Corticosteroids, Inhaled Review

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Corticosteroids, Inhaled Review

Overview

The National Asthma Education and Prevention Program (NAEPP) have defined asthma as a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. In susceptible individuals, inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness and coughing. These episodes are usually associated with airflow obstruction that is often reversible either spontaneously or with treatment. The inflammation also causes an increase in bronchial hyper-responsiveness (BHR) to a variety of stimuli.

Studies have demonstrated the efficacy of the inhaled corticosteroids in improving lung function, reducing symptoms, reducing frequency and severity of exacerbations, and improving the quality of life (QoL) of patients with asthma.[1,2,3,4,5] Based on this evidence, the 2002 National Heart, Lung, and Blood Institute, National Institutes of Health (NHLBI, NIH) Global Initiative for Asthma (GINA) state that "inhaled glucocorticoids are the preferred treatment for patients with persistent asthma at all levels of severity".[6] To help health care professionals bridge the gap between current knowledge and practice, the NHLBI's NAEPP has prepared clinical guidelines for the management of asthma. An updated guideline is also available for the treatment of asthma in pregnancy.[7]

Stepwise Approach for Managing Persistent Asthma from the NAEPP Expert Panel Report-2 [9]

Severity	**Adults and Children Older Than Five Years of Age**	**Infants and Young Children Five Years of Age and Younger**
Step 4 Severe Persistent	high-dose corticosteroids AND long-acting inhaled $beta_2$-agonist	high-dose inhaled corticosteroid AND long-acting inhaled $beta_2$-agonist
Step 3 Moderate Persistent	low-to-medium dose inhaled corticosteroids AND long-acting inhaled $beta_2$-agonist	low-dose inhaled corticosteroid and long-acting inhaled $beta_2$-agonist OR medium-dose inhaled corticosteroid
Step 2 Mild Persistent	low-dose inhaled corticosteroid	low-dose inhaled corticosteroid with nebulizer or MDI with holding chamber $\pm$ face mask or DPI
Step 1 Mild Intermittent	no daily medications needed	no daily medications needed

MDI = metered-dose inhaler DPI=dry-powder inhaler

The updated 2006 GINA guidelines now recommend a new classification scheme based on level of asthma control.[10] These revised GINA guidelines offer a new stepwise treatment approach to achieving control using the patient's current level of control as the start point. If the patient is not controlled on the current regimen, treatment should be stepped up until control is achieved. If control is maintained for at least three months on the current regimen, treatment can be stepped down to the lowest step and dosage that maintains control.

Levels of Asthma Control [11]

Characteristic	**Controlled (All of the following)**	**Partly Controlled (Any present in past week)**	**Uncontrolled**
Daytime symptoms	≤2 times per week	>2 times per week	>2 features of partly controlled asthma in any week
Limitations of activities	None	Any	
Nocturnal symptoms/awakening	None	Any	
Need for reliever/rescue treatment	≤2 times per week	>2 times per week	
Lung function (PEF or FEV1)	Normal	<80% predicted or personal best	
Exacerbations	None	Any within 1 year	Any within 1 week

Stepwise Approach to Asthma Control [12]

	Adults and Children Older Than Six Years of Age
Step 1	PRN reliever medication Recommended: rapid acting ß$_2$-agonist Alternatives: inhaled anticholinergic , short-acting oral ß$_2$-agonist or short-acting theophylline
Step 2	One controller AND a PRN reliever medication Recommended controller: low-dose inhaled corticosteroid (ICS) Alternative controller: leukotriene modifier
Step 3	One or two controllers AND a PRN reliever medication Recommended for adolescents and adults: low-dose ICS AND inhaled long acting ß$_2$-agonist Recommended for children: medium dose ICS Alternative controllers: low-dose ICS AND leukotriene modifier, OR, low-dose sustained-release theophylline
Step 4	Two or more controllers AND a PRN reliever medication
Step 5	Additional controller options AND a PRN reliever medication) Recommended controllers for patients who remain severely uncontrolled on Step 4 medications: Oral corticosteroids Anti-IgE treatment (omalizumab – Xolair)

Pharmacology

Corticosteroids decrease the metabolism of the anti-inflammatory compound arachidonic acid and reduce the synthesis of proinflammatory prostaglandins and leukotrienes. In addition, they increase the number and responsiveness of beta-adrenergic receptors. Because systemic corticosteroids have a high incidence of adverse reactions, inhaled corticosteroids are preferred for maintenance therapy of asthma.

