Drug Class Review
on
Inhaled Corticosteroids

Final Report

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Richard A. Hansen, PhD
Gerald Gartlehner, MD, MPH
Kathleen N. Lohr, PhD
Shannon Carson, MD
Tim Carey, MD, MPH

RTI-UNC Evidence-based Practice Center
Cecil G. Sheps Center for Health Services Research
University of North Carolina at Chapel Hill
725 Airport Road, CB# 7590
Chapel Hill, NC 27599-7590

Tim Carey, MD, MPH, Director

CECIL G. sheps CENTER
FOR HEALTH SERVICES RESEARCH
UNIVERSITY OF NORTH CAROLINA AT CHAPEL HILL

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INTRODUCTION

A. Overview

Asthma and chronic obstructive pulmonary disease (COPD) are characterized by airflow limitation. Although asthma and COPD may co-exist in some individuals, each differs in pathogenesis and therapeutic response and should be considered different disease entities.[1] Asthma is characterized by episodic symptoms of airflow obstruction that are at least partially reversible.[2] In most cases, asthma is associated with a family history, early onset, varying symptoms, and diurnal variations. COPD differs from asthma in that airflow limitation is usually progressive, irreversible, and associated with an abnormal inflammatory response to noxious particles or gases; it is primarily caused by smoking.[3] Compared to the early onset of asthmatic symptoms for most patients, COPD usually is diagnosed mid-life or later. Symptomatic and spirometric classification of asthma and COPD severity are described in Table 1.

Table 1. Classification of asthma and COPD severity

	Daytime Symptoms	Nighttime Symptoms	FEV1* % Predicted
Asthma†			
Severe Persistent	Continual	Frequent	≤ 60%
Moderate Persistent	Daily	> 1 night/week	> 60% - < 80%
Mild Persistent	> 2/week but < 1/day	> 2 nights/month	≥ 80%
Mild Intermittent	≤ 2 days/week	≤ 2 nights/month	≥ 80%
COPD††			
Very Severe	-	-	< 30%
Severe	-	-	≥ 30% - < 50%
Moderate	-	-	≥ 50% - < 80%
Mild	-	-	≥ 80%

* FEV1 - Forced expiratory volume over 1 second
† National Asthma Education and Prevention Program: Expert Panel Report (update 2002)[4]
†† American Thoracic Society: Standards for the Diagnosis and Management of Patients with COPD (2004)[3]

Asthma and COPD are burdensome diseases. In the United States, more than 7 percent of adults and 12 percent of children are affected by asthma.[5] In 2000 asthma accounted for approximately 10.4 million outpatient visits, 1.8 million visits to the emergency department, 500,000 hospitalizations, and 4,487 deaths.[5] Although the prevalence of COPD in the US is slightly lower than the prevalence of asthma (approximately 5.5%), COPD accounts for a larger portion of health care utilization and mortality. In 2000 COPD accounted for approximately 20.7 million outpatient visits, 3.4 million visits to the emergency department, 6.3 million hospitalizations, and 116,513 deaths.[6]

Because asthma and COPD have different pathogenesis and therapeutic response, treatment guidelines differ for the two. Current treatment guidelines for asthma suggest that daily long-term control medications are necessary to prevent exacerbations and chronic symptoms. Inhaled corticosteroids (ICSs) are preferred because of their ability to control the underlying inflammatory processes. Leukotriene inhibitors/receptor blockers are alternative orally administered anti-inflammatory medications but are less effective than inhaled steroids.[7] Patients with moderate or severe disease usually require additional medication, such as a long-acting inhaled β_2-agonist. All patients with asthma

require a short-acting bronchodilator medication for managing acute symptoms or exacerbations.[4]

Current treatment guidelines for COPD are not as clear, in part because only smoking cessation is reliably shown to slow the rate of decline in lung function.[8] Some medications, however, can reduce or alleviate symptoms, increase exercise capacity, reduce the number and severity of exacerbations, and improve health status.[3] Although the Food and Drug Administration (FDA) has not approved ICSs as monotherapy for the treatment of COPD, they are believed to improve some clinical outcomes.[3] Bronchodilators – β-agonists, anticholinergic drugs, and methylxanthines – also are believed to provide some benefit and have been linked to improvements in lung function, dyspnea, exercise endurance, and health-related quality of life.[3] A recent review suggests that inhaled combinations of long-acting β_2-agonists and corticosteroids are slightly more efficacious than individual therapies.[9]

In general, ICSs are favored over oral corticosteroids because their anti-inflammatory effect is directed at the airways, which reduces the risk of unwanted systemic effects. Five different ICSs currently are available in the United States and Canada: beclomethasone dipropionate, budesonide, flunisolide, fluticasone propionate and triamcinolone acetonide; their generic name, trade name, manufacturer, dosage form with corresponding device, strength, and labeled uses are summarized in Table 2.

Product formulation and delivery device vary among products; ICSs can be delivered via nebulization, pressurized metered dose inhaler (MDI), or dry powder inhaler (DPI). MDIs historically have contained chlorofluorocarbons (CFCs), a substance known to harm public health and the environment by destroying ozone in the upper atmosphere; the Environmental Protection Agency has discouraged their use. The Montreal protocol calls for a ban on CFC-containing inhalers effective January 1, 2005, although it is possible that this date will be extended if all products do not have an alternative delivery device approved by this time.

Table 2. Inhaled corticosteroid trade names, manufacturers, formulations, and labeled uses

Generic Name	US Trade Name	Manufacturer	Dosage Form/Device	Strength	Labeled Uses
Beclomethasone dipropionate	QVAR®	Ivax / 3M	MDI (HFA)	40 mcg/puff 80 mcg/puff	Asthma (age ≥ 5 yrs) - Maintenance - Systemic corticosteroid reduction
	Vanceril®†	Schering-Plough	MDI*	42 mcg/puff 84 mcg/puff	Asthma (age ≥ 5 yrs) - Maintenance - Systemic corticosteroid reduction
Budesonide	Pulmicort Turbuhaler®	AstraZeneca	DPI	200 mcg/dose	Asthma (age ≥ 6 yrs) - Maintenance - Systemic corticosteroid reduction
	Pulmicort Respules®	AstraZeneca	Inhalation suspension	500 mcg 1,000 mcg 2,000 mcg	Asthma (age 1-8 yrs)

Flunisolide	AeroBid® AeroBid®-M	Forest / 3M	MDI* MDI-menthol*	250 mcg/puff	Asthma (age ≥ 6 yrs) - Maintenance - Systemic corticosteroid reduction
	Bronalide††	Boehringer Ingelheim (Canada)	MDI*	250 mcg/puff	Asthma (age ≥ 6 yrs) - Maintenance - Systemic corticosteroid reduction
Fluticasone propionate	Flovent®	GlaxoSmithKline	MDI*	44 mcg/puff 110 mcg/puff 220 mcg/puff	Asthma (age ≥ 4 yrs) - Maintenance - Systemic corticosteroid reduction
	Flovent® Rotadisk†††	GlaxoSmithKline	DPI – blister pack (4) for use in diskhaler	50 mcg/dose 100 mcg/dose 250 mcg/dose	Asthma (age ≥ 4 yrs) - Maintenance - Systemic corticosteroid reduction
	Flovent® Diskus†	GlaxoSmithKline	DPI – breath activated inhalation device	50 mcg/dose 100 mcg/dose 250 mcg/dose	Asthma (age ≥ 4 yrs) - Maintenance - Systemic corticosteroid reduction
Triamcinolone acetonide	Azmacort®	Aventis	MDI* – with spacer mouthpiece	100 mcg/dose	Asthma (age ≥ 6 yrs) - Maintenance - Systemic corticosteroid reduction

* Contains chlorofluorocarbons (CFCs), substances known to destroy ozone in the upper atmosphere
† Currently, not available from the manufacturer
†† Not available in the U.S.
††† Discontinued by manufacturer; supplies should be depleted by end of 1st quarter 2005 at which time Flovent® HFA will replace Flovent®
HFA – Hydrofluoroalkane propellant
MDI – Metered dose inhaler
DPI – Dry powder inhaler

ICS products differ in their pharmacokinetic (e.g., plasma half-life, volume of distribution, plasma clearance, and rate of first-pass metabolism) and pharmacodynamic properties (e.g., receptor affinity, dose-response characteristics, and duration of action) as well as in characteristics of the delivery device (e.g., output, particle size distribution, efficiency of lung delivery, and ease of use).[10] The use of spacers also can alter the amount of drug deposited per actuation. Although clinical comparative trials suggest 6-fold differences in potencies among available products, one review article suggests that currently no evidence supports differences in efficacy when administered at equipotent doses.[11] Some believe, however, that safety and tolerability may differ when used at equipotent doses. Additionally, product formulation and relative potencies lead to dramatic differences in the number of actuations (e.g., number of puffs) required to deliver equipotent doses.

No single study is sufficient to provide the information required to make clinical decisions about the superiority of one ICS over another.[10] Table 3 summarizes comparable dosing regimens recommended by the 2002 update of the National Asthma Education and Prevention Program (NAEPP) Expert Panel Report.[4]

Table 3. Estimated comparative daily dosages for inhaled corticosteroids[4]

Drug	Low Daily Dose		Medium Daily Dose		High Daily Dose	
	Adult	Child*	Adult	Child*	Adult	Child*
Beclomethasone CFC**	**168-504mcg**	**84-336mcg**	**504-840mcg**	**336-672 mcg**	**> 840mcg/d**	**> 672mcg**
42 mcg/puff	4-12 puffs/d	2-8 puffs/d	13-20 puffs/d	8-16 puffs/d	> 20 puffs/d	> 16 puffs/d
84 mcg/puff	2-6 puffs/d	1-4 puffs/d	7-10 puffs/d	4-8 puffs/d	> 10 puffs/d	> 8 puffs/d
beclomethasone HFA	**80-240mcg**	**80-160mcg**	**240-480mcg**	**160-320mcg**	**> 480mcg**	**> 320mcg**
40 mcg/puff	2-6 puffs/d	2-4 puffs/d	6-12 puffs/d	4-8 puffs/d	> 12 puffs/d	> 8 puffs/d
80 mcg/puff	1-3 puffs/d	1-2 puffs/d	3-6 puffs/d	2-4 puffs/d	> 6 puffs/d	> 4 puffs/d
budesonide CFC†	**400-1200mcg**	**400-800mcg**	**1200-2400mcg**	**800-1600mcg**	**> 2400mcg**	**> 1600mcg**
200 mcg/dose	2-6 puffs/d	2-4 puffs/d	6-12 puffs/d	4-8 puffs/d	> 12 puffs/d	> 8 puffs/d
budesonide DPI (Turbuhaler)	**200-600mcg**	**200-400mcg**	**600-1200mcg**	**400-800mcg**	**> 1200mcg**	**> 800mcg**
200 mcg/dose	1-3 puffs/d	1-2 puffs/d	3-6 puffs/d	2-4 puffs/d	> 6 puffs/d	> 4 puffs/d
budesonide suspension (Respules)		**500mcg**		**1000mcg**		**2000mcg**
0.25 mg/2ml inhalation		4 ml/d		8 ml/d		16 ml/d
0.5 mg/2ml inhalation		2 ml/d		4 ml/d		8 ml/d
Flunisolide	**500-1000mcg**	**500-750mcg**	**1000-2000mcg**	**750-1250mcg**	**> 2000mcg**	**> 1250mcg**
250 mcg/puff	2-4 puffs/d	2-3 puffs/d	4-8 puffs/d	4-5 puffs/d	> 8 puffs/d	> 5 puffs/d
Fluticasone MDI**	**88-264mcg**	**88-176mcg**	**264-660mcg**	**176-440mcg**	**> 660mcg**	**> 440mcg**
44 mcg/puff	2-6 puffs/d	2-4 puffs/d	6-15 puffs/d	4-10 puffs/d	> 15 puffs/d	> 10 puffs/d
110 mcg/puff	1-2 puffs/d	1 puff/d	2-6 puffs/d	1-4 puffs/d	> 6 puffs/d	> 6 puffs/d
220 mcg/puff	1 puff/d	NA	1-3 puffs/d	1-2 puffs/d	> 3 puffs/d	> 2 puffs/d
Fluticasone DPI (Rotadisk; Diskus)**	**100-300mcg**	**100-200mcg**	**300-600mcg**	**200-400mcg**	**> 600mcg**	**> 400mcg**
50 mcg/dose DPI	2-6 puffs/d	2-4 puffs/d	6-12 puffs/d	4-8 puffs/d	> 12 puffs/d	> 8 puffs/d
100 mcg/dose DPI	1-3 puffs/d	1-2 puffs/d	3-6 puffs/d	2-4 puffs/d	>6 puffs/d	> 4 puffs/d
250 mcg/dose DPI	1 puff/d	NA	1-2 puffs/d	1 puff/d	> 2 puffs/d	> 1 puff/d
Triamcinolone MDI**	**400-1000mcg**	**400-800mcg**	**1000-2000mcg**	**800-1200mcg**	**> 2000mcg**	**> 1200mcg**
100 mcg/puff	4-10 puffs/d	4-8 puffs/d	10-20 puffs/d	8-12 puffs/d	> 20 puffs/d	> 6 puffs/d

* Children ≤ 12 years of age

** Beclomethasone = beclomethasone dipropionate; fluticasone = fluticasone propionate; triamcinolone = triamcinolone acetonide

† Not available in the US; estimated dosing equivalency from Thorsson et al.[12] and Agertoft & Pedersen[13]

CFC – Contains chlorofluorocarbons; substances known to destroy ozone in the upper atmosphere

HFA – Hydrofluoroalkane propellant

MDI – Metered dose inhaler

DPI – Dry powder inhaler

Because potencies and delivery vary between ICSs, it is difficult to compare clinically equivalent drug, dose, and device combinations. We use the NAEPP comparative dosing (Table 3) to guide our evaluation of equivalent dosing; although on a milligram-for-milligram basis some studies may compare non-equivalent doses, we consider low, medium, and high doses of one product to be equivalent to low, medium, and high doses of a second product, respectively. The NAEPP comparative dosing estimates are not evidence-based but, rather, based on expert opinion. Consequently, we use this information merely as a guide for making drug-drug comparisons; we do not use this information to draw conclusions about the quality or external validity of a study. Furthermore, we do not consider the number of puffs or actuations required to deliver an equivalent dose even though this may be a factor in adherence and/or clinical decision-making.

B. Scope and key questions

The purpose of this review is to help policy makers and clinicians make informed choices about the use of ICSs in the treatment of asthma and COPD. We compare the efficacy, effectiveness, and safety (adverse events) of ICS medications; specifically, we focus on five ICSs (beclomethasone, budesonide, flunisolide, fluticasone, and triamcinolone) and their respective delivery methods. We examine the role of these agents in treating adult or pediatric outpatients with asthma and adult outpatients with COPD. Although some studies have demonstrated the efficacy of combination therapy,[7] we do not evaluate combination therapies where the effect of the ICS cannot be separately evaluated. Furthermore, we evaluate studies with only intermediate outcomes (e.g. respiratory parameters) only if no evidence on health outcomes is available. We do not consider the issue of patient convenience (i.e., some products may require 10 to 15 additional puffs per day to deliver an equipotent dose).

The participating organizations of the Drug Effectiveness Review Project (DERP) are responsible for ensuring that the scope of the review reflects the populations, drugs, and outcome measures of interest to their constituencies. The Oregon Evidence-based Practice Center initially prepared preliminary key questions identifying the populations, interventions, and outcomes of interest, and based the eligibility criteria for studies on them. Representatives of organizations participating in the DERP, in conjunction with experts in the fields of health policy, pulmonary medicine, pharmacotherapy, and research methods reviewed, revised, and approved the questions and outcome measures. The participating organizations approved the following key questions:

1. For outpatients with asthma or COPD, do inhaled corticosteroids differ in effectiveness?

2. For outpatients with asthma or COPD, do inhaled corticosteroids differ in safety or adverse events?

3. Are there subgroups of patients based on demographics (age, racial groups, and sex), other medications, comorbidities, or pregnancy for which one inhaled corticosteroid is more effective or associated with fewer adverse events than another?

The first key question specifically addresses the issue of effectiveness: do ICSs differ in their effects under real-life circumstances. This report addresses both efficacy (i.e., do ICSs differ in their effects under ideal or highly controlled circumstances) and effectiveness. We distinguish between *efficacy* studies and *effectiveness* studies; studies conducted in primary care or office-based settings that use less stringent eligibility criteria (i.e., broad range of population characteristics and disease severity) and long follow-up periods (i.e., greater than one year) are characterized as *effectiveness* studies. Studies conducted in highly selected populations over shorter periods of time are characterized as *efficacy* studies. We summarize the results of efficacy and effectiveness studies separately as the results of effectiveness studies are more applicable to the average patient than results from highly selected populations (i.e., efficacy studies).

For each of the three key questions we evaluate specific outcomes measures (where appropriate) as reported in Table 4. For efficacy and effectiveness we focus on randomized controlled trials and systematic reviews that compare one ICS to another; for safety we evaluate randomized controlled trials and observational studies. When sufficient head-to-head evidence was not available, we evaluate placebo-controlled evidence on health outcomes, specific adverse events, or efficacy/effectiveness for medications not already approved by the FDA for the stated disorder. We base dose and device comparisons on recommendations provided by the 2002 Expert Panel Report of the National Asthma Education and Prevention Program.[4] Studies are grouped by disease state (asthma or COPD), generalizing efficacy/effectiveness, safety, and tolerability only to the disease state for which it was studied.

Table 4. Outcome measures and study eligibility criteria

Outcome	Outcome Measures	Study Eligibility Criteria
Efficacy / Effectiveness	• Alleviation of symptoms - Rate of asthma episodes - COPD exacerbations - Days/nights with symptoms • Quality of life • Ability to participate in work, school, sports, or physical activity • Emergency department / urgent medical care visits • Hospitalization • Mortality • FEV1/PEFR (COPD only)	• Head-to-head randomized controlled clinical trials or meta-analyses comparing one ICS to another • When sufficient evidence was not available for head-to-head trials within a specific diagnostic group we evaluated placebo-controlled trials

Safety / Tolerability	• Overall adverse effect reports
	• Withdrawals because of adverse effects
	• Serious adverse event reports
	• Specific adverse events or withdrawals because of specific adverse events, including:
	  • *Osteoporosis*
	  • *Growth retardation*
	  • *Acute adrenal crisis*
	  • *Cataracts*
	  • *Ocular hypertension & open-angle glaucoma*
		• Head-to-head randomized controlled clinical trials or meta-analyses comparing one ICS to another
		
		• When sufficient evidence was not available for head-to-head trials within a specific diagnostic group, we evaluated:
		
		  • placebo-controlled trials
		  • observational studies

COPD – Chronic obstructive pulmonary disease
ICS – Inhaled corticosteroid
FEV1 – Forced expiratory volume over 1 second
PEFR – Peak expiratory flow rate

METHODS

A. Literature Search

We searched MEDLINE, Embase, The Cochrane Library, and the International Pharmaceutical Abstracts to identify articles relevant to each key question; we used either Medical Subject Headings (MeSH or MH) as search terms when available or key words

when appropriate. We combined terms for selected indications (asthma, chronic obstructive pulmonary disease), drug interactions, and adverse events with a list of five specific ICSs (beclomethasone, budesonide, flunisolide, fluticasone, and triamcinolone). We limited the electronic searches to "human" and "English language;" we searched sources from 1980 to 2004 (April) to delimit literature relevant to the scope of our topic (see Appendix A for complete search strategy).

We used the National Library of Medicine publication type tags to identify reviews, randomized controlled trials (RCTs), and meta-analyses; we also manually searched reference lists of pertinent and relevant review articles and letters to the editor. All citations were imported into an electronic database (ProCite5.0). Additionally, we hand-searched the Center for Drug Evaluation and Research (CDER) database to identify unpublished research submitted to the FDA.

Further, the Center for Evidence-based Policy at the Oregon Health and Science University (OHSU) contacted pharmaceutical manufacturers and invited them to submit dossiers, including citations, using a protocol available at www.ohsu.edu/drugeffectiveness. We received dossiers from two pharmaceutical companies.

Our searches found 488 citations, unduplicated across databases; we found an additional 392 articles from manually reviewing the reference lists of pertinent review articles. We included four studies originating from pharmaceutical dossiers; all other studies submitted from pharmaceutical dossiers were present in our other searches. The total number of citations included in the database was 880.

B. Study Selection

Two persons independently reviewed abstracts; if both reviewers agreed that the trial did not meet eligibility criteria, it was excluded. We obtained the full text of all remaining articles. Records were considered for exclusion if they did not meet pre-established eligibility criteria with respect to study design or duration, patient population, interventions, outcomes, and comparisons to ICS medications outside our scope of interest.

For this review, results from well-conducted, 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 one ICS with another. RCTs of at least 6 weeks' duration and an outpatient study population with a total sample size greater than 40 participants were eligible for inclusion. If head-to-head trials were available we did not examine placebo-controlled trials in detail. We viewed FDA approval as evidence for general efficacy; therefore, we did not review placebo-controlled trials for FDA-approved indications except when outcome measures assessed quality of life or other health outcomes that are not generally required for FDA approval and study duration was longer than 12 weeks.

If no head-to-head evidence was published, we reviewed placebo-controlled trials for indications of interest that had not already been approved by the FDA. We reviewed all placebo-controlled trials for indications without FDA approval to provide an overview of efficacy without taking drug equivalency into account. In other words, we did not evaluate the dosage of one drug relative to the dosage of an alternative drug in a different trial. High dosages or drugs with greater potency may yield greater treatment effects

compared to placebo than do low or medium dosages or drugs with lower potency. In addition, study populations, disease severity, and inhalation devices differ considerably across placebo-controlled trials. Comparisons of treatment effects across trials must, therefore, be made cautiously.

For adverse events we included both experimental and observational studies. For observational studies we included those with large sample sizes (> 100 patients) that lasted at least 1 year and reported an included outcome.

We initially reviewed studies with health outcomes as the primary outcome measures. Outcomes were alleviation of symptoms, functional capacity, emergency department or urgent care visits, hospitalization, and mortality. If no study measuring health outcomes was available for a particular indication or population subgroup, we included intermediate outcomes (e.g., changes in respiratory parameters). Safety outcomes included overall and specific adverse events (e.g., growth suppression, osteoporosis, hypothalamus-pituitary-adrenal axis suppression), withdrawals attributable to asthma attacks or COPD exacerbations, and drug interactions.

We included meta-analyses in the evidence report if we found them to be relevant for a key question and of good or fair methodological quality (based on the QUORUM[14] statement); we did not review individual studies if they were included in a high-quality meta-analysis. We excluded meta-analyses that were not based on a comprehensive systematic literature search or did not maintain the units of the studies in their statistical analyses. We checked our database to guarantee that our literature search had detected trials included in any meta-analyses that we discarded and obtained any missing articles.

If we could not find sufficient evidence of efficacy or effectiveness from at least one randomized, double-blinded head-to-head trial for an indication of interest, we reviewed placebo-controlled trials and controlled open-label trials for this specific indication. The strength of evidence of these results for comparing different drugs must be rated lower, however, than results from the most preferred type of trial. Findings of placebo-controlled trials are hard to compare across studies because disparate populations may respond differently.

We included in total 314 articles on an abstract level and retrieved 215 of those as full text articles for background information or to be reviewed for inclusion into the evidence report. Studies included as abstracts but not retrieved as full text articles were mainly placebo-controlled trials with respect to key questions or indications for which sufficient (i.e. at least one fair head-to-head trial) evidence from head-to-head trials was available.

C. Data Abstraction

We designed and used a structured data abstraction form to ensure consistency in appraisal for each study. Trained reviewers abstracted data from each study and assigned an initial quality rating. A senior reviewer read each abstracted article, evaluated the completeness of the data abstraction, and confirmed the quality rating. We abstracted the following data from included trials: study design, eligibility criteria, intervention (drugs, dose, duration), additional medications allowed, methods of outcome assessment, population characteristics, sample size, loss to follow-up, withdrawals attributed to adverse events, results, and adverse events reported. We recorded intention-to-treat results if available.

D. Quality Assessment

We assessed the internal validity (quality) of trials based on predefined criteria (Appendix B) developed by the US Preventive Services Task Force (ratings: good-fair-poor)[15] and the National Health Service Centre for Reviews and Dissemination.[16] External validity (generalizability) was assessed and reported but did not influence quality ratings.

Two independent reviewers assigned quality ratings; they resolved any disagreements by discussion and consensus or by consulting a third, independent party. Elements of internal validity assessment included, among others, randomization and allocation concealment, similarity of compared groups at baseline, use of intention-to-treat analysis, and overall and differential loss to follow-up.

Loss to follow-up was defined as the number of persons randomized who did not reach the endpoint of the study,[17] independent of the reason and the use of intention-to-treat analysis. We adopted no formal cut-off point of loss to follow-up since many studies defined withdrawals due to acute worsening of the disease as an outcomes measure.

Trials that had a fatal flaw in one or more categories were rated poor quality and not included in the analysis of the evidence report; trials that met all criteria were rated good quality. The majority of trials received a quality rating of fair. This includes studies that presumably fulfilled all quality criteria but did not report their methodologies to an extent that answered all our questions. Therefore, the "fair quality" category includes trials with quite different strengths and weaknesses and a range of validity.

RESULTS

We identified 880 citations from searches and reviews of reference lists. We identified four additional trials from dossiers submitted by pharmaceutical companies. In total we included 63 studies: 46 RCTs, 6 systematic reviews or meta-analyses, 15 observational studies, and one study of other design. Furthermore, we retrieved 61 articles for background information.

Reasons for exclusions were based on eligibility criteria or methodological criteria (Figure 1, QUORUM Tree). Six studies that met the eligibility criteria but were later rated as poor quality for internal validity were excluded from the analysis (Appendix C). The main reasons for a poor quality rating among RCTs were lack of adequate randomization and a high rate of post-randomization exclusion. Among meta-analyses lack of a systematic literature search was the main reasons for exclusion. A lack of systematic literature search leads to a selected spectrum of trials and, subsequently, to biased results. Similarly, pooling data of trials without maintaining the units of the individual trials during statistical analysis fails to preserve randomization and introduces bias and confounding.[17]

Of the 63 included studies, 54 percent were financially supported by pharmaceutical companies and 23 percent were funded by governmental agencies or independent funds. We could not determine a funding source for 23 percent of the studies included.

Studies reviewed for this report utilized a spectrum of abbreviations to describe drugs, tests, methods, symptoms, and measurement scales. Table 5 summarizes common abbreviations found in our review.

Table 5. Common abbreviations

Abbreviation	Full name
ACTH	Adrenocorticotropin
AHR	airway hyperresponsiveness
AQLQ	Asthma Quality of Life Questionnaire
BDP	beclomethasone dipropionate
BHR	bronchial hyper-responsiveness
BIS	budesonide inhalation suspension
BMD	bone mineral density
BUD	budesonide
CAT	conventional asthma therapy
CFC	Chlorofluorocarbon
CI	confidence interval
COOP/WONCA	functional assessment scales created by Dartmouth Primary Care Cooperative Info Group and World Organization of Family Doctors
Delta GV	changes in growth velocity
DPI	dry powder inhaler
ECG	Electrocardiogram
ED	emergency department
EH	Easyhaler
EIA	exercise-induced asthma
FEF	forced expiratory flow
FEV1	forced expired volume in one second
FLUN	flunisolide
FLUP	fluticasone propionate
FSII	Functional Status IIR Questionnaire
FVC	forced vital capacity
GOLD	Global initiative in Obstructive Lung Disease
HFA	Hydrofluoroalkane
HPA	hypothalamo-pituitary-adrenal function
HR	hazard ratio
HRQL	health-related quality of life
ICS	inhaled corticosteroid
ITT	intent to treat
LABA	long-acting beta-agonist
LM	leukotriene modifiers
LOCF	last observation carried forward
LTRA	leukotriene receptor antagonist
LWA-20	Living with Asthma Questionnaire
MDI	metered dose inhaler
MED	minimal effective dose
NHLBI	National Heart, Lung and Blood Institute
NR	not reported
N/A	not applicable
OCS	oral corticosteroid
OR	odds ratio
PEF	peak expiratory flow
PEFR	peak expiratory flow rate
PFM	peak flow meter
PMDI	pressurized metered dose inhaler
QOL-PAC	Quality of Life of Parents of Asthmatic Children Questionnaire
RR	relative risk
SF-36	Medical Outcomes Study Short Form-36

SGRQ	St. George Respiratory Questionnaire
SLP-C	Sleep Scale Children Questionnaire
SM	salmeterol
TIC	Turbuhaler Inhalation Computer
TRIA	triamcinolone acetonide
VC	vital capacity
WMD	weighted mean differences

Key Question 1
For outpatients with asthma or COPD, do inhaled corticosteroids differ in effectiveness?

We included 29 RCTs and three meta-analyses; 19 of the RCTs were head-to-head trials and 10 were placebo-controlled trials. No study was characterized as an effectiveness trial; all included efficacy studies were conducted in narrowly defined populations and/or were limited to less than one year of follow-up.

I. Asthma

The following drugs are currently approved by the FDA for the treatment of asthma in adults and pediatrics: beclomethasone, budesonide, fluticasone, flunisolide, and triamcinolone. Budesonide is the only ICS approved for use in children younger than 4 years of age; no ICS is approved for children younger than one year of age.

A. Description of studies

One meta-analysis[18] and 19 RCTs[19,20-23,24,25,26,27,28-34,35-37] compared the efficacy of one ICS to another for treating patients with asthma (Table 6 and Evidence Table 1). One trial compared beclomethasone to budesonide; one meta-analysis and six RCTs compared beclomethasone to fluticasone; two RCTs compared beclomethasone to triamcinolone; two RCTs compared budesonide to flunisolide; one meta-analysis and five RCTs compared budesonide to fluticasone; two RCTs compared fluticasone to triamcinolone. Based on National Asthma Education and Prevention Program equipotent dose estimates (Table 3), 15 head-to-head trials (79%) compared equipotent doses and 4 trials (21%) compared non-equipotent doses.[25,27,30,31,34,36,37] Of the 15 head-to-head trials that compared equivalent doses, 4 (27%) compared high dose to high dose, 7 (47%) compared medium dose to medium dose, 3 (20%) compared low dose to low dose; and 1 trial compared both low and medium doses. The most commonly used delivery devices were pressurized MDIs; nine studies (47%) compared MDI to MDI; four studies (21%) compared DPI to DPI; four studies (21%) compared MDI to DPI; two studies (11%) compared nebulized therapy.

Ten placebo-controlled studies provided additional evidence on quality of life, functional capacity, and hospitalizations; three studies compared medium or low doses of beclomethasone to placebo;[38,39,40] three studies compared low doses of budesonide to placebo;[41,42,43] four placebo controlled studies compared a range of different fluticasone doses to placebo.[44-47] Studies used a variety of delivery devices including nebulizers, face masks, MDIs, and DPIs.

Three observational studies,[48,49,50] not eligible for inclusion in our review of efficacy, assessed the risk of life-threatening asthma attacks, hospitalizations, or all-cause mortality in ICS-treated populations compared to non-ICS-treated populations. Overall, ICS users were at lower risk for fatal or near-fatal asthma attacks and were less likely to

have an asthma-related hospitalization. The ICS protective effect was strongest when observed at high doses used over a longer period of time.[48] However, because ICS use was addressed as a class, this does not provide evidence of comparative efficacy. Although these studies provide fair[50] to good[48,49] evidence on the relationship between ICS use and asthma-related hospitalizations or death, they do not contribute to comparative assessments.[49]

B. Study populations

Nineteen RCTs compared one ICS to another for a total of 5,391 patients. Most studies were conducted in adult populations (persons 18 to 80 years of age); five studies were conducted in a pediatric population (persons 4 to 19 years of age) and four studies were conducted in a mixed pediatric and adult population (age ≥ 12 years). Asthma severity varied from mild to severe; eight studies (42%) were conducted in patients with mild persistent to moderate persistent asthma, three (16%) in patients with mild persistent to severe persistent asthma, two (11%) in patients with moderate persistent asthma, three (16%) in patients with moderate persistent to severe persistent asthma, and three (16%) in patients classified as having severe persistent asthma. Smoking status was not reported among pediatric populations. Five of 14 studies (36%) that evaluated an adult population excluded individuals with a recent or current history of smoking; eight (57%) allowed participants to smoke, and one (7%) did not report smoking status. Among the studies that allowed and reported smoking, 10 to 24 percent of participants were characterized as smokers.

We included 10 placebo-controlled trials[38,39-44,45,46,47] that evaluated specific health outcomes not commonly reported in head-to-head trials. Four trials (40%) were conducted in a pediatric population, two (20%) in an adult population (≥ 18 years), and four (40%) in a mixed population of adolescents and adults. Most trials were conducted in a population with mixed asthma severity; three (30%) were conducted specifically in a population with severe persistent asthma. Most placebo-controlled studies included in our review either did not allow smoking or did not report the number of smokers enrolled in the study.

In both head-to-head and placebo-controlled trials other asthma medications commonly were allowed if maintained at a constant dose; all trials allowed the use of a short-acting β-agonist. Most trials excluded patients who required a change in concomitant asthma medications or needed a burst of oral corticosteroids. Two head-to-head trials[19] and one placebo-controlled trial[40] conducted in pediatric populations allowed concomitant treatment with prednisone (1 mg/kg body weight); one study[40] excluded patients who required more than one course of prednisone per month or more than four courses during the year. None of the studies that allowed transient use of oral corticosteroids reported oral steroid use as an outcome measure. One placebo-controlled trial[51,46] was conducted in an oral-steroid-dependent population and reported oral corticosteroid sparing differences between ICS- and non-ICS-treated patients.

C. Outcome measures

In the majority of studies, the primary endpoints were changes from baseline in forced expiratory volume over one second (FEV1 (L)) or peak expiratory flow (PEF (L/min)). We view these measures of lung function as intermediate outcomes because

they are not always reliably related to changes in health outcomes.[52] The health outcomes we review were measured often as secondary outcomes; consequently, studies may at times be limited in their ability to detect clinically relevant differences in health outcomes.

Health outcome measures frequently included patient-reported asthma symptom scores and β-agonist use. The most frequently used symptom scale assessed symptoms on a 4-point scale; scale design and definition were not the same in all trials and are difficult to compare. Some studies characterized symptoms and rescue medication use as symptom-free days or β-agonist-free days; some studies recorded the number of nighttime awakenings or the quality of sleep. Most studies did not assess quality of life; studies that did measure quality of life commonly used the Asthma Quality of Life Questionnaire (AQLQ).[53] Several studies used general health status instruments such as the Medical Outcomes Study Short Form-36 (SF-36) to measure quality of life.

Commonly, assessments were made through the use of daily patient diaries. Physician assessments generally were limited to lung function tests (e.g., FEV1 or forced vital capacity (FVC)) or laboratory parameters (e.g., serum cortisol). All studies assessing quality of life used validated instruments or measurement scales.

D. Methodological quality

The overall quality of the 19 head-to-head trials and 10 placebo-controlled trials included in our review was fair to good. Only one efficacy study was excluded because of a poor quality rating for internal validity, which may reflect poor reporting rather than poor internal validity. Most trials received a quality rating of fair. The method of randomization and allocation concealment was specified only rarely. Loss to follow-up commonly was reported, although the number of randomized participants lacking an endpoint assessment varied between studies. Most trials (80%) used an ITT analysis; two (8%) did not use an ITT analysis and we could not ascertain if three (12%) used an ITT analysis.

E. Sponsorship

Of 19 head-to-head trials, 10 placebo-controlled trials, and 1 systematic review, 20 (67%) were funded by pharmaceutical companies; seven trials (23%) did not report the source of funding but at least one author had a primary affiliation with a pharmaceutical company. Only three studies (10%) were funded primarily by sources other than pharmaceutical companies. We were unable to identify a relationship between sponsorship and study quality or outcomes; because of the large number of industry-funded trials a relationship likely would not be apparent.

F. Head-to-head comparisons

Beclomethasone vs. budesonide

One fair-rated RCT compared beclomethasone to budesonide.[19,19] This Italian study randomized 127 children and adolescents ages 6 to 14 years with mild-to-moderate persistent asthma to 800 mcg/day beclomethasone or 1,000 mcg/day budesonide. Both drugs were administered twice daily via a Pari Boy® (Pari GmbH, Starnberg, Germany) nebulizer. Although NAEPP comparative dosing estimates are not available for nebulized beclomethasone, assuming that the complete dose of beclomethasone was

available upon nebulization (i.e., drug loss at mouthpiece does not need to be accounted for), compared doses were equivalent. The study duration was 4 weeks; loss to follow-up was 7 percent with a 10 percentage point differential loss to follow-up between beclomethasone-treated and budesonide-treated patients (beclomethasone 12%; budesonide 2%). Oral prednisone (1 mg/kg body weight) was allowed if inhaled therapy did not maintain acceptable control of asthma symptoms; the authors did not report the number of participants requiring oral prednisone. At endpoint there were no differences in β-agonist use, nocturnal awakenings, diurnal dyspnea, or patient- or parent-rated asthma symptoms on a 0- to 4-point scale between beclomethasone- and budesonide-treated patients.

Beclomethasone vs. flunisolide

We did not identify any head-to-head trial that compared beclomethasone to flunisolide.

Beclomethasone vs. fluticasone

One systematic review compared beclomethasone and budesonide to fluticasone;[18] of the 42 studies included in this review, 20 (48%) compared beclomethasone to fluticasone. Comparisons were stratified by oral corticosteroid use, study design, and fluticasone: beclomethasone/budesonide dose ratios of 1:2 or 1:1. The pooled treatment effect of fluticasone was compared to the pooled treatment effect for beclomethasone and budesonide. For the parallel group studies conducted at dose ratios of 1:2 or 1:1, individual studies and pooled estimates suggest no difference in asthma symptoms, β-agonist use, or the number of asthma exacerbations. Although we rated the quality of this review as good, the comparison of fluticasone to the combined effect of beclomethasone and budesonide limits possible conclusions regarding the *specific* comparison of beclomethasone to fluticasone.

One good-rated[20] and six fair-rated[21,22-26] head-to-head trials comparing beclomethasone to fluticasone met the inclusion/exclusion criteria for our review. The single good-rated trial compared beclomethasone 400 mcg/day (MDI-HFA) to fluticasone 400 mcg/day (MDI) in 172 adults ages 18 to 65 years with mild to severe asthma; both doses were considered of medium potency.[20] This 6-week trial was conducted in 30 general practice sites in the United Kingdom and the Republic of Ireland; overall loss to follow-up was 7.6 percent. At endpoint improvement in asthma symptoms (6-point scale), β-agonist use, sleep disturbance scores (5-point scale), and asthma-related quality of life (AQLQ) were not significantly different between beclomethasone- and fluticasone-treated patients.

Six fair-rated RCTs compared beclomethasone to fluticasone.[21-26] Only one trial was conducted exclusively in a population of children and adolescents;[23] most trials were conducted in populations over the age of 12 years. Asthma severity ranged from mild- to severe-persistent with the majority of trials conducted in populations with moderate or severe asthma. Doses ranged from low to high; all studies compared equipotent doses of beclomethasone and fluticasone. In most trials study duration was 6 weeks or less; one study followed participants for 12 weeks[26] and one study followed participants for 1 year.[22] All trials assessed β-agonist use and asthma symptoms or symptom score.

The majority of trials reported no difference between beclomethasone- and fluticasone-treated patients in asthma symptom score, the percentage of symptom-free days and nights, and β-agonist use. Four trials found fluticasone to be significantly better than beclomethasone on at least one evaluated outcome measure: percentage without asthma exacerbation ($P < 0.05$),[22] β-agonist free days ($P = 0.01$),[23] nighttime symptoms ($P < 0.05$),[25] days without symptoms ($P = 0.027$),[26] asthma symptom score ($P = 0.024$),[26] and β-agonist use ($P = 0.004$).[26] One trial reported significantly more β-agonist free days among beclomethasone-treated patients compared to fluticasone-treated patients ($P = 0.05$).[24] One trial reported no difference in exercise symptoms[23] and one trial reported no difference in nighttime awakenings between beclomethasone- and fluticasone-treated patients.[26]

Beclomethasone vs. triamcinolone

One good-rated[27] and one fair-rated[29] study compared beclomethasone to triamcinolone. The good-rated 16-center American study compared low-dose beclomethasone (336 mcg/day) without spacer to low-dose triamcinolone (800 mcg/day) with built-in spacer and placebo in 329 adults ages 18 to 65 years over 8 weeks; doses were equivalent and concomitant medications, other than β-agonists, were not allowed. Overall loss to follow-up was 24.6 percent; significantly more placebo-treated patients did not complete the study (beclomethasone 14.5%, triamcinolone 16.8%, placebo 42%). No significant differences in β-agonist use or nighttime awakenings due to asthma symptoms were reported for the active treatments. Compared to beclomethasone-treated patients, significantly more triamcinolone-treated patients reported asthma symptoms ($P = 0.028$).

A fair-rated American study compared low-dose beclomethasone (336 mcg/day) to low-dose triamcinolone (800 mcg/day) and placebo in 17 asthma and allergy centers.[29] A total of 339 adults ages 18 to 65 with mild to moderate asthma who currently were using an ICS were randomized to 8 weeks of treatment with beclomethasone, triamcinolone, or placebo. Other than albuterol for rescue no other asthma medications were permitted. Loss to follow-up was 33.9 percent with the highest number of participants lost from the placebo group (beclomethasone 24.6%, triamcinolone 23.4%, placebo 53.5%). No differences in symptom reduction (4-point scale) between beclomethasone- and triamcinolone-treated patients were reported; both were significantly better than placebo ($P < 0.01$). Additionally, no differences in weekly β-agonist use among beclomethasone-, triamcinolone-, and placebo-treated patients were reported.

Budesonide vs. flunisolide

Two fair-rated trials compared budesonide to flunisolide; one 4 week multicenter Italian study compared nebulized doses of budesonide (1000 mcg/day) to flunisolide (1000 mcg/day) in 133 children and adolescents ages 6 to 14 years with mild- to moderate-persistent asthma;[30] one 6 week multicenter Canadian study compared budesonide (1200 mcg/day) to flunisolide (1500 mcg/day) in 154 adults with moderate persistent asthma.[28] Although NAEPP comparative dosing estimates are not available to characterize the nebulized flunisolide doses utilized in the Italian study, in general, doses were equivalent in both studies. The Italian study allowed oral prednisone (1 mg/kg body

weight) for breakthrough asthma symptoms (frequency of oral prednisone use was not reported) while the Canadian study did not allow oral steroids. At endpoint no significant differences were reported in either study between budesonide- and flunisolide-treated patients in improvement in asthma symptom scores or β-agonist use. One study reported a significantly greater reduction in nocturnal awakenings for flunisolide-treated patients ($P < 0.001$) than for budesonide-treated patients.[30]

Budesonide vs. fluticasone

One previously discussed systematic review for the comparison of beclomethasone with fluticasone also compared budesonide to fluticasone.[18] Twenty-one studies compared fluticasone to budesonide, although pooled analyses reflect the comparison of fluticasone with the combined effect of beclomethasone and budesonide. Pooled analyses reflect no difference between fluticasone and beclomethasone/budesonide in asthma symptoms, β-agonist use, or the number of asthma exacerbations. Conclusions regarding the specific comparison of budesonide with fluticasone are limited.

