102. Ringdal N, Swinburn P, Backman R, et al. A blinded comparison of fluticasone propionate with budesonide via powder devices in adult patients with moderate-to-severe asthma: A clinical evaluation. *Mediators of Inflammation.* 1996;5(5):382-389.
103. Ukena D, Biberger C, Steinijans V, et al. Ciclesonide is more effective than budesonide in the treatment of persistent asthma. *Pulm Pharmacol Ther.* 2007;20(5):562-570.
104. Vermetten FA, Boermans AJ, Luiten WD, Mulder PG, Vermue NA. Comparison of salmeterol with beclomethasone in adult patients with mild persistent asthma who are already on low-dose inhaled steroids. *J Asthma.* 1999;36(1):97-106.
105. Volmer T, Kielhorn A, Weber HH, Wiessmann KJ. Cost effectiveness of fluticasone propionate and flunisolide in the treatment of corticosteroid-naive patients with moderate asthma. *Pharmacoeconomics.* Nov 1999;16(5 Pt 2):525-531.
106. von Berg A, Engelstatter R, Minic P, et al. Comparison of the efficacy and safety of ciclesonide 160 microg once daily vs. budesonide 400 microg once daily in children with asthma. *Pediatr Allergy Immunol.* Aug 2007;18(5):391-400.
107. Wardlaw A, Larivee P, Eller J, Cockcroft DW, Ghaly L, Harris AG. Efficacy and safety of mometasone furoate dry powder inhaler vs fluticasone propionate metered-dose inhaler in asthma subjects previously using fluticasone propionate. *Ann Allergy Asthma Immunol.* Jul 2004;93(1):49-55.
108. Weiss KB, Liljas B, Schoenwetter W, Schatz M, Luce BR. Effectiveness of budesonide administered via dry-powder inhaler versus triamcinolone acetonide administered via pressurized metered-dose inhaler for adults with persistent asthma in managed care settings. *Clin Ther.* Jan 2004;26(1):102-114.
109. Worth H, Muir JF, Pieters WR. Comparison of hydrofluoroalkane-beclomethasone dipropionate Autohaler with budesonide Turbuhaler in asthma control. *Respiration.* 2001;68(5):517-526.
110. Padukudru M, Parthasarathi G, Sabin T. Health-related quality of life assessment using St. George's respiratory questionnaire in asthmatics on inhaled corticosteroids. *Lung India.* 2012 January-March 2012;29(1):35.
111. Ayers ML, Mejia R, Ward J, Lentine T, Mahler DA. Effectiveness of salmeterol versus ipratropium bromide on exertional dyspnoea in COPD. *European Respiratory Journal.* Jun 2001;17(6):1132-1137.
112. Vermeulen JH, Gyurkovits K, Rauer H, Engelstatter R. Randomized comparison of the efficacy and safety of ciclesonide and budesonide in adolescents with severe asthma. *Respir Med.* Oct 2007;101(10):2182-2191.
113. Riccioni G, Della Vecchia R, Di Ilio C, D'Orazio N. Effect of the two different leukotriene receptor antagonists, montelukast and zafirlukast, on quality of life: a 12-week randomized study. *Allergy Asthma Proc.* Nov-Dec 2004;25(6):445-448.
114. Kubavat AH, Khippal N, Tak S, et al. A randomized, comparative, multicentric clinical trial to assess the efficacy and safety of zileuton extended-release tablets with montelukast sodium tablets in patients suffering from chronic persistent asthma. *Am J Ther.* Mar-Apr 2013;20(2):154-162.
115. Campbell LM, Anderson TJ, Parashchak MR, Burke CM, Watson SA, Turbitt ML. A comparison of the efficacy of long-acting beta 2-agonists: eformoterol via Turbohaler and salmeterol via pressurized metered dose inhaler or Accuhaler, in mild to moderate asthmatics. Force Research Group. *Respir Med.* Apr 1999;93(4):236-244.

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116. Everden P, Campbell M, Harnden C, et al. Eformoterol Turbohaler compared with salmeterol by dry powder inhaler in asthmatic children not controlled on inhaled corticosteroids. *Pediatr Allergy Immunol.* Feb 2004;15(1):40-47.
117. Vervloet D, Ekstrom T, Pela R, et al. A 6-month comparison between formoterol and salmeterol in patients with reversible obstructive airways disease. *Respir Med.* Jun 1998;92(6):836-842.
118. Rutten-van Molken MP, van Doorslaer EK, Till MD. Cost-effectiveness analysis of formoterol versus salmeterol in patients with asthma. *Pharmacoeconomics.* Dec 1998;14(6):671-684.
119. Dahl R, Chung KF, Buhl R, et al. Efficacy of a new once-daily long-acting inhaled beta2-agonist indacaterol versus twice-daily formoterol in COPD. *Thorax.* 2010;65(6):473-479.
120. Gross NJ, Nelson HS, Lapidus RJ, et al. Efficacy and safety of formoterol fumarate delivered by nebulization to COPD patients. *Respir Med.* Feb 2008;102(2):189-197.
121. Hanania NA, Darken P, Horstman D, et al. The efficacy and safety of fluticasone propionate (250 microg)/salmeterol (50 microg) combined in the Diskus inhaler for the treatment of COPD. *Chest.* 2003 2003;124(3):834-843.
122. Korn S, Kerwin E, Atis S, et al. Indacaterol once-daily provides superior efficacy to salmeterol twice-daily in COPD: a 12-week study. *Respir Med.* 2011;105(5):719-726.
123. Kornmann O, Dahl R, Centanni S, et al. Once-daily indacaterol versus twice-daily salmeterol for COPD: a placebo-controlled comparison. *Euro Respir J.* 2011;37(2):273-279.
124. Novartis Pharmaceuticals Inc. A 52-week treatment, multi-center, randomized, open label, parallel group study to assess the long term safety and efficacy of Indacaterol (300 µg o.d.) using salmeterol (50 µg b.i.d.) as an active control in Japanese patients with chronic obstructive pulmonary disease (COPD) NCT00876694. 2011. http://clinicaltrials.gov/ct2/show/results/NCT00876694.
125. Hanania NA, Donohue JF, Nelson H, et al. The safety and efficacy of arformoterol and formoterol in COPD. *COPD.* Feb 2010;7(1):17-31.
126. Condemi JJ. Comparison of the efficacy of formoterol and salmeterol in patients with reversible obstructive airway disease: a multicenter, randomized, open-label trial. *Clin Ther.* Sep 2001;23(9):1529-1541.
127. Aalber R, Backer V, Kava T, et al. Adjustable maintenance dosing with budesonide/formoterol compared with fixed-dose salmeterol/fluticasone in moderate to severe asthma. *Curr Med Res Opin.* 2004 2004;20(2):225-240.
128. Aalbers R. Fixed or adjustable maintenance-dose budesonide/formoterol compared with fixed maintenance-dose salmeterol/fluticasone propionate in asthma patients aged >or=16 years: post hoc analysis of a randomized, double-blind/open-label extension, parallel-group study. *Clin Drug Investig.* 2010;30(7):439-451.
129. Busse WW, Shah SR, Somerville L, Parasuraman B, Martin P, Goldman M. Comparison of adjustable- and fixed-dose budesonide/formoterol pressurized metered-dose inhaler and fixed-dose fluticasone propionate/salmeterol dry powder inhaler in asthma patients. *J Allergy Clin Immunol.* Jun 2008;121(6):1407-1414, 1414 e1401-1406.
130. Dahl R, Chuchalin A, Gor D, Yoxall S, Sharma R. EXCEL: A randomised trial comparing salmeterol/fluticasone propionate and formoterol/budesonide combinations in adults with persistent asthma. *Respir Med.* Jul 2006;100(7):1152-1162.