The selection of a delivery system is a critical factor in determining clinical success of inhaled corticosteroid therapy. Delivery systems can significantly affect both topical and systemic activity of inhaled corticosteroids.[13,14] Poor inhaler technique has been reported in up to 89 percent of patients.[15]

Metered dose inhalers (MDIs) are pressurized spray inhalers, available in suspension and solution, for which the user has to press down on the metal canister to release the medicine and then breathe in. Metered-dose inhalers deliver approximately 15 to 35 percent of the administered dose to the lungs. Spacer chambers can be attached to MDIs to make them easier to use by people who find it hard to coordinate the press-and-breathe action. When using the spacer, the user can take several breaths to inhale the medicine, which is held in the chamber, so that it is more likely that the right amount of medicine will reach the airways.

Dry-powder inhalers (DPIs) are breath-actuated devices that release the medicine in the form of a dry powder when the user breathes in. Each manufacturer uses a different brand of DPI for their individual products. Although DPIs minimize the potential difficulties in coordinating the press-and-breathe action of the MDI, these delivery systems tend to result in more dosage variations than MDIs at low inspiratory flow rates (less than 20 L/min).

Nebulizer therapy is not the recommended form of administration for any patient.[16] It is considered inferior to an MDI with spacer because of the inconvenience, less effective drug deposition, higher risk of side effects and potentially higher cost. However, for young children under age six who may not have the coordination to use the MDI with spacer, the nebulizer serves as an alternative.

Salmeterol is a long acting beta-agonist that is combined with a corticosteroid (fluticasone) in the combination product, Advair®. Salmeterol selectively binds to the $beta_2$-receptors in the bronchial smooth muscle leading to bronchial relaxation and a decrease in the release of mediators of immediate hypersensitivity from mast cells.

Formoterol is a long acting beta-agonist that is combined with a corticosteroid (budesonide) in the combination product, Symbicort. Similar to salmeterol, formoterol has selective affinity for the $beta_2$-receptors in the bronchial smooth muscle.

FDA-Approved Indications and Dosage Forms

Drug	Manufacturer	Device	Propellant	Doses per container	Dose delivered (mcg)	Age (yrs)	Indication
Corticosteroids							
beclomethasone inhalation aerosol (QVAR™)[17]	IVAX	MDI	HFA	100	40, 80	≥5	Maintenance treatment of asthma as prophylactic therapy • For asthma patients requiring systemic corticosteroid administration to reduce or eliminate the need for systemic corticosteroids
budesonide inhalation powder (Pulmicort Flexhaler®)	AstraZeneca	DPI (Flexhaler®)	--	60, 120	80, 160	≥6	
budesonide inhalation powder (Pulmicort Turbuhaler®)[18]	AstraZeneca	DPI (Turbuhaler®)	--	200	200	≥6	
flunisolide inhalation aerosol (Aerobid®, Aerobid-M®)[20]	Forest	MDI	3 CFCs	100	250	≥6	
fluticasone inhalation aerosol (Flovent®)[21]	GlaxoSmithKline	MDI	2 CFCs	60, 120	44, 110, 220	≥12	
fluticasone inhalation aerosol (Flovent HFA®)[22]	GlaxoSmithKline	MDI	HFA	120	44, 110, 220	≥4	
triamcinolone inhalation aerosol (Azmacort®)[23]	Abbott	MDI	1 CFC	240	100	≥6	
budesonide inhalation suspension (Pulmicort Respules®)[24]	AstraZeneca	2 ml Respule® via jet nebulizer	--	1	250, 500	1-8	Maintenance treatment of asthma as prophylactic therapy
mometasone furoate inhalation powder (Asmanex®)[25]	Schering-Plough	DPI (Twisthaler®)	--	30, 60, 120	220	=12	Maintenance treatment of asthma as prophylaxis or to reduce the oral corticosteroid requirement