Five fair-rated head-to-head trials compared budesonide to fluticasone;[31-35] two were conducted in children and adolescent populations;[32,34] four were conducted in patients with moderate to severe asthma[31-33,35] and one study randomized patients with less severe asthmatic symptoms.[34] Two trials evaluated nonequivalent doses; in both fluticasone was given at a higher dose than budesonide.[31,34] All but one study[31] used a dry-powder formulation of both budesonide and fluticasone. Two trials were 8 weeks or less in duration;[31,34] one was 12 weeks,[35] one 20 weeks,[32,32] and one 24 weeks.[33] All trials assessed β-agonist use and asthma symptoms or symptom score.

Two trials (40%) reported no difference between budesonide- and fluticasone-treated patients in asthma symptom score, the percentage of symptom-free days and nights, and β-agonist use. Three trials (60%) found fluticasone to be significantly better than budesonide on at least one evaluated outcome measure; symptom-free days ($P < 0.05$),[31,33] nighttime β-agonist use ($P < 0.05$),[31] β-agonist-free days ($P = 0.02$),[33] days absent from work ($P = 0.012$),[33] and disruption in physical activity ($P = 0.03$).[34] Two of the three trials that found fluticasone to be superior to budesonide on at least one outcome measure utilized higher doses of fluticasone.[31,34] Given the mixed evidence for this comparison and the fact that two of the three trials that reported significant differences were conducted with more potent doses of fluticasone, evidence favors no differences between equipotent doses of budesonide and fluticasone. Additionally, one trial reported no differences between budesonide and fluticasone in sleep disturbances or days of school missed.[34]

Budesonide vs. triamcinolone

We did not identify any head-to-head trial that compared budesonide to triamcinolone.

Flunisolide vs. fluticasone

We did not identify any head-to-head trial that compared flunisolide to fluticasone.

Flunisolide vs. triamcinolone

We did not identify any head-to-head trial that compared flunisolide to triamcinolone.

Fluticasone vs. triamcinolone

Two similarly designed fair-rated trials conducted in 24 outpatient centers compared fluticasone (500 mcg/day) to triamcinolone (800 mcg/day) and placebo over 24 weeks;[36,37] both were conducted in moderate to severe patients with asthma age 12 years or older.[36,37] Fluticasone was administered via DPI; triamcinolone via MDI with attached spacer. In both trials, fluticasone doses were characterized as medium and triamcinolone doses were characterized as low. Patients were allowed to continue theophylline at fixed doses. Overall loss to follow-up was greater than 50 percent in both trials; one trial had more than a 15 percentage point differential loss to follow-up between fluticasone- and triamcinolone-treated patients.[37]

No differences were found at endpoint between fluticasone- and triamcinolone-treated patients in asthma symptom scores (4-point scale). Fluticasone-treated patients consistently had less β-agonist use than triamcinolone-treated patients.[36,37] Inconsistent evidence supports fewer nighttime awakenings for fluticasone-treated patients compared to triamcinolone-treated patients.[37] One trial reported significantly better AQLQ scores for fluticasone-treated patients compared to triamcinolone-treated patients.[37] Significant differences favoring fluticasone over triamcinolone are not unexpected given the more potent doses of fluticasone utilized in these studies.

G. Placebo-controlled trials

We included 10 placebo-controlled trials[38,39-44,45-47] that evaluated health outcomes not commonly reported in the head-to-head comparisons. One trial[40,45] reported functional capacity (e.g., ability to participate in work, school, sports, or physical activity); seven[38,39,42,44,45-47] reported quality of life; two[41,45] measured sleep disturbance; and one[41] measured time parents spend caring for their child's asthma and hospital admissions. A list of excluded placebo-controlled trials is noted in Appendix D.

Beclomethasone vs. placebo

We identified one good-rated multinational trial[38] and one fair-rated American trial[39] that measured health-related quality of life using the AQLQ. Both trials reported significantly better scores on each of the four domains of the AQLQ for beclomethasone-treated patients compared to placebo-treated patients ($P < 0.003$). Additionally, we identified one placebo-controlled trial that assessed functional impairment and school days missed because of asthma.[40] This 12-month trial reported diary card assessment of school absence and activities affected by asthma in 241 children ages 6 to 14 years randomized to beclomethasone, salmeterol, or placebo. The percentage of children missing school because of asthma and the percentage of days with activities affected by asthma were not statistically different between beclomethasone- and placebo-treated patients.

Budesonide vs. placebo

Two good- and one fair-rated placebo-controlled trials assessed outcome measures not commonly reported in head-to-head studies; one[42,54] assessed quality of life (AQLQ), two[41,43] reported hospitalizations attributable to asthma, and one[43] assessed symptoms of depression. One[41] trial reported parental sleep disturbance and time caring for a child's asthma. Compared to placebo, patients treated with budesonide had significantly better quality of life,[42] fewer asthma-related hospitalizations,[41,43] and lower depression scores (fewer symptoms of depression).[43] Parents of asthmatic children treated with budesonide reported fewer parental sleep disturbances and less time at night caring for their child's asthma.[41]

Flunisolide vs. placebo

`We did not identify any trials comparing flunisolide to placebo that measured health-related quality of life, functional impairment, or hospitalizations.

Fluticasone vs. placebo

`Four trials comparing fluticasone to placebo assessed quality of life, health status, or functional capacity.[44,45-47] One trial[45] was conducted in a pediatric population, and three[44,46,47] in mixed adolescent and adult populations. In all trials fluticasone performed significantly better than placebo on select outcome measures; health-related quality of life (AQLQ, quality of life of parents with asthmatic children questionnaire (QOL-PAC)),[45,47] general health status (SF-36, living with asthma questionnaire (LWA-20)),[44,47] and functional capacity (functional status IIR questionnaire (FSII)).[44,45]

Triamcinolone vs. placebo

We did not identify any trials comparing triamcinolone to placebo that measured health-related quality of life, functional impairment, or hospitalizations.

H. Summary of the evidence

Nineteen head-to-head trials and one systematic review compared one ICS to another and 10 placebo-controlled trials provided additional evidence on health outcomes (Table 6 and Evidence Table 1). No trial was considered to be an effectiveness trial; all included studies were characterized as efficacy trials.

The body of evidence for the comparison of beclomethasone and budesonide with fluticasone is fair to good; one systematic review and seven RCTs compared beclomethasone to fluticasone; one systematic review and five RCTs compared budesonide to fluticasone. The body of evidence for the comparisons of beclomethasone with budesonide, beclomethasone with triamcinolone, budesonide with flunisolide, and fluticasone with triamcinolone is limited to fewer studies. We did not identify any head-to-head trial that compared beclomethasone with flunisolide, budesonide with triamcinolone, flunisolide with fluticasone, or flunisolide with triamcinolone. Evidence on quality of life, functional capacity, and hospitalizations rarely are reported in head-to-head trials; we identified 10 placebo-controlled trials that provide additional evidence on these outcome measures.

Effectiveness

We did not identify any study with a high degree of generalizability. All included studies were conducted in highly selected populations with well-defined asthma severity.

Efficacy

Most efficacy studies provide fair evidence that, at equipotent doses administered through comparable delivery devices, ICSs do not differ in their ability to control asthma symptoms and reduce the need for additional rescue medication. Several studies comparing beclomethasone and budesonide with fluticasone contradict this evidence, though some of these studies utilize nonequivalent doses. The most conclusive evidence of this relationship is provided by a systematic review that compares the pooled effect of beclomethasone and budesonide with fluticasone; this review reported no difference in asthma symptoms, asthma exacerbations, or β-agonist use.

The body of evidence for health-related quality of life, functional capacity, work absences, and hospitalizations is limited to 4 head-to-head trials and 10 placebo-controlled trials. Among the head-to-head comparisons, one trial compared beclomethasone and fluticasone and found no difference in health-related quality of life between beclomethasone- and fluticasone-treated patients; one study compared budesonide with fluticasone and reported significantly fewer work absences for fluticasone-treated patients. One study compared fluticasone with triamcinolone and found significantly more improvement in quality of life in fluticasone-treated patients; one compared budesonide with fluticasone and found no difference in missed school among children and adolescents but fewer disruptions in physical activity for fluticasone-treated patients compared to budesonide-treated patients. Although evidence from placebo-controlled trials is insufficient to compare one ICS with another, we found consistent evidence to suggest that, compared to placebo, beclomethasone, budesonide, and fluticasone improve health-related quality of life. We did not identify any study that evaluated health-related quality of life in flunisolide- or triamcinolone-treated patients. Based on a single study beclomethasone- and placebo-treated patients do not differ in the number of school days missed or activities affected by asthma. Consistent evidence from two placebo-controlled trials suggests that budesonide-treated patients have fewer hospitalizations; no other study reported emergency department visits or hospitalizations.

Table 6. Summary of efficacy trials in adult and pediatric outpatients with asthma

Author, Year	Age (years)	N	Duration (weeks)	Equivalent Dosing	Results	Quality Rating
beclomethasone vs. budesonide						
Terzano et al., 2000[19]	6-14	127	4	Yes	No difference in symptoms, β-agonist use, or nocturnal dyspnea	Fair
beclomethasone vs. fluticasone						
Adams et al., 2004[18] (SR)	≥ 2	11,479	≥ 1	N/A	No difference in symptoms, exacerbations, or β-agonist use	Good
Barnes et al., 1993[21]	18-78	154	6	Yes	No difference in symptoms or β-agonist use	Fair
Fabbri et al., 1993[22]	17-80	274	52	Yes	FLUP > BDP in % without exacerbations; No difference in symptoms or β-agonist use	Fair
Fairfax et al., 2001[20]	18-65	172	6	Yes	No difference in symptoms, β-agonist use, sleep disturbance, or AQLQ	Good
Gustafsson et al., 1993[23]	4-19	398	6	Yes	FLUP > BDP in % of β-agonist-free days; no difference in symptom-free days, nights, or exercise symptoms	Fair
Leblanc et al., 1994[24]	18-80	261	4	Yes	BDP > FLUP for % β-agonist free-days; no difference in symptom-free days/nights or overall β-agonist use	Fair
Lundback et al., 1993[25]	15-91	585	6	Yes	FLUP > BDP for night symptoms; BDP > FLUP for daytime symptoms; no difference in symptom-free days/nights, or β-agonist use	Fair
Raphael et al., 1999[26]	≥ 12	399	12	Yes	FLUP > BDP in days without symptoms, asthma symptom score, and β-agonist use; No difference in nighttime awakenings	Fair
beclomethasone vs. triamcinolone						
Berkowitz et al., 1998[29]	18-65	339	8	Yes	No difference in symptoms or β-agonist use	Fair
Bronsky et al., 1998[27]	18-65	329	8	Yes	BDP>TRIA for asthma symptoms; no difference in nighttime awakenings or β-agonist use	Good
budesonide vs. flunisolide						
Newhouse et al., 2000[28]	18-75	154	6	Yes	No difference in symptoms, nocturnal awakenings, or β-agonist use	Fair
Terzano et al., 2001[30]	6-14	133	4	Yes	FLUN>BUD for reduction in nocturnal awakenings; no difference in symptoms, diurnal dyspnea, or β-agonist use	Fair
budesonide vs. fluticasone						
Adams et al., 2004[18] (SR)	≥ 2	11,479	≥ 1	N/A	No difference in symptoms, exacerbations, or β-agonist use	Good
Ayres et al., 1995[31]	18-70	225	6	No FLUP>BUD	FLUP>BUD for symptom-free days and nighttime β-agonist use; no difference in symptoms, symptom-free nights, or daytime β-agonist use	Fair
Ferguson et al., 1998[32]	4-12	333	20	Yes	No difference in symptoms or β-	Fair

					agonist use	
Heinig et al., 1999[33]	18-75	395	24	Yes	FLUP>BUD symptom-free days, β-agonist-free days, and fewer days absent from work; no difference in symptom scores or exacerbations	Fair
Hoekx et al., 1996[34]	4-13	229	8	No FLUP>BUD	No difference in symptom-free days/nights, mean symptom score, β-agonist use, sleep, or missed school ; FLUP>BUD disruption in physical activity	Fair
Ringdal et al., 1996[35]	18-75	518	12	Yes	No difference in symptoms, exacerbations, or β-agonist use	Fair
fluticasone vs. triamcinolone						
Condemi et al., 1997[36]	≥ 12	291	24	No FLUP>TRIA	FLUP>TRIA in β-agonist use/β-agonist-free days; no difference in symptoms or symptom-free days	Fair
Gross et al., 1998[37]	≥ 12	304	24	No FLUP>TRIA	FLUP>TRIA in β-agonist use, nighttime awakenings, and AQLQ (statistically but not clinically); no difference in symptom scores	Fair
beclomethasone vs. placebo*						
Juniper et al., 1999[39]	18-65	347	12	N/A	Placebo-patients had a decrease in quality of life (AQLQ) but BDP-patients experienced little change	Fair
Malmstrom et al., 1999[38]	15-85	895	12	N/A	BDP better than placebo for patient & physician global evaluation and quality of life (AQLQ)	Good
Simons et al., 1997[40]	6-14	241	52	N/A	No difference in school missed or activities affected by asthma	Fair
budesonide vs. placebo*						
Banov et al., 2003[54,42]	18-70	177	12	N/A	BUD>placebo for overall quality of life and all four domains of AQLQ	Good
Childhood Asthma Management Program Research Group, 2000[43]	5-12	1,041	208-312	N/A	BUD patients had fewer urgent care visits, fewer hospitalizations, and lower depression scores	Good
Connett et al., 1993[41]	1-3	40	26	N/A	BUD>placebo for parental sleep disturbance, time caring for child's asthma, and hospital admissions	Fair
fluticasone vs. placebo*						
Mahajan et al., 1997[44,55]	≥12	342	12	N/A	FLUP>placebo in physical functioning and role-physical (SF-36), as well as LWA-20 questions and sleep-related items	Fair
Mahajan et al., 1998[45,56]	4-11	325	52	N/A	FLUP>placebo in FSII and SLP-C; higher doses of FLUP>placebo on QOL-PAC	Fair
Nelson et al., 1999[47]	12-77	111	16	N/A	FLUP>placebo in each of the four domains of the AQLQ	Fair
Okamoto et al., 1996[46,51]	≥12	96	16	N/A	FLUP>placebo in physical functioning, role-physical, role-emotional, general health perception, and physical	Fair

component summary scores

* For placebo-controlled trials we did not evaluate exacerbations, symptoms, or β-agonist use; included outcomes were quality of life, ability to participate in work or school activities, resource utilization, and mortality
SR – systematic review
N/A – not applicable
BDP – beclomethasone dipropionate
BUD – budesonide
FLUN – flunisolide
FLUP – fluticasone propionate
TRIA – triamcinolone acetonide
AQLQ – asthma quality of life questionnaire
SF-36 – medical outcomes study short-form 36-item questionnaire
LWA-20 – living with asthma 20-item questionnaire
FSII – functional status IIR questionnaire
SLP-C – sleep scale children questionnaire
QOL-PAC – quality of life of parents with asthmatic children questionnaire

II. COPD

Currently no ICSs are approved by the FDA for the treatment of COPD.

A. Description of studies

We did not find any head-to-head trials comparing one ICS to another. We found nine placebo-controlled trials, one high-quality prospective cohort study, and three meta-analyses assessing the efficacy of individual ICSs or ICSs as a class (Table 7 and Evidence Table 2). Five trials measured quality of life, one assessed hospitalizations, and all reported on mortality. One study examined the effects of the discontinuation of ICS treatment.

B. Study populations

Patients were generally smokers or former smokers with a clinical diagnosis of COPD. Only the Copenhagen City Lung Study enrolled smokers identified as having mild COPD during a random population survey and subsequent respiratory screening.[57] Severity of COPD varied from mild to severe across studies; inclusion criteria generally intended to exclude patients with asthma or significant bronchodilator responsiveness. Patients with a history of asthma, allergic disease, or sudden onset of breathlessness were excluded from all studies. Further, FEV1 reversibility after bronchodilator use was frequently assessed before enrollment. Cut-off criteria varied across studies from 10 percent FEV1 reversibility after bronchodilator use to 15 percent. Some trials additionally examined total serum IgE (Immunoglobin E), eosinophils, alpha1-antitrypsin deficiency, or skin test results to exclude patients with allergic features or alpha 1-antitrysin deficiency.

C. Outcome measures

Except for the EUROSCOP study[58] all trials assessed health outcomes such as exacerbation rates, respiratory symptoms, or withdrawals due to worsening COPD symptoms. Five placebo-controlled studies determined differences in quality of life. Two meta-analyses and the cohort study focused on all-cause mortality and exacerbation rates. All studies reported FEV1 decline as a primary outcome.

D. Methodological quality

Study quality varied with high loss to follow up presenting a consistent problem for longer-term studies. Some "fair" ratings are probably more attributable to inadequate reporting than to methodological flaws. Randomization methods and blinding were generally adequate; all studies used a double-dummy design (i.e., using an identical container for active treatment and placebo) to guarantee blinding; method of allocation concealment was rarely reported. The main reasons for poor internal validity were large post-randomization exclusions for trials and lack of systematic literature search for meta-analyses.

E. Sponsorship

Six trials (47%) were funded by pharmaceutical companies; two studies (15%) did not report the source of funding. Five trials (38%) were funded primarily by governmental agencies or independent funds.

F. Head-to-head comparisons

We did not identify any head-to-head trials.

G. Placebo-controlled trials

Because of the limited number of studies assessing health outcomes for COPD, we also reviewed changes in the decline of FEV1 as an intermediate outcome. Furthermore, because no ICS is FDA-approved for the treatment of COPD, we summarize evidence on the general efficacy of ICSs as a class for the treatment of COPD. This, however, does not provide evidence on the comparative efficacy and tolerability of ICSs.

ICSs as a class

One good[59] and one fair[60] meta-analysis determined the long-term effects of ICS treatment on COPD exacerbations, all-cause mortality, and FEV1 decline. Alsaeedi et al. included nine trials (five on budesonide, two on fluticasone, one on beclomethasone, and one on triamcinolone) with durations of at least 6 months conducted in populations with stable COPD;[61] in total 3,976 patients with COPD were included in the analysis. ICS therapy reduced the rate of exacerbations significantly by about 30% (RR: 0.70; 95% CI: 0.58 to 0.84). Benefits were similar in patients who were and were not receiving systemic corticosteroids during the run-in phase; no dose-response effect could be demonstrated. The relative risk for all-cause mortality favored ICS treatment but did not reach statistical significance (RR: 0.84; 95% CI: 0.60 to 1.18). Data on FEV1 decline could not be pooled in this study. A small meta-analysis[60] using individual patient data from three studies on beclomethasone and budesonide did not support findings of the Alsaeedi et al. study regarding exacerbation rates; prebronchodilator FEV1 decline was significantly slower in the ICS group compared to the placebo group (+ 0.034 ml/year; P = 0.026). If dose was included in the model, a significant treatment effect was maintained only for the high-dose group (+ 0.039l/year; 95% CI: 0.008 to 0.070); this estimate was based on very small numbers. Findings regarding a slower FEV1 decline in ICS-treated patients are consistent, however, with another good meta-analysis which pooled results of seven trials with more than 2 years of ICS treatment to determine differences in FEV1 decline compared to placebo.[61] Results presented a modest but statistically significant difference in FEV1 decline favoring ICS treatment (+ 7.7 ml/ year; 95% CI: 1.3 to 14.2; P = 0.01).

A high-quality prospective cohort study did not meet our formal eligibility criteria;[62] nevertheless, we present the results because mortality and hospitalizations are outcomes that are more difficult to assess in RCTs which generally enroll fewer patients. This cohort study followed 8,033 patients with COPD for a mean of 544 days; 2,686 patients received ICS. Results presented no significant reduction in all-cause mortality for ICS-treated patients (Hazard Ratio: 0.87; 95% CI: 0.72 to 1.05). Stratification did not reveal an association between ICS dose and death. These findings support results from the Alsaeedi et al. meta-analysis.[59] Results did not find a reduction, however, in exacerbation rates or hospitalization for ICS treated patients compared to patients not on ICS treatment. Findings contradict earlier reports of lower quality observational studies based on secondary analysis of large databases which presented improved mortality rates

for ICS-treated patients.[63-65] These studies did not meet eligibility criteria for key question one and might have been affected by immortal time bias.

Beclomethasone vs. placebo

We did not identify any placebo-controlled trial that compared beclomethasone to placebo.

Budesonide vs. placebo

A fair rated multinational RCT enrolled 812 patients with moderate to severe COPD for 1 year.[66] Patients were randomized to budesonide/formoterol (640/18 mcg / day), budesonide (800 mcg / day), formoterol (18 mcg / day), or placebo. Results revealed no significant differences in health-related quality of life (SGRQ) and exacerbation rates between budesonide and placebo. Budesonide and budesonide/formoterol significantly reduced the use of oral steroids compared to placebo ($P < 0.05$). Significantly more patients in the placebo group than in the active treatment groups withdrew because of worsening COPD symptoms. FEV1 was higher in the budesonide group than in the placebo (+ 5%; $P = 0.005$).

The EUROSCOP study, a fair multinational, multi-center, randomized European trial enrolled 1,277 smokers with mild COPD to compare the FEV1 decline in patients treated with 800 mcg budesonide (DPI) with those receiving placebo;[67] all patients were current smokers. Study duration was three years; no health outcomes were assessed. Results presented a modestly slower decline of postbronchodilator FEV1 in the budesonide group (140 ml/ 3 years vs. 180 ml / 3 years; $P = 0.05$). However, this difference was based on an increase of FEV1 in budesonide-treated patients during the first six months (+ 17 ml/year). The slopes of FEV1 decline were similar for both treatment groups from nine months to the endpoint.

Three additional smaller trials assessed the efficacy of budesonide compared to placebo.[57,58,68] Study durations were from 6,[68] 24,[58] and 36 months.[57] Findings were generally consistent with other evidence; no significant differences could be detected in exercise capacity, quality of life, exacerbations, or FEV1 decline. Only one study reported significant improvements in symptom scores (Standardized Symptom Score Questionnaire; $P < 0.05$) and lower withdrawal rates (5% vs. 27.8%; $P < 0.05$) for active treatment than for placebo after 2 years.[58]

Flunisolide vs. placebo

We did not identify any placebo-controlled trial that compared flunisolide to placebo.

Fluticasone vs. placebo

The ISOLDE trial randomized 751 patients in the United Kingdom with moderate to severe COPD to 1000 mcg fluticasone (MDI) or placebo;[69-72] the study duration was 3 years; all patients were current or former smokers. The main outcome measure was decline in FEV1. Fluticasone-treated patients had significantly fewer exacerbations (0.99 / year vs. 1.32 / year; $P = 0.026$) than placebo-treated patients; this treatment effect was confined, however, to patients with moderate to severe disease. In patients with milder COPD no statistically significant difference could be detected.

Patients on fluticasone presented a slower deterioration of quality of life (SGRQ, SF-36; P = 0.004). Furthermore, more patients in the placebo than in the fluticasone group withdrew as a result of respiratory disease (25% vs. 19%; P = 0.034). No significant difference in FEV1 decline between fluticasone (50 ml / year) and placebo (59 ml / year) could be detected.

One good multinational trial[73] and one fair Dutch trial[74] enrolled patients with mild to moderate COPD to placebo and either 6 months of 1000 mcg fluticasone (MDI)[73] or 24 months of 500 mcg fluticasone (DPI).[74] Neither trial found any reduction in exacerbations in the active treatment group compared to placebo. The study with the higher dosage reported less severe exacerbations in the fluticasone group (P < 0.001) and a prolonged walking distance compared to placebo.

Another Dutch trial examined the discontinuation of 1000 mcg fluticasone (DPI) in 244 patients with moderate to severe COPD after 4 of months maintenance therapy.[75] Patients who switched to placebo had a higher rate of exacerbations than patients maintaining fluticasone therapy (HR: 1.5; 95% CI 1.05 to 2.1). Time until the first exacerbation was significantly longer in the fluticasone group (75.2 days vs. 42.7 days; 95% CI: 15.4 to 53.8); patients on fluticasone reported a higher quality of life (SGRQ) than placebo-treated patients. No differences in exercise tolerance tests and in Borg breathlessness scores were noted.

Triamcinolone vs. placebo

The Lung Health Study Group enrolled 1,116 patients with mild to moderate COPD in a fair multi-center trial that lasted 40 months.[76] Patients were randomly assigned to 1200 mcg triamcinolone (MDI) or placebo (MDI); 90 percent of the participants were current smokers. Results revealed no differences between treatment groups in health-related quality of life (SF-36), hospitalizations, and mortality. Furthermore, no significant differences in postbronchodilator FEV1 decline could be detected (triamcinolone: 44.2 ml/year; placebo: 47.0 ml/year). Patients in the placebo group reported more dyspnea than those in the triamcinolone group (P = 0.02; American Thoracic Society-Division of Lung Diseases Questionnaire) and more new or increased respiratory symptoms (28.2 / 100 person-years vs. 21.1 / 100 person-years; P = 0.005).

H. Summary of the evidence

We did not find any head-to-head trials comparing one ICS to another. Evidence from placebo-controlled trials was too heterogeneous to allow conclusions on the comparative efficacy of ICSs.

We found several trials and meta-analyses assessing the general efficacy of individual ICSs or ICSs as a class in the treatment of COPD (Table 7).

Effectiveness

We did not identify any study with a high degree of generalizability.

Efficacy

The evidence is insufficient to draw any firm conclusions about the comparative efficacy or tolerability of ICSs for the treatment of COPD. Consistent fair to good

evidence exists that ICS treatment does not reduce overall mortality in patients with COPD.

The body of evidence on the effect of ICS treatment on exacerbation rates is mixed. A good meta-analysis reported a statistically significant reduction of exacerbation rates for ICS-treated patients compared to patients on placebo.[59] A smaller meta-analysis[60] and a good prospective cohort study[62] did not support this finding. Most efficacy trials reported no reduction in exacerbation rates. Only one large study with a high-dose treatment of fluticasone indicated a statistically significant reduction in exacerbation rates. This treatment effect, however, was confined to patients with moderate to severe COPD. An equally large trial, assessing medium-dose budesonide, did not find a significant reduction of exacerbations in patients with moderate to severe disease.[66] Two other trials examining high-dose fluticasone[73] and high-dose triamcinolone[76] reported a significantly lower rate of severe exacerbations in actively-treated patients than in placebo-treated patients with mild to moderate COPD.

One study assessing high-dose fluticasone[69] in patients with moderate to severe COPD reported significantly greater quality of life scores in patients on fluticasone than on placebo. Two other trials conducted in individuals with mild to moderate disease did not detect a statistically significant difference in quality of life between fluticasone and placebo. None of the other trials examining other ICSs report significant differences in quality of life between active treatment and placebo.

The majority of individual trials did not report statistically significant differences in FEV1 decline between active treatments and placebo. Two meta-analysis found a modest but statistically significant difference in FEV1 decline favoring ICS treatment.[61,60] The treatment effect (+7.7 ml/year) reported in the better study,[61] however, is small and the clinical significance questionable.

Table 7. Summary of efficacy trials in adult outpatients with COPD

Author, Year	Age (years)	N	Duration	Results	Quality Rating
ICS vs. placebo					
Alsaeedi et al., 2002[59] (SR)	≥ 52	3976	1966-2001	ICS significantly reduced rate of exacerbations No differences in all-cause mortality	Good
Sutherland et al., 2003[61] (SR)	NR	3715	1966-2003	FEV1 decline significantly slower in ICS group	Fair
Van Grunsven et al.,1999[60] (SR)	≥ 40	183	1983-1996	No differences in exacerbations or all-cause mortality FEV1 decline significantly slower in ICS group	Fair
budesonide vs. placebo					
Bourbeau et al., 1998[68]	≥ 40	79	6 months	No differences in exacerbations, FEV1 decline, or quality of life	Fair
Pauwels et al., 1999[67]	30-65	1277	3 years	FEV1 decline significantly slower in ICS group	Fair
Renkema et al., 1996[58]	≥ 70	58	2 years	No differences in exacerbations, FEV1 decline, or quality of life	Fair
Szafranski et al., 2003[66]	≥ 40	812	1 year	No differences in exacerbations or quality of life FEV1 decline significantly slower in ICS group	Fair
Vestbo et al., 1999[57]	30-70	290	3 years	No differences in exacerbations, FEV1 decline, or respiratory symptoms	Fair
fluticasone vs. placebo					
Burge et al., 2000[69]	40-75	751	3 years	Significantly fewer exacerbations in patients with severe disease in ICS group Slower decline in quality of life in ICS group	Fair
Paggiaro et al., 1998[73]	50-75	281	6 months	No differences in exacerbations or quality of life	Good
van der Valk et al., 2002[75]	40-75	244	6 months	Significantly fewer exacerbations in the ICS group than in the withdrawal group	Good
van Grunsven et al., 2003[74]	18-75	48	24 months	No differences in exacerbations or quality of life FEV1 decline significantly slower in ICS group	Fair
Cohort study: ICS – no ICS					
Fan et al., 2003[62]	≥ 45	8033	544 days	No differences in all-cause mortality or hospitalizations	N/A

SR – systematic review
NR – not reported
N/A – not applicable
ICS – inhaled corticosteroid
FEV1 – forced expiratory volume over 1 second

Key Question 2
For outpatients with asthma or COPD, do inhaled corticosteroids differ in safety or adverse events?

Most studies that examined the efficacy of one ICS relative to another also determined differences in adverse events; methods of adverse events assessment differed greatly. Few studies used objective scales such as the UKU-SES (Utvalg for Kliniske Undersogelser Side Effect Scale) or the adverse reaction terminology from the World Health Organization (WHO). 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; most published studies were post hoc analyses or retrospective reviews of databases. For specific adverse events we included observational studies if the sample size was larger than 100 and the study duration was at least 1 year (Tables 8-12, Evidence Table 3).

A. Tolerability and discontinuation rates

Of 19 head-to-head studies reviewed for this report, 4 (21%) reported statistically significant differences in at least one adverse event. No trial reported differences in discontinuation rates because of adverse events. All trials reported the number of participants identified as having at least one adverse event; because of inconsistent reporting of the number of participants with specific events versus any event, the overall rate of adverse events cannot be compared (range: 4% - 78%).

Rhinitis, oral candidiasis, sore throat, hoarseness, headache, cough, bronchitis, and upper respiratory infection were reported commonly as adverse events. In most of the head-to-head trials we reviewed oral candidiasis, rhinitis, cough, hoarseness, bronchitis, and sore throat were reported in fewer than 10 percent of ICS-treated patients. Upper respiratory tract infections were reported by 3 to 32 percent of study participants; studies reporting higher upper respiratory tract infection rates commonly were conducted in pediatric populations.[23,32,34] Except for four trials, rates of individual adverse events were not statistically significantly different. Two studies reported a significantly higher incidence of sore throat for fluticasone-treated patients than beclomethasone-treated;[23,25] one study reported significantly more upper respiratory infections in triamcinolone-treated patients than in beclomethasone-treated,[27] and one reported oral candidiasis in significantly more fluticasone-treated patients than in triamcinolone-treated.[36] Although three of the four trials to report significant differences compared nonequivalent ICS doses,[25,27,36] the higher rate of specific events was reported for the lower-dose ICS in two of the three studies with a dose differential.[25,27]

B. Specific adverse events

i. Bone density/osteoporosis

One systematic review evaluated seven placebo-controlled trials that studied the effect of ICSs on markers of bone function and metabolism.[77] The authors reviewed two studies that collected fracture data[78,79] and three studies that measured bone mineral density (BMD).[78-80] Pooled results showed no significant effect of ICSs in patients with asthma or COPD on BMD or fractures.[77]

Our review includes two of the trials[78,79] included in the Jones et al.[77] review as well as five additional studies.[43,81,82,83,84] We excluded one study[85] from the Jones et al.[77] review because it relied on an insufficient sample size of ICS users. In total our review includes one good-rated RCT,[43] two fair-rated RCTs,[78,79] one fair-rated prospective cohort study,[81] two good-rated case-control studies,[82,83] and one cross-sectional evaluation of patients followed in a pediatric clinic.[84]

Four studies evaluated the risk of fracture[78,79,82,83] and five measured BMD as an intermediate outcome of osteoporosis.[43,78,79,81,84] Only one study compared one ICS to another,[79] three compared one ICS to placebo,[43,78,84] and three studies compared one ICS or any ICS to a population that did not use an ICS.[81,82,83] Most studies evaluated the risk of bone weakening over 2 to 6 years; no study was designed specifically to assess lifetime or long-term cumulative ICS exposure.

One study comparing beclomethasone to budesonide measured BMD and vertebral fractures; this open-label trial randomized 374 adult patients with asthma to beclomethasone, budesonide, or placebo.[79] Patients were titrated to the minimal effective dose following a pre-specified management plan; subjects who required more than three courses of oral corticosteroids were withdrawn. At 2 years, no significant differences in BMD were reported between beclomethasone-, budesonide-, or placebo-treated patients. We did not identify any other trial that compared the risk of bone weakening between one ICS and another.

Six studies comparing an ICS-exposed population to an ICS-unexposed population provide mixed evidence of an association between ICS use and loss of BMD or osteoporosis;[43,78,79,81,82,83,84] three (50%) of these studies measured bone fractures.[78,82,83] Two good-rated case-control studies reported a small dose-dependent increase in risk of fractures for ICS-treated patients compared to patients that had not been exposed to an ICS;[82,83] one RCT reported no increase in the risk of fractures in budesonide-treated COPD patients compared to placebo.[78] Three studies found no difference in BMD between budesonide-treated and placebo-treated patients; one study randomized 1,041 patients with asthma to budesonide, nedocromil, or placebo,[43] one study randomized 1,277 persons with COPD to budesonide or placebo,[78] and one cross-sectional study evaluated pediatric patients followed in an asthma clinic over 3 to 6 years.[84] A prospective cohort study conducted in 109 premenopausal women found a small association between triamcinolone use and reduction in BMD at the total hip and trochanter; an estimated bone loss of 0.00044 g/cm^2 per puff per year of treatment was reported.[81] In this study, however, a Chronolog dosing system was utilized making it difficult to generalize findings to commercially available triamcinolone. Furthermore,

studies comparing an ICS-exposed population to an ICS-unexposed population or a single ICS to placebo provide only general evidence, rather than comparative evidence.

Table 8. Summary of studies on bone density or osteoporotic fractures

Author, Year	N	Design	Population	Results	Quality Rating
Agertoft & Pedersen, 1998[84]	157	Cross-sectional	Asthma (pediatric)	No difference between BUD and placebo (3-6 years use) in BMD	N/A
Childhood Asthma Management Program Research Group, 2000[43]	1041	RCT	Asthma (pediatric)	No difference in bone density between BUD- and placebo-treated patients	Good
Hubbard et al., 2002[83]	16,341	Case-control	Asthma & COPD (adult)	Non-specific ICS use associated with a small increase in the risk of hip fracture	Good
Israel et al., 2001[81]	109	Prospective cohort	Women (age 18-45)	TRIA associated with dose-related decline in BMD (total hip and trochanter) of 0.00044 g/cm^2 per puff/year	Fair
Johnell et al., 2002[67,78]	1277	RCT	COPD (adult)	No difference in bone density between BUD and placebo over 3 years; no difference in bone density or vertebral fractures in subgroup of 912 smokers	Fair
Lee & Weiss 2004[82]	40,157	Nested case-control	COPD (adult)	Nonspecific ICS use associated with increased risk of fractures at high doses	Good
Tattersfield et al., 2001[79]	374	RCT (open label)	Asthma (adult)	No difference in BMD/fractures between BDP, BUD, and placebo over 2 years	Fair

N/A – not applicable
ICS – inhaled corticosteroid
COPD – chronic obstructive pulmonary disease
BDP – beclomethasone dipropionate
BUD – budesonide
TRIA – triamcinolone acetonide
RCT – randomized controlled trial

ii. Growth retardation

The use of ICSs in children includes the risk of delayed growth. Two head-to-head trials comparing fluticasone to beclomethasone[86] and fluticasone to budesonide[87] assessed differences in growth.

A fair 1-year multinational head-to-head trial determined differences in growth velocity comparing a medium dose of fluticasone (400 mcg/day) to a medium dose of beclomethasone (400 mcg/day)[86] in 343 pre-pubertal children with asthma. ITT analysis revealed that adjusted mean growth velocity was significantly greater in fluticasone than in beclomethasone-treated patients (+0.70 cm/year; 95% CI: 0.13 to 1.26; $P < 0.02$).

A Finnish RCT compared growth velocity in 60 children treated with either a low dose of fluticasone (200 mcg/day) or a low dose of budesonide (400 mcg/day) over 1 year.[87] Fluticasone-treated children had significantly less reduction in growth velocity than the budesonide-treated group (height SD (standard deviation) score: 0.03 vs. 0.23; $P < 0.05$); the authors did not provide absolute numbers in centimeters of differences in growth.

Five additional studies provide general evidence of growth retardation for ICSs. A good meta-analysis assessed differences in short-term growth velocity in 273 children

with mild to moderate asthma treated with either beclomethasone (mean 400 mcg/day) or placebo for 7 to 12 months.[88] Growth velocity decreased significantly in the actively treated group (-1.54 cm per year; 95% CI: -1.15 to 1.94) compared to the placebo group. One additional placebo controlled trial assessing growth velocity under low-dose fluticasone treatment (50 mcg/day; 100 mcg/d) did not find any significant differences in linear growth compared to placebo after 1 year of treatment.[89] However, the lower range of this dosage (50 – 87 mcg/d) is considered sub-therapeutic according to the NAEPP Expert Panel Report (Table 3).[2]

A good RCT, the CAMP study, allocated 1,041 asthmatic children to budesonide, nedocromil, or placebo;[43] the median follow-up time was 4.3 years. The mean increase in height was significantly less in budesonide-treated patients than in placebo-treated patients (-1.1 cm; 22.7 cm vs. 23.8 cm; P = 0.005). This analysis was performed on an intent-to-treat basis, providing a more conservative than an "as treated" analysis. The differences in growth occurred, however, primarily during the first year of treatment. After two years of treatment growth velocity was basically identical between groups.

A fair long-term European observational study examined the impact of budesonide therapy on growth in children.[90,91] Agertoft and colleagues conducted a prospective cohort study which followed 216 children on budesonide (mean: 430 mcg/day) and 62 asthmatic children on asthma therapy without ICS for 3 to 7 years.[90,91] Primary outcome measures did not present significant differences between treatment groups in height or weight at study endpoint. Investigators assessed patients again after they had been on budesonide for a mean of 9.2 years.[91] By then 142 subjects in the budesonide group had reached adult height. No differences could be detected in adult height between budesonide-treated children, control subjects, and healthy siblings.

Table 9. Summary of studies on growth retardation

Author, Year	N	Design	Population	Duration	Results	Quality Rating
Agertoft et al. 1994[90]	278	Prospective cohort study	Children with asthma	3-6 years	No differences in height between BUD group and asthmatic children without ICS treatment	Fair
Agertoft et al. 2000[91]	332	Prospective cohort study	Children with asthma	9.2 years	No differences in adult height between BUD group, healthy siblings, and asthmatic children without ICS treatment	Fair
Allen et al 1998[89]	268	RCT	Children with asthma	1 year	No differences in height and growth velocity between FLUP and placebo	Fair
Childhood Asthma Management Program Research Group, 2000[43]	1041	RCT	Children with asthma	4.3 years	Significant reduction in growth for BUD-treated children	Good
De Benedictis et al. 2001[86]	343	RCT	Pre-pubertal children with asthma	1 year	Greater growth velocity in FLUP than in BDP group	Fair

Kannisto et al. 2000[87]	75	RCT	Children with asthma	1 year	Greater growth velocity in FLUP than in BUD group	Fair
Sharek et al. 2004[88] (SR)	273	Meta-analysis	Children with asthma	More than 3 months	Reduction in growth for BDP compared to placebo	Good

SR – systematic review
N/A – not applicable
ICS – inhaled corticosteroid
BDP – beclomethasone dipropionate
BUD – budesonide
FLUP – fluticasone propionate
RCT – randomized controlled trial

iii. Acute adrenal crisis

The use of ICSs includes the risk of altered hypothalamic-pituitary axis (HPA axis) functioning[92,93] and the rare possibility of resultant adrenal suppression. Various case reports indicate that acute adrenal insufficiency crisis is an extremely rare but potentially fatal adverse event of ICS treatment.[94-96] One report states that most reported adrenal crises (94%) occurred in children taking fluticasone (500–2000mcg/day).[96] However, in most cases dosing was likely outside approved labeling. These case reports did not meet eligibility criteria for this report.

We did not find any controlled studies or large database studies reporting on the comparative frequency of adrenal insufficiency crisis in patients treated with ICS. However, multiple studies report on adrenal suppression during ICS therapy using urinary cortisol levels and results of dynamic stimulation tests as intermediate outcomes. We did not review results of these studies for this report. It is unclear to what extent results from sensitive studies of HPA axis suppression can be extrapolated to assess differences in risks for clinically significant adrenal suppression.

iv. Cataracts

The association between systemic corticosteroids and cataracts, especially at high doses administered over extended periods of time, is well-documented in both children[97] and adults.[98] Systemic corticosteroid-induced cataracts typically are located on the posterior side of the lens and are referred to as posterior subcapsular cataracts (PSC); we reviewed studies that compared the risk of PSC in ICS-treated populations to non-ICS-treated populations.

No study compared the risk of developing PSC between one ICS and another. One placebo-controlled trial[43] and five observational studies[84,99-102] evaluated the risk of developing cataracts between ICS- and non-ICS-treated patients. One placebo-controlled trial[43] and one observational study[84] compared budesonide to placebo; all other studies compared nonspecific ICS use to no ICS use.[99,100,101,102] Two studies[43,84] were conducted in pediatric populations, one[99] in a mixed population of children and adults, and three[100-102] evaluated adult populations (≥ 40 years).

Two studies reported no significant differences in the development of PSC between budesonide-treated patients and placebo or matched controls;[43,84] both studies were conducted in children. A third study that included a pediatric population found no increase in the risk of developing cataracts between ICS-treated patients and controls in persons younger than 40 years; a dose-, duration-, and age-related increase in risk was

observed for persons older than 40 years of age.[99] Consistent evidence from two case-control studies[100,102] and one cross-sectional study[101] conducted in adult populations reported an increased risk of cataracts for ICS-treated patients compared to controls. In general, both case-control studies[100,102] found the risk of cataracts increased at higher ICS doses and longer duration of treatment; one study reported a higher relative risk for ICS doses greater than 1,600 mcg/day[102] and one study reported a higher relative risk for budesonide or beclomethasone doses greater than 1,000 mcg/day.[100]

Most studies did not control for or did not report previous exposure to systemic corticosteroids, a known cause of cataracts. Only one observational study controlled for previous exposure to systemic corticosteroids; controlling for systemic corticosteroid use and other potential confounders had little effect on the magnitude of the associations in this study.[101]

Table 10. Summary of studies on posterior subcapsular cataracts

Author, Year	N	Design	Population	Results	Quality Rating
Agertoft et al., 1998[84]	268	Prospective cohort	Children (age 5-16)	No significant differences in PSC between BUD-treated children and matched controls	Fair
Childhood Asthma Management Program Research Group, 2000[43]	1041	RCT	Asthma (pediatric)	No significant differences in PSC between BUD-, nedocromil-, or placebo-treated children	Good
Cumming et al., 1997[101]	3654	Cross-sectional	Adults (age 49-97)	Increased risk of nuclear and PSC among ICS users	N/A
Garbe et al., 1998[100]	25,545	Case-control	RAMQ age ≥ 70 years	Increased risk of cataract extraction for ICS users only at high dose and duration	Good
Jick et al., 2001[99]	201,816 (3,581)	Cohort + case-control	GPRD (age 3-90)	Dose-, duration-, and age-related increased risk of cataracts among ICS users; no increase in risk for age < 40	Good
Smeeth et al., 2003[102]	30,958	Case-control	GPRD age ≥ 40 years	Dose- and duration-related increased risk of cataracts among ICS users	Good

RCT – randomized controlled trial
ICS – inhaled corticosteroid
PSC – posterior subcapsular cataracts
BUD – budesonide
RAMQ – regi de l'assurance maladie du Quebec database
GPRD – general practice research database

v. Ocular hypertension and open-angle glaucoma

Prolonged use of systemic corticosteroids also has been linked to ocular hypertension and increased risk of open-angle glaucoma; we reviewed studies that evaluated this risk in ICS-treated populations.