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131. Kuna P. Treatment comparison of budesonide/formoterol with salmeterol/fluticasone propionate in adults aged > or =16 years with asthma: post hoc analysis of a randomized, double-blind study. *Clin Drug Investig.* 2010;30(9):565-579.
132. Kuna P, Peters MJ, Manjra AI, et al. Effect of budesonide/formoterol maintenance and reliever therapy on asthma exacerbations. *Int J Clin Pract.* May 2007;61(5):725-736.
133. Maspero JF, Nolte H, Cherrez-Ojeda I. Long-term safety of mometasone furoate/formoterol combination for treatment of patients with persistent asthma. *J Asthma.* Dec 2010;47(10):1106-1115.
134. Price D, Wiren A, Kuna P. Cost-effectiveness of budesonide/formoterol for maintenance and reliever asthma therapy. *Allergy.* Oct 2007;62(10):1189-1198.
135. Calverley PM, Kuna P, Monso E, et al. Beclomethasone/formoterol in the management of COPD: a randomised controlled trial. *Respir Med* 2010;104(12):1858-1868.
136. Castro-Rodriguez JA, Rodrigo GJ. The role of inhaled corticosteroids and montelukast in children with mild-moderate asthma: Results of a systematic review with meta-analysis. *Archives of Disease in Childhood.* May 2010;95 (5):365-370.
137. Ducharme FM, Di Salvio F. Anti-leukotriene agents compared to inhaled corticosteroids in the management of recurrent and/or chronic asthma in adults and children. *Cochrane Database of Systematic Reviews, 2004, Issue 1, Art. No.: CD002314. DOI:10.1002/14651858.CD002314.pub2.*
138. Halpern MT, Khan ZM, Stanford RH, Spayde KM, Golubiewski M. Asthma: resource use and costs for inhaled corticosteroid vs leukotriene modifier treatment--a meta-analysis. *J Fam Pract.* May 2003;52(5):382-389.
139. Amer Lung Assoc Asthma Clinical R, Anthonisen N, Holbrook JT, Peters SP, Wise RA, et al. Randomized comparison of strategies for reducing treatment in mild persistent asthma. *New England Journal of Medicine* 2007;356(20):2027-2039.
140. Baumgartner RA, Martinez G, Edelman JM, et al. Distribution of therapeutic response in asthma control between oral montelukast and inhaled beclomethasone. *Eur Respir J.* Jan 2003;21(1):123-128.
141. Becker AB, Kuznetsova O, Vermeulen J, et al. Linear growth in prepubertal asthmatic children treated with montelukast, beclomethasone, or placebo: a 56-week randomized double-blind study. *Ann Allergy Asthma Immunol.* Jun 2006;96(6):800-807.
142. Bleecker ER, Welch MJ, Weinstein SF, et al. Low-dose inhaled fluticasone propionate versus oral zafirlukast in the treatment of persistent asthma. *J Allergy Clin Immunol.* Jun 2000;105(6 Pt 1):1123-1129.
143. Brabson JH, Clifford D, Kerwin E, et al. Efficacy and safety of low-dose fluticasone propionate compared with zafirlukast in patients with persistent asthma. *Am J Med.* Jul 2002;113(1):15-21.
144. Busse W, Raphael GD, Galant S, et al. Low-dose fluticasone propionate compared with montelukast for first-line treatment of persistent asthma: a randomized clinical trial. *J Allergy Clin Immunol.* Mar 2001;107(3):461-468.
145. Busse W, Wolfe J, Storms W, et al. Fluticasone propionate compared with zafirlukast in controlling persistent asthma: a randomized double-blind, placebo-controlled trial. *J Fam Pract.* Jul 2001;50(7):595-602.
146. Covar RA, Szefler SJ, Zeiger RS, et al. Factors associated with asthma exacerbations during a long-term clinical trial of controller medications in children. *J Allergy Clin Immunol.* Oct 2008;122(4):741-747 e744.

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147. Garcia ML, Wahn U, Gilles L, Swern A, Tozzi CA, Polos P. Montelukast, compared with fluticasone, for control of asthma among 6- to 14-year-old patients with mild asthma: the MOSAIC study. *Pediatrics.* Aug 2005;116(2):360-369.
148. Israel E, Chervinsky PS, Friedman B, et al. Effects of montelukast and beclomethasone on airway function and asthma control. *J Allergy Clin Immunol.* Dec 2002;110(6):847-854.
149. Kim KT, Ginchansky EJ, Friedman BF, et al. Fluticasone propionate versus zafirlukast: effect in patients previously receiving inhaled corticosteroid therapy. *Ann Allergy Asthma Immunol.* Nov 2000;85(5):398-406.
150. Laviolette M, Malmstrom K, Lu S, et al. Montelukast added to inhaled beclomethasone in treatment of asthma. Montelukast/Beclomethasone Additivity Group. *Am J Respir Crit Care Med.* Dec 1999;160(6):1862-1868.
151. Lu S, Liu N, Dass SB, Reiss TF. A randomized study comparing the effect of loratadine added to montelukast with montelukast, loratadine, and beclomethasone monotherapies in patients with chronic asthma. *J Asthma.* Jun 2009;46(5):465-469.
152. Malmstrom K, Rodriguez-Gomez G, Guerra J, et al. Oral montelukast, inhaled beclomethasone, and placebo for chronic asthma. A randomized, controlled trial. Montelukast/Beclomethasone Study Group. *Ann Intern Med.* Mar 16 1999;130(6):487-495.
153. Meltzer EO, Lockey RF, Friedman BF, et al. Efficacy and safety of low-dose fluticasone propionate compared with montelukast for maintenance treatment of persistent asthma. *Mayo Clin Proc.* May 2002;77(5):437-445.
154. Ostrom NK, Decotiis BA, Lincourt WR, et al. Comparative efficacy and safety of low-dose fluticasone propionate and montelukast in children with persistent asthma. *J Pediatr.* Aug 2005;147(2):213-220.
155. Price D, Popov TA, Bjermer L, et al. Effect of montelukast for treatment of asthma in cigarette smokers. *J Allergy Clin Immunol.* Mar 2013;131(3):763-771.
156. Rand C, Bilderback A, Schiller K, Edelman JM, Hustad CM, Zeiger RS. Adherence with montelukast or fluticasone in a long-term clinical trial: results from the mild asthma montelukast versus inhaled corticosteroid trial. *J Allergy Clin Immunol.* Apr 2007;119(4):916-923.
157. Sorkness CA, Lemanske RF, Jr., Mauger DT, et al. Long-term comparison of 3 controller regimens for mild-moderate persistent childhood asthma: the Pediatric Asthma Controller Trial. *J Allergy Clin Immunol.* Jan 2007;119(1):64-72.
158. Stelmach I, Bobrowska-Korzeniowska M, Majak P, Stelmach W, Kuna P. The effect of montelukast and different doses of budesonide on IgE serum levels and clinical parameters in children with newly diagnosed asthma. *Pulm Pharmacol Ther.* 2005;18(5):374-380.
159. Szefler SJ, Baker JW, Uryniak T, Goldman M, Silkoff PE. Comparative study of budesonide inhalation suspension and montelukast in young children with mild persistent asthma. *J Allergy Clin Immunol.* Nov 2007;120(5):1043-1050.
160. Szefler SJ, Phillips BR, Martinez FD, et al. Characterization of within-subject responses to fluticasone and montelukast in childhood asthma. *J Allergy Clin Immunol.* Feb 2005;115(2):233-242.