FDA-Approved Indications and Dosage Forms (continued)

Drug	Manufacturer	Device	Propellant	Doses per container	Dose delivered (mcg)	Age (yrs)	Indication
Corticosteroid/Bronchodilator Combinations							
budesonide/ formoterol (Symbicort)[28]	AstraZeneca	MDI	HFA	120	80/4.5, 160/4.5	≥12	Maintenance treatment of asthma
fluticasone/ salmeterol inhalation powder (Advair Diskus)[29]	GlaxoSmithKline	DPI (Diskus®)	--	60	100/50, 250/50, 500/50	≥4	• Maintenance treatment of asthma • COPD associated with chronic bronchitis (250/50 only)
fluticasone/ salmeterol inhalation aerosol (Advair HFA)[30]	GlaxoSmithKline	MDI	HFA	120	45/21, 115/21, 230/21	≥12	Maintenance treatment of asthma

Pharmacokinetics

Several comparative studies have demonstrated that, when given in equipotent anti-inflammatory doses, fluticasone and budesonide have less systemic effect, as measured by plasma cortisol, than the other agents.[32,33,34,35,36] There is, however, considerable intersubject variability in the rate of absorption of these agents from the lungs.[37]

The NAEPP guidelines provide information regarding the relative potencies and dosages of each of the available agents. It should be noted that these are not the FDA approved doses, but rather those doses shown to be clinically effective and recommended by the NHLBI. Mometasone (Asmanex) was not available at the time of publication.

NAEPP Expert Panel Report-2 Estimated Comparative Daily Dosages for Inhaled Corticosteroids (mcg/day)[38]

Drug	Adults			Children		
	Low Dose	Medium Dose	High Dose	Low Dose	Medium Dose	High Dose
beclomethasone MDI (QVAR)	80-240	240-480	>480	80-160	160-320	>320
budesonide DPI (Pulmicort)	200-600	600-1,200	>1,200	200-400	400-800	>800
budesonide suspension (Pulmicort Respules)	--	--	--	0.5 mg	1 mg	1mg
flunisolide MDI (Aerobid, M)	500-1,000	1,000-2,000	>2,000	500-750	1,000-1,250	>1,250
fluticasone MDI (Flovent)	88-264	264-660	>660	88-176	176-440	>440
triamcinolone MDI (Azmacort)	400-1,000	1,000-2,000	>2,000	400-800	800-1,200	>1,200

All of the agents are recommended for twice daily use, except for triamcinolone, which is usually given three or four times daily, although some patients may respond to twice daily dosing.

In addition, the 2006 GINA guidelines suggest the following equipotent dosages for ICS [39]:

Drug	Adults			Children		
	Low Dose	Medium Dose	High Dose	Low Dose	Medium Dose	High Dose
beclomethasone MDI (QVAR)	200-500	>500-1000	>1000-2000	100-200	>200-400	>400
budesonide DPI (Pulmicort Turbuhaler)	200-400	>400-800	>800-1600	100-200	>200-400	>400
flunisolide MDI (Aerobid, M)	500-1000	>1000-2000	>2000	500-750	>750-1250	>1250
fluticasone MDI (Flovent)	100-250	>250-500	>500-1000	100-200	>200-500	>500
mometasone DPI (Asmanex)	200-400	>400-800	>800-1200	100-200	>200-400	>400
triamcinolone MDI (Azmacort)	400-1000	>1000-2000	>2000	400-800	>800-1200	>1200

Onset of Action

Drug	Onset of Action	Maximum Benefit
Corticosteroids		
beclomethasone MDI (QVAR)[40]	1-2 weeks	3-4 weeks
budesonide DPI (Pulmicort Turbuhaler, Flexhaler)[41 42]	24 hours	1-2 weeks
budesonide suspension (Pulmicort Respules)[43]	2-8 days	4-6 weeks
flunisolide MDI (Aerobid)[45]	1-4 weeks	--
fluticasone MDI (Flovent, HFA)[46, 47,48]	24 hours – variable time to onset	1-2 weeks or longer
mometasone DPI (Asmanex)[51]	1-2.5 hours	1-2 weeks or longer
triamcinolone MDI (Azmacort)[52]	1 week	2 weeks or longer
Corticosteroid/Bronchodilator Combinations		
budesonide/formoterol (Symbicort)[54]	15 minutes	2 weeks or longer
fluticasone/salmeterol DPI (Advair)[55]	30 – 60 minutes	1 week or longer
fluticasone/salmeterol (Advair HFA)[56]	30 – 60 minutes	1 week or longer