No study compared one ICS to another for the risk of ocular hypertension or open-angle glaucoma. One fair-rated case-control study of 48,118 Canadians age 66 years and older[103] and one cross-sectional population-based eye study of 3,654 Australians 49 to 97 years of age[104] compared the risk of increased intraocular pressure or open-angle glaucoma between ICS- and non-ICS-treated patients. Both studies reported

a dose-related increase in the risk of open-angle glaucoma for ICS-treated patients compared to patients that had not used an ICS.[103,104] In one study this relationship was observed only among current users of high doses of ICSs prescribed regularly for 3 or more months (OR 1.44; 95% C.I. 1.01 to 2.06);[103] another study found an association between ever using ICSs and findings of elevated intraocular pressure or glaucoma only in subjects with a glaucoma family history (OR 2.8; 95% CI 1.2 to 6.8).[104] Both studies adjusted for age, sex, oral steroid use, history of diabetes, and history of hypertension.

Table 11. Summary of studies on ocular hypertension or open-angle glaucoma

Author, Year	N	Design	Population	Results	Quality Rating
Garbe et al., 1997[103]	48,118	Case-control	RAMQ age ≥ 66 years	≥ 3 months of high-dose ICS associated with an increased risk of open-angle glaucoma and ocular hypertension	Fair
Mitchell et al., 1999[104]	3654	Cross-sectional	Adults (age 49-97)	Dose-related increased risk of elevated IOP and open-angle glaucoma for ICS users with glaucoma family history	N/A

N/A – not applicable
ICS – inhaled corticosteroid
IOP – intraocular pressure
RAMQ – regi de l'assurance maladie du Quebec database

Summary of the Evidence

Bone density/osteoporosis

Overall the evidence of an association between ICS products and osteoporosis is mixed. The strongest evidence comes from four studies that measure fractures;[78,79,82,83] of these, two found no increase in risk for ICS-treated patients[78,79] and two reported a slight increase in the risk of fracture for ICS-treated patients.[82] Additionally, evidence of an ICS-associated reduction in BMD comes from one small prospective cohort study in premenopausal women;[81] four studies suggest no relationship between ICS use and reduction in BMD.[43,67,79,84] We view BMD as an intermediate outcome measure of osteoporosis; although a causal relationship exists between loss of BMD and risk of fractures due to osteoporosis, the clinical significance of modest changes in BMD is often questionable.

Growth retardation

Two head-to-head trials provide fair evidence that short-term growth velocity is reduced significantly less with fluticasone treatment compared to beclomethasone[86] and budesonide[87] treatment. In addition, a meta-analysis reports a significant reduction in growth for beclomethasone compared to placebo.[88] Most of these studies address only ICS treatment duration up to 1 year. A long-term observational study did not detect differences in linear growth and adult height in budesonide-treated patients compared to asthmatic children without ICS treatment and healthy siblings.[90,91] Evidence from other placebo controlled trials is insufficient to draw firm conclusions about comparative

differences in growth. Further, insufficient evidence exists to determine if long-term treatments with ICSs lead to a reduction in 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.[94-96] Evidence from intermediate outcomes can not be extrapolated reliably to form conclusions about the comparative frequency of acute adrenal crisis for ICSs.

Cataracts

No study compared the risk of developing PSC between one ICS and another. General evidence of an association between ICS use and PSC is fair. No significant differences have been reported in the risk of PSC in children, adolescents, and adults less than 40 years of age between ICS users and controls. In older adults, however, an increase in the risk of developing cataracts was reported among individuals who took ICSs; increased risk was related to dose and duration of treatment. 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 one ICS and another. Two observational studies provide consistent evidence of a dose-related increase in risk for ICS-treated patients. Overall, existing evidence of an association between ICS use and increased intraocular pressure or open-angle glaucoma is fair to poor and further evidence is lacking.

Key Question 3
Are there subgroups of patients based on demographics (age, racial groups, sex), other medications (drug-drug interactions), comorbidities (drug-disease interactions), or pregnancy for which one inhaled corticosteroid is more effective or associated with fewer adverse events?

We did not find any studies that directly compared the efficacy, effectiveness, or tolerability of ICSs between subgroups and the general population. In head-to-head comparisons, no subgroups based on age, racial groups, sex, other medications, or comorbidities were studied. Several studies, however, used subgroups as the study population; results can provide indirect evidence for some aspects of key question three. Several observational studies and small-scale clinical trials address drug-drug interactions, drug-disease interactions, and ICS-related risk in pregnancy (Evidence Table 4).

I. Demographics

A. Age

An age-based analysis of efficacy, effectiveness, or tolerability was not conducted for any subgroup of older or younger patients. In general, populations in COPD studies were older than populations in asthma studies, primarily because of the demographics of the disease. One COPD study comparing budesonide to placebo was conducted in a population 70 years and older;[58] results were consistent with similar studies conducted in younger populations. Five head-to-head asthma trials were conducted specifically in children and adolescents;[19,23,32,30,34] results did not differ consistently from studies conducted in older populations. No study was conducted in children younger than 6 months of age. Most studies conducted in children younger than 4 years of age compared budesonide to placebo.

Although no head-to-head trial specifically addressed the relationship of age with drug and device combination, product formulation and inhaler device have been shown to effect proper use of inhaled products, especially in young children and older people.[105] Specifically, inhaler technique and dose delivery for DPI products (e.g., Turbuhaler®) have been shown to be inconsistent in children younger than 5 years of age.[106,105] In persons older than 75 years of age, breath-activated devices and DPIs were more likely to be used correctly than MDIs with large volume spacers.[107]

B. Racial groups

We did not find any study that directly compared the efficacy and tolerability of ICSs between one ethnic population and another. Although evidence suggests that access to health care and treatment compliance differs among ethnic groups,[108,109] no evidence supports specific differences between one ICS and another.

C. Sex

We did not find any study that directly compared the efficacy and tolerability of ICSs between males and females. One prospective cohort study evaluated the risk of osteoporosis in premenopausal women using triamcinolone and found a dose-related decline in BMD.[81] 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.

II. Other medications

No large-scale RCT investigated the likelihood of adverse interaction between an ICS and another drug. Two studies that did not meet the inclusion criteria for our review suggest the potential for interaction.[110,111] One small study conducted in 10 healthy volunteers[110] and a case report of a 70-year-old asthmatic woman[111] reported a potential interaction between budesonide and itraconazole, a potent inhibitor of cytochrome P450; this interaction has the potential to increase plasma cortisol, which can lead to Cushing's syndrome and adrenal insufficiency. Although little documentation exists to support the clinical relevance of this interaction, the potential for interaction between ICSs and inhibitors of the cytochrome P450 isoenzyme 3A4 (CYP3A4) is included in the product labeling for budesonide and fluticasone. Because beclomethasone, flunisolide, and triamcinolone also are eliminated by CYP3A4, the potential for interaction with drugs that inhibit this isoenzyme likely applies to all ICSs. Drugs known to inhibit CYP3A4

include amiodarone, cimetidine, clarithromycin, delavirdine, diltiazem, dirithromycin, disulfiram, erythromycin, fluoxetine, fluvoxamine, indinavir, itraconazole, ketoconazole, nefazodone, nevirapine, propoxyphene, quinupristin-dalfopristin, ritonavir, saquinavir, telithromycin, verapamil, zafirlukast, and zileuton. However, the clinical significance of these 'potential' interactions is questionable.

III. Comorbidities

We did not find any study that directly compared the efficacy, effectiveness, or tolerability of one ICS with another in populations with specific comorbidities. Because mixed evidence supports an increased risk of osteoporotic fractures, cataracts, and glaucoma in ICS-treated patients (especially at high doses), ICSs should be used cautiously in populations at increased risk for these conditions. No evidence implicates different risks between one ICS and another.

IV. Pregnancy

Inadequate control of asthma during pregnancy has been associated with higher rates of prematurity, intrauterine growth retardation, lower birth weight, perinatal death, and preeclampsia.[112,113] Use of ICSs is believed to help reduce this risk, although it may be associated with other harmful effects. FDA approved labeling classifies medications by the potential for risk during pregnancy. Budesonide is the only ICS labeled as a pregnancy category B – no well-controlled studies have been conducted in women but animal studies have found little to no risk. Other ICS products are given a more cautious classification; beclomethasone, flunisolide, fluticasone, and triamcinolone are labeled as pregnancy category C – 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.

For pregnant women, we did not identify any RCT that compared one ICS to another or any that compared an ICS to placebo. Five observational studies[114,115,116,117,118] and one RCT[119] evaluated ICS-related risk during pregnancy. Only two of the six studies met the inclusion criteria for our review,[115,117] one RCT compared beclomethasone to theophylline and placebo but failed to report the placebo comparisons,[119] one prospective cohort study was excluded because of insufficient focus on ICS use,[114] one retrospective cohort study was excluded because of poor exposure measurement and uncontrolled confounders,[118] and one case-series analysis was excluded because it relied on a small sample of ICS users.[116] Of the two studies included in our review (Table 12), one study specifically assessed budesonide-treated mothers[115] and one study compared ICS-treated mothers to non-ICS-treated mothers.[116,117] In both studies no significant differences were observed between ICS- and non-ICS-treated mothers. Compared to infants whose mothers did not use an ICS, infants born to mothers treated with an ICS had no significant differences in gestational age, birth weight, and length. Additionally, the rate of preterm delivery, congenital malformation, and stillbirth was similar for ICS- and non-ICS-treated patients. Results of excluded studies were consistent with included studies. Inadequate information exists to determine if risks associated with ICSs differs among ICSs.

Table 12. Summary of studies in pregnant women

Author, Year	N	Design	Population	Results	Quality Rating
Norjavaara & Gerhardsson de Verdier 2003[115]	293,948	Database review	Pregnant women (Swedish)	No difference in gestational age, birth weight, length, rate of stillbirths, or multiple births for children born to BUD-treated mothers	N/A
Schatz et al., 2004[117]	2,123	Retrospective cohort	Pregnant asthmatic women	No increase in perinatal risks for ICS-treated asthmatic pregnant women	Fair

ICS – inhaled corticosteroid
BUD – budesonide

SUMMARY

Table 13. Key questions and summary of the evidence

Key Question 1: Efficacy / Effectiveness	Quality of Evidence	Conclusion
Asthma	Fair	Nineteen head-to-head trials compared the efficacy of one ICS to another. Ten placebo-controlled trials provide additional evidence on health outcomes not commonly reported in head-to-head trials. No study was characterized as an effectiveness trial. Overall, efficacy studies provide fair evidence that, at equipotent doses administered through comparable delivery devices, ICSs do not differ in their ability to control asthma symptoms and reduce the need for additional rescue medication. Several studies comparing beclomethasone and budesonide with fluticasone contradict this evidence; however, a good-rated systematic review comparing the pooled effect of beclomethasone and budesonide to fluticasone found no differences in asthma symptoms, β-agonist use, or the number of asthma exacerbations. Ten placebo-controlled trials provide fair evidence that beclomethasone, budesonide, and fluticasone improve quality of life and/or functional status. Evidence comparing one ICS to another is poor. Four head-to-head trials that compared fluticasone to beclomethasone, budesonide, or triamcinolone reported quality of life or functional status; three of the four trials found fluticasone to be significantly better than the comparison ICS in quality of life, disruptions in physical activity, and work absences. However, two of the three trials that reported significant differences utilized more potent doses of fluticasone than the comparator ICS.
COPD	Poor	We identified no head-to head trials. In other trials, significant differences in study characteristics make this evidence insufficient to identify differences among treatments. Consistent fair to good evidence exists that ICS treatment does not reduce overall mortality in patients with COPD . The majority of the studies did not find significant differences in QOL between various ICS treatments and placebo. Only one trial reported a significantly slower decline of QOL in patients with severe COPD on high-dose fluticasone than on placebo. The body of evidence on the effect of ICS treatment on exacerbation rates is mixed. A good meta-analysis reported that the use of ICS reduced the rate of exacerbations significantly by about 30 %; however, a fair meta-analysis and a good cohort study do not support this finding. Only one large individual study with a high-dose treatment of fluticasone indicated a statistically significant reduction in exacerbation rates. Fair evidence from 2 meta-analyses exist that ICS treatment leads to a modestly slower decline of FEV1. The effect size, however, is small and the clinical significance questionable.were identified.

Table 13. Key questions and summary of the evidence (cont.)

Key Question 2: Adverse Events	Quality of Evidence	Conclusion
Tolerability and discontinuation	Fair	The overall incidence rate of adverse events is similar among ICSs. Taking the whole body of evidence into consideration, discontinuation rates because of adverse events do not differ significantly.
Bone Density / Osteoporosis	Fair	Overall, evidence of an association between ICS products and osteoporosis is mixed. Conflicting evidence from three observational studies suggests especially at higher doses an increased risk of fractures and reduction of BMD. Evidence from controlled trials and observational studies is insufficient to draw conclusions about one ICS compared to another.
Growth retardation	Fair to poor	Evidence of an association between ICS use and final adult height is limited to one observational study that did not detect differences in growth and adult height in budesonide-treated patients compared to asthmatic children without ICS treatment and healthy siblings.[91] Evidence is insufficient to determine if long-term treatment with ICSs other than budesonide lead to a reduction in adult height. Short-term (< 1 year) evidence from two head-to-head trials provides fair evidence that growth velocity is significantly less reduced with fluticasone treatment compared to beclomethasone and budesonide treatment. In addition, a meta-analysis reports a significant reduction in growth for beclomethasone compared to placebo. Evidence from controlled trials and observational studies is insufficient to compare final adult height for one ICS compared to another.
Acute Adrenal Crisis	Poor	Evidence from randomized trials and observational studies is insufficient to draw conclusions about a higher risk of acute adrenal crisis
Cataracts	Fair to poor	No study compared the risk of developing cataracts between one ICS and another. General evidence of an association between ICS use and cataracts is mixed. Overall, the body of evidence suggests that any ICS-related increase in the risk of cataracts is related to higher doses, longer duration of treatment, and older age.
Ocular hypertension and open-angle glaucoma	Fair to poor	No study compared the risk of ocular hypertension or open-angle glaucoma between one ICS and another. Two observational studies provide consistent evidence of a dose-related increase in risk for ICS-treated patients.

Table 13. Key questions and summary of the evidence (cont.)

Key Question 3: Subgroups	Quality of Evidence	Conclusion
Age	Fair to poor	Only indirect evidence suggests that ICSs do not differ in efficacy and tolerability in pediatric or older populations compared to the general population. Evidence is insufficient to draw conclusions about one ICS compared to another in pediatric or older populations.
Ethnicity	Poor	Evidence is insufficient to draw conclusions about ethnicity and treatment effects.
Sex	Poor	Evidence is insufficient to draw conclusions about sex and treatment effects.
Comorbidities	Poor	We could not find any studies comparing the efficacy and tolerability of ICS between a population with a comorbidity and one without the same comorbidity.
Pregnancy	Fair to poor	No study evaluated the risk of preterm delivery, congenital malformation, stillbirth, or reduction in birth weight/length for one ICS compared to another. Consistent evidence suggests that babies born to ICS-treated mothers are not at increased risk.

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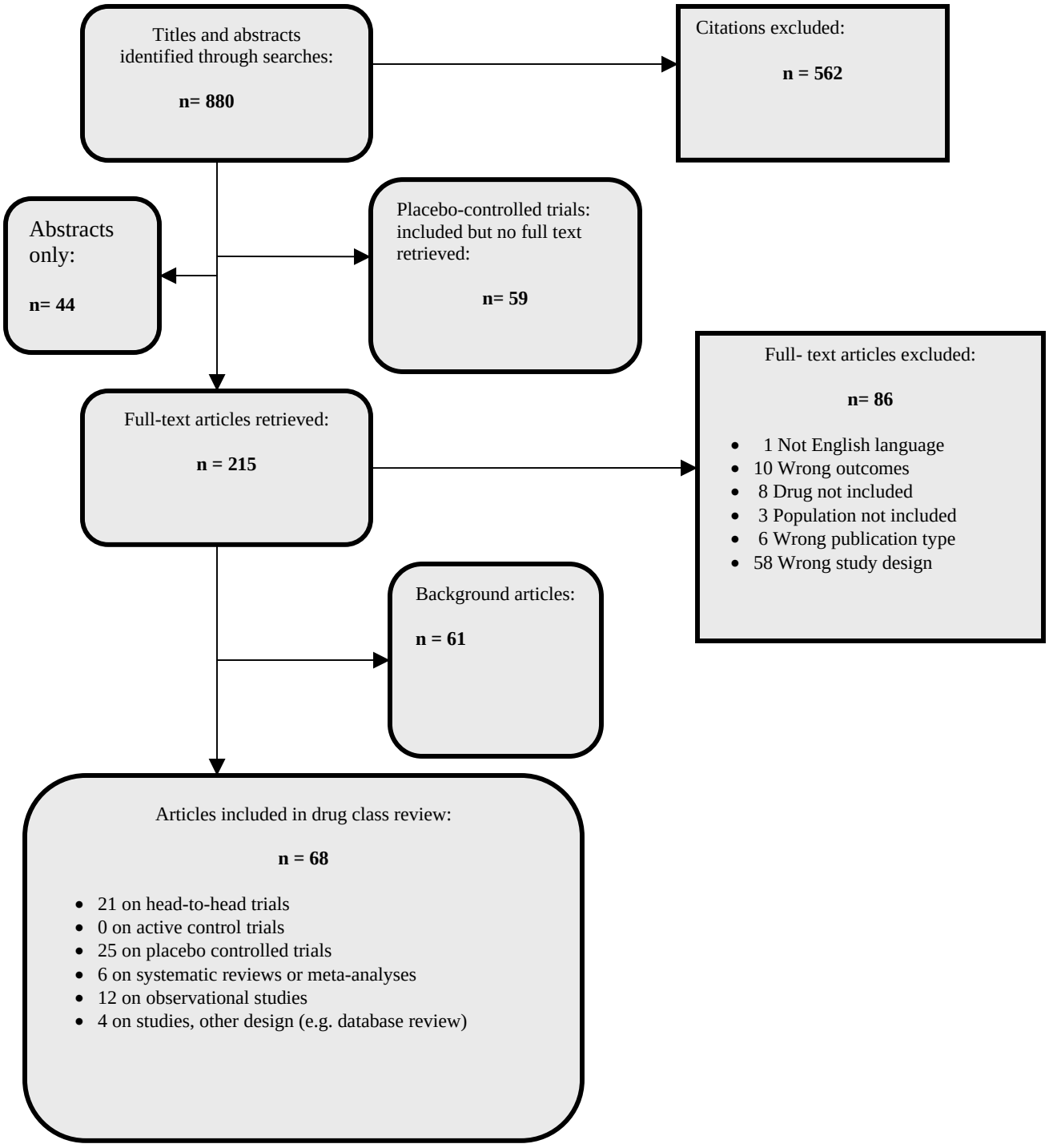
Figure 1. Literature search results



EVIDENCE TABLES

Evidence Table 1. Asthma Inhaled Corticosteroids

STUDY:	**Authors: Adams et al.**[18] **Year: 2004** **Country:** Multinational (14)
FUNDING:	NHS Research and Development UK (Cochrane Collaboration)
DESIGN:	**Study design:** Systematic Review **Number of patients:** 11,479
AIMS OF REVIEW:	To compare safety and efficacy of inhaled fluticasone to inhaled budesonide or beclomethasone in adults and children with chronic asthma
STUDIES INCLUDED IN META-ANALYSIS	Yes; analyses stratified by pre-study oral corticosteroid use, dose ratio (either 1:1 or 1:2), and parallel group vs. crossover group design
TIME PERIOD COVERED:	Up to 1999; update to this review will include studies through 2002
CHARACTERISTICS OF INCLUDED STUDIES:	48 studies included; all were RCTs, 58% were multi-centered; 75% were of parallel group design; 65% were described as double-blind; 3 studies were graded as high quality
CHARACTERISTICS OF INCLUDED POPULATIONS:	Mostly western European populations with mild to severe asthma recruited from primary and secondary care settings

Authors: Adams et al. **Year: 2004**	
CHARACTERISTICS OF INTERVENTIONS:	Intervention duration ranged from 1 month to longer than 1 year; majority of studies featured randomization to either FLUP vs. BUD or BDP at constant doses throughout study period; in one third of studies subjects received an equal 1:1 dose while in the remaining studies the dose ratio was 1:2; delivery devices used included MDI with or without spacer and DPI
MAIN RESULTS:	**<u>Non-oral corticosteroid treated asthmatics: at a dose ratio of 1:2 in parallel group design</u>** **Intermediate Outcomes**: Weighted mean difference (WMD) • FEV1 0.11 L (95% CI: 0.01 to 0.20; n = 1107) favoring FLUP • AM PEF 13 L/min (95% CI: 5 to 22; n = 2087) favoring FLUP • PM PEF 11 L/min (95% CI: 1 to 20; n = 1698) favoring FLUP **Health Outcomes**: • No difference in symptoms between treatments or rescue medication use; only limited pooling was possible • No difference in asthma exacerbations (OR 0.76 (95% CI: 0.53 to 1.09; n = 2890) **<u>Non-oral corticosteroid treated asthmatics: at a dose ratio of 1:1 in parallel group design</u>** **Intermediate Outcomes:** • FEV1 0.01 L (95% CI: –0.15 to 0.16; n = 479) showing no difference • AM PEF 12.2 L/min (95% CI: –8.06 to 32.30; n = 2087) showing no difference **Health Outcomes:** • No difference in asthma exacerbations OR 0.45 (95% CI: 0.14 to 1.47 with significant heterogeneity); OR = 0.28 (95% CI: 0.13 to 0.6 without heterogeneity if Heinig 1999 study is excluded) • No difference in asthma symptoms or rescue medication use, only limited pooling was possible

Authors: Adams et al. **Year: 2004**	
ADVERSE EVENTS:	**1: 2 dose ratio** • Sore throat/pharyngitis higher in FLUP than BDP/BUD, OR 2.16 (95% CI: 1.42 to 3.28; n = 1,919, significant) • Heterogeneity • Hoarseness no difference, OR 0.92 (95% CI: 0.38 to 2.22; n = 1,524) • Oral candidiasis no difference, OR 1.11 (95% CI: 0.63 to 1.96; n = 2,808, significant heterogeneity) • AM plasma cortisol no difference WMD 12 nmol/L (95% CI: –38 to 62) **1:1 dose ratio** • Sore throat no difference, OR 1.71 (95% CI: 0.94 to 3.10; n = 835) • Oral candidiasis no difference, OR 0.84 (95% CI: 0.52 to 1.34; n = 1,320) • Hoarseness higher in FLUP, OR 2.43 (95% CI: 1.10 to 5.39; n = 676)
COMPREHENSIVE LITERATURE SEARCH STRATEGY:	Yes
STANDARD METHOD OF APPRAISAL OF STUDIES:	Yes
QUALITY RATING:	**Good**

Asthma *Inhaled Corticosteroids*

STUDY:	**Authors: Ayres et al.**[31] **Year: 1995** **Country:** Multinational (13)		
FUNDING:	NR (one author affiliated with Glaxo Research and Development)		
DESIGN:	**Study design:** RCT **Setting:** Multi-center (66) **Sample size:** 671		
INTERVENTION: **Dose:** **Dosing range:** **Device:** **Duration:** **Sample size:**	**fluticasone** 1000 mcg/day High MDI 6 weeks 225	**fluticasone** 2000 mcg/day High MDI 6 weeks 225	**budesonide** 1600 mcg/day Medium MDI 6 weeks 221
Comparable dosing:	No; budesonide in the MDI is less potent than DPI		
INCLUSION:	Severe but stable asthma requiring beta-2 agonist and high dose inhaled corticosteroids; no admissions for asthma or changes in prophylactic medications within previous month; asthma symptoms despite continuing treatment; continued symptoms and evidence of reversibility during run-in period		
EXCLUSION:	Alteration of normal asthma medications during run-in period; taking systemic corticosteroids > 10 mg daily or investigational medications during the month preceding the trial; concomitant disease likely to affect evaluation; pregnancy or lactation; current smokers and past smokers with > 10 pack year history		
OTHER MEDICATIONS/ INTERVENTIONS:	Salbutamol as needed; pre-trial asthma medications (except inhaled steroids) at a constant dose allowed; spacer device allowed		
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Asthma classification:** Severe persistent		
	fluticasone 1000 mcg	**fluticasone 2000 mcg**	**budesonide**
Mean age (years):	51 (median)	48 (median)	50 (median)
Sex:	53% female	50% female	52% female
Ethnicity:	91% white	91% white	93% white
Other population characteristics:			
• use of long acting beta-2 agonist	11%	9%	8%
• use of fixed dose oral steroid	13%	12%	10%

<table>
<tr><td colspan="4">Authors: Ayres et al.
Year: 1995</td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">Primary Outcome Measures:
Patient recorded daily and nightly symptom scores rated on a scale from 0-3 and % symptom free days and nights; frequency of additional beta-2-agonist use and % rescue medication free days and nights; patient recorded daily AM and PM PEF; clinic measured PEF, FEV1, FVC
Secondary Outcome Measures:
Serum cortisol and measures of bone turnover
Timing of assessments: Daily for patient assessed outcomes; Baseline, 3 weeks, 6 weeks, and 2 weeks post study-endpoint for clinic-based measures</td></tr>
<tr><td>RESULTS:</td><td colspan="3">Health Outcome Measures:
No change in median day time symptom scores for any of the 3 treatments*
FLUP 1000 mcg had more symptom free days than BUD (P < 0.05)*
No difference in symptom free nights, nighttime asthma score, rescue free days, frequency of daytime rescue, or rescue free nights*
More budesonide treated patients required nighttime rescue: FLUP 1000 mcg 48%; FLUP 2000 mcg 50%; BUD 38% (P < 0.05)*
No difference in % of patients with exacerbations or % patients requiring oral corticosteroids*
Intermediate Outcome Measures:
All treatments increased the mean PEF; Patients taking FLUP improved their mean morning PEF and mean evening PEF more than those on BUD (P < 0.05)*
No difference in mean serum cortisol levels and markers of bone turnover</td></tr>
<tr><td>ANALYSIS:</td><td colspan="3">ITT: NR
Post randomization exclusions: NR</td></tr>
<tr><td>ATTRITION (overall):</td><td colspan="3">Overall loss to follow-up: NR
Loss to follow-up differential high: Unable to determine</td></tr>
<tr><td>ATTRITION (treatment specific):</td><td><u>fluticasone 1000 mcg</u></td><td><u>fluticasone 2000 mcg</u></td><td><u>budesonide</u></td></tr>
<tr><td>Loss to follow-up:</td><td>NR</td><td>NR</td><td>NR</td></tr>
<tr><td>Withdrawals due to adverse events:</td><td>NR</td><td>NR</td><td>NR</td></tr>
<tr><td>Withdrawals due to lack of efficacy:</td><td>NR</td><td>NR</td><td>NR</td></tr>
<tr><td>ADVERSE EVENTS:</td><td><u>fluticasone 1000 mcg</u></td><td><u>fluticasone 2000 mcg</u></td><td><u>budesonide</u></td></tr>
<tr><td>Overall adverse effects reported:</td><td>137 patients (61%)</td><td>110 patients (49%)</td><td>112 patients (51%)</td></tr>
<tr><td>Significant differences in events:</td><td>NR</td><td>NR</td><td>NR</td></tr>
<tr><td>QUALITY RATING:</td><td colspan="3">Fair</td></tr>
</table>

*primary outcome measures

Asthma *Inhaled Corticosteroids*

STUDY:	**Authors: Banov et al.**[54, 42] **Year: 2001, 2003** **Country:** US		
FUNDING:	AstraZeneca		
DESIGN:	**Study design:** RCT **Setting:** Multi-center (19 centers) **Sample size:** 177		
INTERVENTION: **Dose:** **Dosing range:** **Device:** **Duration:** **Sample size:**	**budesonide** 400 mcg/day Low DPI (Turbuhaler) 12 weeks 90	**placebo** N/A N/A DPI (Turbuhaler) 12 weeks 87	
Comparable dosing:	N/A		
INCLUSION:	ICS naïve; 18-70 years of age; at least 6 month history of asthma; reversible airway obstruction (> 12% increase in FEV1 after albuterol; prebronchodilator FEV1 50% - 85% of predicted; symptom score >1 for at least 7 of the 14 baseline days; nonsteroidal asthma medication in the six months prior to the study		
EXCLUSION:	Asthma hospitalization; used inhaled, oral, or parenteral steroid within 12 weeks; required oral steroid for > 30 days in past year; other significant disease; alcohol or drug abuse; smoking; pregnant/lactating		
OTHER MEDICATIONS/ INTERVENTIONS:	Albuterol; other prescription medications considered necessary for patient welfare		
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Asthma classification:** Mild-severe persistent		
	budesonide	**placebo**	
Mean age (years):	36.3	35.2	
Sex:	48.9% female	43.7% female	
Ethnicity:			
• white	92.2%	93.1%	
• black	6.7%	5.7%	
Other population characteristics:			
• baseline beta-agonist use	5.0 puffs/day	5.6 puffs/day	

Authors: Banov et al. **Year: 2001, 2003**			
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** FEV1 change from baseline **Secondary Outcome Measures:** Morning and evening PEFR change from baseline; morning and evening asthma symptom scores; patient discontinuation rates; albuterol use; AQLQ **Timing of assessments:** PEFR and asthma scores recorded daily by patient; lung capacity measured at baseline and weeks 2, 4, 8, and 12; AQLQ administered at baseline and weeks 4 and 12		
RESULTS:	**Health Outcome Measures:** • Asthma symptom scores were significantly lower in the BUD group than the placebo group (P = 0.012) (daytime) and (P = 0.001) (evening) • Albuterol use was significantly lower in the BUD group than the placebo group (P = 0.003) • Overall AQLQ score and each of the four domains of the AQLQ score was significantly more improved in the BUD group than the placebo group (P < 0.05; moderate clinical benefit) **Intermediate Outcome Measures:** • Increase in mean FEV1 was significantly greater for BUD than placebo (P = 0.007) • PEFR improvement was significantly greater for BUD than placebo (AM P = 0.037; PM P = 0.01)		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** Yes (3)		
ATTRITION (*overall*): **ATTRITION (*treatment specific*):** **Loss to follow-up:** **Withdrawals due to adverse events:** **Withdrawals due to lack of efficacy:**	**Overall loss to follow-up:** 18 (10%) **Loss to follow-up differential high:** No **budesonide** 8 (8.9%) 3 (3.3%) 1 (1.1%)	 **placebo** 10 (11.5%) 4 (4.6%) 3 (3.4%)	
ADVERSE EVENTS: **Overall adverse effects reported:** **Significant differences in events:**	**budesonide** NR NR	**placebo** NR NR	
QUALITY RATING:	**Good**		

*primary outcome measures

Asthma *Inhaled Corticosteroids*

STUDY:	**Authors: Barnes et al.**[21] **Year: 1993** **Country:** Multinational (7)		
FUNDING:	NR (one author affiliated with Glaxo)		
DESIGN:	**Study design:** RCT **Setting:** Multi-center (18 outpatient clinics) **Sample size:** 154		
INTERVENTION: **Dose:** **Dosing range:** **Device:** **Duration:** **Sample size:**	**fluticasone** 1000 mcg/day High MDI 6 weeks 82	**beclomethasone** 2000 mcg/d High MDI 6 weeks 72	
Comparable dosing:	Yes		
INCLUSION:	Clinical history of severe asthma; required 1.5 – 2.0 mg/d of beclomethasone or budesonide and inhaled beta-2 agonist therapy; patients had to have at least two of the following: morning PEFR < 70% of predicted, >15% reversibility in FEV1 following inhalation of a beta-2 agonist, or > 20 % diurnal variation in PEFR		
EXCLUSION:	Medication changes during the run-in (except beta-2 agonist); treatment with systemic corticosteroids within one month of the study; treatment with other investigational drugs within four weeks of the study; hypersensitivity to inhaled corticosteroids; concomitant diseases; pregnancy		
OTHER MEDICATIONS/ INTERVENTIONS:	Inhaled salbutamol as required; continued other asthma medications		

Authors: Barnes et al. **Year: 1993**			
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Asthma classification:** Severe persistent		
	fluticasone	**beclomethasone**	
Median age (years):	50	52	
Sex:	46% female	43% female	
Ethnicity:			
• white	95%	99%	
Other population characteristics:			
• smokers	17%	24%	
• methylxanthines	46%	43%	
• used spacer	32%	31%	
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Morning and evening PEFR **Secondary Outcome Measures:** Diurnal variation in PEFR; day and night asthma symptoms; Salbutamol use; clinic measured PEFR, FEV1, and FVC **Timing of assessments:** Morning and evening PEFR, asthma symptoms, and salbutamol use recorded daily by patient; clinic measurements were made at the end of the run-in period, at 3 and 6 weeks, and two weeks following the end of study		
RESULTS:	**Health Outcome Measures:** • No difference in asthma symptom improvement or salbutamol use between FLUP and BDP **Intermediate Outcome Measures:** • No difference in morning or evening PEFR between FLUP and BDP* • A statistically greater reduction in the diurnal variation of PEFR in FLUP patients compared to BDP patients ($P < 0.04$)		

Authors: Barnes et al. **Year: 1993**			
ANALYSIS:	**ITT:** No **Post randomization exclusions:** Yes		
ATTRITION (*overall*):	**Overall loss to follow-up:** 18 (12%) **Loss to follow-up differential high:** No		
ATTRITION (*treatment specific*):	**fluticasone**	**beclomethasone**	
Loss to follow-up:	13 (16%)	5 (7%)	
Withdrawals due to adverse events:	2 (2%)	2 (3%)	
Withdrawals due to lack of efficacy:	6 (7%)	3 (4%)	
ADVERSE EVENTS:	**fluticasone**	**beclomethasone**	
Overall adverse effects reported:	43 (52%)	37 (51%)	
Significant differences in events:	none	none	
QUALITY RATING:	**Fair**		

*primary outcome measures

Asthma *Inhaled Corticosteroids*

STUDY:	**Authors: Berkowitz et al.** [29] **Year: 1998** **Country:** USA		
FUNDING:	Schering Corporation		
DESIGN:	**Study design:** RCT **Setting:** Multi-center (17 asthma/allergy centers) **Sample size:** 339		
INTERVENTION:	**beclomethasone**	**triamcinolone**	**placebo**
Dose:	336 mcg/day	800 mcg/day	N/A
Dosing range:	Low	Low	N/A
Device:	MDI	MDI with tube extender	N/A
Duration:	8 weeks	8 weeks	8 weeks
Sample size:	114	111	114
Comparable dosing:	Yes		
INCLUSION:	Ages 18-65; history of asthma at least 2 years prior to study; FEV1 of 50-90% of predicted at baseline with evidence of reversibility; requirement for and use of inhaled corticosteroids during 1 month prior to study		
EXCLUSION:	Other pulmonary condition; other clinically significant diseases that could interfere with the conduct or evaluation of the study; history of smoking during prior 12 months; history of respiratory infection during prior 30 days; abnormal results from a physical exam or ECG that would affect patient safety; history of assisted ventilation or admission to an ICU, ED, or hospital for severe asthma exacerbations		
OTHER MEDICATIONS/ INTERVENTIONS:	Albuterol		
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Asthma classification:** Mild-moderate		
	beclomethasone	**triamcinolone**	**placebo**
Mean age (years):	36.1	40.3	38.3
Sex:	62.2% female	63.8% female	61.0% female
Ethnicity:	86.7% white	87.2% white	95.1% white
Other population characteristics:	NR	NR	NR

Authors: Berkowitz et al. **Year: 1998**			
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Mean change in FEV1 **Secondary Outcome Measures:** FEF 25-75; FVC; clinic measured PEF; patient measured PEF; asthma symptoms; rescue medication use; asthma exacerbations; nighttime awakenings **Timing of assessments:** Daily for patient assessed outcomes; every 4 weeks for clinic measured outcomes		
RESULTS:	**Health Outcome Measures:** • No difference in symptom reduction between active treatments; both were significantly better than placebo (P < 0.01) • No difference in weekly use of albuterol between BDP, TRIA, and placebo **Intermediate Outcome Measures:** • Mean change in FEV1: BDP: 0.27; TRIA: 0.22; placebo: – 0.06; (P < 0.05 for each active treatment vs. placebo)* • No difference in mean increases in FEF 25-75, FVC, and clinic measured PEF between active treatments; both significantly better than placebo (P < 0.05 for all measures)		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** Yes		
ATTRITION (*overall*):	**Overall loss to follow-up:** 115 (33.9%) **Loss to follow-up differential high:** No (differential for placebo comparison high)		
ATTRITION (*treatment specific*):	**beclomethasone**	**triamcinolone**	**placebo**
Loss to follow-up:	28 (24.6%)	26 (23.4%)	61 (53.5%)
Withdrawals due to adverse events:	11 (9.8%)	9 (8.3%)	18 (15.8%)
Withdrawals due to lack of efficacy:	7 (6.1%)	9 (8.1%)	30 (26.3%)
ADVERSE EVENTS:	**beclomethasone**	**triamcinolone**	**placebo**
Overall adverse effects reported:	56 (50%)	62 (57.4%)	61 (55.5%)
Significant differences in events:	none	none	none
QUALITY RATING:	**Fair**		

*primary outcome measures

Asthma *Inhaled Corticosteroids*

STUDY:	**Authors: Bronsky et al.**[27] **Year: 1998** **Country:** USA		
FUNDING:	Schering Corporation		
DESIGN:	**Study design:** RCT **Setting:** Multi-center (16 centers) **Sample size:** 329		
INTERVENTION: **Dose:** **Dosing range:** **Device:** **Duration:** **Sample size:**	**beclomethasone** 336 mcg/day Medium MDI without spacer 8 weeks 110	**triamcinolone** 800 mcg/day Low MDI with spacer 8 weeks 107	**placebo** N/A N/A MDI 8 weeks 112
Comparable dosing:	Yes		
INCLUSION:	18-65 years of age; history of asthma beginning at least 2 years prior to enrollment; FEV1 on day 1 between 50% and 90% of predicted value following 8-hour beta-2 agonist withholding period; airway reversibility within last 12 months or on day 1 as shown by an increase in FEV1 $\geq$ 15% within 20 minutes of albuterol MDI or 2.5 mg albuterol delivered by nebulization; maintained on ICS for 30 days		
EXCLUSION:	History of smoking; chronic lung disease other than asthma; recurrent hospital admissions for severe asthma exacerbations; other clinically significant disease; presence of respiratory infection within preceding 30 days; hypersensitivity to any medication; abnormal physical exam or electrocardiogram		
OTHER MEDICATIONS/ INTERVENTIONS:	Albuterol; other concomitant medications not allowed		

<table>
<tr><td colspan="4">Authors: Bronsky et al.
Year: 1998</td></tr>
<tr><td rowspan="2">POPULATION CHARACTERISTICS:</td><td colspan="3">Groups similar at baseline: Yes
Asthma classification: Mild to moderately severe</td></tr>
<tr><td></td><td><u>beclomethasone</u></td><td><u>triamcinolone</u></td><td><u>placebo</u></td></tr>
<tr><td>Mean age (years):</td><td>37.4</td><td>38.6</td><td>36.2</td></tr>
<tr><td>Sex:</td><td>54.9% female</td><td>49.5% female</td><td>54.0% female</td></tr>
<tr><td>Ethnicity:</td><td></td><td></td><td></td></tr>
<tr><td>• white</td><td>91.2%</td><td>88.7%</td><td>89.7%</td></tr>
<tr><td>• black</td><td>3.9%</td><td>8.2%</td><td>8.0%</td></tr>
<tr><td>• other</td><td>4.9%</td><td>5.1%</td><td>2.3%</td></tr>
<tr><td>Other population characteristics:</td><td></td><td></td><td></td></tr>
<tr><td>• disease duration (mean years)</td><td>20.5</td><td>21.0</td><td>20.2</td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">Primary Outcome Measures: FEV1; PEFR; FVC

Secondary Outcome Measures: Daytime and nighttime asthma symptoms (diary); albuterol use; number of nighttime awakenings; number of attacks

Timing of assessments: Baseline, days 28 and 56</td></tr>
<tr><td>RESULTS:</td><td colspan="3">Health Outcome Measures:
• BDP-treated patients reported fewer asthma symptoms than TRIA-treated patients (P = 0.028)
• No significant difference in rescue medication use at endpoint between active treatment groups
• No significant differences in nighttime awakenings due to asthma symptoms

Intermediate Outcome Measures:
• Both active treatment groups improved significantly compared to placebo (P < 0.1)*
• BDP had greater mean improvements in FEV1 than TRIA throughout the study but no significant difference in FEV1 at endpoint was reported*
• Subgroup analysis did not report differences in efficacy in patients with mild to moderate and moderate to severe asthma</td></tr>
</table>

Authors: Bronsky et al. **Year: 1998**			
ANALYSIS:	**ITT:** Yes (but not reported for efficacy results) **Post randomization exclusions:** Yes		
ATTRITION (*overall*):	**Overall loss to follow-up**: 81 (24.6%) **Loss to follow-up differential high:** No		
ATTRITION (*treatment specific*):	**beclomethasone**	**triamcinolone**	**placebo**
Loss to follow-up:	16 (14.5%)	18 (16.8%)	47 (42%)
Withdrawals due to adverse events:	3 (2.7%)	9 (8.4%)	20 (17.9%)
Withdrawals due to lack of efficacy:	1 (0.9%)	1 (0.9%)	19 (17.0%)
ADVERSE EVENTS:	**beclomethasone**	**triamcinolone**	**placebo**
Overall adverse effects reported:	53 (48.2%)	54 (50.9%)	67 (59.8%)
Significant differences in events:			
• Respiratory infections	11 (10.4%)	3 (2.7%)	NR
QUALITY RATING:	**Good**		

*primary outcome measures

Asthma *Inhaled Corticosteroids*

STUDY:	**Authors: Childhood Asthma Management Program (CAMP) Research Group**[43] **Year: 2000** **Country:** Multinational (US and Canada)		
FUNDING:	NIH; National Center for Research Resources; various pharmaceutical companies		
DESIGN:	**Study design:** RCT **Setting:** Multi-center (8 sub-specialty outpatient clinics) **Sample size:** 1,041		
INTERVENTION:	**budesonide**	**placebo**	**nedocromil**
Dose:	400 mcg/day	N/A	16 mg/day
Dosing range:	Low-medium	N/A	N/A
Device:	MDI	MDI	MDI
Duration:	Mean 4.3 years	Mean 4.3 years	Mean 4.3 years
Sample size:	311	418	312
Comparable dosing:	N/A		
INCLUSION:	Age 5-12; mild to moderate asthma defined by presence of symptoms or beta-agonist use twice weekly or use of daily medication for asthma; methacholine dose ≤ 12.5 mg/ml to cause a 20% decrease in FEV1		
EXCLUSION:	No other clinically significant conditions		
OTHER MEDICATIONS/ INTERVENTIONS:	Albuterol for rescue therapy as needed or for prevention of exercise induced symptoms; short courses of oral corticosteroids as needed for exacerbations; addition of beclomethasone to study medications allowed if asthma control was inadequate; tapering of study medications was allowed for remission		
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Asthma classification:** Mild-moderate persistent		
	budesonide	**placebo**	**nedocromil**
Mean age (years):	9.0	9.0	8.8
Sex:	41.8% female	44.0% female	34.0% female
Ethnicity:			
• white	64.6%	69.9%	69.9%
• black	14.1%	13.4%	12.2%
Other population characteristics:	NR	NR	NR