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Copyright Drug Effectiveness Review Project. All rights reserved.

161. Wang L, Hollenbeak CS, Mauger DT, et al. Cost-effectiveness analysis of fluticasone versus montelukast in children with mild-to-moderate persistent asthma in the Pediatric Asthma Controller Trial. *J Allergy Clin Immunol.* Jan 2011;127(1):161-166, 166.e161.
162. Williams B, Noonan G, Reiss TF, et al. Long-term asthma control with oral montelukast and inhaled beclomethasone for adults and children 6 years and older. *Clin Exp Allergy.* Jun 2001;31(6):845-854.
163. Yurdakul AS, Taci N, Eren A, Sipit T. Comparative efficacy of once-daily therapy with inhaled corticosteroid, leukotriene antagonist or sustained-release theophylline in patients with mild persistent asthma. *Respir Med.* Dec 2003;97(12):1313-1319.
164. Zeiger RS, Bird SR, Kaplan MS, et al. Short-term and long-term asthma control in patients with mild persistent asthma receiving montelukast or fluticasone: a randomized controlled trial. *Am J Med.* Jun 2005;118(6):649-657.
165. Horner CC, Mauger D, Strunk RC, et al. Most nocturnal asthma symptoms occur outside of exacerbations and associate with morbidity. *J Allergy Clin Immunol.* Nov 2011;128(5):977-982.e971-972.
166. Zeiger RS, Szefler SJ, Phillips BR, et al. Response profiles to fluticasone and montelukast in mild-to-moderate persistent childhood asthma. *J Allergy Clin Immunol.* Jan 2006;117(1):45-52.
167. Kavuru M, Melamed J, Gross G, et al. Salmeterol and fluticasone propionate combined in a new powder inhalation device for the treatment of asthma: a randomized, double-blind, placebo-controlled trial. *J Allergy Clin Immunol.* Jun 2000;105(6 Pt 1):1108-1116.
168. Corren J, Korenblat PE, Miller CJ, O'Brien CD, Mezzanotte WS. Twelve-week, randomized, placebo-controlled, multicenter study of the efficacy and tolerability of budesonide and formoterol in one metered-dose inhaler compared with budesonide alone and formoterol alone in adolescents and adults with asthma. *Clin Ther.* May 2007;29(5):823-843.
169. Lundback B, Ronmark E, Lindberg A, et al. Control of mild to moderate asthma over 1-year with the combination of salmeterol and fluticasone propionate. *Respir Med.* Jan 2006;100(1):2-10.
170. Murray J, Rosenthal R, Somerville L, et al. Fluticasone propionate and salmeterol administered via Diskus compared with salmeterol or fluticasone propionate alone in patients suboptimally controlled with short-acting beta2-agonists. *Ann Allergy Asthma Immunol.* Oct 2004;93(4):351-359.
171. Nathan RA, Rooklin A, Schoaf L, et al. Efficacy and tolerability of fluticasone propionate/salmeterol administered twice daily via hydrofluoroalkane 134a metered-dose inhaler in adolescent and adult patients with persistent asthma: a randomized, double-blind, placebo-controlled, 12-week study. *Clin Ther.* Jan 2006;28(1):73-85.
172. Edin HM, Andersen LB, Schoaf L, Scott-Wilson CA, Ho SY, Ortega HG. Effects of fluticasone propionate and salmeterol hydrofluoroalkane inhalation aerosol on asthma-related quality of life. *Ann Allergy Asthma Immunol.* Apr 2009;102(4):323-327.
173. Nelson HS, Wolfe JD, Gross G, et al. Efficacy and safety of fluticasone propionate 44 microg/salmeterol 21 microg administered in a hydrofluoroalkane metered-dose inhaler as an initial asthma maintenance treatment. *Ann Allergy Asthma Immunol.* Sep 2003;91(3):263-269.
174. Noonan M, Rosenwasser LJ, Martin P, O'Brien CD, O'Dowd L. Efficacy and safety of budesonide and formoterol in one pressurised metered-dose inhaler in adults and

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adolescents with moderate to severe asthma: a randomised clinical trial. *Drugs.* 2006;66(17):2235-2254.

175. Shapiro G, Lumry W, Wolfe J, et al. Combined salmeterol 50 microg and fluticasone propionate 250 microg in the diskus device for the treatment of asthma. *Am J Respir Crit Care Med.* Feb 2000;161(2 Pt 1):527-534.

176. Nathan RA, Dorinsky P, Rosenzweig JR, Shah T, Edin H, Prillaman B. Improved ability to perform strenuous activities after treatment with fluticasone propionate/salmeterol combination in patients with persistent asthma. *J Asthma.* 2003;40(7):815-822.

177. Lazarus SC, Boushey HA, Fahy JV, et al. Long-acting beta2-agonist monotherapy vs continued therapy with inhaled corticosteroids in patients with persistent asthma: a randomized controlled trial. *Jama.* May 23-30 2001;285(20):2583-2593.

178. Deykin A, Lazarus SC, Fahy JV, et al. Sputum eosinophil counts predict asthma control after discontinuation of inhaled corticosteroids. *J Allergy Clin Immunol.* Apr 2005;115(4):720-727.

179. Nathan RA, Pinnas JL, Schwartz HJ, et al. A six-month, placebo-controlled comparison of the safety and efficacy of salmeterol or beclomethasone for persistent asthma. *Ann Allergy Asthma Immunol.* Jun 1999;82(6):521-529.

180. Simons FE. A comparison of beclomethasone, salmeterol, and placebo in children with asthma. Canadian Beclomethasone Dipropionate-Salmeterol Xinafoate Study Group. *N Engl J Med.* Dec 4 1997;337(23):1659-1665.

181. Verberne AA, Frost C, Roorda RJ, van der Laag H, Kerrebijn KF. One year treatment with salmeterol compared with beclomethasone in children with asthma. The Dutch Paediatric Asthma Study Group. *Am J Respir Crit Care Med.* Sep 1997;156(3 Pt 1):688-695.

182. Pearlman DS, Peden D, Condemi JJ, et al. Efficacy and safety of fluticasone propionate/salmeterol HFA 134A MDI in patients with mild-to-moderate persistent asthma. *J Asthma.* 2004;41(8):797-806.

183. Nathan RA, D'Urzo A, Blazhko V, Kaiser K. Safety and efficacy of fluticasone/formoterol combination therapy in adolescent and adult patients with mild-to-moderate asthma: a randomised controlled trial. *BMC polm.* 2012;12:67.