Clinical Trials

Search Strategy

Articles were identified through searches performed on PubMed, www.ifpma.org/clinicaltrials and review of information sent by manufacturers. Search strategy included the use of all drugs in this class. Randomized, controlled comparative trials are considered the most relevant in this category. Criteria for study inclusion in this review are the following: English language, human studies, analyze the data consistently with the study question, randomly allocate participants to comparison groups, include follow-up (endpoint assessment) at least 80 percent of those entering the investigation, and have clearly stated, predetermined outcome measure of known or probable clinical importance. Studies were determined to be free of bias. Unbiased studies were then reviewed for validity and importance. The majority of clinical drug trials are sponsored and/or funded by pharmaceutical manufacturers. While objective criteria were used to ensure that the studies included are free of bias, the potential influence of manufacturer sponsorship/funding must be considered.

beclomethasone (QVAR) MDI versus fluticasone/salmeterol (Advair) DPI

In an evaluation of step-down therapy, 39 patients with uncontrolled moderate-to-severe asthma were treated with beclomethasone DPI 1,000 mcg twice daily for four weeks and then randomized to medium-dose beclomethasone MDI 200 mcg twice daily or low-dose fluticasone/salmeterol 100/50 mcg DPI twice daily for eight weeks in a double-blind, double-dummy, parallel-group design.[57] The primary outcome was the provocative dose of methacholine producing a 20 percent fall in FEV_1 (methacholine PD20). Secondary outcomes were lung function, surrogate inflammatory markers, diary card responses, QoL, and safety.

There was a 0.9 doubling dose improvement in methacholine PD20 comparing asthma before versus after beclomethasone. Beclomethasone maintained this improvement, whereas fluticasone/salmeterol produced a further improvement, amounting to a significant 1.1 doubling dose difference at eight weeks for fluticasone/salmeterol versus beclomethasone. Suppression of plasma and urinary cortisol and serum osteocalcin levels occurred with beclomethasone DPI, but values returned to baseline levels within one month of beclomethasone or fluticasone/salmeterol administration.

budesonide (Pulmicort) DPI versus fluticasone/salmeterol (Advair) DPI

A randomized, double-blind study compared the efficacy and tolerability of low-dose fluticasone/salmeterol 100/50 mcg twice daily with medium-dose budesonide 400 mcg twice daily in 349 patients with symptomatic, mild to moderate asthma.[58] After 12 weeks of treatment, patients in the fluticasone/salmeterol arm had a mean morning peak expiratory flow (PEF) of 426 L/min and evening PEF of 435 L/min compared to 415 L/min and 424 L/min in the budesonide group ($p=0.022$ and $p=0.008$, respectively). There were no differences in any other efficacy or tolerability parameters (symptom scores, use of rescue medication, spirometry, exacerbations).

budesonide (Pulmicort) DPI/formoterol (Foradil) DPI versus fluticasone/salmeterol (Advair) DPI

In the Evaluation of Different Inhaled Combination Therapies (EDICT) trial, medium-dose fluticasone/salmeterol DPI 250/50 mcg twice daily was compared with formoterol (a long-acting $beta_2$-agonist) DPI 12 mcg twice daily and high-dose budesonide DPI 800 mcg twice daily given concurrently.[59] The 428 patients in this study were moderate-to-severe, symptomatic asthmatics who were uncontrolled on existing corticosteroid therapy. This study used a randomized, double-blind, double-dummy, parallel-group design, consisting of a two-week run-in period on current corticosteroid therapy (1,000 to 1,600 mcg/day of beclomethasone or equivalent) and a 12-week treatment period. Improvement in mean morning PEF was similar in both groups and, like mean evening PEF, increased by a clinically significant amount (more than 20 L/min) from baseline in each treatment group. The mean rate of exacerbations was significantly lower in the fluticasone/salmeterol group compared with the budesonide/formoterol group (0.472 versus 0.735, respectively; $p<0.001$). Patients in the fluticasone/salmeterol group also experienced significantly fewer nocturnal symptoms, with a higher median percentage of symptom-free nights ($p=0.04$), nights with a symptom score less than two ($p=0.03$), and nights with no awakenings ($p=0.02$). Both treatments were well tolerated, with a similar low incidence of adverse events.