<table>
<tr><td colspan="4">Authors: CAMP
Year: 2000</td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">Primary Outcome Measures: Mean change in post-bronchodilator FEV1 (% of predicted value)

Secondary Outcome Measures: Spirometry measures; methacholine challenge; PEF; asthma symptoms; nighttime awakenings; beta-agonist use; use of prednisone and time to first use; use of additional BUD or other asthma medicine; school absences; urgent care or hospital visits; height; bone mineral density; skeletal maturation; Childhood Depression Inventory; eye exam for cataract development

Timing of assessments: Daily patient assessment; bi-annual spirometry; annual methacholine challenge and psychological development; 4-month height, weight, and Tanner stage all at study end</td></tr>
<tr><td>RESULTS:</td><td colspan="3">Health Outcome Measures:
Compared to placebo BUD-treated patients had fewer hospitalizations (P = 0.04), fewer urgent care visits (P < 0.001), less prednisone use (P < 0.001), fewer symptoms (P = 0.005), less albuterol use (P < 0.001), and more episode free days (P = 0.01)
No differences between BUD and placebo in the number of nighttime awakenings per month
Larger decrease in Children’s Depression Inventory in BUD group than placebo group (P = 0.01)
No difference between BUD and placebo in fractures, BMD, or posterior subcapsular cataracts
Significantly greater increase in height for placebo-treated patients compared to BUD (P = 0.005)
Intermediate Outcome Measures:
No difference in post-bronchodilator improvement in FEV1 between BUD and placebo*
Larger adjusted mean change in % predicted pre-bronchodilator FEV1 in BUD group (P = 0.02)
Airway responsiveness to methacholine favors BUD (P < 0.001)</td></tr>
<tr><td>ANALYSIS:</td><td colspan="3">ITT: Yes
Post randomization exclusions: NR</td></tr>
<tr><td>ATTRITION (overall):</td><td colspan="3">Overall loss to follow-up: 1.6% (at least one outcome measure)
Loss to follow-up differential high: No</td></tr>
<tr><td>ATTRITION (treatment specific):
Loss to follow-up:
Withdrawals due to adverse events:
Withdrawals due to lack of efficacy:</td><td><u>budesonide</u>
1.6%
NR
NR</td><td><u>placebo</u>
1.7%
NR
NR</td><td><u>nedocromil</u>
1.6%
NR
NR</td></tr>
</table>

Authors: CAMP **Year: 2000**			
ADVERSE EVENTS:	**budesonide**	**placebo**	**nedocromil**
Overall adverse effects reported:	NR	NR	NR
Significant differences in events:			
• Change in height (cm) (P = 0.005)	22.7	23.8	23.7
QUALITY RATING:	**Good**		

*primary outcome measures

Asthma *Inhaled Corticosteroids*

STUDY:	**Authors: Condemi et al.**[36] **Year: 1997** **Country:** USA		
FUNDING:	Glaxo Wellcome Inc., Research Triangle Park, NC		
DESIGN:	**Study design:** RCT **Setting:** Multi-center (24 outpatient centers) **Sample size:** 291		
INTERVENTION:	**fluticasone**	**triamcinolone**	**placebo**
Dose:	500 mcg/day	800 mcg/day	N/A
Dosing range:	Medium (adult) High (child)	Low	N/A
Device:	DPI (Diskhaler)	MDI	Diskhaler and Azmacort
Duration:	24 weeks	24 weeks	24 weeks
Sample size:	95	101	95
Comparable dosing:	No; FLUP dose considered medium-high, TRIA dose considered low		
INCLUSION:	Nonsmokers; at least 12 years old; met American Thoracic Society criteria for asthma; required inhaled corticosteroid therapy for at least 4 weeks preceding the study; FEV1 of 50-80% of predicted value; 1 documented urgent or emergency care visit within 12 months of screening.		
EXCLUSION:	Use of methotrexate or gold salts; use of inhaled cromolyn or nedocromil; use of oral, intranasal, or injectable corticosteroids within 4 weeks of trial; significant illness; pregnancy		
OTHER MEDICATIONS/ INTERVENTIONS:	Albuterol; theophylline		
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Asthma classification:** Mild-severe persistent		
	fluticasone	**triamcinolone**	**placebo**
Mean age (years):	34	37	37
Sex:	46% female	58% female	48% female
Ethnicity:			
• white	91%	89%	93%
• black	5%	5%	5%
• other	4%	6%	2%
Other population characteristics:			
• mean % predicted FEV1	68%	67%	66%

Authors: Condemi et al. **Year: 1997**			
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Morning predose FEV1; morning PEF; probability of remaining in the study (patients withdrawn because of lack of efficacy); albuterol use; nighttime awakenings; asthma symptom scores **Secondary Outcome Measures:** Clinic measured pulmonary function tests; rescue medication free days; symptom free days **Timing of assessments:** Patient measures performed daily; clinic measures performed at baseline, after weeks 1 and 2, then once every two weeks for 1 month, and then once every 3 weeks for the remainder of the study		
RESULTS:	**Health Outcome Measures:** • Patients taking FLUP had significantly less albuterol use than patients taking TRIA (P < 0.05)* • Patients taking FLUP had significantly more rescue medication free days (P < 0.05)* • No difference in nighttime awakenings* • No difference in asthma symptom scores* • No difference in symptom free days **Intermediate Outcome Measures:** • Patients taking FLUP had significantly greater FEV1 improvement than TRIA (P < 0.05)* • Patients taking FLUP had significantly greater PEF improvement than TRIA (P < 0.05)* • No difference in the probability of remaining in the study between FLUP and TRIA*		
ANALYSIS:	**ITT:** Yes (LOCF) **Post randomization exclusions:** NR		
ATTRITION (*overall*):	**Overall loss to follow-up:** 146 (50%) **Loss to follow-up differential high:** Yes (but major differences are compared to placebo)		
ATTRITION (*treatment specific*):	**fluticasone**	**triamcinolone**	**placebo**
Loss to follow-up:	32 (34%)	45 (45%)	69 (73%)
Withdrawals due to adverse events:	4 (4%)	5 (5%)	8 (8%)
Withdrawals due to lack of efficacy:	16 (17%)	27 (27%)	57 (60%)
ADVERSE EVENTS:	**fluticasone**	**triamcinolone**	**placebo**
Overall adverse effects reported:	14 (15%)	8 (8%)	12 (13%)
Differences in specific events:			
• Candidiasis (P = 0.035)	8 (8%)	3 (3%)	1 (1%)

QUALITY RATING:	**Fair**

*primary outcome measures

Asthma ***Inhaled Corticosteroids***

STUDY:	**Authors: Connett et al.**[41] **Year: 1993** **Country:** UK		
FUNDING:	Royal Alexandra Hospital Rocking Horse Appeal		
DESIGN:	**Study design:** RCT **Setting:** Referral hospital **Sample size:** 40		
INTERVENTION: **Dose:** **Dosing range:** **Device:** **Duration:** **Sample size:**	**budesonide** 400 mcg/d Low-medium MDI/Nebuhaler/Facemask 26 weeks 20	**placebo** N/A N/A MDI/Nebuhaler/Facemask 26 weeks 20	
Comparable dosing:	N/A		
INCLUSION:	Age 1-3 years; 6-month history of troublesome asthma; responsive to bronchodilators (assessed by parental opinion); symptoms on at least 3 days/week during run-in period; able to use devices during the run-in period		
EXCLUSION:	Chest x-ray findings suggestive of other causes of wheezing; respiratory tract infection; treatment with inhaled or oral corticosteroids in the previous 2 weeks		
OTHER MEDICATIONS/ INTERVENTIONS:	Terbutaline to a maximum of 4 puffs/day (250 mcg/puff) in any 4 hours as needed; nebulized terbutaline or oral corticosteroids for exacerbations		
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** No: significantly more females in the BUD group **Asthma classification:** Severe-persistent		
	budesonide	**placebo**	
Mean age (years):	1.7 years	1.9 years	
Sex:	45% female	25% female	
Ethnicity:	NR	NR	
Other population characteristics:			
• smoking	11 (55%)	9 (45%)	

Authors: Connett et al. **Year: 1993**			
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Nighttime cough **Secondary Outcome Measures:** Other day and nighttime asthma symptoms; parental sleep disturbance due to child's asthma symptoms at night; activity limitation due to asthma symptoms; use of study medication; time spent caring for child's asthma; amount oral corticosteroids used (mg/patient); number of prescriptions per patient for asthma **Timing of assessments:** Daily for parental assessed outcomes; every 6 weeks for clinic assessed outcomes		
RESULTS:	**Health Outcome Measures:** • Parental sleep was disturbed less frequently for BUD-treated children (P = 0.07) • No difference in days per week of limited activity • No difference in day time spent caring for child's asthma • Significantly less nighttime spent caring for child's asthma (P < 0.03) • Three hospital admissions for BUD-treated patients and eight hospital admissions for placebo-treated patients		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** Yes (4)		
ATTRITION (*overall*): **ATTRITION (*treatment specific*):** **Loss to follow-up:** **Withdrawals due to adverse events:** **Withdrawals due to lack of efficacy:**	**Overall loss to follow-up:** 14 (35%) **Loss to follow-up differential high:** No **budesonide** 7 (35%) NR 3 (15%)	**placebo** 7 (35%) NR 6 (30%)	
ADVERSE EVENTS: **Overall adverse effects reported:** **Significant differences in events:** • Hospital admissions: (P = NR)	**budesonide** 1 (5%) 3 (15%)	**placebo** 0 (0%) 8 (40%)	
QUALITY RATING:	**Fair**		

Asthma ***Inhaled Corticosteroids***

STUDY:	**Authors: Ernst et al.**[48] **Year: 1992** **Country:** Canada		
FUNDING:	Boehringer Ingelheim Pharmaceuticals, Canada Ltd.		
DESIGN:	**Study design:** Case control study **Setting:** Population-based Saskatchewan 1978-1987 **Sample size:** 784		
INTERVENTION:	**no beclomethasone**	**< 1 canister beclomethasone/month**	**≥ 1 canister beclomethasone/month**
Dose:	N/A	N/A	N/A
Dosing range:	N/A	N/A	N/A
Device:	N/A	N/A	N/A
Duration:	N/A	N/A	N/A
Sample size:	515	232	37
Comparable dosing:	N/A		
INCLUSION:	Case patients were 44 patients that experienced asthma death, 85 that experienced near-death, and 655 controls with at least one asthma hospitalization matched for age and date of entry into the dataset		
EXCLUSION:	NR		
OTHER MEDICATIONS/ INTERVENTIONS:	N/A		
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** N/A **Asthma classification:** Moderate persistent to severe persistent		
	no beclomethasone	**< 1 canister beclomethasone/month**	**≥ 1 canister beclomethasone/month**
Mean Age (years):	28	33	38
Sex:	43.7% female	47% female	35.1% female
Ethnicity:	NR	NR	NR
Other Medications:			
• inhaled beta-agonist	78.8%	94.8%	97.3%
• oral beta-agonist	29.3%	28.9%	16.2%
• theophylline	50.5%	79.3%	51.4%
• oral corticosteroids	18.6%	55.2%	45.9%

<table>
<tr><td colspan="4">Authors: Ernst et al.
Year: 1992</td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">Primary Outcome Measures: OR of life threatening asthma attacks in patients using beclomethasone relative to nonusers

Secondary Outcome Measures: None

Timing of assessments: N/A</td></tr>
<tr><td>RESULTS:</td><td colspan="3">Health Outcome Measures:
Patients administered, on average, one or more MDI of beclomethasone per month over a one year period had a significantly lower risk of fatal and near-fatal asthma; OR: 0.1 (95% CI: 0.02 to 0.6)
Intermediate Outcome Measures:
None</td></tr>
<tr><td>ANALYSIS:</td><td colspan="3">ITT: N/A
Post randomization exclusions: N/A</td></tr>
<tr><td>ATTRITION (overall):</td><td colspan="3">Overall loss to follow-up: N/A
Loss to follow-up differential high: N/A</td></tr>
<tr><td>ATTRITION (treatment specific):</td><td><u>no beclomethasone</u></td><td><u>< 1 canister beclomethasone/month</u></td><td><u>≥ 1 canister beclomethasone/month</u></td></tr>
<tr><td>Loss to follow-up:</td><td>N/A</td><td>N/A</td><td>N/A</td></tr>
<tr><td>Withdrawals due to adverse events:</td><td>N/A</td><td>N/A</td><td>N/A</td></tr>
<tr><td>Withdrawals due to lack of efficacy:</td><td>N/A</td><td>N/A</td><td>N/A</td></tr>
<tr><td>ADVERSE EVENTS:
Overall adverse effects reported:
Significant differences in events:</td><td colspan="3">
N/A
N/A</td></tr>
<tr><td>QUALITY RATING:</td><td colspan="3">Good</td></tr>
</table>

Asthma ***Inhaled Corticosteroids***

STUDY:	**Authors: Fabbri et al.**[22] **Year: 1993** **Country:** Multinational (10 countries)		
FUNDING:	Glaxo Group Research Ltd.		
DESIGN:	**Study design:** RCT **Setting:** Multi-center (25) **Sample size:** 274		
INTERVENTION: **Dose:** **Dosing range:** **Device:** **Duration:** **Sample size:**	**fluticasone** 1500 mcg/day High MDI 1 year (12 weeks for diary) 142	**beclomethasone** 1500 mcg/day High MDI 1 year (12 weeks for diary) 132	
Comparable dosing:	Yes		
INCLUSION:	Age 17-80; moderate to severe asthma; currently receiving at least 1000 mcg/d of BDP or BUD; continued evidence of asthma (symptoms, FEV1, reversibility) at end of run-in		
EXCLUSION:	Treatment with ≥ 2000 mcg/d of BDP or BUD; systemic corticosteroids within 1 month prior to study or on > 3 occasions during 6 months prior to study; treatment with other investigational drugs within 4 weeks prior to study; concomitant disease likely to complicate the evaluation; pregnancy/lactation		
OTHER MEDICATIONS/ INTERVENTIONS:	Spacer devices allowed at discretion of individual physicians.		
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes; more females in beclomethasone group but not significant **Asthma classification:** Symptomatic moderate to severe		
	fluticasone	**beclomethasone**	
Mean age (years): *(range reported)*	17-77	19-80	
Sex:	36% female	52% female	
Ethnicity:	96% white	98% white	
Other population characteristics:			
• smoker	13%	8%	
• pre-study methylxanthine	55%	55%	

Authors: Fabbri et al. **Year: 1993**	
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Patient assessed AM and PM PEF; asthma symptom scores; rescue beta-agonist use; clinic measured PEF, FEV1, FVC; asthma exacerbations defined as increasing asthma symptoms requiring a change in therapy other than inhaled beta-agonist rescue therapy **Secondary Outcome Measures:** Urinary free cortisol; serum cortisol; candida swab **Timing of assessments:** During first 3 months patients had clinic measures every 4 weeks and performed daily PEF/symptom scores; then clinic visits every 3 months
RESULTS:	**Health Outcome Measures:** • No difference in day or night symptoms between treatment groups at week 12 • No difference in % of beta-agonist free days or nights between groups at week 12 • No overall difference in number of times per week beta-agonist medication used at week 12 • Total number of asthma exacerbations (FLUP 33 vs. BDP 62 (no P value given)) • % of patient with exacerbation (FLUP 16% vs. BDP 28% (P < 0.05)) • % of patients with severe exacerbation (FLUP 2% vs. BDP 10% (P < 0.02)) **Intermediate Outcome Measures:** • 12 week adjusted mean difference in AM PEF 15 L/min favoring FLUP (95% CI: 6 to 25, P < 0.005) • 12 week adjusted mean difference in PM PEF 10 L/min favoring FLUP (95% CI: 0 to 19, P < 0.05) • 1 year adjusted mean difference in clinic PEF 20 L/min favoring FLUP (95% CI: 1 to 40, P< 0.05) • 1 year adjusted mean difference in FEV1 0.15 L favoring FLUP (95% CI: 0.01 to 0.29, P < 0.05) • No difference in adjusted mean difference at 1 year for FVC

Authors: Fabbri et al. **Year: 1993**			
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** NR		
ATTRITION (*overall*):	**Overall loss to follow-up:** 43 (15.7%) **Loss to follow-up differential high:** No		
ATTRITION (*treatment specific*):	**fluticasone**	**beclomethasone**	
Loss to follow-up:	25 (17.6%)	18 (13.6%)	
Withdrawals due to adverse events:	11 (8%)	11 (8%)	
Withdrawals due to lack of efficacy:	NR	NR	
ADVERSE EVENTS:	**fluticasone**	**beclomethasone**	
Overall adverse effects reported:	276 (70%)	267 (73%)	
Significant differences in events:	none	none	
QUALITY RATING:	**Fair**		

Asthma *Inhaled Corticosteroids*

STUDY:	**Authors: Fairfax et al.**[20] **Year: 2001** **Country:** UK and Ireland		
FUNDING:	3M Pharmaceuticals		
DESIGN:	**Study design:** RCT **Setting:** Multi-center (30 general practice sites) **Sample size:** 172		
INTERVENTION: **Dose:** **Dosing range:** **Device:** **Duration:** **Sample size:**	**fluticasone** 400 mcg/day Medium MDI 6 weeks 84	**beclomethasone** 400 mcg/day Medium MDI (HFA) 6 weeks 88	
Comparable dosing:	Yes		
INCLUSION:	18-65 years old; taking 100-250 mcg/day FLUP; at least a 4 week history of clinically diagnosable asthma; PEFR of 50-90% of predicted value		
EXCLUSION:	Use of oral corticosteroids, intramuscular or injectable steroids; use of beta-blockers, salmeterol, formoterol, or monoamine oxidase inhibitors within 4 weeks of trial; significant illness; pregnancy; using a nasal steroid at a dose >400 mcg/day; use of an investigational drug within 4 weeks of trial		
OTHER MEDICATIONS/ INTERVENTIONS:	Beta-2 agonists as required		
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Asthma classification:** Mild; moderate; severe		
	fluticasone	**beclomethasone**	
Mean age (years):	39.5	40.6	
Sex:	60.7% female	59.1% female	
Ethnicity:	NR	NR	
Other population characteristics:			
• mean % predicted PEFR	75.2%	75.0%	
• current smokers	26.2%	22.7%	

Authors: Fairfax et al. **Year: 2001**			
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Mean change in morning PEFR at weeks 5 to 6 **Secondary Outcome Measures:** Asthma symptom and sleep disturbance scores; beta-2 agonist use; FEV1; AQLQ **Timing of assessments:** PEFR, asthma symptoms, sleep disturbance and beta-2 agonist use was measured daily; FEV1 was measure at baseline and weeks 3 and 6, AQLQ was completed at day 1 and week 6		
RESULTS:	**Health Outcome Measures:** • No difference in mean change from baseline in severity of asthma symptoms • No difference in mean change from baseline in sleep disturbance scores between • No difference in mean change from baseline in beta-2 agonist use • No difference in mean change in AQLQ scores; mean increase from baseline 0.47 points **Intermediate Outcome Measures:** • No difference in mean change from baseline in morning PEFR* • No difference in mean plasma cortisol levels		
ANALYSIS:	**ITT:** Yes (LOCF) **Post randomization exclusions:** NR		
ATTRITION (*overall*):	**Overall loss to follow-up:** 13 (7.6%) **Loss to follow-up differential high:** No		
ATTRITION (*treatment specific*): **Loss to follow-up:** **Withdrawals due to adverse events:** **Withdrawals due to lack of efficacy:**	**fluticasone** 5 (6%) NR NR	**beclomethasone** 8 (9.1%) NR NR	
ADVERSE EVENTS: **Overall adverse effects reported:** **Differences in specific events:**	**fluticasone** 31 (37%) none	**beclomethasone** 36 (41%) none	
QUALITY RATING:	**Good**		

*primary outcome measures

Asthma *Inhaled Corticosteroids*

STUDY:	**Authors: Ferguson et al.**[32] **Year: 1998** **Country:** Canada, Denmark, Finland, Netherlands, Indonesia, South Africa		
FUNDING:	Glaxo Wellcome Inc., Mississauga, Ontario, Canada		
DESIGN:	**Study design:** RCT **Setting:** Multi-center **Sample size:** 333		
INTERVENTION: **Dose:** **Dosing range** **Device:** **Duration:** **Sample size:**	**fluticasone** 400 mcg/day Medium DPI (Diskus) 20 weeks 166	**budesonide** 800 mcg/day Medium DPI (Turbuhaler) 20 weeks 167	
Comparable dosing:	Yes		
INCLUSION:	4-12 years old; prepubertal; Taking moderate to high doses of ICS to control symptoms for at least 1 month prior to study; using beta-adrenergic medication for relief of symptoms when necessary; daily symptom score of 1 or greater or PEF ≤ 85% of predicted on at least 4 of 7 consecutive days		
EXCLUSION:	Children who had received combination bronchodilators or systemic corticosteroids; significant illness; used an investigational drug		
OTHER MEDICATIONS/ INTERVENTIONS:	Albuterol as required; concurrent asthma and non-asthma medications were permitted except for long-acting beta-adrenergic drugs, combination bronchodilators, or other corticosteroid formulations		
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Asthma classification:** Moderate; severe		
	fluticasone	**budesonide**	
Mean age (years): **Sex:** **Ethnicity:** **Other population characteristics:** • mean morning PEF	8.2 31% female NR 236 +/- 72	7.9 35 % female NR 229 +/- 74	

Authors: Ferguson et al. **Year: 1998**			
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Mean morning PEF during the last 7 treatment days **Secondary Outcome Measures:** Day and night asthma symptom scores; percentage of symptom free nights; albuterol use; change in height; serum cortisol levels; FEV1 **Timing of assessments:** PEF, asthma symptoms, sleep disturbance, and albuterol use were recorded daily; height and FEV1 were measured at baseline, weeks 8, 16, and 20, and 2 weeks after the study; serum cortisol was measured at baseline and the end of the study		
RESULTS:	**Health Outcome Measures:** • No difference in improvement of daytime (P = 0.73) and nighttime (P = 0.34) asthma symptom scores • No difference in albuterol use for daytime (P = 0.181) and nighttime (P = 0.59) • Linear growth velocity was statistically greater for FLUP compared to BDP (P < 0.01) • No difference in serum cortisol levels **Intermediate Outcome Measures:** • The treatment difference in morning PEF was significantly different between the two (P < 0.01), with FLUP having the greater improvement in PEF*		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** Yes		
ATTRITION (*overall*): **ATTRITION (*treatment specific*):** **Loss to follow-up:** **Withdrawals due to adverse events:** **Withdrawals due to lack of efficacy:**	**Overall loss to follow-up:** 25 (7.5%) **Loss to follow-up differential high:** No **fluticasone** 15 (9%) 0 NR	**budesonide** 10 (6%) 1 NR	
ADVERSE EVENTS: **Overall adverse effects reported:** **Differences in specific events:**	**fluticasone** 4 (2%) none	**budesonide** 10 (6%) none	
QUALITY RATING:	**Fair**		

*primary outcome measures

Asthma ***Inhaled Corticosteroids***

STUDY:	**Authors: Gross et al.**[37] **Year: 1998** **Country:** USA		
FUNDING:	Glaxo Wellcome, Inc.		
DESIGN:	**Study design:** RCT **Setting:** Multi-center (24 respiratory care or allergy clinics) **Sample size:** 304		
INTERVENTION:	**fluticasone**	**triamcinolone**	**placebo**
Dose:	500 mcg/d	800 mcg/d	N/A
Dosing range:	Medium	Low	N/A
Device:	DPI	MDI	MDI
Duration:	24 weeks	24 weeks	24 weeks
Sample size:	100	101	103
Comparable dosing:	No		
INCLUSION:	Nonsmokers at least 12 years old with asthma and required BDP or TRIA (8-12 actuations daily) for at least 4 weeks before study; FEV1 of 50-80% of predicted normal values; had to have at least 1 documented urgent or emergent care visit or home treatment for asthma within 12 months of study		
EXCLUSION:	Pregnant or lactating; use of methotrexate, gold salts, inhaled cromolyn sodium, inhaled nedocromil, oral, intranasal or injectable corticosteroids within 4 weeks of study commencement; significant concomitant illness; immunotherapy requiring a change in dosage regimen within 12 weeks		
OTHER MEDICATIONS/ INTERVENTIONS:	Prescription or OTC drugs that might effect course of asthma not allowed; albuterol aerosol PRN; theophylline if part of established regimen; albuterol had to be withheld at least 6 hours & theophylline 24-36 hours before clinic visits		

<table>
<tr><td colspan="4">Authors: Gross et al.
Year: 1998</td></tr>
<tr><td>POPULATION CHARACTERISTICS:</td><td colspan="3">Groups similar at baseline: No; significantly more patients in the TRIA group were treated with theophylline
Asthma classification: Mild to moderate</td></tr>
<tr><td></td><td><u>fluticasone</u></td><td><u>triamcinolone</u></td><td><u>placebo</u></td></tr>
<tr><td>Mean age (years):</td><td>38</td><td>38</td><td>38</td></tr>
<tr><td>Sex:</td><td>49% female</td><td>45% female</td><td>43% female</td></tr>
<tr><td>Ethnicity:</td><td></td><td></td><td></td></tr>
<tr><td>• white</td><td>91%</td><td>92%</td><td>92%</td></tr>
<tr><td>• black</td><td>5%</td><td>2%</td><td>5%</td></tr>
<tr><td>• other</td><td>4%</td><td>6%</td><td>3%</td></tr>
<tr><td>Other population characteristics:</td><td></td><td></td><td></td></tr>
<tr><td>• tobacco use</td><td>35%</td><td>35%</td><td>25%</td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">Primary Outcome Measures: FEV1; probability of remaining in the study over time; PEF, nighttime awakenings; asthma symptom scores; quality of life (AQLQ); albuterol use

Secondary Outcome Measures: Plasma cortisol concentrations

Timing of assessments: Baseline visit then weekly for first 2 weeks, every 2 weeks for 1 month, then every 3 weeks for remainder of 24 week study</td></tr>
<tr><td>RESULTS:</td><td colspan="3">Health Outcome Measures:
• No significant differences between FLUP and TRIA in symptom scores*
• AQLQ scores were significantly higher in the FLUP group than in the TRIA group (P = 0.007), however the difference did not reach 0.5, indicative of a clinically meaningful difference*
• More patients on TRIA than on FLUP were withdrawn because of unstable asthma (33% vs. 17%); over time, FLUP patients had a significantly greater probability of remaining in the study than TRIA patients (P = 0.008)*
• FLUP-treated patients used significantly less albuterol and had fewer nighttime awakenings than TRIA- or placebo-treated patients (P < 0.001)*</td></tr>
</table>

<table>
<tr><td colspan="4">Authors: Gross et al.
Year: 1998</td></tr>
<tr><td>RESULTS:</td><td colspan="3">Intermediate Outcome Measures:
• FLUP- and TRIA- patients had significantly higher FEV1 compared to placebo (P ≤ 0.009)*
• Patients treated with FLUP experienced significantly greater FEV1 improvements compared to TRIA patients throughout study (P ≤ 0.035) and at endpoint (0.32 L vs. 0.03 L; P < 0.001)*
• At endpoint mean increase in morning PEF over baseline values in patients receiving FLUP = 18 L/min compared with mean decrease of 3 L/min = TRIA and 24 L/min = placebo (P < 0.001)*</td></tr>
<tr><td>ANALYSIS:</td><td colspan="3">ITT: Yes
Post randomization exclusions: NR</td></tr>
<tr><td>ATTRITION (overall):</td><td colspan="3">Overall loss to follow-up: 54%
Loss to follow-up differential high: Yes</td></tr>
<tr><td>ATTRITION (treatment specific):</td><td><u>fluticasone</u></td><td><u>triamcinolone</u></td><td><u>placebo</u></td></tr>
<tr><td>Loss to follow-up:</td><td>33%</td><td>49%</td><td>79%</td></tr>
<tr><td>Withdrawals due to adverse events:</td><td>NR</td><td>NR</td><td>NR</td></tr>
<tr><td>Withdrawals due to lack of efficacy:</td><td>17%</td><td>33%</td><td>65%</td></tr>
<tr><td>ADVERSE EVENTS:</td><td><u>fluticasone</u></td><td><u>triamcinolone</u></td><td><u>placebo</u></td></tr>
<tr><td>Overall adverse effects reported:</td><td>20 (20%)</td><td>5 (5%)</td><td>5 (5%)</td></tr>
<tr><td>Significant differences in events:</td><td>none</td><td>none</td><td>none</td></tr>
<tr><td>QUALITY RATING:</td><td colspan="3">Fair</td></tr>
</table>

*primary outcome measures

Asthma ***Inhaled Corticosteroids***

STUDY:	**Authors: Gustafsson et al.**[23] **Year: 1993** **Country:** Multinational (11)		
FUNDING:	NR (1 author affiliated with Glaxo)		
DESIGN:	**Study design:** RCT **Setting:** Multi-center (32 outpatient clinics) **Sample size:** 398		
INTERVENTION: **Dose:** **Dosing range:** **Device:** **Duration:** **Sample size:**	**fluticasone** 200 mcg/day Medium (child) MDI (with Volumatic spacer) 6 weeks 197	**beclomethasone** 400 mcg/day Medium (child) MDI (with Volumatic spacer) 6 weeks 201	
Comparable dosing:	Yes		
INCLUSION:	History of asthma and either receiving inhaled corticoids 400 mcg/day or a demonstrated need for this dosage as indicated by uncontrolled symptoms and evidence of reversibility; ability to use MDI, PFM, and spacer		
EXCLUSION:	Use of corticosteroids in prior month or on more than 3 occasions in the prior 3 months; lower respiratory tract infection within 14 days; unstable asthma during the run-in period; hospital admission for respiratory condition in previous month		
OTHER MEDICATIONS/ INTERVENTIONS:	Beta-2 agonist; other usual asthma medications kept at constant doses.		
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Asthma classification:** Mild; moderate persistent		
	fluticasone	**beclomethasone**	
Mean age (years):	10	11	
Sex:	43.7% female	43.3% female	
Ethnicity:	97.5% white	95% white	
Other population characteristics:			
• using inhaled corticosteroids	72%	62%	
• using methylxanthines	9%	16%	

Authors: Gustafsson et al. **Year: 1993**			
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Patient measured symptoms on scale of 0-4 (daytime, nighttime, and with exercise); change in % symptom free days, nights, and exercise; use of beta-2 agonist and change in % rescue medication free days; daily AM and PM PEFR; PEFR prior to taking study med or using salbutamol; clinic measured PEF and FEV1 **Secondary Outcome Measures:** Serum cortisol **Timing of assessments:** Daily for patient measured outcomes, baseline, middle, end, and 2 weeks after study end-point for clinic-based measures		
RESULTS:	**Health Outcome Measures:** • No difference in % with symptom free days or nights* • % with symptom-free exercise: FLUP 87%, BDP 81% (P = 0.04)* • No difference in changes in median day, night, or exercise symptom scores* • Increase in % of rescue beta-2 agonist free days: FLUP 87%, BDP 80% (P = 0.01)* • Use of rescue medication per day: FLUP 13%, BDP 16% (P = 0.04)* **Intermediate Outcome Measures:** • No difference in mean change % predicted AM PEF: FLUP 6.2, BDP 4.5 (P = 0.07)* • Mean change % predicted PM PEF: FLUP 5.5, BDP 3.6 (P = 0.03)* • No difference in mean change % predicted FEV1 or PEFR* • No difference on serum cortisol measures		
ANALYSIS:	**ITT:** NR **Post randomization exclusions:** NR		
ATTRITION (*overall*): **ATTRITION (*treatment specific*):** **Loss to follow-up:** **Withdrawals due to adverse events:** **Withdrawals due to lack of efficacy:**	**Overall loss to follow-up:** 9 (2.3%) **Loss to follow-up differential high:** No		
	fluticasone 4 (2%) 3 (1.5%) NR	**beclomethasone** 5 (2.5%) 3 (1.5%) NR	
ADVERSE EVENTS: **Overall adverse effects reported:** **Significant differences in events:** • Sore throat (P < 0.001)	**fluticasone** 99 (50.3%) 16 (8%)	**beclomethasone** 95 (47.3%) 2 (1%)	
QUALITY RATING:	**Fair**		

*primary outcome measures

Asthma *Inhaled Corticosteroids*

STUDY:	**Authors: Heinig et al.**[33] **Year: 1999** **Country:** Multinational (Belgium, Canada, Denmark, The Netherlands)		
FUNDING:	Glaxo Wellcome		
DESIGN:	**Study design:** RCT **Setting:** Multi-center (47) **Sample size:** 395		
INTERVENTION: **Dose:** **Dosing Range:** **Device:** **Duration:** **Sample size:**	**fluticasone** 2000 mcg/day High DPI 24 weeks 198	**budesonide** 2000 mcg/day High DPI 24 weeks 197	
Comparable dosing:	No; Both high doses but relative potency of fluticasone is much greater		
INCLUSION:	Age 18-75 years; history of asthma within the previous 12 months or pre-study evidence of reversible airways disease; requiring or responding to high-dose inhaled corticosteroids (FLUP or BUD)		
EXCLUSION:	Serious systemic disease; treatment with oral corticosteroids or research medication within previous 1 month; pregnancy/lactation.		
OTHER MEDICATIONS/ INTERVENTIONS:	Methylxanthines; anticholinergics; nedocromil; cromoglycate; ketotifen; long acting beta-agonists (as long as all doses remained unchanged during the study); intra-nasal corticosteroids; anti-fungal lozenges; salbutamol as needed for rescue; oral steroids per investigators discretion		
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes; more smokers in BUD group **Asthma classification:** Severe		
	fluticasone	**budesonide**	
Mean age (years):	49	47	
Sex:	49.5% female	49.7% female	
Ethnicity:	97.4% white	95.9 % white	
Other population characteristics:			
• current smoker	24%	35%	
• concurrent medication	39%	34%	

Authors: Heinig et al. **Year: 1999**	
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Clinic measured FEV1, FVC, and PEF; patient recorded daily AM and PM PEF; daily and nightly asthma symptom scores; % symptom free days and nights; use of inhaled rescue salbutamol **Secondary Outcome Measures:** Number, severity and time to asthma exacerbations; serum cortisol; serum markers of bone turnover **Timing of assessments:** Daily for patient assessed measures; baseline, 4 weeks, and every 8 weeks thereafter until study end-point for clinic based measures
RESULTS:	**Health Outcomes:** • % symptom free days overall: 31.5% FLUP vs. 22.8% BUD (P = 0.02)* • % rescue medication free days overall: 42.7% FLUP vs. 33.7% BUD (P = 0.02)* • No difference between groups in % of patients with exacerbations • Time to resolution of exacerbation shorter with FLUP (11.0 vs. 14.7 days; P = 0.04)* • Fewer days absent from work due to exacerbation with FLUP (P = 0.01)* • No difference between groups in mean duration of individual exacerbations • Mean differences in overall daytime and nighttime symptom scores at endpoint: NR* **Intermediate Outcomes:** • FLUP treated subjects had greater adjusted mean increases in FEV1, FVC, PEF* • No difference in adjusted mean daily PEF (trend towards fluticasone present)* • No differences in amount of serum cortisol decrease between treatments • No differences in serum markers of bone turnover
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** No

Authors: Heinig et al. **Year: 1999**			
ATTRITION (*overall*):	**Overall loss to follow-up:** NR **Loss to follow-up differential high:** NR		
ATTRITION (*treatment specific*):	**fluticasone**	**budesonide**	
Loss to follow-up:	NR	NR	
Withdrawals due to adverse events:	NR	NR	
Withdrawals due to lack of efficacy:	NR	NR	
ADVERSE EVENTS:	**fluticasone**	**budesonide**	
Overall adverse effects reported:	155 patients (78.3 %)	152 patients (77.2 %)	
Significant differences in events:	none	none	
QUALITY RATING:	**Fair**		

*primary outcome measures

Asthma *Inhaled Corticosteroids*

STUDY:	**Authors: Hoekx et al.**[34] **Year: 1996** **Country:** Multinational (4)		
FUNDING:	NR (one author affiliated with Glaxo Wellcome Research and Development)		
DESIGN:	**Study design:** RCT; **Setting:** Multi-center (22) **Sample size:** 229		
INTERVENTION: **Dose:** **Dosing range:** **Device:** **Duration:** **Sample size:**	**fluticasone** 400 mcg/day Medium Diskhaler 8 weeks 119	**budesonide** 400 mcg/day Low Turbuhaler 8 weeks 110	
Comparable dosing:	No		
INCLUSION:	Outpatient children using 200 – 400 mcg/d of inhaled corticosteroids and using beta-agonist therapy as required; meet at least 2 of the following criteria: daytime or nighttime symptoms on 4 out of 7 days; wakening during the night or early morning on 1 or more occasions; PEFR $\leq$ 75% of predicted on 4 of 7 days; at least 15% reversibility in FEV1 or PEFR in response to beta-agonist therapy		
EXCLUSION:	Oral or parental corticosteroids in previous 3 months; unable to use delivery devices or peak flow meter; suffered infection or seasonal allergy likely to affect asthma during trial; known hypersensitivity; use of investigational drug in previous month		
OTHER MEDICATIONS/ INTERVENTIONS:	Beta-agonists		
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Asthma classification:** Mild to moderate		
	fluticasone	**budesonide**	
Mean age (years):	5-13 (range)	4-12 (range)	
Sex:	32% female	32% female	
Ethnicity:	NR	NR	
Other population characteristics:			
• mean dose of corticosteroid at entry	355 mcg	351 mcg	
• mean % predicted PEFR	98%	97%	

<table>
<tr><td colspan="4">Authors: Hoekx et al.
Year: 1996</td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">Primary Outcome Measures: Daily PEF; % symptom-free days and nights; % days with normal activity; symptom and activity score (instruments not specified); use of rescue medication; parent report of asthma impact on child
Secondary Outcome Measures: Clinic measured PEF and FEV1
Timing of assessments: Daily for patient-assessed measures; baseline; 2, 4, 8, and 10 weeks post-baseline for clinic-based measures; at baseline and study-end for parental assessment of asthma impact on child</td></tr>
<tr><td>RESULTS:</td><td colspan="3">Health Outcomes:
No difference in % of symptom free days and nights
No difference in % of days with normal activity
No difference in mean symptom or activity scores
No difference in % of rescue medication free days
Parent report of impact of asthma: no difference in sleep or days of missed school or parental work; FLUP treated group had significantly less disruption in physical activities as compared to BUD treated group (P = 0.03)
Intermediate Outcomes:
No difference in clinic measured PEF or FEV1
Adjusted mean AM PEF weeks 1 – 8: FLUP 104% vs. BUD 101% (P < 0.01)
Adjusted mean PM PEF weeks 1 – 8: FLUP 106% vs. BUD 103% (P < 0.02)</td></tr>
<tr><td>ANALYSIS:</td><td colspan="3">ITT: NR
Post randomization exclusions: NR</td></tr>
<tr><td>ATTRITION (overall):</td><td colspan="3">Overall loss to follow-up: 8 (3.5%)
Loss to follow-up differential high: No</td></tr>
<tr><td>ATTRITION (treatment specific):
Loss to follow-up:
Withdrawals due to adverse events:
Withdrawals due to lack of efficacy:</td><td><u>fluticasone</u>
NR
2 (1.7%)
NR</td><td><u>budesonide</u>
NR
3 (2.7%)
NR</td><td></td></tr>
<tr><td>ADVERSE EVENTS:
Overall adverse effects reported:
Significant differences in events:</td><td><u>fluticasone</u>
75 patients (63%)
NR</td><td><u>budesonide</u>
76 patients (69%)
NR</td><td></td></tr>
<tr><td>QUALITY RATING:</td><td colspan="3">Fair</td></tr>
</table>

Asthma ***Inhaled Corticosteroids***

STUDY:	**Authors: Juniper et al.**[39] **Year: 1999** **Country:** USA		
FUNDING:	3M Pharmaceuticals		
DESIGN:	**Study design:** RCT **Setting:** Multi-center (27 sites) **Sample size:** 347		
INTERVENTION:	**HFA beclomethasone**	**CFC beclomethasone**	**placebo**
Dose:	400 mcg/day	800 mcg/day	N/A
Dosing range:	Medium	Medium	N/A
Device:	MDI	MDI	MDI
Duration:	12 weeks	12 weeks	12 weeks
Sample size:	113	117	117
Comparable dosing:	Yes		
INCLUSION:	Nonsmoking adults; ages 18-65; had symptomatic asthma despite treatment with bronchodilators or ICS; evidence of active asthma during the run-in defined as morning PEF between 50% and 85% of predicted and either sleep disturbance, asthma symptoms, or twice daily beta-agonist use		
EXCLUSION:	Clinically significant disease; acute respiratory tract infection within 4 weeks of study; taking any other medication (other than beta-agonist)		
OTHER MEDICATIONS/ INTERVENTIONS:	Beta-agonist bronchodilator permitted as needed		
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** No **Asthma classification:** Moderate persistent		
	HFA beclomethasone	**CFC beclomethasone**	**placebo**
Mean age (years):	32.5	34.8	34.6
Sex:	59.3% female	53.8% female	47% female
Ethnicity:	NR	NR	NR
Other population characteristics:			
• ICS use at baseline	31%	39.3%	41.0%
• baseline beta-agonist use (P < 0.001)	3.8 puffs/day	3.4 puffs/day	2.9 puffs/day

<table>
<tr><td colspan="4">Authors: Juniper et al.
Year: 1999</td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">Primary Outcome Measures: AQLQ

Secondary Outcome Measures: PEF; asthma symptoms; bronchodilator use

Timing of assessments: AQLQ completed after run-in, following a 7-12 day oral steroid treatment, and after 12 weeks of study drug treatment; secondary measures recorded daily</td></tr>
<tr><td>RESULTS:</td><td colspan="3">Health Outcome Measures:
Patients receiving placebo experienced deterioration in AQLQ score; those receiving either type of BDP experienced little change in AQLQ score; the difference between either BDP formulation and placebo was significant (P ≤ 0.003)*; trend favoring HFA BDP
Intermediate Outcome Measures:
Change in overall AQLQ was weakly correlated with change in FEV1 (r = 0.305)
HFA and CFC-BDP achieved similar asthma control (PEF, asthma symptom scores)</td></tr>
<tr><td>ANALYSIS:</td><td colspan="3">ITT: Yes
Post randomization exclusions: Yes</td></tr>
<tr><td>ATTRITION (overall):</td><td colspan="3">Overall loss to follow-up: 13.7% (16)
Loss to follow-up differential high: Yes (between active treatment and placebo)</td></tr>
<tr><td>ATTRITION (treatment specific):</td><td><u>HFA beclomethasone</u></td><td><u>CFC beclomethasone</u></td><td><u>placebo</u></td></tr>
<tr><td>Loss to follow-up:</td><td>12 (10.6%)</td><td>12 (10.3%)</td><td>37 (32%)</td></tr>
<tr><td>Withdrawals due to adverse events:</td><td>NR</td><td>NR</td><td>NR</td></tr>
<tr><td>Withdrawals due to lack of efficacy:</td><td>5 (4.4%)</td><td>5 (4.3%)</td><td>33 (28.2%)</td></tr>
<tr><td>ADVERSE EVENTS:
Overall adverse effects reported:
Significant differences in events:</td><td colspan="3">NR</td></tr>
<tr><td>QUALITY RATING:</td><td colspan="3">Fair</td></tr>
</table>