184. Meltzer EO, Kuna P, Nolte H, Nayak AS, Laforce C. Mometasone furoate/formoterol reduces asthma deteriorations and improves lung function. *Eur Respir J.* Feb 2012;39(2):279-289.

185. Nathan RA, Nolte H, Pearlman DS. Twenty-six-week efficacy and safety study of mometasone furoate/formoterol 200/10 microg combination treatment in patients with persistent asthma previously receiving medium-dose inhaled corticosteroids. *Allergy Asthma Proc.* Jul-Aug 2010;31(4):269-279.

186. Spencer S, Karner C, Cates CJ, Evans DJ. Inhaled corticosteroids versus long-acting beta(2)-agonists for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev.* 2011(12):CD007033.

187. Doherty DE, Tashkin DP, Kerwin E, et al. Effects of mometasone furoate/formoterol fumarate fixed-dose combination formulation on chronic obstructive pulmonary disease (COPD): results from a 52-week Phase III trial in subjects with moderate-to-very severe COPD. *Int J Chron Obstruct Pulmon Dis.* 2012;7:57-71.

188. Tashkin DP, Doherty DE, Kerwin E, et al. Efficacy and safety of a fixed-dose combination of mometasone furoate and formoterol fumarate in subjects with moderate

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to very severe COPD: results from a 52-week Phase III trial. *Int J Chron Obstruct Pulmon Dis.* 2012;7:43-55.

189. Edelman JM, Turpin JA, Bronsky EA, et al. Oral montelukast compared with inhaled salmeterol to prevent exercise-induced bronchoconstriction. A randomized, double-blind trial. Exercise Study Group. *Ann Intern Med.* Jan 18 2000;132(2):97-104.

190. Jenkins CR, Thien FC, Wheatley JR, Reddel HK. Traditional and patient-centred outcomes with three classes of asthma medication. *Eur Respir J.* Jul 2005;26(1):36-44.

191. Bateman ED, Kornmann O, Schmidt P, Pivovarova A, Engel M, Fabbri LM. Tiotropium is noninferior to salmeterol in maintaining improved lung function in B16-Arg/Arg patients with asthma. *J Allergy Clin Immunol.* Aug 2011;128(2):315-322.

192. Peters SP, Kunselman SJ, Icitovic N, et al. Tiotropium bromide step-up therapy for adults with uncontrolled asthma. *N Engl J Med.* Oct 28 2010;363(18):1715-1726.

193. Chong J, Karner C, Poole P. Tiotropium versus long-acting beta-agonists for stable chronic obstructive pulmonary disease. *Cochrane Database Syst Rev.* 2012;9.

194. Briggs DD, Jr., Covelli H, Lapidus R, Bhattycharya S, Kesten S, Cassino C. Improved daytime spirometric efficacy of tiotropium compared with salmeterol in patients with COPD. *Pulm Pharmacol Ther.* 2005;18(6):397-404.

195. Brusasco V, Hodder R, Miravitlles M, Korducki L, Towse L, Kesten S. Health outcomes following treatment for six months with once daily tiotropium compared with twice daily salmeterol in patients with COPD.[Erratum appears in Thorax. 2005 Feb;60(2):105]. *Thorax.* 2003;58(5):399-404.

196. Vogelmeier C, Hederer B, Glaab T, et al. Tiotropium versus salmeterol for the prevention of exacerbations of COPD. *N Engl J Med.* 2011;364(12):1093-1103.

197. Vogelmeier C, Kardos P, Harari S, Gans SJ, Stenglein S, Thirlwell J. Formoterol mono- and combination therapy with tiotropium in patients with COPD: a 6-month study. *Respir Med.* 2008;102(11):1511-1520.

198. Donohue JF, Fogarty C, Lotvall J, et al. Once-daily bronchodilators for chronic obstructive pulmonary disease: indacaterol versus tiotropium. *Am J Respir Crit Care Med.* 2010;182(2):155-162.

199. Buhl R, Dunn LJ, Disdier C, et al. Blinded 12-week comparison of once-daily indacaterol and tiotropium in COPD. *Eur Respir J.* 2011;38(4):797-803.

200. Decramer ML, Chapman KR, Dahl R, et al. Once-daily indacaterol versus tiotropium for patients with severe chronic obstructive pulmonary disease (INVIGORATE): A randomised, blinded, parallel-group study. *The Lancet Respiratory Medicine.* Vol 12013:524-533.

201. Hoogendoorn M, Al MJ, Beeh KM, et al. Cost-effectiveness of tiotropium versus salmeterol: the POET-COPD trial. *The European respiratory journal.* Mar 2013;41(3):556-564.

202. Bousquet J, Aubier M, Sastre J, et al. Comparison of roflumilast, an oral anti-inflammatory, with beclomethasone dipropionate in the treatment of persistent asthma. *Allergy.* Jan 2006;61(1):72-78.

203. Sin DD, Man J, Sharpe H, Gan WQ, Man SF. Pharmacological management to reduce exacerbations in adults with asthma: a systematic review and meta-analysis. *Jama.* Jul 21 2004;292(3):367-376.

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Copyright Drug Effectiveness Review Project. All rights reserved.

204. Ni Chroinin M, Lasserson TJ, Greenstone I, Ducharme FM. Addition of long-acting beta-agonists to inhaled corticosteroids for chronic asthma in children. *Cochrane Database of Systematic Reviews.* 2009;3.

205. Ducharme FM, Ni Chroinin M, Greenstone I, Lasserson TJ. Addition of long-acting beta2-agonists to inhaled steroids versus higher dose inhaled steroids in adults and children with persistent asthma. *Cochrane Database Syst Rev.* 2010;4:CD005533.

206. Jaeschke R, O'Byrne PM, Mejza F, et al. The safety of long-acting beta-agonists among patients with asthma using inhaled corticosteroids: systematic review and metaanalysis. *Am J Respir Crit Care Med.* Nov 15 2008;178(10):1009-1016.

207. Bateman ED, Bantje TA, Joao Gomes M, et al. Combination therapy with single inhaler budesonide/formoterol compared with high dose of fluticasone propionate alone in patients with moderate persistent asthma. *Am J Respir Med.* 2003;2(3):275-281.

208. Bateman ED, Jacques L, Goldfrad C, Atienza T, Mihaescu T, Duggan M. Asthma control can be maintained when fluticasone propionate/salmeterol in a single inhaler is stepped down. *J Allergy Clin Immunol.* Mar 2006;117(3):563-570.

209. Bergmann KC, Lindemann L, Braun R, Steinkamp G. Salmeterol/fluticasone propionate (50/250 microg) combination is superior to double dose fluticasone (500 microg) for the treatment of symptomatic moderate asthma. *Swiss Med Wkly.* Jan 24 2004;134(3-4):50-58.

210. Bisgaard H, Le Roux P, Bjamer D, Dymek A, Vermeulen JH, Hultquist C. Budesonide/formoterol maintenance plus reliever therapy: a new strategy in pediatric asthma. *Chest.* Dec 2006;130(6):1733-1743.

211. Bouros D, Bachlitzanakis N, Kottakis J, et al. Formoterol and beclomethasone versus higher dose beclomethasone as maintenance therapy in adult asthma. *Eur Respir J.* Sep 1999;14(3):627-632.