budesonide/formoterol (Symbicort) versus budesonide

A double blind, randomized, parallel-group study was conducted to compare the efficacy and safety of low-dose budesonide/formoterol (80/4.5 mcg) twice daily versus low-dose budesonide 200 mcg twice daily in 467 adult patients with mild to moderate asthma not fully controlled on low dose inhaled corticosteroid use alone.[60] Improvements were maintained over the 12 weeks of the study in asthma control days (17 percent increase in budesonide/formoterol patients versus 10 percent in budesonide patients), greater reduction in reliever medication use and symptom free days in patients using budesonide/formoterol. Mean PEF after 12 weeks, 378 and 388 in the morning and evening, respectively per budesonide/formoterol group, while the budesonide alone group was 369 and 381 in the morning and evening, respectively. ($p=0.002$ and $p=0.001$ for morning and evening, respectively).

budesonide/formoterol (Symbicort) versus budesonide (Pulmicort) versus formoterol (Foradil) versus budesonide+formoterol versus placebo

A 12-week, randomized, double-blind, double-dummy, placebo-controlled study was conducted to compare the efficacy and safety of budesonide/formoterol (Symbicort) to each of its individual ingredients (budesonide, formoterol, or budesonide+formoterol) as well as to placebo.[61] Five hundred ninety-six patients ages 12 years and older with moderate to severe persistent asthma and previously receiving an ICS were placed on budesonide 160 mcg twice daily. After two weeks, they were randomized to budesonide/formoterol 160/4.5 mcg twice daily; budesonide 160 mcg twice daily + formoterol 4.5 mcg twice daily; budesonide 160 mcg twice daily; formoterol 4.5 mcg twice daily; or placebo twice daily. The primary efficacy endpoints were mean change from baseline of FEV_1 and mean change from baseline in 12-hour FEV_1. The results were similar in the budesonide/formoterol and the budesonide+formoterol groups in all measures. The Symbicort group showed greater improvement in FEV_1 ($p=0.049$) than the individual budesonide, formoterol and placebo. Also, fewer patients on Symbicort experienced worsening asthma symptoms ($p=0.025$). All of the treatments were well tolerated with similar safety profiles.

budesonide/formoterol (Symbicort) versus formoterol (Pulmicort) versus terbutaline

In a 12 month, double-blind, parallel-group study of 3,394 patients (aged 12 years or older) maintained on budesonide/formoterol, the efficacy and safety of three reliever strategies were compared: terbutaline 0.4 mg daily, formoterol 4.5 mcg daily and budesonide/formoterol 160/4.5 mcg daily.[62] The primary outcome was time to first severe exacerbation, defined as an event resulting in hospitalization, ER visit or both, or the need for oral corticosteroids for three days or more. The time to first severe exacerbation was longer with as-needed budesonide/formoterol versus formoterol. The rate of severe exacerbations was 37, 29, and 19 per 100 patients per year with as-needed terbutaline, formoterol and budesonide/formoterol respectively. Asthma control days increased to a similar extent in all treatment groups. As-needed formoterol did not significantly improve symptoms compared with as-needed terbutaline. All treatments were well tolerated.

fluticasone (Flovent) versus fluticasone/salmeterol (Advair)