*primary outcome measures

Asthma ***Inhaled Corticosteroids***

STUDY:	**Authors: Leblanc et al.**[24] **Year: 1994** **Country:** Multinational		
FUNDING:	NR (one author affiliated with Glaxo)		
DESIGN:	**Study design:** RCT **Setting:** NR **Sample size:** 261		
INTERVENTION: **Dose:** **Dosing range:** **Device:** **Duration:** **Sample size:**	**fluticasone** 200 mcg/day Low MDI 4 weeks 129	**beclomethasone** 400 mcg/d Low MDI 4 weeks 132	
Comparable dosing:	Yes		
INCLUSION:	Mild to moderate asthma; PEF variability of >20 % during run-in or a beta-agonist response of > 15%; symptoms on at least 4 days or nights of run-in		
EXCLUSION:	Requiring more than 400 mcg/d of BUD or BDP or oral corticosteroids during month prior to study; intolerance of short-acting beta-agonists; severe concurrent disease; pregnancy/lactation		
OTHER MEDICATIONS/ INTERVENTIONS:	Salbutamol MDI for rescue medication; spacer device allowed; all pre-study medication (except rescue beta-agonist) continued		
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Asthma classification:** Mild-moderate		
	fluticasone	**beclomethasone**	
Mean age (years):	46 (median)	46 (median)	
Sex:	46% female	48 % female	
Ethnicity:	97% white	97% white	
Other population characteristics:			
• pre-study use of methylxanthines	42%	52%	
• pre-study use of ICS	61%	60%	

Authors: Leblanc et al. **Year: 1994**			
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Patient assessed AM and PM PEF; day and night symptoms; use of rescue medication; clinic measured PEF, FEV1, and FVC **Secondary Outcome Measures:** Plasma cortisol **Timing of assessments:** Daily for patient measured outcomes; every 2 weeks for clinic measured outcomes		
RESULTS:	**Health Outcome Measures:** • No difference in increase in % of symptom free days or nights between groups • BDP treated subjects had larger increase in % of rescue medication free days (BDP 17% vs. FLUP 12%, P = 0.05) • No difference in number of rescue medication inhalations used **Intermediate Outcome Measures:** • No differences in adjusted mean increases or % predicted AM and PM PEF between groups • No differences in adjusted mean increases or % predicted clinic measured PEF, FEV1 or FVC • Differences in plasma cortisol between groups (increase of 27 nmol/L in FLUP group vs. decrease of 41 nmol/L in BDP group, P < 0.01)		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** Unable to determine		
ATTRITION (*overall*): **ATTRITION (*treatment specific*):** **Loss to follow-up:** **Withdrawals due to adverse events:** **Withdrawals due to lack of efficacy:**	**Overall loss to follow-up:** 10 (3.8%) **Loss to follow-up differential high:** No **<u>fluticasone</u>** 5 (3.8%) 0 2 (1.6%)	**<u>beclomethasone</u>** 5 (3.8%) 1 (0.8%) 4 (3%)	
ADVERSE EVENTS: **Overall adverse effects reported:** **Significant differences in events:**	**<u>fluticasone</u>** 31 (24% of patients) none	**<u>beclomethasone</u>** 46 (35% of patients) none	
QUALITY RATING:	**Fair**		

Asthma *Inhaled Corticosteroids*

STUDY:	**Authors: Lundback et al.**[25] **Year: 1993** **Country:** Multinational		
FUNDING:	NR (one author affiliated with Glaxo)		
DESIGN:	**Study design:** RCT **Setting:** Multi-center (47 centers) **Sample size:** 585		
INTERVENTION: **Dose:** **Dosing range:** **Device:** **Duration:** **Sample size:**	**fluticasone** 500 mcg/day Medium MDI 6 weeks (42 week continuation) 193 (329)	**fluticasone** 500 mcg/day Medium DPI (Diskhaler) 6 weeks 198	**beclomethasone** 1000 mcg/day High MDI 6 weeks (42 week continuation) 194 (160)
Comparable dosing:	No		
INCLUSION:	Currently taking 400-1000 mcg ICS/day; beta-agonist therapy		
EXCLUSION:	Treatment with systemic corticosteroid during past month; serious disease other than asthma; pregnancy/lactation; use of investigational drugs within previous four weeks; no hospital admittance for respiratory disease during the past month; no change in prophylactic medication during the past month		
OTHER MEDICATIONS/ INTERVENTIONS:	Spacer device allowed at physician discretion; continue other asthma medications at same dose; salbutamol as needed; amphotericin lozenges as needed for candidiasis		
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Asthma classification:** Moderate persistent		
	fluticasone (MDI)	**fluticasone (DPI)**	**beclomethasone**
Mean age (years):	46	45	46
Sex:	48% female	45% female	49% female
Ethnicity:	97% white	97% white	99% white
Other population characteristics:			
• spacer used	58%	59%	61%
• smokers	16%	12%	10%
• methylxanthines	23%	26%	23%

Authors: Lundback et al. **Year: 1993**			
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** PEFR; FVC; FEV1; % symptom free days and nights; day and nighttime asthma symptoms; use of rescue medication **Secondary Outcome Measures:** Blood sample for cortisol determination and routine testing **Timing of assessments:** Daily patient record cards; investigator assessment: weeks 3, 6, 8		
RESULTS:	**Health Outcomes Measures:** • No differences in the percentage of symptom free days and nights; improvement for all • Median daytime asthma symptom score was lower for BDP than for either the FLUP MDI or DPI (P = 0.03) • Median nighttime asthma symptom score was better for FLUP (DPI) than BDP (P < 0.05) • No differences in the use of rescue medications; all treatments reduced the need for rescue • No significant differences between FLUP (MDI) and BDP after 12 months continuation **Intermediate Outcome Measures:** • No differences in changes of FEV1 or FVC between any of the treatment groups • PEFRs were not significantly different when assessed on the patient card; clinical assessment after 6 weeks presented a significantly greater effect of FLUP (DPI) than BDP (mean difference 19 L/min; P = 0.013)		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** NR		
ATTRITION (*overall*):	**Overall loss to follow-up:** 55 (9.4%) **Loss to follow-up differential high:** No		
ATTRITION (*treatment specific*):	**fluticasone (MDI)**	**fluticasone (disk)**	**beclomethasone**
Loss to follow-up:	18 (9.3%)	17 (8.6%)	20 (10.3%)
Withdrawals due to adverse events:	7 (3.6%)	8 (4.0%)	11 (5.7%)
Withdrawals due to lack of efficacy:	6 (3.1%)	7 (3.5%)	5 (2.6%)
ADVERSE EVENTS:	**fluticasone (MDI)**	**fluticasone (disk)**	**beclomethasone**
Overall adverse effects reported:	97 (50%)	87 (44%)	89 (46%)
Significant differences in events:			
• Sore throat (P < 0.05)*	10 (5%)*	4 (2%)	2 (1%)
QUALITY RATING:	**Fair**		

*primary outcome measures

Asthma *Inhaled Corticosteroids*

STUDY:	**Authors: Mahajan et al.**[44, 55] **Year: 1997** **Country:** USA			
FUNDING:	Glaxo Wellcome Inc.			
DESIGN:	**Study design:** RCT **Setting:** Multi-center (20 sites) **Sample size:** 342			
INTERVENTION:	**fluticasone (50)**	**fluticasone (100)**	**fluticasone (250)**	**placebo**
Dose:	100 mcg/d	200 mcg/d	500 mcg/d	N/A
Dosing range:	Low	Low	Medium	N/A
Device:	DPI	DPI	DPI	DPI
Duration:	12 weeks	12 weeks	12 weeks	12 weeks
Sample size:	89	84	91	78
Comparable dosing:	N/A			
INCLUSION:	Males or females ≥ 12 years of age with asthma and FEV1 between 50-80% of predicted value; used daily pharmacotherapy for asthma for at least 6 months, inhaled BDP or TRIA for at least 1 month, and oral or inhaled beta-sympathomimetic bronchodilators for at least 2 weeks preceding study entry			
EXCLUSION:	Pregnancy; lactation; methotrexate or gold salts; inhaled cromolyn; oral corticosteroids within 4 weeks of enrollment; significant concomitant illness			
OTHER MEDICATIONS/ INTERVENTIONS:	Albuterol; all other ICS discontinued			
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Asthma classification:** Moderate			
	fluticasone (50)	**fluticasone (100)**	**fluticasone (250)**	**placebo**
Mean age (years):	34	36	36	36
Sex:	39% female	35% female	37% female	46% female
Ethnicity:				
• white	93%	93%	92%	94%
• black	4%	4%	3%	1%
• other	2%	3%	4%	5%
Other population characteristics:	NR	NR	NR	NR

Authors: Mahajan et al. **Year: 1997**				
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** SF-36A; Living With Asthma Questionnaire (LWA-20); 2-item scale related to sleep loss/number of nighttime awakenings, FEV1, PEF **Secondary Outcome Measures:** NR **Timing of assessments:** HRQL at baseline and weeks 1, 2, 6 and 12			
RESULTS:	**Health Outcome Measures:** • All three FLUP regimens had significantly better SF-36 scores at endpoint than placebo ($P < 0.001$) • At endpoint all 3 FLUP groups had significantly lower scores on the LWA-20, indicating better health status, compared with placebo ($P < 0.01$) • Mean changes in scores from baseline to endpoint showed significant ($P < 0.05$) improvement in asthmatic-specific QOL in FLUP100 and FLUP250, while placebo scores decreased significantly ($P < 0.05$) • FLUP-treated patients had significantly higher sleep scores compared to placebo ($P < 0.0001$) **Intermediate Outcome Measures:** • FLUP treated patients experienced an increased FEV1 (+ 0.42 to 0.47 L) from baseline to endpoint, whereas placebo patients had a decreased FEV1 (- 0.22 L; $P < 0.001$)			
ANALYSIS:	**ITT:** No (for HRQL); Yes (for FEV1) **Post randomization exclusions:** Yes			
ATTRITION (*overall*): **ATTRITION (*treatment specific*):**	**Overall loss to follow-up:** 18.4% for HRQL; 28.9% for FEV1 **Loss to follow-up differential high:** Yes; biggest differential with placebo			
	fluticasone (50)	**fluticasone (100)**	**fluticasone (250)**	**placebo**
Loss to follow-up:	21%	23%	10%	67%
Withdrawals due to adverse events:	13%	13%	7%	65%
Withdrawals due to lack of efficacy:	2%	2%	1%	1%
ADVERSE EVENTS:	**fluticasone (50)**	**fluticasone (100)**	**fluticasone (250)**	**placebo**
Overall adverse effects reported:	10 (11%)	10 (12%)	11 (12%)	3 (4%)
Significant differences in events:	none	none	none	none
QUALITY RATING:	**Fair**			

*primary outcome measures

Asthma *Inhaled Corticosteroids*

STUDY:	**Authors: Mahajan et al.**[45] **Year: 1998** **Country:** USA		
FUNDING:	Glaxo Wellcome Inc.		
DESIGN:	**Study design:** RCT **Setting:** Multi-center (number of sites not given) **Sample size:** 325		
INTERVENTION:	**fluticasone 100 mcg/d**	**fluticasone 200 mcg/d**	**placebo**
Dose:	100 mcg/d	200 mcg/d	N/A
Dosing range:	Low	Low	N/A
Device:	DPI (Diskhaler)	DPI (Diskhaler)	DPI (Diskhaler)
Duration:	52 weeks	52 weeks	52 weeks
Sample size:	111	108	106
Comparable dosing:	N/A		
INCLUSION:	Boys between 4 and 11 years old; girls between 4 and 9 years old; mild to moderate asthma; FEV1 of at least 60% of predicted normal value; patients treated with ICS and/or beta-agonists in previous month		
EXCLUSION:	NR		
OTHER MEDICATIONS/ INTERVENTIONS:	Albuterol as needed.		
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Asthma classification:** Mild to moderate persistent		
	fluticasone 100 mcg/d	**fluticasone 200 mcg/d**	**placebo**
Mean age (years):	8.5	8.2	8.5
Sex:	74% female	76% female	75% female
Ethnicity:			
• white	88%	90%	84%
• black	8%	4%	11%
• Hispanic	2%	4%	2%
• other	2%	2%	3%
Other population characteristics:			
• FEV1 % predicted	86%	88%	89%

Authors: Mahajan et al. **Year: 1998**			
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Functional Status IIR (FSII); Sleep Scale Children (SLP-C); Quality of Life of Parents with Asthmatic Children (QOL-PAC) **Secondary Outcome Measures:** None **Timing of assessments:** Questionnaires completed at baseline, and weeks 24 and 52		
RESULTS:	**Health Outcome Measures:** • Placebo patients experienced deterioration in FSII score, while FLUP patients experienced an improvement in FSII score; differences between FLUP and placebo were significant ($P \leq 0.05$)* • Placebo patients experienced deterioration in SLP-C score, while FLUP patients experienced an improvement in SLP-C score; difference between FLUP and placebo were significant ($P \leq 0.01$)* • For the QOL-PAC, parents of both children in both FLUP groups showed significant improvement in Burden scale score ($P < 0.05$); for the Subjective Norms and Social scales only parents in the higher dose FLUP group (200 mcg/day) had improved scores compared to placebo ($P < 0.05$)* **Intermediate Outcome Measures:** • None		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** Yes		
ATTRITION (*overall*): **ATTRITION (*treatment specific*):**	**Overall loss to follow-up:** 62 (19%) **Loss to follow-up differential high:** Unable to determine		
	fluticasone 100 mcg/d	**fluticasone 200 mcg/d**	**placebo**
Loss to follow-up:	NR	NR	NR
Withdrawals due to adverse events:	NR	NR	NR
Withdrawals due to lack of efficacy:	4 (4%)	4 (4%)	20 (19%)
ADVERSE EVENTS:	**fluticasone 100 mcg/d**	**fluticasone 200 mcg/d**	**placebo**
Overall adverse effects reported:	NR	NR	NR
Significant differences in events:	NR	NR	NR
QUALITY RATING:	**Fair**		

*primary outcome measures

Asthma ***Inhaled Corticosteroids***

STUDY:	**Authors: Malmstrom et al.**[38] **Year: 1999** **Country:** Multinational (19 countries)		
FUNDING:	Merck Research Laboratories		
DESIGN:	**Study design:** RCT **Setting:** Multi-center (36 clinical centers) **Sample size:** 895		
INTERVENTION:	**montelukast**	**beclomethasone**	**placebo**
Dose:	10 mg/day	400 mcg/day	N/A
Dosing range:	N/A	Low	N/A
Device:	Oral tablets	MDI - Spacer Device	Tablets and spacer device
Duration:	12 weeks	12 weeks	12 weeks
Sample size:	387	251	257
Comparable dosing:	N/A		
INCLUSION:	Healthy; non-smoking; 15 years of age or older; asthma for 1 year prior to study; FEV1 between 50% and 85% of predicted value; increase of 15% in FEV1 after beta-agonist on two of three visits; asthma symptom score of at least 64 out of 336; an average of 1 puff/day beta-agonist		
EXCLUSION:	Use of inhaled or oral corticosteroids, cromolyn, or nedocromil within 4 weeks of initial evaluation; use of long acting beta-agonists, antimuscarinics, and newly instituted theophylline within 2 weeks		
OTHER MEDICATIONS/ INTERVENTIONS:	Beta-agonists as needed; theophylline if taking prior to study (but longer than 2 weeks)		
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Asthma classification:** Mild-severe persistent		
	montelukast	**beclomethasone**	**placebo**
Median age (years):	35	35	36
Sex:	60% female	65% female	57% female
Ethnicity:			
• white	54%	47%	53%
• Hispanic	32%	34%	31%
Other population characteristics:			
• theophylline users	10.3%	9.6%	10.5%

Authors: Malmstrom et al. **Year: 1999**			
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Daytime asthma score (7-point scale); FEV1 **Secondary Outcome Measures:** Morning and evening PEFR; beta-agonist use; nocturnal awakenings; AQLQ; worsening asthma episodes **Timing of assessments:** Lung function measured every three weeks during treatment phase; PEFR and asthma symptoms recorded daily		
RESULTS:	**Health Outcome Measures:** • Daytime symptom scores were significantly improved in BDP compared to placebo (P < 0.001)* • Beta-agonist use was significantly reduced in BDP compared to placebo (P < 0.001) • Nocturnal awakenings were significantly reduced in BDP compared to placebo (P < 0.001) • Asthma attacks were significantly reduced in BDP compared to placebo (P < 0.001) • Patient & physician global evaluation better with BDP than placebo (P < 0.001) • Significantly greater improvement in AQLQ for BDP compared to placebo (P < 0.001) **Intermediate Outcome Measures:** FEV1 was significantly improved in BDP compared to placebo (P < 0.001)		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** Yes		
ATTRITION (*overall*):	**Overall loss to follow-up:** 93 (10.4%) **Loss to follow-up differential high:** No		
ATTRITION (*treatment specific*):	**montelukast**	**beclomethasone**	**placebo**
Loss to follow-up:	33 (8.5%)	18 (7.2%)	42 (16.3%)
Withdrawals due to adverse events:	8 (2%)	5 (2%)	11 (4%)
Withdrawals due to lack of efficacy:	NR	NR	NR
ADVERSE EVENTS:	**montelukast**	**beclomethasone**	**placebo**
Overall adverse effects reported:	NR	NR	NR
Significant differences in events:			
• Worsening asthma (P < 0.05)*	98 (25%)	48 (19%)	99 (39%)
QUALITY RATING:	**Good**		

*primary outcome measures

Asthma ***Inhaled Corticosteroids***

STUDY:	**Authors: Nelson et al.**[47] **Year: 1999** **Country:** USA		
FUNDING:	Glaxo Wellcome Inc.		
DESIGN:	**Study design:** RCT **Setting:** Multi-center (13 sites) **Sample size:** 111		
INTERVENTION: **Dose:** **Dosing range:** **Device:** **Duration:** **Sample size:**	**fluticasone** 1000 mcg/d high DPI 16 weeks 41	**fluticasone** 2000 mcg/d high DPI 16 weeks 36	**placebo** N/A N/A DPI 16 weeks 34
Comparable dosing:	Yes		
INCLUSION:	12 years of age or older with chronic asthma; required regular maintenance treatment with oral corticosteroids over preceding 6 months; stable minimum dose of oral prednisone 5-40mg/day or 10-80mg every other day for ≥ 2 weeks prior to study; prior use of beta-2 agonists; prior use of ICS not required but permitted; FEV1 of 40-80% of predicted values; 15% or greater reversibility in FEV1		
EXCLUSION:	Life-threatening asthma or other severe concurrent disease; used intranasal, ophthalmologic, injectable or topical (except < 1% cream) corticosteroids; participated in previous clinical trial involving FLUP inhalation powder; used any prescription or OTC medication that might have affected asthma or treatment; used cromolyn sodium, nedocromil, ipratropium bromide, atropine within 1 month before study or methotrexate, gold salts, troleandomycin, azathioprine, cyclosporine within 3 months before study		
OTHER MEDICATIONS/ INTERVENTIONS:	Theophylline or salmeterol if started before study with no change in dose or dosing regimen; albuterol; oral prednisone		

<table>
<tr><td colspan="4">Authors: Nelson et al.
Year: 1999</td></tr>
<tr><td rowspan="2">POPULATION CHARACTERISTICS:</td><td colspan="3">Groups similar at baseline: Yes
Asthma classification: Moderate to severe</td></tr>
<tr><td></td><td><u>fluticasone 1000 mcg</u></td><td><u>fluticasone 2000 mcg</u></td><td><u>placebo</u></td></tr>
<tr><td></td><td>Mean age (years):
Sex:
Ethnicity:
Other population characteristics:
• mean prednisone dosage (mg)</td><td>49
61% female
NR

15.44</td><td>50
58% female
NR

13.58</td><td>49
62% female
NR

13.03</td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">Primary Outcome Measures: Change in prednisone dosage

Secondary Outcome Measures: FEV; PEF; quality of life; albuterol use; asthma symptom scores

Timing of assessments: NR</td></tr>
<tr><td>RESULTS:</td><td colspan="3">Health Outcome Measures:
• Quality of Life scores were statistically and clinically (> 0.5 points) significantly greater in the active treatment groups compared to placebo (P < 0.03)
• Compared to placebo, both doses of FLUP improved asthma symptom scores and reduced the need for beta-agonist use (P < 0.1)

Intermediate Outcome Measures:
• Oral prednisone was eliminated by 75% and 89% of the twice daily FLUP 1000 or 2000 mcg treated patients (placebo: 9%; P < 0.001)
• FEV1, PEF, and albuterol use improved significantly with FLUP treatment (P < 0.009)</td></tr>
</table>

Authors: Nelson et al. **Year: 1999**			
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** NR		
ATTRITION (*overall*): **ATTRITION (*treatment specific*):**	**Overall loss to follow-up:** 48 (43%) **Loss to follow-up differential high:** Yes; but not between active treatment groups		
	fluticasone 1000 mcg	**fluticasone 2000 mcg**	**placebo**
Loss to follow-up:	12 (29%)	6 (17%)	30 (88%)
Withdrawals due to adverse events:	NR	NR	NR
Withdrawals due to lack of efficacy:	12%	8%	79%
ADVERSE EVENTS:	**fluticasone 1000 mcg**	**fluticasone 2000 mcg**	**placebo**
Overall adverse effects reported:	13 (32%)	20 (56%)	5 (15%)
Significant differences in events:	NR	NR	NR
QUALITY RATING:	**Fair**		

*primary outcome measures

Asthma ***Inhaled Corticosteroids***

STUDY:	**Authors: Newhouse et al.**[28] **Year: 2000** **Country:** Canada		
FUNDING:	Forest Laboratories, Inc.		
DESIGN:	**Study design:** RCT **Setting:** Multi-center (17) **Sample size:** 154		
INTERVENTION: **Dose:** **Dosing range:** **Device:** **Duration:** **Sample size:**	**flunisolide** 1500 mcg/day Medium MDI with Aerochamber 6 weeks 75	**budesonide** 1200 mcg/day Medium DPI with Turbuhaler 6 weeks 79	
Comparable dosing:	Yes		
INCLUSION:	Age 18-75; documented history of moderate stable asthma requiring a dose ≥ 800 mcg/d and ≤ 2000 mcg/d of BDP; FLUP or BUD and the use of salbutamol; FEV1 of 40-85% of predicted; evidence of at least 12% reversibility after beta-2 agonist therapy; use of inhaled corticosteroid for at least 30 days		
EXCLUSION:	Significant pulmonary disease other than asthma; other significant illness; hospitalization for asthma exacerbation within 6 prior weeks; immunotherapy other than maintenance; upper respiratory tract infection within 30 days; systemic corticosteroids on 2 or more occasions within prior 3 months; unstable asthma; long-acting beta-agonist in prior 2 weeks		
OTHER MEDICATIONS/ INTERVENTIONS:	Other inhaled corticosteroids, antileukotrienes; oral steroids; cromolyn/nedocromil; nasal steroids; oral beta-2 agonists; long acting beta-2 agonists; ipratropium; theophylline; formoterol		
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Asthma classification:** Moderate persistent		
	flunisolide	**budesonide**	
Mean age (years):	44.0	42.8	
Sex:	60% female	57% female	
Ethnicity:	91% white	92% white	
• current smoker	5.3%	5.1%	

Authors: Newhouse et al. **Year: 2000**			
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Change in pre-bronchodilator FEV1; change in mean rescue salbutamol usage **Secondary Outcome Measures:** Change in AM and PM PEF; clinical asthma score; mean number of nocturnal awakenings due to asthma that required salbutamol **Timing of assessments:** Weeks 2 and 6		
RESULTS:	**Health Outcome Measures:** • No difference in change in salbutamol usage (puffs/day) (FLUN 0.4, BUD 0.1, P = 0.333)* • No difference in change in asthma symptom score • No difference in number of nocturnal awakenings due to asthma **Intermediate Outcome Measures:** • No difference in change in FEV1 from baseline (FLUN -0.07, BUD -0.02, P = 0.544)* • No difference in change in AM or PM PEF		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** Yes (1)		
ATTRITION (*overall*):	**Overall loss to follow-up:** 14 (9%) **Loss to follow-up differential high:** Yes but < 15 percentage point differential		
ATTRITION (*treatment specific*): **Loss to follow-up:** **Withdrawals due to adverse events:** **Withdrawals due to lack of efficacy:**	**flunisolide** 11 (14.6%) NR NR	**budesonide** 3 (3.8%) NR NR	
ADVERSE EVENTS: **Overall adverse effects reported:** **Significant differences in events:**	**flunisolide** 54.4% of patients none	**budesonide** 54.4% of patients none	
QUALITY RATING:	**Fair**		

*primary outcome measures

Asthma *Inhaled Corticosteroids*

STUDY:	**Authors: Noonan et al.**[51]**; Okamoto et al.**[46] **Year: 1995, 1996** **Country:** US		
FUNDING:	Glaxo Research Institute		
DESIGN:	**Study design:** RCT followed by 1 year open-label treatment phase **Setting:** Multi-center (16) **Sample size:** 96		
INTERVENTION: **Dose:** **Dosing range:** **Device:** **Duration:** **Sample size:**	**fluticasone** 1500 mcg/day High MDI 16 weeks (+ 1 year open label) 32	**fluticasone** 2000 mcg/day High MDI 16 weeks (+ 1 year open label) 32	**placebo** N/A N/A MDI 16 weeks (+ 1 year open label) 32
Comparable dosing:	N/A		
INCLUSION:	Age ≥ 12 years; asthma as defined by ATS; requiring oral corticosteroid daily or every other day for at least 6 months prior to study and taking doses of 5-20 mg every day or 10-40 mg every other day during the previous 2 weeks; FEV1 40-80%; documented attempts to reduce oral corticosteroid dose		
EXCLUSION:	Pregnancy/lactation; smoking history greater than 10-pack years; requirement for intranasal corticosteroids; use of methotrexate, gold salts, or troleandomycin within prior 3 months		
OTHER MEDICATIONS/ INTERVENTIONS:	Oral prednisone dose was tapered according to defined criteria starting at week 3; during open label period, all subjects received FLUP 2000 mcg/d which could be tapered down to 500 mcg/d		
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** No; unequal gender between groups; baseline PEF different **Asthma classification:** Severe persistent		
	fluticasone 1500 mcg/d	**fluticasone 2000 mcg/d**	**placebo**
Mean age (years):	53	50	52
Sex:	72% female	31% female	53% female
Ethnicity:	NR	NR	NR
Other population characteristics:			
• baseline AM and PM PEF	307/342	378/422	332/367

Authors: Noonan et al.; Okamoto et al. **Year: 1995, 1996**			
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** SF-36 (specifically the 8 individual domain scores, the physical and mental component summary scores (PCS and MCS); the health-transition item) **Secondary Outcome Measures:** Requirement for oral corticosteroids, correlations of SF-36 with FEV1 **Timing of assessments:** Baseline, 16 weeks, and every 4 months during 1 year open-label phase		
RESULTS:	**Health Outcome Measures:** **16 weeks** • FLUP 2000 mcg/day > placebo on physical functioning (P < 0.001), role-physical (P = 0.001), and general health perception (P = 0.02)* • FLUP 1500 mcg/day > placebo on role emotional (P = 0.01)* • FLUP 2000 mcg/day > FLUP 1500 mcg/day in physical functioning and role physical (P < 0.05)* • FLUP 2000 mcg/day > FLUP 1500 mcg/day and placebo in PCS scores; no difference in MCS • % of subjects to come off oral prednisone: FLUP 2000 mcg/d 88%, FLUP 1500 mcg/d 69%, placebo 3% (P < 0.001) **Intermediate Outcome Measures:** • Mean change in FEV1 higher in FLUP 2000 mcg/d (0.52 L) compared to placebo (-0.17 L) and FDP 1500 mcg/d (0.18 L), (P < 0.05 for both comparisons) Mean change in FEV1 higher in FLUP 1500 mcg/d compared to placebo (P < 0.05)		
ANALYSIS:	**ITT:** Yes (LOCF) **Post randomization exclusions:** Yes; 14 subjects did not complete the study		
ATTRITION (*overall*):	**Overall loss to follow-up:** 14.6% (14) **Loss to follow-up differential high:** Unable to determine		
ATTRITION (*treatment specific*):	**fluticasone 1500 mcg/d**	**fluticasone 2000 mcg/d**	**placebo**
Loss to follow-up:	NR	NR	NR
Withdrawals due to adverse events:	0	0	0
Withdrawals due to lack of efficacy:	NR	NR	NR
ADVERSE EVENTS:	**fluticasone 1500 mcg/d**	**fluticasone 2000 mcg/d**	**placebo**
Overall adverse effects reported:	17 (53.1%)	14 (43.8%)	5 (15.6%)
Significant differences in events:	0	0	0
• Candidiasis/plaques	14 (43.8%)	9 (28.1%)	3 (9.4%)
QUALITY RATING:	**Fair**		

*primary outcome measures

Asthma ***Inhaled Corticosteroids***

STUDY:	**Authors: Raphael et al.**[26] **Year: 1999** **Country:** USA			
FUNDING:	Glaxo Wellcome			
DESIGN:	**Study design:** RCT **Setting:** Multi-center (23 primary care and asthma specialty centers) **Sample size:** 399			
INTERVENTION: **Dose:** **Dosing range:** **Device:** **Duration:** **Sample size:**	**fluticasone** 176 mcg/day Low MDI 12 weeks 99	**fluticasone** 440 mcg/day Medium MDI 12 weeks 101	**beclomethasone** 336 mcg/day Low MDI 12 weeks 104	**beclomethasone** 672 mcg/day Medium MDI 12 weeks 95
Comparable dosing:	Yes			
INCLUSION:	Nonsmokers aged 12 or older; established diagnosis of chronic asthma requiring daily ICS; FEV1 45% to 80% below normal value; reversible lung function with albuterol			
EXCLUSION:	Systemic corticosteroids leukotriene modifiers, sodium cromoglycate, or nedocromil sodium for 1 month before study			
OTHER MEDICATIONS/ INTERVENTIONS:	Theophylline; salmeterol; albuterol; no spacer allowed			

Authors: Raphael et al. **Year: 1999**				
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Asthma classification:** Mild to severe persistent (most were moderate persistent)			
	fluticasone (low)	**fluticasone (mid)**	**beclomethasone (low)**	**beclomethasone (mid)**
Mean age (years):	38.4	37.8	41.5	39.8
Sex:	54% female	52% female	68% female	59% female
Ethnicity:				
• white:	92%	95%	90%	96%
• black	6%	4%	6%	3%
• other	2%	<1%	4%	1%
Other population characteristics:				
• salmeterol	27%	26%	23%	23%
• theophylline	29%	16%	19%	15%
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** FEV1; morning and evening PEF; use of supplemental albuterol; asthma symptom scale; nighttime awakenings caused by asthma **Secondary Outcome Measures:** NR **Timing of assessments:** Daily diary; FEV1: baseline, weeks 1, 2, 4, 6, 8, 10, 12			
RESULTS:	**Health Outcome Measures:** • Combined FLUP treatments significantly reduced albuterol use compared to combined BDP (0.9 vs. 0.5 puffs/d; P = 0.004)* • Asthma symptom scores were significantly lower under FLUP treatments than under BDP treatments (P = 0.024)* • FLUP patients had significantly more days without symptoms than BDP patients (P = 0.027)* • Night awakenings due to asthma were not significantly different* **Intermediate Outcome Measures:** • FEV1 showed a significantly greater improvement under low (0.311 vs. 0.181; P = 0.048) and medium (0.361 vs. 0.211; P = 0.034) FP treatment than under BDP treatment* • FP had a significantly greater improvement of PEF than BDP (P < 0.004)* • No significant dose effects for any outcome variables			

Authors: Raphael et al. **Year: 1999**				
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** No			
ATTRITION (*overall*):	**Overall loss to follow-up:** 111 (28%) **Loss to follow-up differential high:** Yes			
ATTRITION (*treatment specific*):	**fluticasone (low)**	**fluticasone (mid)**	**beclomethasone (low)**	**beclomethasone (mid)**
Loss to follow-up:	27 (27%)	22 (21%)	40 (40%)	22 (23%)
Withdrawals due to adverse events:	3 (3%)	3 (3%)	3 (3%)	3 (3%)
Withdrawals due to lack of efficacy:	17 (17%)	16 (15%)	26 (26%)	16 (17%)
Other:	7 (7%)	3 (3%)	10 (10%)	4 (4%)
ADVERSE EVENTS:	**fluticasone (low)**	**fluticasone (mid)**	**beclomethasone (low)**	**beclomethasone (mid)**
Overall adverse effects reported:	NR	NR	NR	NR
Specific differences in events:	none	none	none	none
QUALITY RATING:	**Fair**			

*primary outcome measures

Asthma *Inhaled Corticosteroids*

STUDY:	**Authors: Ringdal et al.**[35] **Year: 1996** **Country:** Multinational		
FUNDING:	NR (2 authors affiliated with Glaxo Wellcome)		
DESIGN:	**Study design:** RCT **Setting:** Multi-center **Sample size:** 518		
INTERVENTION: **Dose:** **Dosing range:** **Device:** **Duration:** **Sample size:**	**fluticasone** 800 mcg/day High DPI 12 weeks 256	**budesonide** 1600 mcg/day High DPI 12 weeks 262	
Comparable dosing:	Yes		
INCLUSION:	Age 18-75; history of reversible airways obstruction treated with a constant dose of ICS for 4 weeks prior to study; FEV1 45-90% of predicted with response to beta-agonist; require 2 or more doses of rescue beta-agonist or asthma symptoms on at least 4 of the last 7 days of the run-in		
EXCLUSION:	Unstable asthma; receipt of oral corticosteroids; upper respiratory infection; hospital admission for respiratory disease during 4 weeks prior to study; requiring 16 or more doses of rescue beta-agonist during the last 6 days of run-in; concomitant disease which would interfere with assessment; alcohol or drug abuse; pregnancy/lactation		
OTHER MEDICATIONS/ INTERVENTIONS:	Short acting beta-agonist allowed for rescue; other concomitant asthma medications (except oral corticosteroid) were allowed permitting they were at a constant dose for 4 weeks prior to study		
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Asthma classification:** Moderate-severe persistent		
	fluticasone	**budesonide**	
Mean age (years):	47.6	48.3	
Sex:	42.6% female	49.6% female	
Ethnicity:	88.7% white	90.8% white	
Other population characteristics: • smoker	16.8%	20.6%	

Authors: Ringdal et al. **Year: 1996**			
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Patient assessed AM PEF **Secondary Outcome Measures:** PM PEF; day and nighttime symptom severity; use of rescue beta-agonist; clinic measured PEF, FEV1, FVC; exacerbation rate defined as either requiring ≥ 8 doses of rescue beta-agonist or PEF < 85% of predicted on 3 days during any 6 day period **Timing of assessments:** Daily for patient assessed measures, baseline, 4, 8 and 12 weeks for clinic based measures		
RESULTS:	**Health Outcome Measures:** • No differences in day or night asthma symptom scores between treatment groups • No difference in percentage of days without rescue beta-agonist use between treatment groups • No difference in numbers of patients reporting exacerbations between groups **Intermediate Outcome Measures:** • Mean change in AM PEF (FLUP 21.1 L/min vs. BUD 11.2 L/min, P = 0.003)*. • Mean change in PM PEF (FLUP 13.8 L/min vs. BUD 6.8 L/min, P = 0.04) • Mean change in clinic PEF (FLUP 24.8 L/min vs. BUD 20.9 L/min, P = 0.005) • Mean change in clinic FEV1 (FLUP 0.12 L vs. BUD 0.06 L, P = 0.008) • Mean change in clinic FVC (FLUP 0.07 L vs. BUD 0.02 L, P = 0.02)		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** NR		
ATTRITION (*overall*):	**Overall loss to follow-up:** 49 (9.5%) **Loss to follow-up differential high:** No		
ATTRITION (*treatment specific*): **Loss to follow-up:** **Withdrawals due to adverse events:** **Withdrawals due to lack of efficacy:**	**fluticasone** 25 (9.8%) 10 (3.9%) 2 (0.8%)	**budesonide** 24 (9.2%) 13 (5.0%) 1 (0.4%)	
ADVERSE EVENTS: **Overall adverse effects reported:** **Significant differences in events:**	**fluticasone** 61.7% of patients none	**budesonide** 61.5% of patients none	
QUALITY RATING:	**Fair**		

*primary outcome measures

Asthma *Inhaled Corticosteroids*

STUDY:	**Authors: Simons**[40] **Year: 1997** **Country:** Canada		
FUNDING:	Glaxo Wellcome		
DESIGN:	**Study design:** RCT **Setting:** Multi-center (number of sites NR) **Sample size:** 241		
INTERVENTION:	**beclomethasone**	**salmeterol**	**placebo**
Dose:	400 mcg/day	100 mcg/d	N/A
Dosing range:	Medium	N/A	N/A
Device:	Diskhaler (DPI)	Diskhaler	Diskhaler
Duration:	1 year	1 year	1 year
Sample size:	81	80	80
Comparable dosing:	Yes		
INCLUSION:	Age 6-14 years; clinically stable asthma; < 1 month treatment with inhaled or oral glucocorticoids for asthma; no glucocorticoid treatment within three months of enrollment; FEV1 greater than 70% of predicted after bronchodilator had been withheld for 6 hours; 10% increase in FEV1 30 minutes after inhalation of albuterol; Less than 8 mg of metacholine/ml necessary to decrease FEV1 by 20%		
EXCLUSION:	Any emergency department visits or hospitalizations within three months of study; history of life-threatening asthma; history of adverse reactions to study medication		
OTHER MEDICATIONS/ INTERVENTIONS:	Albuterol permitted as needed; other medications being taken prior to study also permitted if dosage unchanged		
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Asthma classification:** Mild to moderate persistent		
	beclomethasone	**salmeterol**	**placebo**
Mean age (years):	9.6	8.8	9.5
Sex:	41% female	40% female	45% female
Ethnicity:	NR	NR	NR
Percent taking other asthma meds	22%	26%	26%

Authors: Simons **Year: 1997**			
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Airway responsiveness (measured by metacholine-challenge tests) **Secondary Outcome Measures:** Daily PEFR; asthma symptoms; albuterol use; height; school days missed; activities affected by asthma **Timing of assessments:** Airway responsiveness measured at baseline, 3,6,9, and 12 months of study drug treatment, and 2 weeks after study drugs discontinued; PEFR, asthma symptoms, and albuterol use recorded daily; height measured at 1,3,6,9, and 12 months		
RESULTS:	**Health Outcome Measures:** • Significantly more beta-agonist free days and nights for BDP compared with placebo (P < 0.001) • Significantly higher percentage of BDP-treated children did not require beta-agonist (P = 0.03) • Increase in height in the BDP group was significantly less than the placebo group (P = 0.018) • No significant differences in the number of school days missed or activities affected by asthma between BDP and placebo **Intermediate Outcome Measures:** • BDP group had significantly greater improvement in airway responsiveness than the placebo group (P < 0.001)		
ANALYSIS:	**ITT:** No **Post randomization exclusions:** NR		
ATTRITION (*overall*): **ATTRITION (*treatment specific*):**	**Overall loss to follow-up:** 60 (25%) **Loss to follow-up differential high:** Yes		
Loss to follow-up:	**beclomethasone** 17%	**salmeterol** 28%	**placebo** 31%
Withdrawals due to adverse events:	4%	5%	4%
Withdrawals due to lack of efficacy:	5%	15%	15%
ADVERSE EVENTS:	**beclomethasone**	**salmeterol**	**placebo**
Overall adverse effects reported:	NR	NR	NR
Significant differences in events:	none	none	none
QUALITY RATING:	**Fair**		

Asthma ***Inhaled Corticosteroids***

STUDY:	**Authors: Sin et al.**[50] **Year: 2001** **Country:** Canada		
FUNDING:	Institute for Clinical Evaluative Sciences		
DESIGN:	**Study design:** Retrospective cohort study **Setting:** Population-based database review **Sample size:** 6,254		
INTERVENTION:	**ICS**	**no ICS**	
Dose:	N/A	N/A	
Dosing range:	Low-medium-high	N/A	
Device:	All devices	N/A	
Duration:	NR	N/A	
Sample size:	3,759	2,495	
Comparable dosing:	N/A		
INCLUSION:	Residents from Ontario; 65 years or older; hospitalized for asthma between 1992 and 1997		
EXCLUSION:	Patients who died in hospital or within 30 days of discharge; patients who were transferred to another hospital		
OTHER MEDICATIONS/ INTERVENTIONS:	All other medications allowed		
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Asthma classification:** Mild intermittent; mild persistent; moderate persistent; severe persistent		
	ICS	**no ICS**	
Mean age (years):	73.9	74.8	
Sex:	70% female	66.9% female	
Ethnicity:	NR	NR	
Other population characteristics:	NR	NR	

<table>
<tr><td colspan="4">Authors: Sin et al.
Year: 2001</td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">Primary Outcome Measures: Association between ICS and all cause mortality or rehospitalization over a 12 months time period

Secondary Outcome Measures: NR

Timing of assessments: N/A</td></tr>
<tr><td>RESULTS:</td><td colspan="3">Health Outcome Measures:
Users of ICS postdischarge were 29% (95% CI: 20% to 38%) less likely to be readmitted to a hospital for asthma and 39% (95% CI: 20% to 53%) less likely to die of any cause over a 1 year period than patients not using ICS*
Intermediate Outcome Measures:
NR</td></tr>
<tr><td>ANALYSIS:</td><td colspan="3">ITT: N/A
Post randomization exclusions: N/A</td></tr>
<tr><td>ATTRITION (overall):</td><td colspan="3">Overall loss to follow-up: N/A
Loss to follow-up differential high: N/A</td></tr>
<tr><td>ATTRITION (treatment specific):
Loss to follow-up:
Withdrawals due to adverse events:
Withdrawals due to lack of efficacy:</td><td><u>ICS</u>
N/A
N/A
N/A</td><td><u>no ICS</u>
N/A
N/A
N/A</td><td></td></tr>
<tr><td>ADVERSE EVENTS:
Overall adverse effects reported:
Significant differences in events:</td><td colspan="3">NR</td></tr>
<tr><td>QUALITY RATING:</td><td colspan="3">Fair</td></tr>
</table>

*primary outcome measures

Asthma ***Inhaled Corticosteroids***

STUDY:	**Authors: Suissa et al.**[49] **Year: 2000** **Country:** Canada		
FUNDING:	Medical Research Council of Canada, Astra Draco, Boehringer Ingelheim Pharm., and Zeneca Pharm.		
DESIGN:	**Study design:** Case control study **Setting:** Population-based Saskatchewan 1975-1991 **Sample size:** 2,747		
INTERVENTION: **Dose:** **Dosing range:** **Device:** **Duration:** **Sample size:**	**case patients (asthma death)** N/A N/A N/A N/A 66	**control patients** N/A N/A N/A N/A 2,681	
Comparable dosing:	N/A		
INCLUSION:	Case patients were the 66 patients that experienced asthma death and the 2,681 matched controls; controls were matched for age, date of entry into the database, length of time in the database, number of beta-agonist canisters used, theophylline use, use of nebulized beta-agonists, use of oral corticosteroids, and hospitalization for asthma		
EXCLUSION:	NR		
OTHER MEDICATIONS/ INTERVENTIONS:	N/A		
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** N/A **Asthma classification:** Severe persistent		
	case patients (asthma death)	**control patients**	
Mean Age (years):	30	28	
Sex:	40.9% female	49.1% female	
Ethnicity:	NR	NR	
ICS use 1 year prior to index date			
• none	47.0%	53.8%	
• 1-5 canisters	51.5%	38.8%	
• ≥ 6 canisters	1.5%	7.4%	