212. Busse W, Koenig SM, Oppenheimer J, et al. Steroid-sparing effects of fluticasone propionate 100 microg and salmeterol 50 microg administered twice daily in a single product in patients previously controlled with fluticasone propionate 250 microg administered twice daily. *J Allergy Clin Immunol.* Jan 2003;111(1):57-65.

213. Chuchalin A, Jacques L, Frith L. Salmeterol/fluticasone propionate via Diskus once daily versus fluticasone propionate twice daily in patients with mild asthma not previously receiving maintenance corticosteroids. *Clin Drug Investig.* 2008;28(3):169-181.

214. Condemi JJ, Goldstein S, Kalberg C, Yancey S, Emmett A, Rickard K. The addition of salmeterol to fluticasone propionate versus increasing the dose of fluticasone propionate in patients with persistent asthma. Salmeterol Study Group. *Ann Allergy Asthma Immunol.* Apr 1999;82(4):383-389.

215. de Blic J, Ogorodova L, Klink R, et al. Salmeterol/fluticasone propionate vs. double dose fluticasone propionate on lung function and asthma control in children. *Pediatr Allergy Immunol.* Dec 2009;20(8):763-771.

216. Gappa M, Zachgo W, Von Berg A, Kamin W, Stern-Strater C, Steinkamp G. Add-on salmeterol compared to double dose fluticasone in pediatric asthma: A double-blind, randomized trial (VIAPAED). *Pediatric Pulmonology.* 2009;44(11):1132-1142.

217. Greening AP, Ind PW, Northfield M, Shaw G. Added salmeterol versus higher-dose corticosteroid in asthma patients with symptoms on existing inhaled corticosteroid. Allen & Hanburys Limited UK Study Group. *Lancet.* Jul 23 1994;344(8917):219-224.

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218. Huchon G, Magnussen H, Chuchalin A, Dymek L, Gonod FB, Bousquet J. Lung function and asthma control with beclomethasone and formoterol in a single inhaler. *Respir Med.* Jan 2009;103(1):41-49.

219. Hyland ME, Crocker GR. Validation of an asthma quality of life diary in a clinical trial. *Thorax.* Jul 1995;50(7):724-730.

220. Ind PW, Dal Negro R, Colman NC, Fletcher CP, Browning D, James MH. Addition of salmeterol to fluticasone propionate treatment in moderate-to-severe asthma. *Respir Med.* May 2003;97(5):555-562.

221. Jarjour NN, Wilson SJ, Koenig SM, Laviolette M, Djukanovic R, et al. Control of airway inflammation maintained at a lower steroid dose with 100/50 mug of fluticasone propionate/saimeterol. *Journal of Allergy and Clinical Immunology.* 2006;118(1):44-52.

222. Jenkins C, Woolcock AJ, Saarelainen P, Lundback B, James MH. Salmeterol/fluticasone propionate combination therapy 50/250 microg twice daily is more effective than budesonide 800 microg twice daily in treating moderate to severe asthma. *Respir Med.* Jul 2000;94(7):715-723.

223. Johansson G, McIvor RA, D'Ambrosio FP, Gratziou C, James MH. Comparison of salmeterol/fluticasone propionate combination with budesonide in patients with mild-to-moderate asthma. *Clinical Drug Investigation.* 2001;21(9):633-642.

224. Juniper EF, Jenkins C, Price MJ, James MH. Impact of inhaled salmeterol/fluticasone propionate combination product versus budesonide on the health-related quality of life of patients with asthma. *Am J Respir Med.* 2002;1(6):435-440.

225. Juniper EF, Svensson K, O'Byrne PM, et al. Asthma quality of life during 1 year of treatment with budesonide with or without formoterol. *Eur Respir J.* Nov 1999;14(5):1038-1043.

226. Kelsen SG, Church NL, Gillman SA, et al. Salmeterol added to inhaled corticosteroid therapy is superior to doubling the dose of inhaled corticosteroids: a randomized clinical trial. *J Asthma.* Dec 1999;36(8):703-715.

227. Kips JC, O'Connor BJ, Inman MD, Svensson K, Pauwels RA, O'Byrne PM. A long-term study of the antiinflammatory effect of low-dose budesonide plus formoterol versus high-dose budesonide in asthma. *Am J Respir Crit Care Med.* Mar 2000;161(3 Pt 1):996-1001.

228. Lalloo UG, Malolepszy J, Kozma D, et al. Budesonide and formoterol in a single inhaler improves asthma control compared with increasing the dose of corticosteroid in adults with mild-to-moderate asthma. *Chest.* May 2003;123(5):1480-1487.

229. Lemanske RF, Jr., Mauger DT, Sorkness CA, et al. Step-up therapy for children with uncontrolled asthma receiving inhaled corticosteroids. *N Engl J Med.* Mar 18 2010;362(11):975-985.

230. Mitchell C, Jenkins C, Scicchitano R, Rubinfeld A, Kottakis J. Formoterol (Foradil) and medium-high doses of inhaled corticosteroids are more effective than high doses of corticosteroids in moderate-to-severe asthma. *Pulm Pharmacol Ther.* 2003;16(5):299-306.

231. Murray JJ, Church NL, Anderson WH, et al. Concurrent use of salmeterol with inhaled corticosteroids is more effective than inhaled corticosteroid dose increases. *Allergy Asthma Proc.* May-Jun 1999;20(3):173-180.

232. O'Byrne PM, Barnes PJ, Rodriguez-Roisin R, et al. Low dose inhaled budesonide and formoterol in mild persistent asthma: the OPTIMA randomized trial. *Am J Respir Crit Care Med.* Oct 15 2001;164(8 Pt 1):1392-1397.