<table>
<tr><td colspan="4">Authors: Suissa et al.
Year: 2000</td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">Primary Outcome Measures: Rate of death from asthma as a function of inhaled corticosteroid use

Secondary Outcome Measures: None

Timing of assessments: N/A</td></tr>
<tr><td>RESULTS:</td><td colspan="3">Health Outcome Measures:
The rate of death decreased by 21% with each additional canister of inhaled corticosteroids used during the previous year (rate ratio: 0.79; 95% CI: 0.65 to 0.97)
Intermediate Outcome Measures:
None</td></tr>
<tr><td>ANALYSIS:</td><td colspan="3">ITT: N/A
Post randomization exclusions: N/A</td></tr>
<tr><td>ATTRITION (overall):</td><td colspan="3">Overall loss to follow-up: N/A
Loss to follow-up differential high: N/A</td></tr>
<tr><td>ATTRITION (treatment specific):
Loss to follow-up:
Withdrawals due to adverse events:
Withdrawals due to lack of efficacy:</td><td><u>case patients (asthma death)</u>
N/A
N/A
N/A</td><td><u>control patients</u>
N/A
N/A
N/A</td><td></td></tr>
<tr><td>ADVERSE EVENTS:
Overall adverse effects reported:
Significant differences in events:</td><td colspan="3">
N/A
N/A</td></tr>
<tr><td>QUALITY RATING:</td><td colspan="3">Good</td></tr>
</table>

Asthma ***Inhaled Corticosteroids***

STUDY:	**Authors: Terzano et al.**[19] **Year: 2000** **Country:** Italy		
FUNDING:	Chiesi Farmaceutici SpA, Parma, Italy		
DESIGN:	**Study design:** RCT **Setting:** Multi-center (10) **Sample size:** 127		
INTERVENTION: **Dose:** **Dosing range:** **Device:** **Duration:** **Sample size:**	**beclomethasone** 800 mcg/day High Nebulizer 4 weeks 66	**budesonide** 1000 mcg/day Medium Nebulizer 4 weeks 61	
Comparable dosing:	No (inhalation dose for BDP estimated and may be comparable)		
INCLUSION:	6-14 years old; persistent asthma that met NHLBI criteria: PEFR > 50% and < 85% predicted		
EXCLUSION:	Children who had oral steroid treatment for more than 12 days in the previous 12 weeks; significant illness; hypersensitivity to the study drugs		
OTHER MEDICATIONS/ INTERVENTIONS:	Beta-2 agonists as required; oral prednisone 1 mg/kg body weight was also allowed		
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Asthma classification:** Mild persistent to moderate persistent		
	beclomethasone	**budesonide**	
Mean age (years): **Sex:** **Ethnicity:** **Other population characteristics:** • mean height • % predicted PEFR (L/min)	9.5 27% female NR 141.9 cm 67.1	10.0 28% female NR 132.9 cm 66.3	

Authors: Terzano et al. **Year: 2000**			
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Final mean of clinic PEFR **Secondary Outcome Measures:** FEV1; FVC; improvement of asthma symptoms; beta-2 agonist use; patient measured PEFR; nocturnal dyspnea **Timing of assessments:** Clinic measured PEFR, FEV1, and FVC were obtained every 2 weeks; asthma symptoms, patient PEFR, and beta-2 agonist use were recorded daily		
RESULTS:	**Health Outcome Measures:** • No difference in the improvement of asthma symptoms • No difference in beta-2 agonist use • No difference in nocturnal dyspnea **Intermediate Outcome Measures:** • No difference in clinic measured PEFR* • No difference in FEV1		
ANALYSIS:	**ITT:** Yes (LOCF) **Post randomization exclusions:** No		
ATTRITION (*overall*): **ATTRITION (*treatment specific*):**	**Overall loss to follow-up:** 9 (7%) **Loss to follow-up differential high:** No		
	beclomethasone	**budesonide**	
Loss to follow-up:	8 (12%)	1 (2%)	
Withdrawals due to adverse events:	0	0	
Withdrawals due to lack of efficacy:	NR	NR	
ADVERSE EVENTS:	**beclomethasone**	**budesonide**	
Overall adverse effects reported:	4 (6%)	2 (3%)	
Differences in specific events:	none	none	
QUALITY RATING:	**Fair**		

*primary outcome measures

Asthma *Inhaled Corticosteroids*

STUDY:	**Authors: Terzano et al.**[30] **Year: 2001** **Country:** Italy		
FUNDING:	Chiesi Farmaceutici SpA, Parma, Italy (one author employee of Chiesi)		
DESIGN:	**Study design:** RCT **Setting:** Multi-center (10) **Sample size:** 133		
INTERVENTION: **Dose:** **Dosing range:** **Device:** **Duration:** **Sample size:**	**flunisolide** 1000 mcg/day Low-Medium Nebulizer 4 weeks 67	**budesonide** 1000 mcg/day Medium Nebulizer 4 weeks 66	
Comparable dosing:	Yes (dosing range for nebulized FLUN is estimated)		
INCLUSION:	6-14 years old; persistent asthma that met NHLBI criteria: PEFR between 50-85% predicted and at least a 15% increase in FEV1 30 minutes following 1 puff of salbutamol		
EXCLUSION:	Children who had oral steroid treatment for more than 12 days in the previous 12 weeks; significant illness; hypersensitivity to the study drugs		
OTHER MEDICATIONS/ INTERVENTIONS:	Beta-2 agonists as required; oral prednisone 1 mg/kg body weight was also allowed		
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Asthma classification:** Mild persistent to moderate persistent		
	flunisolide	**budesonide**	
Mean age (years):	9.6	9.8	
Sex:	29% female	39 % female	
Ethnicity:	NR	NR	
Other population characteristics:			
• baseline morning PEFR	263.3 L/min	262.9 L/min	
• clinic PEFR % predicted	68.4	67.7	

<table>
<tr><td colspan="4">Authors: Terzano et al.
Year: 2001</td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">Primary Outcome Measures: Mean morning PEFR

Secondary Outcome Measures: Evening PEFR; global asthma symptoms (5 point scale); beta-2 agonist use; nocturnal awakening; diurnal dyspnea

Timing of assessments: PEFR, asthma symptoms, sleep disturbance, and beta-2 agonist use recorded daily</td></tr>
<tr><td>RESULTS:</td><td colspan="3">Health Outcome Measures:
No difference in the improvement of asthma symptom scores
No difference in beta-2 agonist use
No difference in diurnal dyspnea
Significant reduction in the number of nocturnal awakenings only for FLUN (P < 0.001)
Intermediate Outcome Measures:
No difference in morning PEFR (P = 0.091)
No difference in evening PEFR (P = 0.089)</td></tr>
<tr><td>ANALYSIS:</td><td colspan="3">ITT: Yes (LOCF)
Post randomization exclusions: Yes (1)</td></tr>
<tr><td>ATTRITION (overall):</td><td colspan="3">Overall loss to follow-up: NR (1 (0.75%) post-randomization exclusion)
Loss to follow-up differential high: No</td></tr>
<tr><td>ATTRITION (treatment specific):
Loss to follow-up:
Withdrawals due to adverse events:
Withdrawals due to lack of efficacy:</td><td><u>flunisolide</u>
1 (1.5%)
NR
NR</td><td><u>budesonide</u>
0 (0%)
NR
NR</td><td></td></tr>
<tr><td>ADVERSE EVENTS:
Overall adverse effects reported:
Differences in specific events:</td><td><u>flunisolide</u>
10 (15%)
none</td><td><u>budesonide</u>
11(17%)
none</td><td></td></tr>
<tr><td>QUALITY RATING:</td><td colspan="3">Fair</td></tr>
</table>

Evidence Table 2. COPD Inhaled Corticosteroids

STUDY:	**Authors**: **Alsaeedi et al.**[59] **Year: 2002**
FUNDING:	NR
DESIGN:	**Study design:** Meta-analysis **Number of patients:** 3,976
AIMS OF REVIEW:	To determine whether ICS improve clinical outcomes for patients with stable COPD
STUDIES INCLUDED IN META-ANALYSIS	Paggiaro et al., 1998; Weir et al., 1999; Pauwels et al., 1999; Renkema et al., 1996; The Lung Health Study Research Group, 2000; Burge et al., 2000; Bourbeau et al., 1998; Senderovitz et al., 1999; Vestbo et al., 1999
TIME PERIOD COVERED:	1966-2001
CHARACTERISTICS OF INCLUDED STUDIES:	Placebo-controlled randomized trials of ICS in stable COPD of at least 6 months
CHARACTERISTICS OF INCLUDED POPULATIONS:	Mean age for all studies greater than or equal to 52 years old; stable COPD

Authors: Alsaeedi et al. **Year: 2002**	
CHARACTERISTICS OF INTERVENTIONS:	Medium to High Dose of ICS; study durations between 6 and 40 months
MAIN RESULTS:	• ICS usage significantly reduced the rate of exacerbations (RR: 0.70; 95% CI: 0.58 to 0.84) • No dose-response effect could be demonstrated • Similar benefits in patients who were and were not pretreated with oral corticosteroids • The relative risk for all cause mortality favored ICS use but did not reach statistical significance (RR 0.84; 95% CI: 0.60 to 1.18)
ADVERSE EVENTS:	ICS usage was associated with significantly higher rates of oral candidiasis (RR: 2.1; 95% CI: 1.5 to 3.1) and skin bruising (RR: 2.1; 95% CI: 1.6 to 2.8)
COMPREHENSIVE LITERATURE SEARCH STRATEGY:	Yes
STANDARD METHOD OF APPRAISAL OF STUDIES:	Yes
QUALITY RATING:	**Good**

COPD ***Inhaled Corticosteroids***

STUDY:	**Authors: Bourbeau et al.**[68] **Year: 1998** **Country:** Canada		
FUNDING:	ASTRA Pharma Inc., Canada		
DESIGN:	**Study design:** RCT **Setting:** Single center (outpatient clinic) **Sample size:** 79		
INTERVENTION: **Dose:** **Dosing range:** **Device:** **Duration:** **Sample size:**	**budesonide** 1600 mcg/d High DPI 6 months 39	**placebo** N/A N/A DPI 6 months 40	
Comparable dosing:	N/A		
INCLUSION:	Age 40 years old or older; smokers or ex-smokers; no history of asthma; no exacerbation 2 months prior to trial; FEV1/FVC ratio of 0.65 or less; prebronchodilator FEV1 less than 65% of predicted; postbronchodilator less than 80%; absence of other serious disease; no inhaled corticosteroids within a month and no oral steroids within 2 months		
EXCLUSION:	Patients who responded to a two week course of oral prednisone; other active lung disease; diabetes; peptic ulcer disease		
OTHER MEDICATIONS/ INTERVENTIONS:	All medications except other ICS		
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** No **COPD classification:** Moderate to severe		
	budesonide	**placebo**	
Mean age (years):	66	66	
Sex:	15% female	28% female	
Ethnicity:	NR	NR	
Other population characteristics:			
• current smoker	33%	45%	

Authors: Bourbeau et al. **Year: 1998**			
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** FEV1 **Secondary Outcome Measures:** Exercise capacity; dyspnea with exertion; quality of life; PEFR; respiratory symptoms **Timing of assessments:** FEV1, exercise capacity, dyspnea with exertion, and quality of life questionnaires were administered at 1, 3, 6 months; morning and evening PEFR and symptom scores were recorded daily for 3 months and then weekly		
RESULTS:	**Health Outcome Measures:** • No difference in exercise capacity, dyspnea with exertion, or quality of life between placebo and budesonide • No difference in respiratory symptoms observed between the two groups **Intermediate Outcome Measures:** • No significant difference between budesonide and placebo in FEV1*		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** NR		
ATTRITION (*overall*):	**Overall loss to follow-up:** 13 (16%) **Loss to follow-up differential high:** Yes		
ATTRITION (*treatment specific*): **Loss to follow-up:** **Withdrawals due to adverse events:** **Withdrawals due to lack of efficacy:**	**budesonide** 3 (8%) 0 NR	**placebo** 10 (25%) 1 (2.5%) NR	
ADVERSE EVENTS: **Overall adverse effects reported:** **Significant differences in events:**	**budesonide** 59% NR	**placebo** 70% NR	
QUALITY RATING:	**Fair**		

*primary outcome measures

COPD ***Inhaled Corticosteroids***

STUDY:	**Authors**: **Burge et al.**[69] **Year: 2000** **Country:** UK **Trial name: ISOLDE**	**Authors**: **Calverley et al.**[70] **Year: 2003**	**Authors**: **Spencer et al.**[71] **Year: 2001**	**Authors: Jones et al.**[72] **Year: 2003**
FUNDING:	Glaxo Wellcome Research and Development, Uxbridge, Middlesex			
DESIGN:	**Study design:** RCT **Setting:** Multi-center (18 hospitals) **Sample size:** 751			

INTERVENTION:	**fluticasone**	**placebo**	
Dose:	1000 mcg/d	N/A	
Dosing range:	High	N/A	
Device:	MDI	MDI	
Duration:	3 years	3 years	
Sample size:	376	375	

Comparable dosing:	N/A
INCLUSION:	Current or former smokers; 40-75 years of age; non-asthmatic chronic obstructive pulmonary disease; baseline FEV1 after bronchodilator at least 0.8 L but less than 85% of predicted normal
EXCLUSION:	FEV1 response to 400 mcg salbutamol exceeded 10% of predicted normal; life expectancy of less than 5 years from concurrent diseases; used beta-blockers
OTHER MEDICATIONS/ INTERVENTIONS:	Nasal and ophthalmic corticosteroids; theophyllines; salbutamol or ipratropium bromide for symptomatic relief

<table>
<tr><td colspan="4">Authors and Year: Burge et al. 2000; Calverley et al. 2003; Spencer et al. 2001; Jones et al. 2003</td></tr>
<tr><td rowspan="5">POPULATION CHARACTERISTICS:</td><td colspan="3">Groups similar at baseline: Yes
COPD classification: Mild and moderate to severe</td></tr>
<tr><td></td><td><u>fluticasone</u></td><td><u>placebo</u></td></tr>
<tr><td>Mean age (years):</td><td>63.7</td><td>63.8</td></tr>
<tr><td>Sex:</td><td>25% female</td><td>26% female</td></tr>
<tr><td>Ethnicity:
Other population characteristics:
• smoked during trial
• former smoker</td><td>NR

36%
47%</td><td>NR

39%
46%</td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">Primary Outcome Measures: Rate of FEV1 decline; frequency of exacerbations; respiratory withdrawals

Secondary Outcome Measures: SGRQ; serum cortisol concentrations

Timing of assessments: FEV1 measured every three months; exacerbations recorded when they occurred; SGRQ and serum cortisol measured every six months</td></tr>
<tr><td>RESULTS:</td><td colspan="3">Health Outcome Measures:
• The mean yearly exacerbation rate was lower in the fluticasone group than the placebo group (0.99/year vs. 1.32/year; P = 0.026)*
• Reduced rate of exacerbations was confined to patients with moderate to severe disease; patients with milder COPD did not show a statistically significant difference to placebo
• More patients withdrew in the placebo group than the fluticasone group due to respiratory disease (25% vs. 19%; P = 0.034)*
• Overall heath status deteriorated faster in the placebo-treated than in the FLUP-treated group as assessed on SGRQ and SF-36 (P = 0.004)
Intermediate Outcome Measures:
• There was no significant difference in the annual rate of FEV1 decline between FLUP (50 ml/year) and placebo (59 ml/year)
• Mean FEV1 after bronchodilator was significantly higher in FLUP than placebo throughout the study (+ 70 ml; P < 0.001)</td></tr>
</table>

Authors and Year: Burge et al. 2000; Calverley et al. 2003; Spencer et al. 2001; Jones et al. 2003			
RESULTS:	**Subgroup analysis** • Patients in the placebo group who withdrew because of exacerbation and respiratory symptoms were more likely to have had severe COPD at baseline than patients who withdrew from the FLUP group		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** Yes		
ATTRITION (*overall*):	**Overall loss to follow-up:** 47% **Loss to follow-up differential high:** No		
ATTRITION (*treatment specific*):	**fluticasone**	**placebo**	
Loss to follow-up:	160 (43%)	195 (53%)	
Withdrawals due to adverse events:	111 (30%)	131 (35%)	
Withdrawals due to lack of efficacy:	NR	NR	
ADVERSE EVENTS:	**fluticasone**	**placebo**	
Overall adverse effects reported:			
• Total serious adverse events	141	148	
• Total deaths	32	36	
Significant differences in events:	none	none	
QUALITY RATING:	**Fair**		

*primary outcome measures

COPD ***Inhaled Corticosteroids***

STUDY:	**Authors: Fan et al.**[62] **Year: 2003** **Country:** USA		
FUNDING:	Department of Veterans Affairs		
DESIGN:	**Study design:** Prospective cohort **Setting:** Multi-center (7 primary care clinics of VA Medical Centers) **Sample size:** 8,033		
INTERVENTION: **Dose:** **Dosing range:** **Device:** **Duration:** **Sample size:**	**all ICS** Varied N/A Varied 544 days (mean follow-up) 2,654	**no ICS** N/A N/A N/A 544 days (mean follow-up) 5,398	
Comparable dosing:	N/A		
INCLUSION:	45 years or older; outpatient clinic visit or inpatient hospitalization with a primary or secondary diagnosis of COPD and using at least 1 pulmonary medication during the 90 day period prior to index visit; participation in the VA Ambulatory Care Quality Improvement Project trial for at least 1 year		
EXCLUSION:	NR		
OTHER MEDICATIONS/ INTERVENTIONS:	Subjects' usual medications		

Authors: Fan et al. **Year: 2003**			
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** No **COPD classification:** NR		
	all ICS	**no ICS**	
Mean age (years):	67.2	66.5	
Sex:	2.1 % female	1.7 % female	
Ethnicity:	79.9 % white	84.6% white	
Other population characteristics:			
• theophylline use	22.0 %	9.0 %	
• anticholinergic use	74.9 %	56.3 %	
• oral corticosteroid use	8.3 %	4.9 %	
• long acting beta-agonist use	2.4 %	0.4%	
• concurrent asthma diagnosis	20.0 %	8.1%	
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** All-cause mortality **Secondary Outcome Measures:** COPD exacerbation (outpatient or inpatient) **Timing of assessments:** Varied		
RESULTS:	**Health Outcome Measures:** • Hazard ratio 0.87 (95% CI: 0.72 to 1.05) for all cause mortality for corticosteroid use vs. non-use* • Other time-dependent analyses and analyses stratified for low vs. medium/high dose show no mortality difference for corticosteroid use vs. non-use • Hazard ratio 0.85 (95% CI: 0.67 to 1.06) for hospitalization due to COPD for corticosteroid use vs. non-use • Sensitivity analysis restricted to subjects without a concomitant asthma diagnosis did not alter results **Intermediate Outcome Measures:** • NR		

Authors: Fan et al. **Year: 2003**			
ANALYSIS:	**ITT:** N/A **Post randomization exclusions:** N/A		
ATTRITION (*overall*): **ATTRITION (*treatment specific*):**	**Overall loss to follow-up:** N/A **Loss to follow-up differential high:** N/A		
	<u>all ICS</u>	**<u>no ICS</u>**	
Loss to follow-up:	N/A	N/A	
Withdrawals due to adverse events:	N/A	N/A	
Withdrawals due to lack of efficacy:	N/A	N/A	
ADVERSE EVENTS: **Overall adverse effects reported:** **Significant differences in events:**	Not studied in this analysis N/A		
QUALITY RATING:	**Good**		

*primary outcome measures

COPD ***Inhaled Corticosteroids***

STUDY:	**Authors: Paggiaro et al.**[73] **Year: 1998** **Country:** Multinational (13 European, New Zealand, South Africa)		
FUNDING:	NR		
DESIGN:	**Study design:** RCT **Setting:** Multi-center (hospital outpatient clinics) **Sample size:** 281		
INTERVENTION: **Dose:** **Dosing range:** **Device:** **Duration:** **Sample size:**	**fluticasone** 1000 mcg/d High MDI 6 months 142	**placebo** N/A N/A MDI 6 months 139	
Comparable dosing:	N/A		
INCLUSION:	Age 50-75; COPD as defined by European Respiratory Society Consensus Statement; at least 10 pack-year smoking history; chronic bronchitis; at least 1 exacerbation per year for the prior 3 years that required a health care visit; high likelihood of experiencing an exacerbation within next 6 months; regular productive cough; FEV1 35-90% of predicted; FEV1/FVC ratio of $\leq$ 0.7; FEV1 reversibility < 15% after beta-agonist		
EXCLUSION:	Abnormal chest radiograph; oral, depot, or > 500 mcg/d of inhaled corticosteroids within prior 4 weeks, antibiotic therapy or admission to hospital in prior 4 weeks; current users of fluticasone		
OTHER MEDICATIONS/ INTERVENTIONS:	Short acting beta-agonists allowed on an “as-needed” basis; continuation of anticholinergics and methylxanthines allowed		

Authors: Paggiaro et al. **Year: 1998**			
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **COPD classification:** Mild to moderate		
	fluticasone	**placebo**	
Mean age (years):	62	64	
Sex:	30% female	22% female	
Ethnicity:	NR	NR	
Other population characteristics:			
• current smoker	49%	49%	
• ex-smoker	51%	50%	
• history of atopy	3%	6%	
• using methylxanthines	36%	32%	
• using anticholinergics	12%	19%	
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Number of patients with at least 1 exacerbation at the end of the treatment period **Secondary Outcome Measures:** Patient assessed PEF, symptoms and beta-agonist use; patient and physician assessment of efficacy; distance walked in 6 minutes; Borg Score for breathlessness; pulmonary function tests **Timing of assessments:** 1, 2, 4 and 6 months		
RESULTS:	**Health Outcome Measures:** • No difference in the number of patients with at least one exacerbation (32% FLUP vs. 37% placebo, P = 0.449)* • Trend toward fewer total and less severe exacerbations in FLUP group (P = 0.067) • Placebo treated subjects' most severe exacerbations were rated as moderate or severe significantly more frequent than FLUP treated subjects' most severe exacerbations (P < 0.001) • Lower median daily cough and sputum volume in FLUP treated subjects as compared to placebo (P = 0.004 and 0.016 respectively) • No difference between groups in breathlessness or use of rescue beta-agonist • Adjusted mean change in distance walked during 6 min (FLUP 27m vs. placebo 8m, P = 0.03) • Physician and patient assessed efficacy favored FLUP (P = 0.003 and 0.004 respectively)		

Authors: Paggiaro et al. **Year: 1998**			
RESULTS:	**Intermediate Outcome Measures:** • Adjusted mean change in daily PEF (15 L/min FLUP vs. –2 L/min placebo, P < 0.001) • Adjusted mean change in clinic PEF (difference 15L/min favoring FLUP, P = 0.048) • Adjusted mean change in FEV1 (0.11 L FLUP vs. –0.04 L placebo, P < 0.001) • Adjusted mean change in FVC (Difference 0.33 L favoring FLUP, P < 0.001) • Adjusted mean change in FEF 25 – 75 (difference 0.14 L favoring FLUP, P < 0.01)		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** No		
ATTRITION (*overall*):	**Overall loss to follow-up:** 46 (16.4%) **Loss to follow-up differential high:** No		
ATTRITION (*treatment specific*):	**fluticasone**	**placebo**	
Loss to follow-up:	19 (13%)	27 (19%)	
Withdrawals due to adverse events:	9 (6.3%)	16 (11.5%)	
Withdrawals due to lack of efficacy:	4 (2.8%)	1 (0.7%)	
ADVERSE EVENTS:	**fluticasone**	**placebo**	
Overall adverse effects reported:	64% of patients	68% of patients	
Significant differences in events:	none	none	
QUALITY RATING:	**Good**		

*primary outcome measures

COPD ***Inhaled Corticosteroids***

STUDY:	**Authors: Pauwels et al.**[67] **Year: 1999** **Country:** Multi-national (9 European countries) **Study name:** EUROSCOP		
FUNDING:	Astra Draco, Sweden		
DESIGN:	**Study design:** RCT **Setting:** Multi-center (39 centers) **Sample size:** 1,277		
INTERVENTION: **Dose:** **Dosing range:** **Device:** **Duration:** **Sample size:**	**budesonide** 800 mcg/day Medium DPI 3 years 634	**placebo** N/A N/A DPI 3 years 643	
Comparable dosing:	N/A		
INCLUSION:	Age 30-65 years; current smokers; at least 5 cigarettes/day and had smoked for at least 10 years or had smoking history of at least 5 pack-years; FEV1 after bronchodilator use 50-100% of predicted normal value; ratio of prebronchodilator FEV1 to slow vital capacity less than 70%		
EXCLUSION:	History of asthma, allergic rhinitis, or allergic eczema; anyone who quit smoking during the smoking cessation treatment program (where participants had been recruited)		
OTHER MEDICATIONS/ INTERVENTIONS:	Beta-blockers; cromones; long-acting inhaled beta 2-adrenergic agonists		
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **COPD classification:** Mild (still smoking)		
	budesonide	**placebo**	
Mean age (years):	52	52	
Sex:	26.5% female	27.8% female	
Ethnicity:	NR	NR	
Other population characteristics:			
• pack-years of smoking	39.4+/- 20.1	39.2+/- 20.1	
• duration of smoking	35.8+/- 7.8	35.9+/- 8.2	

Authors: Pauwels et al. **Year: 1999**			
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** FEV1; bone density **Secondary Outcome Measures:** NR **Timing of assessments:** Every 3 months		
RESULTS:	**Health Outcome Measures:** NR **Intermediate Outcome Measures:** • Decline of FEV1 was significantly less in the BUD-group than in the placebo group over 3 years (140 ml vs. 180 ml; P = 0.05) • No significant difference in changes of bone density over time between treatment groups		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** NR		
ATTRITION (*overall*): **ATTRITION (*treatment specific*):** **Loss to follow-up:** **Withdrawals due to adverse events:** **Withdrawals due to lack of efficacy:**	**Overall loss to follow-up:** 365 (29%) **Loss to follow-up differential high:** No **budesonide** 176 (27.8%) 70 (16.6%) NR	**placebo** 189 (29.4%) 62 (13.2%) NR	
ADVERSE EVENTS: **Overall adverse effects reported:** **Significant differences in events:** • Candidiasis (P < 0.001) • Hoarseness (P < 0.04) • Bruises (P < 0.001)	**budesonide** 330 (52%) 31 (4.9%) 46 (7.3%) 63 (10%)	**placebo** 240 (37%) 10 (1.6%) 28 (4.4%) 27 (4.2%)	
QUALITY RATING:	**Fair**		

*primary outcome measures

COPD ***Inhaled Corticosteroids***

STUDY:	**Authors: Renkema et al.**[58] **Year: 1996** **Country:** The Netherlands		
FUNDING:	Netherlands Asthma Foundation, ASTRA BV Holland, AB DRACO Sweden		
DESIGN:	**Study design:** RCT **Setting:** Pulmonary outpatient clinics **Sample size:** 58		
INTERVENTION:	**budesonide**	**budesonide & prednisolone**	**placebo**
Dose:	1600 mcg/day	1600 mcg & 5mg prednisolone	N/A
Dosing range:	Medium	Medium	N/A
Device:	MDI	MDI	MDI
Duration:	2 years	2 years	2 years
Sample size:	21	19	18
Comparable dosing:	Yes		
INCLUSION:	Non-allergic COPD; FEV1 < 80% of predicted value; residual volume greater than 100% predicted; stable phase of disease; smokers or ex-smokers		
EXCLUSION:	Older than 70 years; corticosteroid therapy; severe concomitant disease; allergies		
OTHER MEDICATIONS/ INTERVENTIONS:	Bronchodilators		
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **COPD classification:** Mild to moderate		
	budesonide	**budesonide & prednisolone**	**placebo**
Mean age (years):	56	58	54
Sex:	0% female	0% female	0% female
Ethnicity:	NR	NR	NR
Other population characteristics:			
• current smokers:	43%	47%	44%

<table>
<tr><td colspan="4">Authors: Renkema et al.
Year: 1996</td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">Primary Outcome Measures: FEV1; VC; exacerbations; standardized symptom score questionnaire

Secondary Outcome Measures: Serum cortisol

Timing of assessments: Bi-monthly</td></tr>
<tr><td>RESULTS:</td><td colspan="3">Health Outcome Measures:
No significant differences in frequency and duration of exacerbations between treatment groups*
Placebo treated patients had a higher number of withdrawals due to pulmonary problems than actively treated patients (27.7% vs. 5%; P = 0.036)
Active treatment groups had significant improvements in symptom scores from baseline (P < 0.05) and compared to placebo treated group (P < 0.05)
Intermediate Outcome Measures:
Actively treated groups had a reduced decline of FEV1 compared to placebo (BUD -30ml, combination -40 ml, placebo -60 ml/yr); however, the differences were not statistically significant*
Mean cortisol level was within normal range for all 3 groups at the end of the study</td></tr>
<tr><td>ANALYSIS:</td><td colspan="3">ITT: No
Post randomization exclusions: Yes</td></tr>
<tr><td>ATTRITION (overall):

ATTRITION (treatment specific):
Loss to follow-up:
Withdrawals due to adverse events:
Withdrawals due to lack of efficacy:</td><td colspan="3">Overall loss to follow-up: 20%
Loss to follow-up differential high: Yes
<table><tr><th><u>budesonide</u></th><th><u>budesonide & prednisolone</u></th><th><u>placebo</u></th></tr><tr><td>2 (9.5%)</td><td>4 (21%)</td><td>5 (27.7%)</td></tr><tr><td>NR</td><td>NR</td><td>NR</td></tr><tr><td>0</td><td>2 (10.5%)</td><td>5 (27.7%)</td></tr></table></td></tr>
<tr><td>ADVERSE EVENTS:
Overall adverse effects reported:
Significant differences in events:</td><td colspan="3">NR
NR
NR</td></tr>
<tr><td>QUALITY RATING:</td><td colspan="3">Fair</td></tr>
</table>

*primary outcome measures

COPD ***Inhaled Corticosteroids***

STUDY:	**Authors: Sutherland et al.**[61] **Year: 2003**
FUNDING:	NIH, The Wellcome Trust
DESIGN:	**Study design:** Meta-analysis **Number of patients:** 3,715
AIMS OF REVIEW:	To assess if inhaled corticosteroids reduce the progression of airflow limitation in COPD
STUDIES INCLUDED IN META-ANALYSIS	Burge et al, 2000[69]; Lung Health Study Research Group, 2000[120]; Pauwels et al, 1999[67]; van Grunsven et al, 1999[60]; Vestbo et al, 1999[57]; Weir et al, 1999[121]
TIME PERIOD COVERED:	1966-2003
CHARACTERISTICS OF INCLUDED STUDIES:	RCTs of ICT treatments for more than 2 years in subjects with COPD; minimum 1 year follow up; change in FEV1 over time primary outcome variable
CHARACTERISTICS OF INCLUDED POPULATIONS:	Patients with mild to severe COPD; subjects were studied when disease was stabilized

Authors: Sutherland et al. **Year: 2003**	
CHARACTERISTICS OF INTERVENTIONS:	Patients treated with any of the following ICS: fluticasone, triamcinolone, budesonide, beclomethasone
MAIN RESULTS:	• ICS treatment significantly slowed FEV1 decline compared to placebo (+7.7 ml / year; 95% CI: 1.3 to 14.2; P = 0.02) • High dose regimens revealed a greater effect (9.9 ml / year; 95% CI: 2.3 to 17.5; P = 0.01)
ADVERSE EVENTS:	NR
COMPREHENSIVE LITERATURE SEARCH STRATEGY:	Yes
STANDARD METHOD OF APPRAISAL OF STUDIES:	Yes
QUALITY RATING:	**Good**

COPD ***Inhaled Corticosteroids***

STUDY:	**Authors**: **Szafranski et al.**[66] **Year: 2003** **Country:** Multinational (Argentina, Brazil, Denmark, Finland, UK, Italy, Mexico, Poland, Portugal, South Africa, Spain)			
FUNDING:	Astra Zeneca			
DESIGN:	**Study design:** RCT **Setting:** Multi-center (89) **Sample size:** 812			
INTERVENTION:	**budesonide/formoterol**	**budesonide**	**formoterol**	**placebo**
Dose:	640/18 mcg/day	800 mcg/d	18 mcg/d	N/A
Dosing range:	Medium (ICS)	Low	N/A	N/A
Device:	DPI	MDI	DPI	NR
Duration:	1 year	1 year	1 year	1 year
Sample size:	208	198	201	205
Comparable dosing:	N/A			
INCLUSION:	Moderate to severe COPD; aged ≥ 40 years; COPD symptoms ≥ 2 years; COPD symptoms ≥ 2/day during at last 7 days; ≥ 10 pack-years smoking history; FEV1 ≤ 50% predicted value; ≥ 1 severe exacerbation during the last 2 – 12 months			
EXCLUSION:	Asthma; allergies; cardiovascular disorders; beta-blocker use; other respiratory disorders; requirement for regular oxygen therapy; exacerbation during run-in			
OTHER MEDICATIONS/ INTERVENTIONS:	Short acting beta-agonists			
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **COPD classification:** Moderate to severe			
	budesonide/formoterol	**budesonide**	**formoterol**	**placebo**
Mean age (years):	64	64	63	65
Sex:	24% female	20% female	24% female	17% female
Ethnicity:	NR	NR	NR	NR
Other population characteristics:				
• current smokers:	30%	36%	38%	34%

<table>
<tr><td colspan="5">Authors: Szafranski et al.
Year: 2003</td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="4">Primary Outcome Measures: Severe exacerbations (use of oral steroids or antibiotics or hospitalizations due to respiratory symptoms); AM and PM COPD symptoms; short acting beta-agonist use; PEF; SGRQ; FEV1

Secondary Outcome Measures: Hematology; ECG; clinical chemistry

Timing of assessments: Daily diary; clinical visits at 1, 2, 3, 6, 9, and 12 months</td></tr>
<tr><td>RESULTS:</td><td colspan="4">Health Outcome Measures:
No significant difference in reduction of severe exacerbations between BUD/formoterol versus BUD and BUD versus placebo; BUD/formoterol had significantly fewer exacerbations than placebo (reduction: 0.758 exacerbations/year (24%); P = 0.035)*
BUD/formoterol and BUD reduced the rates of oral steroid use compared to placebo (P < 0.05)*
No significant differences in HRQOL between BUD and placebo*
Significantly more patients in the placebo group withdrew because of COPD deterioration than in the active treatment groups (P < 0.05)
Intermediate Outcome Measures:
FEV1 was higher in the BUD group than in the placebo group (+ 5%; P = 0.005) and higher in the BUD/formoterol group than in the BUD group (+ 9%; P < 0.001)*</td></tr>
<tr><td>ANALYSIS:</td><td colspan="4">ITT: Yes
Post randomization exclusions: NR</td></tr>
<tr><td>ATTRITION (overall):</td><td colspan="4">Overall loss to follow-up: 33.9%
Loss to follow-up differential high: Yes</td></tr>
<tr><td>ATTRITION (treatment specific):</td><td><u>budesonode/formoterol</u></td><td><u>budesonide</u></td><td><u>formoterol</u></td><td><u>placebo</u></td></tr>
<tr><td>Loss to follow-up:</td><td>59 (28%)</td><td>62 (31%)</td><td>64 (32%)</td><td>90 (44%)</td></tr>
<tr><td>Withdrawals due to adverse events:</td><td>8 (16%)</td><td>7 (13%)</td><td>6 (12%)</td><td>8 (17%)</td></tr>
<tr><td>Withdrawals due to lack of efficacy:</td><td>10 (20%)</td><td>12 (23%)</td><td>14 (29%)</td><td>21 (43%)</td></tr>
<tr><td>ADVERSE EVENTS:
Overall adverse effects reported:
Significant differences in events:</td><td colspan="4">No differences in adverse events between treatment groups and placebo</td></tr>
<tr><td>QUALITY RATING:</td><td colspan="4">Fair</td></tr>
</table>

*primary outcome measures

COPD ***Inhaled Corticosteroids***

STUDY:	**Authors: van der Valk et al.**[75] **Year: 2002** **Country:** The Netherlands		
FUNDING:	Netherlands Asthma Foundation, Amicon Health Insurance, Boehringer Ingelheim, GlaxoSmithKline BV		
DESIGN:	**Study design:** RCT **Setting:** One outpatient pulmonary university clinic **Sample size:** 244		
INTERVENTION: **Dose:** **Dosing range:** **Device:** **Duration:** **Sample size:**	**fluticasone** 1000 mcg/day High DPI 6 months 123	**placebo (ICS discontinuation)** N/A N/A DPI 6 months 121	
Comparable dosing:	N/A		
INCLUSION:	Stable COPD; no history of asthma; no exacerbation within 1 month of enrollment; current or former smoker; age 40 to 75; baseline prebronchodilator FEV1 25% - 80% of predicted; FEV1 reversibility after 80 mcg ipratropium of 12% or less		
EXCLUSION:	Oral steroids or antibiotics; serious medical condition; other active lung disease		
OTHER MEDICATIONS/ INTERVENTIONS:	Nasal corticosteroids; acetylcystein; theopyllines; bronchodilators		
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** More smokers in the placebo group (33% vs. 22%) **COPD classification:** Mild to severe		
	fluticasone	**placebo**	
Mean age (years):	64.1	64.0	
Sex:	14.6% female	16.5% female	
Ethnicity:	NR	NR	
Other population characteristics:			
• current smokers	22.0%	33.3%	

<table>
<tr><td colspan="4">Authors: van der Valk et al.
Year: 2002</td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">Primary Outcome Measures: Exacerbations; health related quality of life (SGRQ, Euroqol 5D); use of health care resources (hospitalization, ER, etc).

Secondary Outcome Measures: FEV1; inspiratory vital capacity; exercise tolerance; Borg Score of Breathlessness
Timing of assessments: Patient diary; clinic visits at 3 and 6 months</td></tr>
<tr><td>RESULTS:</td><td colspan="3">Health Outcome Measures:
More patients in the placebo group developed an exacerbation than in the FLUP group (57% vs. 47.2%; hazard ratio: 1.5; 95% CI: 1.05 to 2.1)*
Mean difference in time to first exacerbation was 34.6 days (72.2 vs. 42.7 days) in favor of FLUP*
FLUP-treated patients had a higher SGRQ total score than placebo-treated patients (+2.48; 95% CI: 0.37 to 4.58)*
No difference in exercise tolerance test
No differences in Borg breathlessness scores
Intermediate Outcome Measures:
Postbronchodilation FEV1 was higher in the FLUP group (+38 ml; p = 0.056)</td></tr>
<tr><td>ANALYSIS:</td><td colspan="3">ITT: Yes
Post randomization exclusions: No</td></tr>
<tr><td>ATTRITION (overall):</td><td colspan="3">Overall loss to follow-up: 0.8%
Loss to follow-up differential high: No</td></tr>
<tr><td>ATTRITION (treatment specific):
Loss to follow-up:
Withdrawals due to adverse events:
Withdrawals due to lack of efficacy:</td><td><u>fluticasone</u>
1 (0.8%)
0
0</td><td><u>placebo</u>
1 (0.8%)
0
0</td><td></td></tr>
<tr><td>ADVERSE EVENTS:
Overall adverse effects reported:
Significant differences in events:</td><td colspan="3">No significant differences in adverse events</td></tr>
<tr><td>QUALITY RATING:</td><td colspan="3">Good</td></tr>
</table>

*primary outcome measures

COPD ***Inhaled Corticosteroids***

STUDY:	**Authors: van Grunsven et al.**[60] **Year: 1999**
FUNDING:	The Dutch Government Organization for Scientific Research
DESIGN:	**Study design:** Meta-analysis (individual patient data) **Number of patients:** 183
AIMS OF REVIEW:	To evaluate the role of ICS in the decline of prebronchodilator FEV1 in patients with moderate to severe COPD
STUDIES INCLUDED IN META-ANALYSIS	Included individual patient data if age 40 and over; bronchodilator response to beta-2-agonist; excluded patients with reversible obstruction, mild obstruction, and never-smokers Inclusion/exclusion criteria applied to: Renkema et al., 1996; Derenne et al., 1995; Kerstjens et al., 1992; studies had to be RCTs with at least 24 months follow-up
TIME PERIOD COVERED:	1983-1996
CHARACTERISTICS OF INCLUDED STUDIES:	Randomized, double-blinded, placebo-controlled clinical trials
CHARACTERISTICS OF INCLUDED POPULATIONS:	Pulmonary symptoms compatible with diagnosis of COPD; age 40 and over; FEV1 following treatment with beta-2 agonist ($\geq$ 400 mcg salbutamol or $\geq$500mcg terbutaline) $\leq$ FEV1 predicted -1.64SD; bronchodilator response to beta-2 agonist ($\geq$ 400 mcg salbutamol or $\geq$ 500 mcg terbutaline) $\leq$ 9% FEV1 predicted; previous or current smoker; patients with asthmatic features were excluded; mean age 61 years; 11% female for ICS, 21% female for placebo; 33% smokers

Authors: van Grunsven et al. **Year: 1999**	
CHARACTERISTICS OF INTERVENTIONS:	Budesonide 1600 mcg/d per MDI; beclomethasone 1500 mcg/d per MDI; beclomethasone 800 mcg/d per MDI
MAIN RESULTS:	• ICS treated patients showed a significant benefit in prebronchodilator FEV1 compared to placebo (+0.034 L/year; 95% CI, 0.005 to 0.063; P = 0.026). • No differences in postbronchodilator FEV1 measurements • No beneficial effect was observed on exacerbation rates; • 17 (18%) ICS patients and 12 (14%) placebo patients dropped out (P = 0.43)
ADVERSE EVENTS:	Cough; dysphonia; sore throat; anorexia; problems with taste and nasal organ; headache. No serious adverse events related to treatment occurred
COMPREHENSIVE LITERATURE SEARCH STRATEGY:	Yes
STANDARD METHOD OF APPRAISAL OF STUDIES:	Method of quality assessment not reported
QUALITY RATING:	**Fair**

COPD ***Inhaled Corticosteroids***

STUDY:	**Authors: van Grunsven et al.**[74] **Year: 2003** **Country:** The Netherlands		
FUNDING:	Dutch Governmental Organization for Scientific Research, Dutch Asthma Foundation, Prevention Fund, GlaxoSmithKline BV		
DESIGN:	**Study design:** RCT **Setting:** Multi-center (10 general practice sites) **Sample size:** 48		
INTERVENTION: **Dose:** **Dosing range:** **Device:** **Duration:** **Sample size:**	**fluticasone** 500 mcg/d N/A DPI 24 months 24	**placebo** N/A N/A N/A 24 months 24	
Comparable dosing:	N/A		
INCLUSION:	Subjects detected through screening program and monitored for 2 years (DIMCA: Detection, Intervention, and Monitoring of COPD and Asthma); age 18-75; no corticosteroid dependence; annual decline of FEV1 of 40-80 ml		
EXCLUSION:	Prior diagnosis of a pulmonary condition; presence of a co-morbid condition with reduced life expectancy; intolerance for inhaled beta-agonist; use of beta-blocking agents; inability to use inhalation devices or peak flow meters		
OTHER MEDICATIONS/ INTERVENTIONS:	Only pulmonary medication allowed was rescue beta-agonist		

<table>
<tr><td colspan="4">Authors: van Grunsven et al.
Year: 2003</td></tr>
<tr><td>POPULATION CHARACTERISTICS:</td><td colspan="3">Groups similar at baseline: No; more smokers, pack-years, and bronchial hyper-responsiveness in FLUP treated group.
COPD classification: Mild persistent; early COPD</td></tr>
<tr><td></td><td><u>fluticasone</u></td><td><u>placebo</u></td><td></td></tr>
<tr><td>Mean age (years):</td><td>46</td><td>47</td><td></td></tr>
<tr><td>Sex:</td><td>50% female</td><td>45.8% female</td><td></td></tr>
<tr><td>Ethnicity:</td><td>NR</td><td>NR</td><td></td></tr>
<tr><td>Other population characteristics:</td><td></td><td></td><td></td></tr>
<tr><td>• smoker</td><td>50%</td><td>33.3%</td><td></td></tr>
<tr><td>• pack-years</td><td>11.9</td><td>5.8</td><td></td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">Primary Outcome Measures: Annual decline in post beta-agonist FEV1

Secondary Outcome Measures: Annual decline in pre beta-agonist FEV1, bronchial hyper-responsiveness; exacerbation rate; number of episodes with aggravated symptoms; use of rescue beta-agonist; COOP/WONCA COPD functional assessment scales

Timing of assessments: Every 3 months for FEV1 and FVC other measures every 6 months.</td></tr>
<tr><td>RESULTS:</td><td colspan="3">Health Outcome Measures:
• No significant differences in number of exacerbations (FLUP 6 vs. Placebo 4), and number of patients with exacerbations (FLUP 5 vs. Placebo 3)
• No difference in the number or severity of respiratory symptoms between groups
• No difference in the number of subjects using rescue beta-agonist between groups

Intermediate Outcome Measures:
• Treatment with FLUP had an early treatment effect in post-bronchodilator FEV1 (at 3 months +125 ml compared to placebo; P = 0.075) that was not maintained during the 2 year follow-up
• Annual decline in post-bronchodilator FEV1/year was higher in the FLUP group than in the placebo group (FLUP –93 ml vs. Placebo – 14 ml, P = 0.001)*
• Annual decline in pre beta-agonist FEV1 (FLUP –85 ml vs. placebo –38 ml, P = 0.08)
• No difference in pre or post beta-agonist FEV1</td></tr>
</table>

Authors: van Grunsven et al. **Year: 2003**			
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** NR		
ATTRITION (*overall*):	**Overall loss to follow-up:** 12 (25%) **Loss to follow-up differential high:** No		
ATTRITION (*treatment specific*):	**fluticasone**	**placebo**	
Loss to follow-up:	6 (25%)	6 (25%)	
Withdrawals due to adverse events:	2 (8.3%)	3 (12.5%)	
Withdrawals due to lack of efficacy:	NR	NR	
ADVERSE EVENTS: **Overall adverse effects reported:** **Significant differences in events:**	14% of all subjects reported adverse events None		
QUALITY RATING:	**Fair**		

*primary outcome measures

COPD ***Inhaled Corticosteroids***

STUDY:	**Authors: Vestbo et al.**[57] **Year: 1999** **Country:** Denmark		
FUNDING:	ASTRA Danmark A/S; ASTRA Pharmaceutical Production AB (Sweden); and the National Union against Lung Diseases		
DESIGN:	**Study design:** RCT **Setting:** Single center (hospital) **Sample size:** 290		
INTERVENTION:	**budesonide**	**placebo**	
Dose:	1200 mcg/d (6 months) then 800 mcg/d (30 months)	N/A	
Dosing range:	Medium	N/A	
Device:	Turbuhaler	Turbuhaler	
Duration:	3 years	3 years	
Sample size:	145	145	
Comparable dosing:	N/A		
INCLUSION:	Participant in the Copenhagen City Heart Study; 30-70 years old; FEV1/FVC ratio of 0.7 or less; FEV1 reversibility after inhalation of 1 mg terbutaline of less than 15% of prebronchodilator FEV1; FEV1 reversibility after 10 days of treatment with oral prednisone of less than 15% of prebronchodilator FEV1		
EXCLUSION:	Long term treatment with oral steroids; pregnancy; other serious systemic disease; chronic alcohol or drug use; participation in other COPD studies within 1 month of inclusion		
OTHER MEDICATIONS/ INTERVENTIONS:	Beta-agonists allowed		
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **COPD classification:** Mild to moderate		
	budesonide	**placebo**	
Mean age (years):	59.0	59.1	
Sex:	41.4% female	37.9% female	
Ethnicity:	NR	NR	
Other population characteristics:			
Smoking Status:			
• current	75.9%	77.2%	
• never	3.4%	4.8%	

Authors: Vestbo et al. **Year: 1999**			
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Rate of FEV1 decline **Secondary Outcome Measures:** Number of COPD exacerbations; respiratory symptoms (recorded by short questionnaire based on the UK Medical Research Council questionnaire) **Timing of assessments:** FEV1 performed every 3 months; respiratory questionnaire every 6 months		
RESULTS:	**Health Outcome Measures:** • No statistical difference in the number of COPD exacerbations between budesonide and placebo • No difference in respiratory symptoms observed between the two groups **Intermediate Outcome Measures:** • No significant difference between budesonide and placebo in rate of FEV1 decline		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** NR		
ATTRITION (*overall*): **ATTRITION (*treatment specific*):** **Loss to follow-up:** **Withdrawals due to adverse events:** **Withdrawals due to lack of efficacy:**	**Overall loss to follow-up:** 89 (31%) **Loss to follow-up differential high:** No		
	budesonide	**placebo**	
	36 (25%)	53 (37%)	
	16 (11%)	17 (12%)	
	NR	NR	
ADVERSE EVENTS: **Overall serious adverse effects reported:** **Significant differences in events:**	Budesonide: 10 (7%); placebo: 34 (23%) Significantly more serious adverse effects occurred in placebo group than budesonide group (P = 0.001)		
QUALITY RATING:	**Good**		

*primary outcome measures

COPD ***Inhaled Corticosteroids***

STUDY:	**Authors: Wise et al.**[76] **Year: 2000** **Country:** USA		
FUNDING:	NIH and Aventis		
DESIGN:	**Study design:** RCT **Setting:** Multi-center (10 centers) **Sample size:** 1116		
INTERVENTION: **Dose:** **Dosing range:** **Device:** **Duration:** **Sample size:**	**triamcinolone** 1200 mcg/day Medium MDI 40 months 559	**placebo** N/A N/A MDI 40 months 557	
Comparable dosing:	N/A		
INCLUSION:	Previously participated in or had been screened for the Lung Health Study; 40–69 years of age; had airway obstruction with ratio of FEV1 to FVC<0.70 and FEV1 value that was 30-90% of predicted value		
EXCLUSION:	Medical conditions such as cancer, recent myocardial infarction, alcoholism, heart failure, insulin-dependent diabetes or mellitus; neuropsychiatric disorders; use bronchodilators or oral or ICS in previous year		
OTHER MEDICATIONS/ INTERVENTIONS:	NR		
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **COPD classification:** Mild-moderate		
	triamcinolone	**placebo**	
Mean age (years):	56.2+/-6.8	56.4+/-6.8	
Sex:	36.0% female	37.9% female	
Ethnicity:	93.7% white	95.9% white	
Other population characteristics:			
• current smoking	90.5%	89.8%	

Authors: Wise et al. **Year: 2000**			
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Rate of FEV1 decline after bronchodilator **Secondary Outcome Measures:** American Thoracic Society-Division of Lung Diseases questionnaire for respiratory symptoms; morbidity and mortality; airway reactivity in response to methacholine; eight aspects of health-related quality of life measured with SF-36 **Timing of assessments:** Baseline, SF-36 yearly, respiratory symptoms every 3 months		
RESULTS:	**Health Outcome Measures:** • Dyspnea more common in placebo group (P = 0.02) • No differences in eight aspects of health-related quality as assessed with SF-36 • Placebo treated patients reported more new or increased respiratory symptoms than TRI-treated patients (28.2/100 person-yrs vs. 21.1/100person-yrs; P = 0.005) • No differences in overall mortality and hospitalizations; more respiratory-related visits (P = 0.03) **Intermediate Outcome Measures:** No significant difference in FEV1 decline between treatment groups (TRI: 44.2+/-2.9 ml/yr; placebo: 47.0+/-3.0 ml/yr)*		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** No		
ATTRITION (*overall*): **ATTRITION (*treatment specific*):** **Loss to follow-up:** **Withdrawals due to adverse events:** **Withdrawals due to lack of efficacy:**	**Overall loss to follow-up:** 66 (5.9%) **Loss to follow-up differential high:** No **triamcinolone** 28 (5.0%) 8 (1.4%) NR	**placebo** 38 (6.8%) 4 (0.72%) NR	
ADVERSE EVENTS: **Overall adverse effects reported:** **Significant differences in events:** • Mouth irritation (P = 0.02)	**triamcinolone** NR 13 (2.3%)	**placebo** NR 6 (1.1%)	
QUALITY RATING:	**Fair**		

*primary outcome measures

Evidence Table 3. Adverse Events Inhaled Corticosteroids

STUDY:	**Authors: Agertoft et al.**[90] **Year: 1994** **Country:** Denmark		
FUNDING:	NR		
DESIGN:	**Study design:** Prospective cohort study **Setting:** Asthma clinic **Sample size:** 278		
INTERVENTION: **Dose:** **Dosing range:** **Device:** **Duration:** **Sample size:**	**budesonide** mean: 430 mcg/day (endpoint) Medium Nebuhaler, Turbuhaler 3-6 years 216	**asthma therapy without ICS** N/A N/A N/A 3-7 years 62	
Comparable dosing:	N/A		
INCLUSION:	Children with mild to moderate asthma; standard treatment of asthma; patients of clinic for at least 1 year		
EXCLUSION:	ICS or oral corticosteroids for more than 2 weeks per year		
OTHER MEDICATIONS/ INTERVENTIONS:	Theophylline; beta-agonists		
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Asthma classification:** Mild intermittent; mild persistent; moderate persistent		
	budesonide	**asthma therapy without ICS**	
Mean age (years):	6.2	6.1	
Sex:	31.5% female	25.8% female	
Ethnicity:	NR	NR	
Other population characteristics:			
• FEV1 (% predicted):	81.3%	79.2%	
• asthma duration (years):	3.7	3.5	

<table>
<tr><td colspan="4">Authors: Agertoft et al.
Year: 1994</td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">Primary Outcome Measures: Growth; weight; FEV1; hospitalizations; concurrent medicine

Secondary Outcome Measures: NR

Timing of assessments: 6-monthly</td></tr>
<tr><td>RESULTS:</td><td colspan="3">Health Outcome Measures:
• No significant differences in height and weight between study groups
• BUD treatment was associated with a significant reduction in the number of annual hospitalizations due to acute severe asthma (0.03 vs. 0.004 visits/child/year; P < 0.001)*
Intermediate Outcome Measures:
• Greater improvement in FEV1 % predicted for BUD group compared to controls (2.51 vs. -8.11; P = 0.019)</td></tr>
<tr><td>ANALYSIS:</td><td colspan="3">ITT: N/A
Post randomization exclusions: N/A</td></tr>
<tr><td>ATTRITION (overall):

ATTRITION (treatment specific):
Loss to follow-up:
Withdrawals due to adverse events:
Withdrawals due to lack of efficacy:</td><td colspan="3">Overall loss to follow-up: NR
Loss to follow-up differential high: NR
<table><tr><td><u>budesonide</u></td><td><u>asthma therapy without ICS</u></td><td></td></tr><tr><td>NR</td><td>NR</td><td></td></tr><tr><td>NR</td><td>NR</td><td></td></tr><tr><td>NR</td><td>NR</td><td></td></tr></table></td></tr>
<tr><td>ADVERSE EVENTS:
Overall adverse effects reported:
Specific adverse events reported:</td><td colspan="3">NR
NR
NR</td></tr>
<tr><td>QUALITY RATING:</td><td colspan="3">Fair</td></tr>
</table>

*primary outcome measures

Adverse Events ***Inhaled Corticosteroids***

STUDY:	**Authors: Agertoft et al.**[84] **Year: 1998** **Country:** Denmark		
FUNDING:	NR		
DESIGN:	**Study design:** Cross sectional study **Setting:** Asthma clinic **Sample size:** 268		
INTERVENTION: **Dose:** **Dosing range:** **Device:** **Duration:** **Sample size:**	**budesonide** Mean daily dose: 504 mcg Low-medium-high MDI or DPI 3 to 6 years 157	**no ICS** N/A N/A N/A 3 to 6 years 111	
Comparable dosing:	N/A		
INCLUSION:	Children with persistent asthma, part of an ongoing prospective study; BUD for > 3 years		
EXCLUSION:	More than 14 days of systemic glucocorticosteroids ever; use of topical or nasal glucocorticosteroids; Control group: ICS more than 2 weeks ever		
OTHER MEDICATIONS/ INTERVENTIONS:	Other asthma medications		
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Asthma classification:** Mild intermittent; mild persistent; moderate persistent; severe persistent		
	budesonide	**no ICS**	
Mean age (years):	10.3	9.9	
Sex:	31% female	45% female	
Ethnicity:	NR	NR	
Other population characteristics:			
• asthma duration (years):	8.3	4.5	
• FEV1 % predicted:	97	81	

<table>
<tr><td colspan="4">Authors: Agertoft et al.
Year: 1998</td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">Primary Outcome Measures: Total body bone mineral density (BMD); total body bone mineral capacity; total bone calcium; body composition

Secondary Outcome Measures: NR

Timing of assessments: Cross sectional; patients were followed prospectively for at least 3 years</td></tr>
<tr><td>RESULTS:</td><td colspan="3">Health Outcome Measures:
• NR

Intermediate Outcome Measures:
• No statistically significant differences between the two groups
• No correlation between any outcome parameter and duration of treatment or dosage</td></tr>
<tr><td>ANALYSIS:</td><td colspan="3">ITT: N/A
Post randomization exclusions: N/A</td></tr>
<tr><td>ATTRITION (overall):</td><td colspan="3">Overall loss to follow-up: N/A
Loss to follow-up differential high: N/A</td></tr>
<tr><td>ATTRITION (treatment specific):</td><td><u>budesonide</u></td><td><u>no ICS</u></td><td></td></tr>
<tr><td>Loss to follow-up:</td><td>N/A</td><td>N/A</td><td></td></tr>
<tr><td>Withdrawals due to adverse events:</td><td>N/A</td><td>N/A</td><td></td></tr>
<tr><td>Withdrawals due to lack of efficacy:</td><td>N/A</td><td>N/A</td><td></td></tr>
<tr><td>ADVERSE EVENTS:
Overall adverse effects reported:
Significant differences in events:</td><td colspan="3">N/A
N/A
N/A</td></tr>
<tr><td>QUALITY RATING:</td><td colspan="3">N/A</td></tr>
</table>

Adverse Events ***Inhaled Corticosteroids***

STUDY:	**Authors: Agertoft et al.**[122] **Year: 1998** **Country:** Denmark		
FUNDING:	NR		
DESIGN:	**Study design:** Prospective cohort study **Setting:** Hospital clinic **Sample size:** 268		
INTERVENTION: **Dose:** **Dosing range:** **Device:** **Duration:** **Sample size:**	**budesonide** Mean: 504 mcg/d Low - High DPI 3-6 years 157	**non-users** NR NR NR 3-6 years 111	
Comparable dosing:	N/A		
INCLUSION:	Children with persistent asthma and no other chronic disease		
EXCLUSION:	Had to be seen in clinic at least every six months for 3-6 years; oral corticosteroids > 2 weeks/year; > 14 days with systemic steroids (ever); control group use of ICS > 2 weeks (ever)		
OTHER MEDICATIONS/ INTERVENTIONS:	Inhaled long and short acting beta-2 agonists; oral beta 2-agonists; theophylline; sodium cromoglycate		
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** NR (figures below are reported 3 years into the study) **Asthma classification:** NR		
	budesonide	**non-users**	
Mean age (years):	10.3	9.9	
Sex:	31% female	45% female	
Ethnicity:	NR	NR	
Other population characteristics:			
• asthma duration	8.3 years	4.5 years	
• FEV1 (% of predicted)	97	81	

<table>
<tr><td colspan="4">Authors: Agertoft et al.
Year: 1998</td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">Primary Outcome Measures: Incidence of cataracts; bruising (number, size and family reported tendency to bruise); family reported hoarseness

Secondary Outcome Measures: NR

Timing of assessments: Every 6 months</td></tr>
<tr><td>RESULTS:</td><td colspan="3">Health Outcome Measures:
No incidence of post subcapsular cataract in either group
No difference in number of bruises, area covered by bruises, tendency to bruise as reported by family between groups
No differences in occurrence of hoarseness or other noticeable voice changes between groups</td></tr>
<tr><td>ANALYSIS:</td><td colspan="3">ITT: N/A
Post randomization exclusions: N/A</td></tr>
<tr><td>ATTRITION (overall):</td><td colspan="3">Overall loss to follow-up: N/A
Loss to follow-up differential high: N/A</td></tr>
<tr><td>ATTRITION (treatment specific):
Loss to follow-up:
Withdrawals due to adverse events:
Withdrawals due to lack of efficacy:</td><td><u>budesonide</u>
N/A
N/A
N/A</td><td><u>non-users</u>
N/A
N/A
N/A</td><td></td></tr>
<tr><td>ADVERSE EVENTS:
Overall adverse effects reported:
Significant differences in events:</td><td colspan="3">N/A</td></tr>
<tr><td>QUALITY RATING:</td><td colspan="3">Fair</td></tr>
</table>

Adverse Events ***Inhaled Corticosteroids***

STUDY:	**Authors: Agertoft et al.**[91] **Year: 2000** **Country:** Denmark		
FUNDING:	Vejle County Hospital Research Fund		
DESIGN:	**Study design:** Prospective cohort study (follow-up of Agertoft et al. 1994) **Setting:** Pediatric hospital **Sample size:** 265		
INTERVENTION:	**budesonide**	**asthma control (no ICS)**	**healthy siblings**
Dose:	412 mcg/day (mean)	N/A	N/A
Dosing range:	Low-high	N/A	N/A
Device:	NR	N/A	N/A
Duration:	9.2 years (mean)	N/A	N/A
Sample size:	142	18	105
Comparable dosing:	N/A		
INCLUSION:	Children with persistent asthma; must have reached adult height		
EXCLUSION:	Current chronic diseases; gestational age less than 32 weeks		
OTHER MEDICATIONS/ INTERVENTIONS:	NR		
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Asthma classification:** Mild intermittent-; mild persistent-; moderate persistent-;		
	budesonide	**asthma control**	**healthy siblings**
Mean age (years):	8.7 (start of treatment)	NR	NR
Sex:	39.4% female	38.9% female	52.9%
Ethnicity:	NR	NR	NR
Other population characteristics:	NR	NR	NR

<table>
<tr><td colspan="4">Authors: Agertoft et al.
Year: 2000</td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">Primary Outcome Measures: Adult height in relation to targeted adult height

Secondary Outcome Measures: Association of adult height with BUD dose; duration of treatment; duration of asthma; FEV1; use of intranasal corticosteroids; height before ICS use

Timing of assessments: At each six-month visit</td></tr>
<tr><td>RESULTS:</td><td colspan="3">Health Outcome Measures:
• BUD-treated children reached targeted adult height to the same extent as their healthy siblings and the control group without ICS*

Intermediate Outcome Measures:
• There was no significant correlation between duration of treatment (P = 0.16) or cumulative dose of BUD (P = 0.14) and the difference between measured and target adult height</td></tr>
<tr><td>ANALYSIS:</td><td colspan="3">ITT: N/A
Post randomization exclusions: N/A</td></tr>
<tr><td>ATTRITION (overall):</td><td colspan="3">Overall loss to follow-up: NR
Loss to follow-up differential high: NR</td></tr>
<tr><td>ATTRITION (treatment specific):
Loss to follow-up:
Withdrawals due to adverse events:
Withdrawals due to lack of efficacy:</td><td><u>budesonide</u>
158 (52.6%)
NR
NR</td><td><u>asthma control</u>
44 (71.0%)
NR
NR</td><td><u>healthy siblings</u>
NR
NR
NR</td></tr>
<tr><td>ADVERSE EVENTS:
Overall adverse effects reported:
Significant differences in events:</td><td colspan="3">NR</td></tr>
<tr><td>QUALITY RATING:</td><td colspan="3">Fair</td></tr>
</table>

*primary outcome measures

Adverse Events ***Inhaled Corticosteroids***

STUDY:	**Authors: Allen et al.**[56] **Year: 1998** **Country:** USA		
FUNDING:	Glaxo Wellcome Inc.		
DESIGN:	**Study design:** RCT **Setting:** Multi-center (19 clinical centers) **Sample size:** 268 (included in growth analysis)		
INTERVENTION:	**fluticasone (50 mcg)**	**fluticasone (100 mcg)**	**placebo**
Dose:	100 mcg/d	200 mcg/d	N/A
Dosing range:	Low (adult)	Low (adult)	N/A
Device:	Diskhaler	Diskhaler	N/A
Duration:	52 weeks	52 weeks	52 weeks
Sample size:	85	96	87
Comparable dosing:	Yes		
INCLUSION:	Children who met American Thoracic Society guidelines for asthma; persistent asthma for at least 3 months; boys aged 4-11 and girls aged 4-9; had normal growth rates; were prepubescent as defined by a sexual maturity rating of 1 in any Tanner classification		
EXCLUSION:	Received intranasal, systemic, or ophthalmic corticosteroids within one month of study; had cataracts, glaucoma, or other significant disease; patients were excluded from the growth analysis if they showed signs of puberty during the study		
OTHER MEDICATIONS/ INTERVENTIONS:	Albuterol syrup and inhaled albuterol as necessary; other anti-asthma medications could be continued		
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Asthma classification:** NR		
	fluticasone (50 mcg)	**fluticasone (100 mcg)**	**placebo**
Mean age (years):	8.1	7.9	8.1
Sex:	27% female	25% female	23% female
Ethnicity:	NR	NR	NR
Other population characteristics:			
• mean baseline height (cm)	128.2	127.2	127.5
• previous ICS use (%)	54	54	55

Authors: Allen et al. **Year: 1998**			
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Height (cm) **Secondary Outcome Measures:** Radiographic determination of bone age **Timing of assessments:** Beginning and end of run-in period, first, second, fourth weeks of study, then every 4 weeks afterward		
RESULTS:	**Health Outcome Measures:** • There was no statistical difference in mean height, mean growth velocity, or mean skeletal age between any of the treatment groups* **Intermediate Outcome Measures:** • None		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** Yes		
ATTRITION (*overall*): **ATTRITION (*treatment specific*):**	**Overall loss to follow-up:** NR **Loss to follow-up differential high:** Yes		
	fluticasone (50 mcg)	**fluticasone (100 mcg)**	**placebo**
Loss to follow-up:	< 20% (not specified)	< 20% (not specified)	34%
Withdrawals due to adverse events:	NR	NR	NR
Withdrawals due to lack of efficacy:	2%	4%	23%
ADVERSE EVENTS:	**fluticasone (50 mcg)**	**fluticasone (100 mcg)**	**placebo**
Overall adverse effects reported:	NR	NR	NR
Significant differences in events:	NR	NR	NR
QUALITY RATING:	**Fair**		

*primary outcome measures

Adverse Events ***Inhaled Corticosteroids***

STUDY:	**Authors: Childhood Asthma Management Program (CAMP) Research Group**[43] **Year: 2000** **Country:** Multinational (US and Canada)		
FUNDING:	NIH; National Center for Research Resources; various pharmaceutical companies		
DESIGN:	**Study design:** RCT **Setting:** Multi-center (8 sub-specialty outpatient clinics) **Sample size:** 1,041		
INTERVENTION:	**budesonide**	**placebo**	**nedocromil**
Dose:	400 mcg/day	N/A	16 mg/day
Dosing range:	Low-medium	N/A	N/A
Device:	MDI	MDI	MDI
Duration:	Mean 4.3 years	Mean 4.3 years	Mean 4.3 years
Sample size:	311	418	312
Comparable dosing:	N/A		
INCLUSION:	Age 5-12; mild to moderate asthma defined by presence of symptoms or beta-agonist use twice weekly or use of daily medication for asthma; methacholine dose ≤ 12.5 mg/ml to cause a 20% decrease in FEV1		
EXCLUSION:	No other clinically significant conditions		
OTHER MEDICATIONS/ INTERVENTIONS:	Albuterol for rescue therapy as needed or for prevention of exercise induced symptoms; short courses of oral corticosteroids as needed for exacerbations; addition of beclomethasone to study medications allowed if asthma control was inadequate; tapering of study medications was allowed for remission		
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Asthma classification:** Mild-moderate persistent		
	budesonide	**placebo**	**nedocromil**
Mean age (years):	9.0	9.0	8.8
Sex:	41.8% female	44.0% female	34.0% female
Ethnicity:			
• white	64.6%	69.9%	69.9%
• black	14.1%	13.4%	12.2%
Other population characteristics:	NR	NR	NR

Authors: CAMP **Year: 2000**	
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Mean change in post-bronchodilator FEV1 (% of predicted value) **Secondary Outcome Measures:** Spirometry measures; methacholine challenge; PEF; asthma symptoms; nighttime awakenings; beta-agonist use; use of prednisone and time to first use; use of additional BUD or other asthma medicine; school absences; urgent care or hospital visits; height; bone mineral density; skeletal maturation; Childhood Depression Inventory; eye exam for cataract development **Timing of assessments:** Daily patient assessment; bi-annual spirometry; annual methacholine challenge and psychological development; 4-month height, weight, and Tanner stage all at study end
RESULTS:	**Health Outcome Measures:** • Significantly greater increase in height for placebo-treated patients compared to BUD-patients (+1.1 cm; P = 0.005) • Compared to placebo, BUD-treated patients had fewer hospitalizations (P = 0.04), fewer urgent care visits (P < 0.001), less prednisone use (P < 0.001), fewer symptoms (P = 0.005), less albuterol use (P < 0.001), and more episode free days (P = 0.01) • No differences between BUD and placebo in the number of nighttime awakenings per month • No difference between BUD and placebo in fractures, BMD, or posterior subcapsular cataracts **Intermediate Outcome Measures:** • No difference in post-bronchodilator improvement in FEV1 between BUD and placebo* • Larger adjusted mean change in % predicted pre-bronchodilator FEV1 in BUD group (P = 0.02) • Airway responsiveness to methacholine favors BUD (P < 0.001) • Larger decrease in Children's Depression Inventory in BUD group than placebo group (P = 0.01)
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** NR

Authors: CAMP **Year: 2000**			
ATTRITION (*overall*):	**Overall loss to follow-up:** 1.6% (at least one outcome measure) **Loss to follow-up differential high:** No		
ATTRITION (*treatment specific*):	**budesonide**	**placebo**	**nedocromil**
Loss to follow-up:	1.6%	1.7%	1.6%
Withdrawals due to adverse events:	NR	NR	NR
Withdrawals due to lack of efficacy:	NR	NR	NR
ADVERSE EVENTS:	**budesonide**	**placebo**	**nedocromil**
Overall adverse effects reported:	NR	NR	NR
Significant differences in events:			
• Change in Height (cm) (P = 0.005)	22.7	23.8	23.7
QUALITY RATING:	**Good**		

*primary outcome measures

Adverse Events ***Inhaled Corticosteroids***

STUDY:	**Authors: Cumming et al.**[101] **Year: 1997** **Country:** Australia		
FUNDING:	Australian Department of Health, Housing and Community Services; Save Sight Institute		
DESIGN:	**Study design:** Observational (Cross-sectional) **Setting:** Population-based (Blue Mountain Region) **Sample size:** 3,313 (90.6% of subjects in the blue mountain eye study)		
INTERVENTION: **Dose:** **Dosing range:** **Device:** **Duration:** **Sample size:**	**ICS users** NR NR NR NR 241	**non-users** NR NR NR NR 2,784	
Comparable dosing:	N/A		
INCLUSION:	Permanent residents of the Blue Mountain Region born before January 1, 1943; 3,025 included in population that did not use systemic corticosteroids		
EXCLUSION:	1,045 subjects did not have eye photographs; history of medication use missing for 341 subjects		
OTHER MEDICATIONS/ INTERVENTIONS:	Use of systemic corticosteroids in addition to inhaled corticosteroids in 111 subjects		
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** N/A **Asthma classification:** N/A		
	ICS Users	**non-users**	
Mean age (years): **Sex:** **Ethnicity:** **Other population characteristics:** • diabetes • hypertension • no sun related skin damage	66.1 54% female NR 9% 51% 78%	66.1 56% female NR 6% 50% 74%	

Authors: Cumming et al. **Year: 1997**	
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Prevalence of cortical, nuclear, and posterior subcapsular cataracts **Secondary Outcome Measures:** N/A **Timing of assessments:** Same time as exposure ascertainment
RESULTS:	**Health Outcome Measures:** • Age and sex adjusted prevalence ratios compared to never users of corticosteroids: ***Any use current or former:*** cortical 1.1 (95% CI: 0.9 to 1.3), nuclear 1.5 (95% CI: 1.2 to 1.9), post subcapsular 1.9 (95% CI: 1.3 to 2.8) ***Former Users:*** cortical 0.9 (95% CI: 0.7 to 2.2), nuclear 1.6 (95% CI: 1.1 to 2.3), post subcapsular 1.1 (95% CI: 0.6 to 2.0) ***Current Users:*** cortical 1.4 (95% CI: 1.1 to 1.7), nuclear 1.5 (95% CI: 1.1 to 2.0), post subcapsular 2.6 (95% CI: 1.7 to 4.0) • Higher cumulative lifetime doses of BDP were associated with higher risk of posterior subcapsular cataracts ($P < 0.001$); adjusting for oral steroid use did not change this significantly
ANALYSIS:	**ITT:** N/A **Post randomization exclusions:** N/A
ATTRITION (*overall*):	**Overall loss to follow-up:** N/A **Loss to follow-up differential high:** N/A
ATTRITION (*treatment specific*): **Loss to follow-up:** **Withdrawals due to adverse events:** **Withdrawals due to lack of efficacy:**	N/A
ADVERSE EVENTS: **Overall adverse effects reported:** **Significant differences in events:**	N/A
QUALITY RATING:	**N/A**

Adverse Events ***Inhaled Corticosteroids***

STUDY:	**Authors: de Benedictis et al.**[86] **Year: 2001** **Country:** Multinational (7 countries)		
FUNDING:	GlaxoSmithKline		
DESIGN:	**Study design:** RCT **Setting:** Multi-center (32) **Sample size:** 343		
INTERVENTION: **Dose:** **Dosing range:** **Device:** **Duration:** **Sample size:**	**fluticasone** 400 mcg/day Medium DPI 52 weeks 170	**beclomethasone** 400 mcg/day Medium DPI 52 weeks 173	
Comparable dosing:	Yes		
INCLUSION:	Pre-pubertal children ages 4-11 (boys) or 4-9 (girls); requiring treatment with 100-200 mcg/d of FLUP or 200-500 mcg/d of BDP or BUD for at least 8 prior weeks and at a constant dose for at least 4 weeks; asthma symptom score of at least 1 or require albuterol at least once daily 4 of last 7 days		
EXCLUSION:	Intermittent asthma; disorders that could affect growth; parenteral or oral steroids; admission to hospital with respiratory disease within prior 4 weeks		
OTHER MEDICATIONS/ INTERVENTIONS:	All other anti-asthma medications permitted provided they remained at a constant dose; also permitted were oral corticosteroids for exacerbations, intranasal corticosteroids, decongestants, antihistamines, and antibiotics		
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Asthma classification:** NR		
	fluticasone	**beclomethasone**	
Mean age (years):	7.6	7.6	
Sex:	33.5% female	22.0% female	
Ethnicity:	82.9% white	84.4% white	
Other population characteristics:	NR	NR	

Authors: de Benedictis et al. **Year: 2001**			
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Growth velocity as measured by stadiometry means **Secondary Outcome Measures:** Asthma symptom scores; beta-agonist use; asthma exacerbation rate; lung function measures **Timing of assessments:** At week 2 and 4, then every 12 weeks until study end		
RESULTS:	**Health Outcome Measures:** Adjusted mean growth velocity greater in FLUP treated subjects (4.76 cm/year) than BDP treated subjects (4.06 cm/year) (Difference 0.70 (95% CI: 0.13 to 1.26 cm, P < 0.02)) • No difference in asthma symptoms between groups • No difference in use of beta-agonist medication between groups • No difference in number of asthma exacerbations between groups **Intermediate Outcome Measures:** • Mean change in AM PEF favors FLUP (difference 8.5 L/min, 95% CI: 2.8 to 14.2 L/min, P = 0.004) • Mean change in PM PEF favors FLUP (difference 8.6 L/min, 95% CI: 3.0 to 14.1 L/min, P = 0.003) • Adjusted mean change in clinic PEF favors FLUP (difference 15.2 L/min, P < 0.001) • Adjusted mean change in FEV1 favors FLUP (difference 0.2 L, P < 0.001) • Adjusted mean change in FVC favors FLUP (difference 0.1 L, P = 0.008) • Adjusted mean change in FEF 25-75 favors FLUP (difference 0.2 L, P = 0.02)		
ANALYSIS:	**ITT:** Yes **Post randomization exclusions:** Yes (66 patients for growth)		
ATTRITION (*overall*):	**Overall loss to follow-up:** 7 (2%) **Loss to follow-up differential high:** No		
ATTRITION (*treatment specific*):	**fluticasone**	**beclomethasone**	
Loss to follow-up:	3 (1.8%)	4 (2.3%)	
Withdrawals due to adverse events:	NR	NR	
Withdrawals due to lack of efficacy:	3 (1.8%)	5 (2.9%)	
ADVERSE EVENTS:	**fluticasone**	**beclomethasone**	
Overall adverse effects reported:	136 patients (80%)	140 patients (80.9%)	
Significant differences in events:			
• Rhinitis	43 patients (25.3%)	20 patients (11.6%)	
QUALITY RATING:	**Fair**		

Adverse Events ***Inhaled Corticosteroids***

STUDY:	**Authors: Garbe et al.**[103] **Year: 1997** **Country:** Canada		
FUNDING:	Fonds de la recherché en sante du Quebec, Montreal		
DESIGN:	**Study design:** Case control study **Setting:** Quebec universal health insurance program database **Sample size:** 48,118		
INTERVENTION:	**ocular hypertension or open angle glaucoma patients**	**control patients**	
Dose:	N/A	N/A	
Dosing range:	N/A	N/A	
Device:	N/A	N/A	
Duration:	N/A	N/A	
Sample size:	9,793	38,325	
Comparable dosing:	N/A		
INCLUSION:	Case patients were RAMQ enrollees ≥ 66 years of age; diagnosis of ocular hypertension or open-angle glaucoma or had received treatment for these conditions; enrolled in RAMQ ≥ 1 year prior to diagnosis; control patients were randomly selected from the same age range also enrolled in RAMQ ≥ 1 year		
EXCLUSION:	Diagnosis of angle-closure glaucoma or secondary glaucoma excluded		
OTHER MEDICATIONS/ INTERVENTIONS:	N/A		

<table>
<tr><td colspan="4">Authors: Garbe et al.
Year: 1997</td></tr>
<tr><td>POPULATION CHARACTERISTICS:</td><td colspan="3">Groups similar at baseline: N/A
Asthma classification: N/A</td></tr>
<tr><td></td><td><u>ocular hypertension or open angle glaucoma patients</u></td><td><u>control patients</u></td><td></td></tr>
<tr><td>Age (years):
• 65-74
• <u>≥</u> 75
Sex:
Inhaled glucocorticoid use:
• beclomethasone
• flunisolide
• budesonide
• triamcinolone
• <u>≥</u> 1 glucocorticoid</td><td>53.2%
46.8%
65.5% female

219 (2.2%)
2 (0.02%)
61 (0.6%)
2 (0.02%)
281 (2.9%)</td><td>55.2%
44.8%
62.1% female

848 (2.2%)
5 (0.01%)
181 (0.5%)
1 (0.003%)
1029 (2.7%)</td><td></td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">Primary Outcome Measures: Odds ratio of ocular hypertension or open-angle glaucoma in patients using inhaled glucocorticoids relative to nonusers

Secondary Outcome Measures: None

Timing of assessments: N/A</td></tr>
<tr><td>RESULTS:</td><td colspan="3">Health Outcome Measures:
• Overall, use of inhaled and nasal glucocorticoids was not associated with an increased risk of ocular hypertension or open-angle glaucoma
• Users of high doses of inhaled steroids prescribed for 3 months or more were at an increased risk with an odds ratio of 1.44 (95% CI: 1.01 to 2.06)

Intermediate Outcome Measures:
• None</td></tr>
<tr><td>ANALYSIS:</td><td colspan="3">ITT: N/A
Post randomization exclusions: N/A</td></tr>
</table>

Authors: Garbe et al. **Year: 1997**			
ATTRITION (*overall*): **ATTRITION (*treatment specific*):** **Loss to follow-up:** **Withdrawals due to adverse events:** **Withdrawals due to lack of efficacy:**	**Overall loss to follow-up:** N/A **Loss to follow-up differential high:** N/A **<u>ocular hypertension or open angle glaucoma patients</u>** N/A N/A N/A	**<u>control patients</u>** N/A N/A N/A	
ADVERSE EVENTS: **Overall adverse effects reported:** **Significant differences in events:**	N/A N/A		
QUALITY RATING:	**Fair**		

Adverse Events ***Inhaled Corticosteroids***

STUDY:	**Authors: Garbe et al.**[100] **Year: 1998** **Country:** Canada		
FUNDING:	Fonds de la Recherche en Sante du Quebec		
DESIGN:	**Study design:** Case-control study **Setting:** Elderly population contained in the provincial health insurance plan database (RAMQ) **Sample size:** 25,545		
INTERVENTION:	**ICS (BDP, BUD, FLUN, TRIA)**	**non-exposed**	
Dose:	Varied	N/A	
Dosing range:	N/A	N/A	
Device:	Varied	N/A	
Duration:	Varied	N/A	
Sample size:	N/A	N/A	
Comparable dosing:	N/A		
INCLUSION:	Registration within the RAMQ database (includes all prescription drugs and medical services for all individuals 65 years and older, 97.3% of this population is registered in the database); at least 5 years of history in the RAMQ database; study represents 10% random sample of this population		
EXCLUSION:	NR		
OTHER MEDICATIONS/ INTERVENTIONS:	NR		
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** No, controls were younger, more likely to be male with fewer comorbidities and use of medical services; and less likely to have used ocular or oral steroids **Asthma classification:** NR		
	cases (n = 3,677)	**controls (n = 21,868)**	
Mean age (years):	NR	NR	
Sex:	67.4% female	57.1% female	
Ethnicity:	NR	NR	
Other population characteristics:	NR	NR	

Authors: Garbe et al. **Year: 1998**	
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Risk of cataract extraction for various levels of exposure to inhaled corticosteroids and for exposure to oral steroids. **Secondary Outcome Measures:** NR **Timing of assessments:** N/A
RESULTS:	**Health Outcome Measures:** • Adjusted OR for cataract extraction according to average daily dose and cumulative treatment duration of ICS (reference group is no treatment) ***≤ 1 year*** Low to Medium dose (< 1000 mcg/day of BDP) 0.94 (95% CI: 0.76 to 1.16) High dose (> 1000 mcg/day of BDP) 0.86 (95% CI: 0.65 to 1.12) ***1-2 years*** Low to Medium dose (< 1000 mcg/day of BDP) 0.79 (95% CI 0.35 to 1.52) High dose (> 1000 mcg/day of BDP) 0.85 (95% CI: 0.35, 2.08) ***>2 years*** Low to Medium dose (< 1000 mcg/day of BDP) 1.63 (95% CI: 0.85 to 3.13) High dose (> 1000 mcg/day of BDP) 3.40 (95% CI: 1.49 to 7.76) • Adjusted OR for cataract extraction according to cumulative treatment duration with oral steroids (reference group is no treatment) ***Up to 1 year*** 1.27 (95% CI: 0.85 to 1.12) ***1-3 years*** 1.98 (95% CI: 1.44 to 2.71) ***> 3 years*** 2.33 (95% CI: 1.61 to 3.38)
ANALYSIS:	**ITT:** N/A **Post randomization exclusions:** N/A
ATTRITION (*overall*):	**Overall loss to follow-up:** N/A **Loss to follow-up differential high:** N/A
ATTRITION (*treatment specific*): **Loss to follow-up:** **Withdrawals due to adverse events:** **Withdrawals due to lack of efficacy:**	N/A
ADVERSE EVENTS:	N/A
QUALITY RATING:	**Good**

Adverse Events ***Inhaled Corticosteroids***

STUDY:	**Authors: Hubbard et al.**[83] **Year: 2002** **Country:** UK		
FUNDING:	Wellcome Trust		
DESIGN:	**Study design:** Case-control study **Setting:** United Kingdom General Practice Research Database (GPRD) **Sample size:** 16,341 cases; 29,889 controls		
INTERVENTION:	**cases (hip fractures)**	**controls**	
Dose:	N/A	N/A	
Dosing range:	N/A	N/A	
Device:	N/A	N/A	
Duration:	1987-1999	1987-1999	
Sample size:	16,341	29,889	
Comparable dosing:	No; assumed all ICS equivalent in dosing		
INCLUSION:	Patients with hip fracture as cases; matched controls by age, sex, general practice, and start date for collection of prescribing data		
EXCLUSION:	NR		
OTHER MEDICATIONS/ INTERVENTIONS:	Other corticosteroids (oral, topical, nasal, injected); analyzed with and without concomitant corticosteroid use		
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Asthma classification:** NR		
	cases	**controls**	
Mean age (years):	79.0	78.9	
Sex:	79% female	79% female	
Ethnicity:	NR	NR	
Other population characteristics:			
• diagnosis of asthma:	3%	3%	
• diagnosis of COPD:	3%	2%	
• diagnosis of asthma & COPD	2%	1%	

<table>
<tr><td colspan="4">Authors: Hubbard et al.
Year: 2002</td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">Primary Outcome Measures: Association of hip fracture to inhaled corticosteroids

Secondary Outcome Measures: Dose relationship

Timing of assessments: N/A</td></tr>
<tr><td>RESULTS:</td><td colspan="3">Health Outcome Measures:
ICS were associated with a small increase in the risk of hip fracture (adjusted OR: 1.19; 95% CI: 1.10 to 1.28)
The relationship between ICS and hip fractures was dose related (P = 0.007)
Association remained significant after patients with oral corticosteroids were removed from analysis (P = 0.013)
Intermediate Outcome Measures:
N/A</td></tr>
<tr><td>ANALYSIS:</td><td colspan="3">ITT: N/A
Post randomization exclusions: N/A</td></tr>
<tr><td>ATTRITION (overall):</td><td colspan="3">Overall loss to follow-up: N/A
Loss to follow-up differential high: N/A</td></tr>
<tr><td></td><td><u>cases</u></td><td><u>controls</u></td><td></td></tr>
<tr><td>ATTRITION (treatment specific):</td><td>N/A</td><td>N/A</td><td></td></tr>
<tr><td>Loss to follow-up:</td><td>N/A</td><td>N/A</td><td></td></tr>
<tr><td>Withdrawals due to adverse events:</td><td>N/A</td><td>N/A</td><td></td></tr>
<tr><td>Withdrawals due to lack of efficacy:</td><td>N/A</td><td>N/A</td><td></td></tr>
<tr><td>ADVERSE EVENTS:
Overall adverse effects reported:
Significant differences in events:</td><td colspan="3">N/A</td></tr>
<tr><td>QUALITY RATING:</td><td colspan="3">Good</td></tr>
</table>