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233. O'Byrne PM, Bisgaard H, Godard PP, et al. Budesonide/formoterol combination therapy as both maintenance and reliever medication in asthma. *Am J Respir Crit Care Med.* Jan 15 2005;171(2):129-136.
234. O'Byrne PM, Naya IP, Kallen A, Postma DS, Barnes PJ. Increasing doses of inhaled corticosteroids compared to adding long-acting inhaled beta2-agonists in achieving asthma control. *Chest.* Dec 2008;134(6):1192-1199.
235. Pauwels RA, Lofdahl CG, Postma DS, et al. Effect of inhaled formoterol and budesonide on exacerbations of asthma. Formoterol and Corticosteroids Establishing Therapy (FACET) International Study Group. *N Engl J Med.* Nov 13 1997;337(20):1405-1411.
236. Peters SP, Prenner BM, Mezzanotte WS, Martin P, O'Brien CD. Long-term safety and asthma control with budesonide/formoterol versus budesonide pressurized metered-dose inhaler in asthma patients. *Allergy Asthma Proc.* Sep-Oct 2008;29(5):499-516.
237. Schermer TR, Albers JM, Verblackt HW, Costongs RJ, Westers P. Lower inhaled steroid requirement with a fluticasone/salmeterol combination in family practice patients with asthma or COPD. *Fam Pract.* Apr 2007;24(2):181-188.
238. Vaessen-Verberne AA, van den Berg NJ, van Nierop JC, et al. Combination therapy salmeterol/fluticasone versus doubling dose of fluticasone in children with asthma. *Am J Respir Crit Care Med.* Nov 15 2010;182(10):1221-1227.
239. van Noord JA, Schreurs AJ, Mol SJ, Mulder PG. Addition of salmeterol versus doubling the dose of fluticasone propionate in patients with mild to moderate asthma. *Thorax.* Mar 1999;54(3):207-212.
240. Verberne AA, Frost C, Duiverman EJ, Grol MH, Kerrebijn KF. Addition of salmeterol versus doubling the dose of beclomethasone in children with asthma. The Dutch Asthma Study Group. *Am J Respir Crit Care Med.* Jul 1998;158(1):213-219.
241. Weinstein SF, Corren J, Murphy K, Nolte H, White M. Twelve-week efficacy and safety study of mometasone furoate/formoterol 200/10 microg and 400/10 microg combination treatments in patients with persistent asthma previously receiving high-dose inhaled corticosteroids. *Allergy Asthma Proc.* Jul-Aug 2010;31(4):280-289.
242. Woolcock A, Lundback B, Ringdal N, Jacques LA. Comparison of addition of salmeterol to inhaled steroids with doubling of the dose of inhaled steroids. *Am J Respir Crit Care Med.* May 1996;153(5):1481-1488.
243. Greenstone IR, Ni Chroinin MN, Masse V, et al. Combination of inhaled long-acting beta2-agonists and inhaled steroids versus higher dose of inhaled steroids in children and adults with persistent asthma. *Cochrane Database Syst Rev.* 2005(4):CD005533.
244. Rodrigo GJ, Plaza Moral V, Garcia Marcos L, Castro Rodriguez JA. Safety of regular use of long-acting beta agonists as monotherapy or added to inhaled corticosteroids in asthma: a systematic review (Provisional abstract). *Pulmonary Pharmacology and Therapeutics.* 2009;22(1):9-19.
245. Baraldi E, Rossi GA, Boner AL, Beclomethasone, Salbutamol Treatment for Children Study G. Budesonide in preschool-age children with recurrent wheezing. *New England Journal of Medicine.* Feb 9 2012;366(6):570-571; author reply 571.
246. Center for Drug Evaluation and Research. Dulera Formo-mometa medical review. 2010. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022518_dulera_toc.cfm.
247. Postma DS, O'Byrne PM, Pedersen S. Comparison of the effect of low-dose ciclesonide and fixed-dose fluticasone propionate and salmeterol combination on long-term asthma control. *Chest.* Feb 2011;139(2):311-318.

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248. Busse WW, O'Byrne PM, Bleecker ER, et al. Safety and tolerability of the novel inhaled corticosteroid fluticasone furoate in combination with the β2 agonist vilanterol administered once daily for 52 weeks in patients >=12 years old with asthma: a randomised trial. *Thorax.* Jun 2013;68(6):513-520.

249. O'Byrne PM, Bleecker ER, Bateman ED, et al. Once-daily fluticasone furoate alone or combined with vilanterol in persistent asthma. *European Respiratory Journal*2013.

250. Welsh EJ, Cates CJ, Poole P. Combination inhaled steroid and long-acting beta2-agonist versus tiotropium for chronic obstructive pulmonary disease. [Review] [30 refs]. *Cochrane Database Syst Rev.* 2010(5):CD007891.

251. Wedzicha JA, Calverley PMA, Seemungal TA, et al. The prevention of chronic obstructive pulmonary disease exacerbations by salmeterol/fluticasone propionate or tiotropium bromide. *Am J Respir Crit Care Med.* Jan 1 2008;177(1):19-26.

252. GlaxoSmithKline. A multicentre, randomised, double-blind, double dummy, parallel group 12-week exploratory study to compare the effect of the salmeterol/fluticasone propionate combination product (SERETIDE) 50/500mcg bd via the DISKUS/ACCUHALER inhaler with tiotropium bromide 18 mcg od via the Handihaler inhalation device on efficacy and safety in patients with chronic obstructive pulmonary disease (COPD). SCO40034. *GlaxoSmithKline Clinical Trial Register.* 2005.

253. GlaxoSmithKline. A Multicenter trial comparing the efficacy and safety of Umeclidinium/Vilanterol 62.5/25 mcg Once Daily with Tiotropium 18 mcg Once Daily over 24 weeks in Subjects with Chronic Obstructive Pulmonary disease (COPD). Study ZEP 1171152013.

254. Fang LZ, Liang X, Zhang JQ, et al. [Combination of inhaled salmeterol/fluticasone and tiotropium in the treatment of chronic obstructive pulmonary disease: a randomised controlled trial]. *Zhonghua jie he he hu xi za zhi = Zhonghua jiehe he huxi zazhi = Chinese journal of tuberculosis and respiratory diseases.* Vol 312008:811-814.

255. Study DB2113374 GSK Data on File submitted via Public Comment. Data available upon request from DERP. GSK 2014. 2014.

256. Ducharme F, Schwartz Z, Kakuma R. Addition of anti-leukotriene agents to inhaled corticosteroids for chronic asthma. *Cochrane Database of Systematic Reviews.* 2004(1).

257. Joos S, Miksch A, Szecsenyi J, et al. Montelukast as add-on therapy to inhaled corticosteroids in the treatment of mild to moderate asthma: a systematic review. *Thorax.* May 2008;63(5):453-462.

258. Price DB, Hernandez D, Magyar P, et al. Randomised controlled trial of montelukast plus inhaled budesonide versus double dose inhaled budesonide in adult patients with asthma. *Thorax.* Mar 2003;58(3):211-216.

259. Price DB, Swern A, Tozzi CA, Philip G, Polos P. Effect of montelukast on lung function in asthma patients with allergic rhinitis: analysis from the COMPACT trial. *Allergy.* Jun 2006;61(6):737-742.

260. Vaquerizo MJ, Casan P, Castillo J, et al. Effect of montelukast added to inhaled budesonide on control of mild to moderate asthma. *Thorax.* Mar 2003;58(3):204-210.

261. Jat GC, Mathew JL, Singh M. Treatment with 400 microg of inhaled budesonide vs 200 microg of inhaled budesonide and oral montelukast in children with moderate persistent asthma: randomized controlled trial. *Ann Allergy Asthma Immunol.* Sep 2006;97(3):397-401.

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262. Chauhan BF, Ben Salah R, Ducharme FM. Addition of anti-leukotriene agents to inhaled corticosteroids in children with persistent asthma. *Cochrane Database of Systematic Reviews*2013.

263. Calhoun WJ, Nelson HS, Nathan RA, et al. Comparison of fluticasone propionate-salmeterol combination therapy and montelukast in patients who are symptomatic on short-acting beta(2)-agonists alone. *Am J Respir Crit Care Med.* Sep 1 2001;164(5):759-763.

264. Maspero J, Guerra F, Cuevas F, et al. Efficacy and tolerability of salmeterol/fluticasone propionate versus montelukast in childhood asthma: A prospective, randomized, double-blind, double-dummy, parallel-group study. *Clin Ther.* Aug 2008;30(8):1492-1504.

265. Pearlman DS, White MV, Lieberman AK, et al. Fluticasone propionate/salmeterol combination compared with montelukast for the treatment of persistent asthma. *Ann Allergy Asthma Immunol.* Feb 2002;88(2):227-235.

266. Pedersen S, Maspero J, Gul N, Sharma R. Components of asthma control and treatment response of individual control criteria in children: analysis of the PEACE study. *Pediatr Pulmonol.* Dec 2011;46(12):1182-1188.

267. Ducharme FM, Lasserson TJ, Cates CJ. Long-acting beta2-agonists versus anti-leukotrienes as add-on therapy to inhaled corticosteroids for chronic asthma. *Cochrane Database Syst Rev.* 2006(4):CD003137.

268. Ducharme F. Addition to inhaled corticosteroids of long-acting beta2-agonists versus anti-leukotrienes for chronic asthma [Systematic Review]. *Cochrane Database Syst Rev.* 2011;8:8.

269. Bjermer L, Bisgaard H, Bousquet J, et al. Montelukast and fluticasone compared with salmeterol and fluticasone in protecting against asthma exacerbation in adults: one year, double blind, randomised, comparative trial. *Bmj.* Oct 18 2003;327(7420):891.

270. Fish JE, Israel E, Murray JJ, et al. Salmeterol powder provides significantly better benefit than montelukast in asthmatic patients receiving concomitant inhaled corticosteroid therapy. *Chest.* Aug 2001;120(2):423-430.

271. Ilowite J, Webb R, Friedman B, et al. Addition of montelukast or salmeterol to fluticasone for protection against asthma attacks: a randomized, double-blind, multicenter study. *Ann Allergy Asthma Immunol.* Jun 2004;92(6):641-648.

272. Nelson HS, Busse WW, Kerwin E, et al. Fluticasone propionate/salmeterol combination provides more effective asthma control than low-dose inhaled corticosteroid plus montelukast. *J Allergy Clin Immunol.* Dec 2000;106(6):1088-1095.

273. Pavord I, Woodcock A, Parker D, Rice L. Salmeterol plus fluticasone propionate versus fluticasone propionate plus montelukast: a randomised controlled trial investigating the effects on airway inflammation in asthma. *Respir Res.* 2007;8:67.

274. Ringdal N, Eliraz A, Pruzinec R, et al. The salmeterol/fluticasone combination is more effective than fluticasone plus oral montelukast in asthma. *Respir Med.* Mar 2003;97(3):234-241.

275. Ceylan E, Gencer M, Aksoy S. Addition of formoterol or montelukast to low-dose budesonide: an efficacy comparison in short- and long-term asthma control. *Respiration.* Nov-Dec 2004;71(6):594-601.

276. Juniper EF, Guyatt GH, Willan A, Griffith LE. Determining a minimal important change in a disease-specific Quality of Life Questionnaire. *Journal of Clinical Epidemiology.* 1994;47(1):81-87.

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Copyright Drug Effectiveness Review Project. All rights reserved.

277. Nelson HS, Nathan RA, Kalberg C, Yancey SW, Rickard KA. Comparison of inhaled salmeterol and oral zafirlukast in asthmatic patients using concommitant inhaled corticosteroids. *Medscape Gn Med.* 2001;3(3).
278. Deykin A, Wechsler ME, Boushey HA, et al. Combination therapy with a long-acting beta-agonist and a leukotriene antagonist in moderate asthma. *Am J Respir Crit Care Med.* Feb 1 2007;175(3):228-234.
279. Tattersfield AE, Town GI, Johnell O, et al. Bone mineral density in subjects with mild asthma randomised to treatment with inhaled corticosteroids or non-corticosteroid treatment for two years. *Thorax.* Apr 2001;56(4):272-278.
280. Medici TC, Grebski E, Hacki M, Ruegsegger P, Maden C, Efthimiou J. Effect of one year treatment with inhaled fluticasone propionate or beclomethasone dipropionate on bone density and bone metabolism: a randomised parallel group study in adult asthmatic subjects. *Thorax.* May 2000;55(5):375-382.
281. Kannisto S, Korppi M, Remes K, Voutilainen R. Adrenal suppression, evaluated by a low dose adrenocorticotropin test, and growth in asthmatic children treated with inhaled steroids. *J Clin Endocrinol Metab.* Feb 2000;85(2):652-657.
282. Macdessi JS, Randell TL, Donaghue KC, Ambler GR, van Asperen PP, Mellis CM. Adrenal crises in children treated with high-dose inhaled corticosteroids for asthma. *Med J Aust.* 2003;178(5):214-216.
283. Dunlop KA, Carson DJ, Shields MD. Hypoglycemia due to adrenal suppression secondary to high-dose nebulized corticosteroid. *Pediatr Pulmonol.* 2002;34(1):85-86.
284. Todd GR, Acerini CL, Ross-Russell R, Zahra S, Warner JT, McCance D. Survey of adrenal crisis associated with inhaled corticosteroids in the United Kingdom. *Arch Dis Child.* 2002;87(6):457-461.
285. Chylack LT, Jr., Gross GN, Pedinoff A. A randomized, controlled trial to investigate the effect of ciclesonide and beclomethasone dipropionate on eye lens opacity. *J Asthma.* Dec 2008;45(10):893-902.
286. Malo JL, Cartier A, Ghezzo H, et al. Skin bruising, adrenal function and markers of bone metabolism in asthmatics using inhaled beclomethasone and fluticasone. *Eur Respir J.* May 1999;13(5):993-998.
287. Lipworth BJ, Kaliner MA, LaForce CF, et al. Effect of ciclesonide and fluticasone on hypothalamic-pituitary-adrenal axis function in adults with mild-to-moderate persistent asthma. *Ann Allergy Asthma Immunol.* Apr 2005;94(4):465-472.
288. Erceg D, Nenadic N, Plavec D, Nogalo B, Turkalj M. Inhaled corticosteroids used for the control of asthma in a "real-life" setting do not affect linear growth velocity in prepubertal children. *Med Sci Monit.* Sep 2012;18(9):CR564-568.
289. Nelson HS, Weiss ST, Bleecker ER, Yancey SW, Dorinsky PM. The Salmeterol Multicenter Asthma Research Trial: a comparison of usual pharmacotherapy for asthma or usual pharmacotherapy plus salmeterol. *Chest.* Jan 2006;129(1):15-26.
290. Prescribing Information for Advair.
291. Prescribing Information for Serevent.
292. Prescribing Information for Foradil.
293. FDA Drug Safety Communication: Drug labels now contain updated recommendations on the appropriate use of long-acting inhaled asthma medications called Long-Acting Beta-Agonists (LABAs). 2010.