*primary outcome measures

Adverse Events ***Inhaled Corticosteroids***

STUDY:	**Authors: Israel et al.**[81] **Year: 2001** **Country:** USA		
FUNDING:	National Heart Lung and Blood Institute, National Center for Research Resources		
DESIGN:	**Study design:** Cohort Study **Setting:** University clinic **Sample size:** 109		
INTERVENTION:	**triamcinolone (4-8 puffs/d)**	**triamcinolone (> 8 puffs/d)**	**no ICS**
Dose:	400-800 mcg/day	> 800 mcg/day	N/A
Dosing range:	Low	> Low	N/A
Device:	MDI	MDI	N/A
Duration:	3 years	3 years	3 years
Sample size:	39	42	28
Comparable dosing:	N/A		
INCLUSION:	Premenopausal women; age between 18 and 45 years; more than 10 menstrual cycles in preceding year		
EXCLUSION:	Diseases affecting bone turnover; drugs known to influence bone metabolism; smoking within the preceding year; low bone density; oral glucocorticosteroids within preceding three months		
OTHER MEDICATIONS/ INTERVENTIONS:	Calcium/vitamin D supplements; oral contraceptives; others NR		
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Asthma classification:** NR		
	triamcinolone (4-8 puffs)	**triamcinolone (> 8 puffs)**	**no ICS**
Mean age (years):	33	37	34
Sex:	100% female	100% female	100 % female
Ethnicity:	NR	NR	NR
Other population characteristics:	NR	NR	NR

<table>
<tr><td colspan="4">Authors: Israel et al.
Year: 2002</td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">Primary Outcome Measures: Bone density of total hip, trochanter, femoral neck, and lumbar spine

Secondary Outcome Measures: Serum calcium, osteocalcin, urinary N-telopeptide, and calcium; physical activity; diet; FEV1

Timing of assessments: 6 months, 1, 2, 3 years</td></tr>
<tr><td>RESULTS:</td><td colspan="3">Health Outcome Measures:
• NR
Intermediate Outcome Measures:
• ICS therapy was associated with a dose-related decline of 0.00044g per square centimeter per puff in bone density at the total hip (P = 0.01) and the trochanter (P = 0.005) but not at the femoral neck or the spine*
• Serum and urinary markers of bone turnover did not predict the degree of bone loss</td></tr>
<tr><td>ANALYSIS:</td><td colspan="3">ITT: N/A
Post randomization exclusions: N/A</td></tr>
<tr><td>ATTRITION (overall):</td><td colspan="3">Overall loss to follow-up: (exclusionary events) 33% (36)
Loss to follow-up differential high: NR</td></tr>
<tr><td>ATTRITION (treatment specific):</td><td><u>triamcinolone (4-8 puffs/d)</u></td><td><u>triamcinolone (> 8 puffs)</u></td><td><u>no ICS</u></td></tr>
<tr><td>Loss to follow-up:</td><td>13 (39%)</td><td>15 (36%)</td><td>8 (29%)</td></tr>
<tr><td>Withdrawals due to adverse events:</td><td>NR</td><td>NR</td><td>NR</td></tr>
<tr><td>Withdrawals due to lack of efficacy:</td><td>NR</td><td>NR</td><td>NR</td></tr>
<tr><td>ADVERSE EVENTS:
Overall adverse effects reported:
Significant differences in events:</td><td colspan="3">NR
NR
NR</td></tr>
<tr><td>QUALITY RATING:</td><td colspan="3">Fair</td></tr>
</table>

*primary outcome measures

Adverse Events ***Inhaled Corticosteroids***

STUDY:	**Authors: Jick et al.**[99] **Year: 2001** **Country:** UK		
FUNDING:	Glaxo Wellcome, Inc.		
DESIGN:	**Study design:** Retrospective cohort and nested case-control study **Setting:** General Practictioners in UK **Sample size:** 201,816 Cohort study; 3,581 Case-control study		
INTERVENTION:	**ICS cohort (BDP, BUD, FLUP)**	**non-exposed cohort**	
Dose:	Varied	Varied	
Dosing range:	N/A	N/A	
Device:	Varied	Varied	
Duration:	Varied	Varied	
Sample size:	103,289	98,527	
Comparable dosing:	N/A		
INCLUSION:	All subjects in UK General Practice Research Database (GPRD) younger than 90 years old with a diagnosis of asthma or COPD and received at least one prescription for BDP, BUD, or FLUP		
EXCLUSION:	Subjects with prescriptions for other steroids (including intranasal but not topical); any subject who had diagnosis of cataract before entry into study		
OTHER MEDICATIONS/ INTERVENTIONS:	N/A		
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** No: older patients in ICS cohort; case-control patients similar **Asthma/COPD classification:** N/A		
	ICS cohort (BDP, BUD, FLUP)	**non-exposed cohort**	
Mean age (years):	Cohort: NR; case-control: 73.1	Cohort: NR; case-control: 73.1	
Sex:	50.1% female	47.3% female	
Ethnicity:	NR	NR	
Other population characteristics:	NR	NR	

<table>
<tr><td colspan="4">Authors: Jick et al.
Year: 2001</td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">Primary Outcome Measures: Database code for cataract recorded after subject entered study

Secondary Outcome Measures: NR

Timing of assessments: N/A</td></tr>
<tr><td>RESULTS:</td><td colspan="3">Health Outcome Measures:
RR 1.3 (95% CI: 1.1 to 1.5) for incidence of cataract in ICS users as compared to non-exposed cohort based on cohort analysis and same RR estimate found in case-control analysis
In case-control analysis, RR estimates increased with increasing numbers of ICS prescriptions (RR 2.5 (95% CI: 1.7 to 3.6) for ≥ 40 prescriptions)
In case-control analysis, age-stratified RR estimates show no increased risk of cataract among ICS users less than 40 years old, regardless of the number of prescriptions
Analysis of individual ICS showed similar increased risk for all drugs</td></tr>
<tr><td>ANALYSIS:</td><td colspan="3">ITT: N/A
Post randomization exclusions: N/A</td></tr>
<tr><td>ATTRITION (overall):</td><td colspan="3">Overall loss to follow-up: N/A
Loss to follow-up differential high: N/A</td></tr>
<tr><td>ATTRITION (treatment specific):
Loss to follow-up:
Withdrawals due to adverse events:
Withdrawals due to lack of efficacy:</td><td><u>ICS cohort (BDP, BUD, FLUP)</u>
N/A
N/A
N/A</td><td><u>non-exposed cohort</u>
N/A
N/A
N/A</td><td></td></tr>
<tr><td>ADVERSE EVENTS:
Overall adverse effects reported:
Significant differences in events:</td><td colspan="3">NR</td></tr>
<tr><td>QUALITY RATING:</td><td colspan="3">Good</td></tr>
</table>

*primary outcome measures

Adverse Events ***Inhaled Corticosteroids***

STUDY:	**Authors: Johnell et al.**[78] **Year: 2002** **Country:** Belgium, Denmark, Finland, Italy, the Netherlands, Norway, Spain, Sweden, UK		
FUNDING:	Astra Zeneca		
DESIGN:	**Study design:** RCT **Setting:** Multi-center (EUROSCOP; 39 centers) **Sample size:** 912		
INTERVENTION: **Dose:** **Dosing range:** **Device:** **Duration:** **Sample size:**	**budesonide** 800 mcg/day Medium DPI 3 years 458	**placebo** N/A N/A DPI 3 years 454	
Comparable dosing:	N/A		
INCLUSION:	Smokers; > 75% compliance with ICS during run-in; mild COPD		
EXCLUSION:	Asthma; allergic rhinitis or eczema; oral corticosteroids for > 4 weeks during preceding 6 months		
OTHER MEDICATIONS/ INTERVENTIONS:	NR		
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **COPD classification:** Mild		
	budesonide	**placebo**	
Mean age (years):	52	52	
Sex:	NR	NR	
Ethnicity:	NR	NR	
Other population characteristics:			
• smoking years:	36.0	36.0	

<table>
<tr><td colspan="4">Authors: Johnell et al.
Year: 2002</td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">Primary Outcome Measures: Vertebral fractures; bone mineral density

Secondary Outcome Measures: Osteocalcin concentrations

Timing of assessments: 6, 12, 24, 36 months</td></tr>
<tr><td>RESULTS:</td><td colspan="3">Health Outcome Measures:
No significant difference in vertebral fractures between treatment groups (BUD: 1.5%; placebo: 0.91%)
Intermediate Outcome Measures:
No significant differences in bone mineral density between BUD and placebo
BUD-treated patients had a significantly lower mean concentration of osteocalcin but no significantly different concentration at endpoint</td></tr>
<tr><td>ANALYSIS:</td><td colspan="3">ITT: No
Post randomization exclusions: NR</td></tr>
<tr><td>ATTRITION (overall):</td><td colspan="3">Overall loss to follow-up: NR
Loss to follow-up differential high: NR</td></tr>
<tr><td>ATTRITION (treatment specific):</td><td><u>budesonide</u></td><td><u>placebo</u></td><td></td></tr>
<tr><td>Loss to follow-up:</td><td>NR</td><td>NR</td><td></td></tr>
<tr><td>Withdrawals due to adverse events:</td><td>NR</td><td>NR</td><td></td></tr>
<tr><td>Withdrawals due to lack of efficacy:</td><td>NR</td><td>NR</td><td></td></tr>
<tr><td>ADVERSE EVENTS:
Overall adverse effects reported:
Significant differences in events:</td><td colspan="3">NR</td></tr>
<tr><td>QUALITY RATING:</td><td colspan="3">Fair</td></tr>
</table>

*primary outcome measures

Adverse Events ***Inhaled Corticosteroids***

STUDY:	**Authors: Kannisto et al.**[87] **Year: 2000** **Country:** Finland		
FUNDING:	Finnish Foundation for Pediatric Research		
DESIGN:	**Study design:** RCT **Setting:** University clinic **Sample size:** 75		
INTERVENTION:	**budesonide**	**fluticasone**	**cromones**
Dose:	800 mcg/day x 2 months; then 400 mcg/day	500 mcg/day x 2 months; then 200 mcg/day	cromolyn 30-60 mg/day nedocromil 12 mg/day
Dosing range:	Medium - low	Medium - low	N/A
Device:	DPI	DPI	MDI or DPI
Duration:	12 months	12 months	12 months
Sample size:	30	30	15
Comparable dosing:	Yes		
INCLUSION:	Asthmatic children		
EXCLUSION:	No ICS and oral steroids during the preceding 12 months		
OTHER MEDICATIONS/ INTERVENTIONS:	NR		
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** No (percentage of females in study groups differs significantly) **Asthma classification:** NR		
	budesonide	**fluticasone**	**cromones**
Mean age (years):	9.3	10.1	8.7
Sex:	57% female	37% female	73% female
Ethnicity:	NR	NR	NR
Other population characteristics:	NR	NR	NR

Authors: Kannisto et al. **Year: 2000**			
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Serum cortisol levels; growth (SD score) **Secondary Outcome Measures:** NR **Timing of assessments:** 2, 4, 6, 12 months		
RESULTS:	**Health Outcome Measures:** • FLUP treated children had significantly less growth reduction than BUD treated children (height SD score: 0.03 vs. 0.23; P < 0.05)* **Intermediate Outcome Measures:** • Overall ACTH tests were abnormal in 23% of children; more BUD-treated children than FLUP-treated children had an abnormal test (30% vs. 18%; P < 0.05)*		
ANALYSIS:	**ITT:** No **Post randomization exclusions:** NR		
ATTRITION (*overall*):	**Overall loss to follow-up:** NR **Loss to follow-up differential high:** NR		
ATTRITION (*treatment specific*):	**budesonide**	**fluticasone**	**cromones**
Loss to follow-up:	N/A	N/A	N/A
Withdrawals due to adverse events:	N/A	N/A	N/A
Withdrawals due to lack of efficacy:	N/A	N/A	N/A
ADVERSE EVENTS:	**budesonide**	**fluticasone**	**cromones**
Overall adverse effects reported:	N/A	N/A	N/A
Differences in specific events:	N/A	N/A	N/A
QUALITY RATING:	**Fair**		

*primary outcome measures

Adverse Events ***Inhaled Corticosteroids***

STUDY:	**Authors: Lee et al.**[82] **Year: 2004** **Country:** USA		
FUNDING:	GlaxoSmithKline		
DESIGN:	**Study design:** Prospective cohort study with nested case control **Setting:** Veterans Affairs hospitals **Sample size:** 40,157 (cohort)		
INTERVENTION:	**cases**	**controls**	
Dose:	21.4% exposed to ICS (mean 156.7 mcg BDP-equivalent)	22.1% exposed to ICS (mean 137.9 mcg BDP-equivalent)	
Dosing range:	Low to high	Low to high	
Device:	All devices	All devices	
Duration:	1.75 years	1,75 years	
Sample size (for case control):	1,708	6,817	
Comparable dosing:	Yes		
INCLUSION:	For cohort study: new diagnosis of COPD within 1 calendar year (10/1998 – 9/1999) Cases: non-vertebral fractures; Controls selected 4:1 from cohort without fractures		
EXCLUSION:	No respiratory-related medication; fracture within 90 days after start of study		
OTHER MEDICATIONS/ INTERVENTIONS:	All other medications allowed		
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes; although on average cases had more comorbidities, used more co-medication, and had a higher number of hospitalizations **COPD classification:** NR		
	cases	**controls**	
Mean age (years):	67.2	67.2	
Sex:	5.6 % female	5.4% female	
Ethnicity:	NR	NR	
Other population characteristics:	NR	NR	

<table>
<tr><td colspan="4">Authors: Lee et al.
Year: 2004</td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">Primary Outcome Measures: Association of ICS use to non-vertebral fractures

Secondary Outcome Measures: NR

Timing of assessments: N/A</td></tr>
<tr><td>RESULTS:</td><td colspan="3">Health Outcome Measures:
Current high dose ICS (> 700 mcg BDP-equivalent) users had an increased risk of fractures compared with patients with no exposure (adjusted OR: 1.68; 95% CI: 1.10 to 2.57)
Exposure to ICS at any time during follow-up was not associated with a higher risk of fractures (adjusted OR: 0.97; 95% CI: 0.84 to 1.11)
Intermediate Outcome Measures:
NR</td></tr>
<tr><td>ANALYSIS:</td><td colspan="3">ITT: N/A
Post randomization exclusions: N/A</td></tr>
<tr><td>ATTRITION (overall):</td><td colspan="3">Overall loss to follow-up: N/A
Loss to follow-up differential high: N/A</td></tr>
<tr><td>ATTRITION (treatment specific):
Loss to follow-up:
Withdrawals due to adverse events:
Withdrawals due to lack of efficacy:</td><td><u>cases</u>
N/A
N/A
N/A</td><td><u>controls</u>
N/A
N/A
N/A</td><td></td></tr>
<tr><td>ADVERSE EVENTS:
Overall adverse effects reported:
Significant differences in events:</td><td colspan="3">N/A</td></tr>
<tr><td>QUALITY RATING:</td><td colspan="3">Good</td></tr>
</table>

*primary outcome measures

Adverse Events ***Inhaled Corticosteroids***

STUDY:	**Authors: Lipworth et al.**[123] **Year: 1999** **Country:** Scotland
FUNDING:	NR
DESIGN:	**Study design:** Systematic review **Number of patients:** Unable to determine
AIMS OF REVIEW:	To appraise the data on systemic adverse effects of inhaled corticosteroids
STUDIES INCLUDED IN META-ANALYSIS	21 studies included in meta-analysis of overnight urinary cortisol levels; 13 studies included in meta-analysis of 8 AM plasma serum cortisol levels; 12 studies evaluated for growth
TIME PERIOD COVERED:	January 1, 1966 - July 31, 1998
CHARACTERISTICS OF INCLUDED STUDIES:	Not clear; the number of studies characterized in table 1 and table 4 do not match studies included in the meta-analysis
CHARACTERISTICS OF INCLUDED POPULATIONS:	One study conducted in children the remainder were conducted in adults

Authors: Lipworth et al. **Year:1999**	
CHARACTERISTICS OF INTERVENTIONS:	Low-High doses of BDP, BUD, FLUP, TRIA via MDI or DPI with or without spacer
MAIN RESULTS:	• Meta-analysis of 21 studies of 24 hour urinary cortisol levels show FLUP with significantly greater slope gradients for adrenal suppression than BDP, BUD, or TRIA which were not significantly different from each other • Meta-analysis of 13 studies of 8 AM serum cortisol show FLUP with a significantly greater slope gradient as compared to BUD and TRIA which were not significantly different from each other • Growth rate, bone metabolism, ocular effects, and skin effects qualitatively summarized
ADVERSE EVENTS:	N/A
COMPREHENSIVE LITERATURE SEARCH STRATEGY:	Yes
STANDARD METHOD OF APPRAISAL OF STUDIES:	No
QUALITY RATING:	**Fair**

Adverse Events ***Inhaled Corticosteroids***

STUDY:	**Authors: Mitchell et al.**[104] **Year: 1999** **Country:** Australia		
FUNDING:	Australian Department of Health and Family Services and the Save Sight Institute, University of Sydney, New South Wales, Australia		
DESIGN:	**Study design:** Cross-sectional **Setting:** Population-based (Blue Mountain Eye Study near Sydney, Australia) **Sample size:** 3,654		
INTERVENTION: **Dose:** **Dosing range:** **Device:** **Duration:** **Sample size:**	**ICS** N/A N/A N/A N/A 370	**no ICS** N/A N/A N/A N/A 3284	
Comparable dosing:	N/A		
INCLUSION:	Permanent residents of the region west of Sydney identified in door to door census ≥ 49 years willing to undergo eye exam (82.4% of population)		
EXCLUSION:	NR		
OTHER MEDICATIONS/ INTERVENTIONS:	All medications allowed		
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** N/A **Asthma classification:** NR		
	ICS	**no ICS**	
Mean age (years):	62.4	64.7	
Sex:	80% female	70% female	
Ethnicity:	NR	NR	
Other population characteristics:			
• ever used oral steroid	28%	5%	
• use of steroid eye drops	1%	1%	

Authors: Mitchell et al. **Year: 1999**			
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Statistical analysis of associations between ICS use and elevated intraocular pressure or glaucoma, by family history, adjusting for other risk factors **Secondary Outcome Measures:** N/A **Timing of assessments:** N/A		
RESULTS:	**Health Outcome Measures:** • Open-angle glaucoma was diagnosed in 108 subjects; elevated intraocular pressure was found in 160 subjects • In persons with family history of glaucoma there was a strong association between ICS use and presence of either glaucoma or elevated intraocular pressure (OR = 2.6, 95% CI: 1.2 to 5.8) • This risk increased with higher doses (OR = 6.3, CI: 1.0 to 38.6) for persons using > 4 puffs/day **Intermediate Outcome Measures:** • NR		
ANALYSIS:	**ITT:** N/A **Post randomization exclusions:** N/A		
ATTRITION (*overall*): **ATTRITION (*treatment specific*):** **Loss to follow-up:** **Withdrawals due to adverse events:** **Withdrawals due to lack of efficacy:**	**Overall loss to follow-up:** N/A **Loss to follow-up differential high:** N/A **ICS** N/A N/A N/A	 **no ICS** N/A N/A N/A	
ADVERSE EVENTS: **Overall adverse effects reported:** **Significant differences in events:**	**ICS** N/A N/A	**no ICS** N/A N/A	
QUALITY RATING:	**N/A**		

*primary outcome measures

Adverse Events ***Inhaled Corticosteroids***

STUDY:	**Authors: Sharek et al.**[88] **Year: 2004**
FUNDING:	
DESIGN:	**Study design:** Meta-analysis **Number of patients:** 273
AIMS OF REVIEW:	To determine whether inhaled beclomethasone causes significant delay in the linear growth in children with asthma
STUDIES INCLUDED IN META-ANALYSIS	Doull et al., 1995; Verberne et al., 1997; Simons et al., 1997
TIME PERIOD COVERED:	Cochrane Airways Group trial register prior to 1999 (specific time period not reported)
CHARACTERISTICS OF INCLUDED STUDIES:	Single or double-blind RCTs comparing beclomethasone delivered by nebulizer, MDI, diskhaler or rotahaler for a minimum of 3 months to placebo or nonsteroidal medication
CHARACTERISTICS OF INCLUDED POPULATIONS:	Children younger than 18 years; diagnosis of asthma; have been off ICS and oral steroids for a minimum of 3 months prior to the study

Authors: Sharek et al. **Year: 2004**	
CHARACTERISTICS OF INTERVENTIONS:	Beclomethasone 400 mcg/day; two used diskhaler and one used an MDI; two studies were placebo controlled and one was salmeterol controlled; doses characterized as high, medium, or low
MAIN RESULTS:	In children with mild to moderate asthma beclomethasone 200 mcg twice daily caused a decrease in linear growth of 1.54 cm per year (95% CI: -1.15 to -1.94); this corresponds to a reduction in growth velocity of approximately 25%; studies lasted a maximum of 54 weeks
ADVERSE EVENTS:	NR
COMPREHENSIVE LITERATURE SEARCH STRATEGY:	Yes
STANDARD METHOD OF APPRAISAL OF STUDIES:	Yes
QUALITY RATING:	**Good**

Adverse Events ***Inhaled Corticosteroids***

STUDY:	**Authors: Smeeth et al.**[102] **Year: 2003** **Country:** UK		
FUNDING:	Gift of Thomas Pocklington; researchers supported by fellowships from MRC and Wellcome Trust		
DESIGN:	**Study design:** Case control **Setting:** General Practice Research Database, UK (population based) **Sample size:** 30,958		
INTERVENTION:	**cases (patients with cataract)**	**controls**	
Dose:	N/A	N/A	
Dosing range:	N/A	N/A	
Device:	N/A	N/A	
Duration:	Mean observation: 4.5 years	Mean observation: 4.5 years	
Sample size:	15,479	15,479	
Comparable dosing:	N/A		
INCLUSION:	GPRD contributors; cases aged at least 40 years old; diagnosed with cataract while registered with a practice participating in the database; at least 180 days of observation prior to diagnosis (index date); controls were matched for age, sex, and practice		
EXCLUSION:	Congenital or traumatic cataract cases		
OTHER MEDICATIONS/ INTERVENTIONS:	Controlled for other corticosteroid exposure		
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** N/A **Asthma classification:** N/A		
	cases (patients with cataract)	**controls**	
Mean age (years):	75.0	75.0	
Sex:	64.6% female	64.6% female	
Ethnicity:	NR	NR	
Other population characteristics:			
• asthma	11.6%	8.0%	
• glaucoma	7.3%	3.7%	
• COPD	8.2%	5.7%	

<table>
<tr><td colspan="4">Authors: Smeeth et al.
Year: 2003</td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">Primary Outcome Measures: OR for cataract in individuals who use ICS

Secondary Outcome Measures: None

Timing of assessments: N/A</td></tr>
<tr><td>RESULTS:</td><td colspan="3">Health Outcome Measures:
Crude OR for the association between any inhaled corticosteroid use and cataract was 1.58 (95% CI: 1.46 to 1.71); adjusted for systemic steroid use 1.32 (95% CI: 1.21 to 1.44)
The risk of cataract increased with dosage and duration of inhaled corticosteroid use</td></tr>
<tr><td>ANALYSIS:</td><td colspan="3">ITT: N/A
Post randomization exclusions: N/A</td></tr>
<tr><td>ATTRITION (overall):</td><td colspan="3">Overall loss to follow-up: N/A
Loss to follow-up differential high: N/A</td></tr>
<tr><td>ATTRITION (treatment specific):
Loss to follow-up:
Withdrawals due to adverse events:
Withdrawals due to lack of efficacy:</td><td><u>cases (patients with cataract)</u>
N/A
N/A
N/A</td><td><u>controls</u>
N/A
N/A
N/A</td><td></td></tr>
<tr><td>ADVERSE EVENTS:
Overall adverse effects reported:
Significant differences in events:</td><td colspan="3">NR</td></tr>
<tr><td>QUALITY RATING:</td><td colspan="3">Good</td></tr>
</table>

*primary outcome measures

Adverse Events ***Inhaled Corticosteroids***

STUDY:	**Authors: Tattersfield et al.**[79] **Year: 2001** **Country:** Multinational (France, New Zealand, Spain, UK)		
FUNDING:	NR		
DESIGN:	**Study design:** RCT, open label, minimum effective dose **Setting:** Multi-center (19 centers) **Sample size:** 374		
INTERVENTION: **Dose:** **Dosing range:** **Device:** **Duration:** **Sample size:**	**budesonide** Mean: 389 mcg/day Low to high DPI 24 months 87	**beclomethasone** Mean: 499 mcg/day Low to high MDI 24 months 74	**no ICS** N/A N/A N/A 24 months 78
Comparable dosing:	Yes		
INCLUSION:	Age 20–60 years; mild asthma; no corticosteroid treatment		
EXCLUSION:	Other medical conditions; drugs that affect bone mineral density; pregnancy; lactation; more than 2 weeks bed rest during previous 6 months		
OTHER MEDICATIONS/ INTERVENTIONS:	Beta 2-agonists; 1% hydrocortisone cream; nasal steroids if other nasal medication was ineffective		
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** Yes **Asthma classification:** Mild intermittent; mild persistent		
	budesonide	**beclomethasone**	**no ICS**
Mean age (years):	37	36	36
Sex:	56% female	56% female	49% female
Ethnicity:	NR	NR	NR
Other population characteristics:			
• current smoker	19%	17%	22%

<table>
<tr><td colspan="4">Authors: Tattersfield et al.
Year: 2001</td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">Primary Outcome Measures: BMD

Secondary Outcome Measures: FEV1; PEF; serum osteocalcin; exacerbations; day or nighttime symptom scores

Timing of assessments: BMD: 6, 12, 24 months</td></tr>
<tr><td>RESULTS:</td><td colspan="3">Health Outcome Measures:
• No significant differences between BUD and BDP for day or nighttime symptom scores
Intermediate Outcome Measures:
• Change in bone mineral density did not differ among treatment groups*
• Mean daily dose of ICS was related to reduction of mineral bone density at the lumbar spine but not at the femoral neck*
• No significant differences in FEV1 or PEF</td></tr>
<tr><td>ANALYSIS:</td><td colspan="3">ITT: No (authors state ITT analysis conducted but not reported)
Post randomization exclusions: No</td></tr>
<tr><td>ATTRITION (overall):</td><td colspan="3">Overall loss to follow-up: 36%
Loss to follow-up differential high: No</td></tr>
<tr><td>ATTRITION (treatment specific):</td><td><u>budesonide</u></td><td><u>beclomethasone</u></td><td><u>no ICS</u></td></tr>
<tr><td>Loss to follow-up:</td><td>30.4% (38)</td><td>38.3% (46)</td><td>39.5% (51)</td></tr>
<tr><td>Withdrawals due to adverse events:</td><td>4.6% (4)</td><td>1.7% (2)</td><td>3.9% (5)</td></tr>
<tr><td>Withdrawals due to lack of efficacy:</td><td>0</td><td>0.8% (1)</td><td>6.2% (8)</td></tr>
<tr><td>ADVERSE EVENTS:</td><td><u>budesonide</u></td><td><u>beclomethasone</u></td><td><u>no ICS</u></td></tr>
<tr><td>Overall adverse effects reported:</td><td>NR</td><td>NR</td><td>NR</td></tr>
<tr><td>Significant differences in events:</td><td></td><td></td><td></td></tr>
<tr><td>• Upper respiratory infections</td><td>20%</td><td>23%</td><td>12%</td></tr>
<tr><td>• Back pain</td><td>7%</td><td>8%</td><td>2%</td></tr>
<tr><td>QUALITY RATING:</td><td colspan="3">Fair</td></tr>
</table>

*primary outcome measures

Evidence Table 4. Subgroups Inhaled Corticosteroids

STUDY:	**Authors: Norjavaara et al.**[115] **Year: 2003** **Country:** Sweden		
FUNDING:	AstraZeneca R&D, Lund, Sweden		
DESIGN:	**Study design:** Retrospective cohort **Setting:** Population-based; Swedish Medical Birth Register **Sample size:** 293,948		
INTERVENTION:	**budesonide**	**controls (all other infants)**	
Dose:	N/A	N/A	
Dosing range:	N/A	N/A	
Device:	N/A	N/A	
Duration:	N/A	N/A	
Sample size:	2,968	290,980	
Comparable dosing:	N/A		
INCLUSION:	Newborn infants registered from 1995-1998 in the Swedish Medical Birth Register; case group consisted of mothers who used budesonide during pregnancy; controls were all other mothers of newborns		
EXCLUSION:	Multiple births and stillbirths		
OTHER MEDICATIONS/ INTERVENTIONS:	Controlled for other asthma medication use (other medication use: NR)		
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** NR **Asthma classification:** NR		
	budesonide	**controls (all other infants)**	
Mean age (years):	N/A	N/A	
Sex:	47.5% female	48.7 % female	
Ethnicity:	NR	NR	
Other population characteristics:	NR	NR	

<table>
<tr><td colspan="4">Authors: Norjavaara et al.
Year: 2003</td></tr>
<tr><td>OUTCOME ASSESSMENT:</td><td colspan="3">Primary Outcome Measures: Gestational age; birth weight; length of infants

Secondary Outcome Measures: Rate of stillbirths; multiple births; caesarean delivery

Timing of assessments: N/A</td></tr>
<tr><td>RESULTS:</td><td colspan="3">Health Outcome Measures: (note: significance tests are compared to ‘all’ births in the population)
• Gestational age was normal but significantly lower in boys whose mothers reported budesonide use in early pregnancy (P < 0.001)*
• Birth weight was normal but lower in girls and boys whose mothers reported budesonide use in early pregnancy (P < 0.01 and P < 0.001, respectively)*
• No difference in birth length was observed after adjustments for mother’s height and gestational age were made
• Rate of stillbirths and multiple births did not differ among groups.
• Rate of caesarean birth was higher in women taking budesonide early in pregnancy (P < 0.05)

Intermediate Outcome Measures: NR</td></tr>
<tr><td>ANALYSIS:</td><td colspan="3">ITT: N/A
Post randomization exclusions: N/A</td></tr>
<tr><td>ATTRITION (overall):</td><td colspan="3">Overall loss to follow-up: N/A
Loss to follow-up differential high: N/A</td></tr>
<tr><td>ATTRITION (treatment specific):
Loss to follow-up:
Withdrawals due to adverse events:
Withdrawals due to lack of efficacy:</td><td><u>budesonide</u>
N/A
N/A
N/A</td><td><u>controls (all other infants)</u>
N/A
N/A
N/A</td><td></td></tr>
<tr><td>ADVERSE EVENTS:
Overall adverse effects reported:
Significant differences in events:</td><td><u>budesonide</u>
N/A
N/A</td><td><u>controls (all other infants)</u>
N/A
N/A</td><td></td></tr>
<tr><td>QUALITY RATING:</td><td colspan="3">Fair</td></tr>
</table>

*primary outcome measures

Subgroups ***Inhaled Corticosteroids***

STUDY:	**Authors: Schatz et al.**[117] **Year: 2004** **Country:** USA		
FUNDING:	National Institute of Child Health and Human Development; National Heart Lung and Blood Institute		
DESIGN:	**Study design:** Retrospective cohort study **Setting:** Patients recruited from 16 centers for two NIH funded studies (RCT & cohort study) **Sample size:** 2,123 asthmatics (1,739 from observational study and 384 from RCT)		
INTERVENTION:	**ICS**	**other asthma medications**	
Dose:	N/A	N/A	
Dosing range:	NR	NR	
Device:	NR	NR	
Duration:	NR	NR	
Sample size:	722	1,401	
Comparable dosing:	N/A		
INCLUSION:	Pregnant women with all levels of asthma severity		
EXCLUSION:	Known multiple gestations; intrauterine fetal demise; major congenital abnormalities; active pulmonary disease other than asthma; inability to schedule ultrasound for gestational age confirmation; or gestational age > 25 weeks and 6 days at intake		
OTHER MEDICATIONS/ INTERVENTIONS:	NR		
POPULATION CHARACTERISTICS:	**Groups similar at baseline:** N/A **Asthma classification:** Mild intermittent; mild persistent; moderate persistent; severe persistent		
	ICS	**other asthma medications**	**overall**
Mean age (years):	NR	NR	23.3
Sex:	100% female	100% female	100% female
Ethnicity:	NR	NR	NR
Other population characteristics:	NR	NR	NR

Authors: Schatz et al. **Year: 2004**	
OUTCOME ASSESSMENT:	**Primary Outcome Measures:** Gestational hypertension; preterm birth; low birth weight; small for gestational age; major malformations **Secondary Outcome Measures:** NR **Timing of assessments:** N/A
RESULTS:	**Health Outcome Measures:** • No association between ICS use and an increase in perinatal risk for asthmatic pregnant women **Intermediate Outcome Measures:** • NR
ANALYSIS:	**ITT:** N/A **Post randomization exclusions:** N/A
ATTRITION (*overall*):	**Overall loss to follow-up:** N/A **Loss to follow-up differential high:** N/A
ATTRITION (*treatment specific*): **Loss to follow-up:** **Withdrawals due to adverse events:** **Withdrawals due to lack of efficacy:**	N/A
ADVERSE EVENTS: **Overall adverse effects reported:** **Significant differences in events:**	 NR NR
QUALITY RATING:	**N/A**

*primary outcome measures

APPENDICES

Appendix A: Search Strategy

Searches were begun in MEDLINE using the search strategy shown below:

#1	Search inhaled corticosteroids	2888
#7	Search "Metered Dose Inhalers"[MeSH] OR "Administration, Inhalation"[MeSH]	13599
#8	Search corticosteroids	146990
#10	Search "Adrenal Cortex Hormones"[MeSH]	128905
#11	Search #7 AND #10	1051
#12	Search #11 OR #1	3212
#23	Search "Beclomethasone"[MeSH] OR "Budesonide"[MeSH] OR "Triamcinolone"[MeSH]	8207
#25	Search #12 OR #23	10616
#28	Search "Asthma"[MeSH] OR "Pulmonary Disease, Chronic Obstructive"[MeSH]	74409
#29	Search #25 AND #28	4095
#33	Search "Treatment Outcome"[MeSH]	185433
#34	Search #33 AND #29	432
#35	Search #33 AND #29 Field: All Fields, Limits: English, Human	392
#36	Search #33 AND #29 Field: All Fields, Limits: English, Randomized Controlled Trial, Human	193
#41	Search #33 AND #29 Field: All Fields, Limits: English, Review, Human	83
#52	Search "Candidiasis, Oral"[MeSH] OR "Safety Management"[MeSH] OR "Osteoporosis"[MeSH] OR "Substance Withdrawal Syndrome"[MeSH] OR "Drug Hypersensitivity"[MeSH] Limits: English, Review, Human	7421
#54	Search "Candidiasis, Oral"[MeSH] OR "Safety Management"[MeSH] OR "Osteoporosis"[MeSH] OR "Substance Withdrawal Syndrome"[MeSH] OR "Drug Hypersensitivity"[MeSH] Field: All Fields, Limits: English, Human	45897
#55	Search Patient Safety Field: All Fields, Limits: English, Human	19363
#56	Search #54 OR #55 Limits: English, Human	64048
#57	Search #29 AND #56 Limits: English, Human	202
#58	Search #29 AND #56 Field: All Fields, Limits: English, Randomized Controlled Trial, Human	66
#60	Search "Case-Control Studies"[MeSH] OR "Cohort Studies"[MeSH] Limits: English, Randomized Controlled Trial, Human	42186

#61	Search #60 AND #57 Limits: English, Randomized Controlled Trial, Human	9
#62	Search #61 OR #58 Limits: English, Randomized Controlled Trial, Human	66
#63	Search Cointerventions: All Fields, Limits: English, Human	29
#64	Search "Estrogenic Steroids, Alkylated"[MeSH] OR "Adrenergic beta-Agonists"[MeSH]	9364
#65	Search #63 OR #64 Limits: English, Human	9372
#66	Search #29 AND #56 Field: All Fields, Limits: English, Randomized Controlled Trial, Human	189

Similar words, terms and phrases were used to conduct searches in the Cochrane Library, EMBASE, and International Pharmaceutical Abstracts. All search results were pooled into one database, and duplicates were removed.

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

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

The methods outlined in this document ensure that the products created in this process are methodologically sound, scientifically defensible, reproducible, and well-documented. This document has been adapted from the Procedure Manual developed by the Methods Work Group of the United States Preventive Services Task Force (version 1.9, September 2001), with additional material from the NHS Centre for Reviews and Dissemination (CRD) report on *Undertaking Systematic Reviews of Research on Effectiveness: CRD's Guidance for Carrying Out or Commissioning Reviews* (2nd edition, 2001) and "The Database of Abstracts of Reviews of Effects (DARE)" in *Effectiveness Matters*, vol. 6, issue 2, December 2002, published by the CRD.

All studies or systematic reviews that are included are assessed for quality, and assigned a rating of "good", "fair" or "poor". Studies that have a fatal flaw in one or more criteria are rated poor quality; studies which meet all criteria, are rated good quality; the remainder are rated fair quality. As the "fair quality" category is broad, studies with this rating vary in their strengths and weaknesses: the results of some fair quality studies are *likely* to be valid, while others are only *probably* valid. A "poor quality" trial is not valid—the results are at least as likely to reflect flaws in the study design as the true difference between the compared drugs.

For Controlled Trials:

Assessment of Internal Validity

1. Was the assignment to the treatment groups really random?
    - Adequate approaches to sequence generation:
        - Computer-generated random numbers
        - Random numbers tables
    - Inferior approaches to sequence generation:
        - Use of alternation, case record numbers, birth dates or week days
    - Not reported

2. Was the treatment allocation concealed?
    - Adequate approaches to concealment of randomization:
        - Centralized or pharmacy-controlled randomization
        - Serially-numbered identical containers
        - On-site computer based system with a randomization sequence that is not readable until allocation
        - Other approaches sequence to clinicians and patients

Inferior approaches to concealment of randomization:
- Use of alternation, case record numbers, birth dates or week days
- Open random numbers lists
- Serially numbered envelopes (even sealed opaque envelopes can be subject to manipulation)

Not reported

3. Were the groups similar at baseline in terms of prognostic factors?

4. Were the eligibility criteria specified?

5. Were outcome assessors blinded to the treatment allocation?

6. Was the care provider blinded?

7. Was the patient kept unaware of the treatment received?

8. Did the article include an intention-to-treat analysis, or provide the data needed to calculate it (i.e., number assigned to each group, number of subjects who finished in each group, and their results)?

9. Did the study maintain comparable groups?

10. Did the article report attrition, crossovers, adherence, and contamination?

11. Is there important differential loss to followup or overall high loss to followup? (give numbers in each group)

<u>Assessment of External Validity (Generalizability)</u>

1. How similar is the population to the population to whom the intervention would be applied?

2. How many patients were recruited?

3. What were the exclusion criteria for recruitment? (Give numbers excluded at each step)

4. What was the funding source and role of funder in the study?

5. Did the control group receive the standard of care?

6. What was the length of followup? (Give numbers at each stage of attrition.)

For Studies Reporting Complications/Adverse Effects

Assessment of Internal Validity

1. Was the selection of patients for inclusion non-biased (Was any group of patients systematically excluded)?

2. Is there important differential loss to followup or overall high loss to followup? (Give numbers in each group.)

3. Were the events investigated specified and defined?

4. Was there a clear description of the techniques used to identify the events?

5. Was there non-biased and accurate ascertainment of events (independent ascertainer; validation of ascertainment technique)?

6. Were potential confounding variables and risk factors identified and examined using acceptable statistical techniques?

7. Did the duration of followup correlate to reasonable timing for investigated events? (Does it meet the stated threshold?)

Assessment of External Validity

1. Was the description of the population adequate?

2. How similar is the population to the population to whom the intervention would be applied?

3. How many patients were recruited?

4. What were the exclusion criteria for recruitment? (Give numbers excluded at each step)

5. What was the funding source and role of funder in the study?

Systematic Reviews:

1. Is there a clear review question and inclusion/exclusion criteria reported relating to the primary studies?

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

2. Is there evidence of a substantial effort to search for all relevant research?

This is usually the case if details of electronic database searches and other identification strategies are given. Ideally, details of the search terms used, date and language restrictions should be presented. In addition, descriptions of hand-searching, attempts to identify unpublished material, and any contact with authors, industry, and research institutes should be provided. The appropriateness of the database(s) searched by the authors should also be considered, e.g. if MEDLINE is searched for a review looking at health education, then it is unlikely that all relevant studies will have been located.

3. Is the validity of included studies adequately assessed?

A systematic assessment of the quality of primary studies should include an explanation of the criteria used (e.g., method of randomization, whether outcome assessment was blinded, whether analysis was on an intention-to-treat basis). Authors may use either a published checklist or scale, or one that they have designed specifically for their review. Again, the process relating to the assessment should be explained (i.e. how many reviewers involved, whether the assessment was independent, and how discrepancies between reviewers were resolved).

4. Is sufficient detail of the individual studies presented?

The review should demonstrate that the studies included are suitable to answer the question posed and that a judgement on the appropriateness of the authors' conclusions can be made. If a paper includes a table giving information on the design and results of the individual studies, or includes a narrative description of the studies within the text, this criterion is usually fulfilled. If relevant, the tables or text should include information on study design, sample size in each study group, patient characteristics, description of interventions, settings, outcome measures, follow-up, drop-out rate (withdrawals), effectiveness results and adverse events.

5. Are the primary studies summarized appropriately?

The authors should attempt to synthesize the results from individual studies. In all cases, there should be a narrative summary of results, which may or may not be accompanied by a quantitative summary (meta-analysis).

For reviews that use a meta-analysis, heterogeneity between studies should be assessed using statistical techniques. If heterogeneity is present, the possible reasons (including chance) should be investigated. In addition, the individual evaluations should be weighted in some way (e.g., according to sample size, or inverse of the variance) so that studies that are considered to provide the most reliable data have greater impact on the summary statistic.

Appendix C: Characteristics of Excluded Studies

Author, Year	Design	N	Intervention	Reason for Exclusion
Allen et al., 1994[124]	Meta-analysis	826	beclomethasone	No systematic literature search
Barnes et al, 1998 [125]	Meta-analysis	3564	beclomethasone, budesonide, fluticasone	No systematic literature search
British Thoracic and Tuberculosis Association, 1976 [126]	RCT	158	beclomethasone, betamethasone	No randomization of initial groups
Mellon, 1999[127]	Pooled data analysis	1018	budesonide	No systematic literature search
Scott et al., 1999[128]	Pooled data analysis	1017	budesonide	No systematic literature search
Weir et al., 1999[121]	RCT	98	beclomethasone	High rate of post-randomization exclusions

Appendix D: Placebo-controlled Trials of Inhaled Corticosteroids (not included)

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APPENDIX F: ACKNOWLEDGEMENTS

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David B. Allen, MD
Professor of Pediatrics
Director of Endocrinology and Residency Training
University of Wisconsin Children's Hospital

James Donohue, MD
Professor of Medicine
Chief of Pulmonary Medicine
University of North Carolina-Chapel Hill

Pierre Ernst, MD
Professor of Medicine
Division of Clinical Epidemiology
McGill University School of Medicine

H. William Kelly, PharmD
Professor Emeritus of Pediatrics
Department of Pediatrics
University of New Mexico

Gail Shapiro, MD
Clinical Professor of Pediatrics
Northwest Asthma and Allergy Center
University of Washington School of Medicine