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294. Cates CJ, Lasserson TJ. Regular treatment with formoterol versus regular treatment with salmeterol for chronic asthma: serious adverse events. *Cochrane Database Syst Rev.* 2009(4):CD007695.
295. Cates CJ, Lasserson TJ. Regular treatment with formoterol and an inhaled corticosteroid versus regular treatment with salmeterol and an inhaled corticosteroid for chronic asthma: serious adverse events. *Cochrane Database Syst Rev.* 2010(1):CD007694.
296. Ruffin RE, Campbell DA, Chia MM. Post-inhalation bronchoconstriction by beclomethasone dipropionate: a comparison of two different CFC propellant formulations in asthmatics. *Respirology.* Jun 2000;5(2):125-131.
297. Cates CJ, Lasserson TJ. Regular treatment with formoterol versus regular treatment with salmeterol for chronic asthma: serious adverse events. *Cochrane Database Syst Rev.* 2013(5).
298. Janson C, Larsson K, Lisspers KH, et al. Pneumonia and pneumonia related mortality in patients with COPD treated with fixed combinations of inhaled corticosteroid and long acting B2 agonist: observational matched cohort study (PATHOS). *BMJ.* 2013;346:f3306.
299. Chauhan BF, Ducharme FM. Anti-leukotriene agents compared to inhaled corticosteroids in the management of recurrent and/or chronic asthma in adults and children. *Cochrane Database of Systematic Reviews.* 2012;5:CD002314.
300. Tashkin DP, Doherty DE, Kerwin E, et al. Efficacy and safety characteristics of mometasone furoate/formoterol fumarate fixed-dose combination in subjects with moderate to very severe COPD: findings from pooled analysis of two randomized, 52-week placebo-controlled trials. *Int J Chron Obstruct Pulmon Dis.* 2012;7:73-86.
301. Suissa S, Patenaude V, Lapi F, Ernst P. Inhaled corticosteroids in COPD and the risk of serious pneumonia. *Thorax.* Vol 682013:1029-1036.
302. Walters EH, Gibson PG, Lasserson TJ, Walters JA. Long-acting beta2-agonists for chronic asthma in adults and children where background therapy contains varied or no inhaled corticosteroid. *Cochrane Database Syst Rev.* 2007(1):CD001385.
303. US Food and Drug Administration. Safety Alert--Serevent (salmeterol xinafoate). 2003:available at www.fda.gov/medwatch/SAFETY/2003/servent.htm; accessed April 2017, 2008.
304. Israel E, Banerjee TR, Fitzmaurice GM, Kotlov TV, LaHive K, LeBoff MS. Effects of inhaled glucocorticoids on bone density in premenopausal women. *N Engl J Med.* Sep 27 2001;345(13):941-947.
305. Lazarus SC, Chinchilli VM, Rollings NJ, et al. Smoking affects response to inhaled corticosteroids or leukotriene receptor antagonists in asthma. *Am J Respir Crit Care Med.* Apr 15 2007;175(8):783-790.
306. Dombrowski MP. Pharmacologic therapy of asthma during pregnancy. *Obstet Gynecol Clin North Am.* 1997;24(3):559-574.
307. Schatz M. Interrelationships between asthma and pregnancy: a literature review. *J Allergy Clin Immunol.* 1999;103(2 Pt 2):S330-336.
308. FDA, Drug label (package insert) and approvel information; available at: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Search_Drug_Name.

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309. Rahimi R, Nikfar S, Abdollahi M. Meta-analysis finds use of inhaled corticosteroids during pregnancy safe: a systematic meta-analysis review. *Hum Exp Toxicol.* Aug 2006;25(8):447-452.
310. Blais L, Beauchesne MF, Lemiere C, Elftouh N. High doses of inhaled corticosteroids during the first trimester of pregnancy and congenital malformations. *J Allergy Clin Immunol.* Dec 2009;124(6):1229-1234 e1224.
311. Cossette B, Forget A, Beauchesne M-F, et al. Impact of maternal use of asthma-controller therapy on perinatal outcomes. *Thorax.* Vol 682013:724-730.
312. Taylor DR, Drazen JM, Herbison GP, Yandava CN, Hancox RJ, Town GI. Asthma exacerbations during long term beta agonist use: influence of beta(2) adrenoceptor polymorphism. *Thorax.* Sep 2000;55(9):762-767.
313. Bleecker ER, Yancey SW, Baitinger LA, et al. Salmeterol response is not affected by beta2-adrenergic receptor genotype in subjects with persistent asthma. *J Allergy Clin Immunol.* Oct 2006;118(4):809-816.
314. Tantisira KG, Silverman ES, Mariani TJ, et al. FCER2: a pharmacogenetic basis for severe exacerbations in children with asthma. *J Allergy Clin Immunol.* Dec 2007;120(6):1285-1291.
315. Palmer CN, Lipworth BJ, Lee S, Ismail T, Macgregor DF, Mukhopadhyay S. Arginine-16 beta2 adrenoceptor genotype predisposes to exacerbations in young asthmatics taking regular salmeterol. *Thorax.* Nov 2006;61(11):940-944.
316. Bleecker ER, Postma DS, Lawrance RM, Meyers DA, Ambrose HJ, Goldman M. Effect of ADRB2 polymorphisms on response to longacting beta2-agonist therapy: a pharmacogenetic analysis of two randomised studies. *Lancet.* Dec 22 2007;370(9605):2118-2125.
317. Bleecker ER, Nelson HS, Kraft M, Corren J, Ortega HG, et al. beta2-Receptor Polymorphisms in Patients Receiving Salmeterol with or without Fluticasone Propionate. *American Journal of Respiratory and Critical Care Medicine.* 2010;181:676-687.
318. Vogelmeier C, Fabbri LM, Rabe KF, et al. Effect of tiotropium vs. salmeterol on exacerbations: GOLD II and maintenance therapy naive patients. *Respir Med.* 2013;107(1):75-83.
319. Norjavaara E, de Verdier MG. Normal pregnancy outcomes in a population-based study including 2,968 pregnant women exposed to budesonide. *J Allergy Clin Immunol.* Apr 2003;111(4):736-742.

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ABBREVIATIONS

Abbreviaton	Term
AD	adjustable dosing
AQLQ	Asthma Quality of Life Questionnaire
ARF	Arformoterol
BDP	beclomethasone dipropionate
BUD	budesonide
CFC	chlorofluorocarbon
CI	confidence interval
CIC	ciclesonide
COPD	chronic obstructive pulmonary disease
DPI	dry powder inhaler
ED	emergency department
eFM	eformoterol
FD	fixed dosing
FEV1	forced expired volume in one second
FLUN	flunisolide
FF	fluticasone furoate
FP	fluticasone propionate
FM	formoterol
FVC	forced vital capacity
GINA	Global Initiative for Asthma
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HFA	hydrofluoroalkane
HPA	hypothalamo-pituitary-adrenal
HR	hazard ratio
IC	indacaterol
ICS	inhaled corticosteroid
IS	inhalation suspension
ITT	intent to treat
LABA	long-acting beta-2 agonist
LM	leukotriene modifiers
LOCF	last observation carried forward
LTRA	leukotriene receptor antagonist
LTSI	leukotriene synthesis inhibitor
MART	maintenance and reliever therapy
MDI	metered dose inhaler
MF	mometasone
ML	Montelukast
NAEPP	National Asthma Education and Prevention Program
NHLBI	National Heart, Lung and Blood Institute
NA	not applicable

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Abbreviaton	Term
NR	not reported
NS	not statistically significant
OCS	oral corticosteroids
OR	odds ratio
PEF	peak expiratory flow
pMDI	pressurized metered dose inhaler
QOL	quality of life
RF	roflumilast
RR	relative risk
SF-36	Medical Outcomes Study Short Form-36
SGRQ	St. George Respiratory Questionnaire
SM	salmeterol
SMART	Symbicort® maintenance and reliever therapy
SMD	standard mean difference (standard difference in means)
TAA	triamcinolone acetonide
TIB	tiotropium bromide
UMB	umeclidinium bromide
VI	vilanterol
WMD	weighted mean difference

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