A one-year, randomized, stratified, double-blind, parallel-group study of 3,421 patients with uncontrolled asthma compared fluticasone and fluticasone/salmeterol in achieving guideline-based measures of control: totally and well-controlled asthma.[63] Treatment was stepped-up until total control was achieved (or maximum 500 mcg corticosteroid twice a day). Significantly more patients in each stratum (previously corticosteroid-free, low- and moderate-dose corticosteroid users) achieved control with salmeterol/fluticasone than fluticasone. Total control was achieved across all strata in 31 percent versus 19 percent of patients after dose escalation ($p<0.001$) and 41 percent versus 28 percent of patients at one year for fluticasone/salmeterol and fluticasone, respectively. Asthma became well controlled in 63 percent versus 50 percent after dose escalation ($p<0.001$) and in 71 percent versus 59 percent of patients at one year. Control was achieved more rapidly and at a lower corticosteroid dose with fluticasone/salmeterol versus fluticasone. Across all strata, 68 percent and 76 percent of the patients receiving fluticasone/salmeterol and fluticasone, respectively, were on the highest dose at the end of treatment. Exacerbation rates (0.07-0.27 per patient per year) and improvement in health status were significantly better with fluticasone/salmeterol.

fluticasone (Flovent) DPI versus salmeterol (Serevent) DPI versus fluticasone/salmeterol (Advair) DPI

In a double-blind, parallel-group, placebo-controlled study, 1,465 patients with COPD were randomized to receive salmeterol 50 mcg twice daily, high-dose fluticasone 500 mcg twice daily, fluticasone/salmeterol 500/50 mcg twice daily, or placebo.[64] After 12 months, all active treatments improved lung function, symptoms, and health status and reduced use of rescue medication and frequency of exacerbations. Combination therapy improved pretreatment FEV_1 significantly more than did placebo (treatment difference 133 mL, 95% CI 105-161, p<0.0001), salmeterol (73 mL, 46-101, p<0.0001), or fluticasone alone (95 mL, 67-122, p<0.0001). Combination treatment produced a clinically significant improvement in health status and the greatest reduction in daily symptoms. All treatments were well tolerated with no difference in the frequency of adverse events, bruising, or clinically significant falls in serum cortisol concentration.

A 12-week, randomized, double-blind study was conducted in patients 12 years (n=267) and older with persistent asthma who were symptomatic while taking as-needed, short-acting $beta_2$-agonists alone.[65] Treatments were administered twice daily via the Diskus device: salmeterol 50 mcg; low-dose fluticasone 100 mcg; or fluticasone 100 mcg with salmeterol 50 mcg. At end point, fluticasone and salmeterol were significantly (p=0.02) more effective than the individual agents used alone in improving morning and evening peak expiratory flow rate and asthma symptoms. In addition, fluticasone and salmeterol effectively reduced rescue albuterol use (p=0.04).

fluticasone (Flovent) versus fluticasone/salmeterol (Advair) plus salmeterol (Serevent) versus montelukast (Singulair)

The Pediatric Asthma Controller Trial (PACT) is a 48 week, double-blind study that compared the effectiveness of three regimens in achieving asthma control in 285 children (ages six to 14 years) with mild to moderate persistent asthma.[66] These school-aged children were randomized to receive fluticasone 100 mcg twice daily (fluticasone monotherapy), fluticasone/salmeterol 100/50 mcg in the morning and salmeterol 50 mcg in the evening (PACT combination), or oral montelukast 5 mg in the evening. The primary outcome was asthma control days. Other endpoints included exacerbations, humanistic measurements, and pulmonary function measurements. Fluticasone monotherapy and PACT combination were comparable in many patient-measured outcomes. However, fluticasone monotherapy was superior for clinic measured indices like FEV_1/FVC (p=0.015) and maximum bronchodilator response (p=0.009). Both fluticasone monotherapy and PACT combination achieved greater improvements in asthma control days than montelukast. However, fluticasone monotherapy was superior to PACT combination in achieving other dimensions of asthma control. The results of this study confirm the current guideline recommendations in treating children with mild to moderate asthma with an FEV_1 greater than 80 percent predicted.

fluticasone/salmeterol (Advair) DPI versus ipratropium bromide/albuterol (Combivent)

A randomized, double-blind, double-dummy, parallel group, multicenter study compared medium-dose fluticasone propionate/salmeterol 250/50 mcg twice daily via DPI with ipratropium bromide/albuterol 36/206 mcg four times daily via metered dose inhaler in 365 symptomatic COPD patients.[67] The study was conducted over eight weeks. Morning pre-dose FEV_1, six-hour serial spirometry, PEF, dyspnea, night-time awakenings, supplemental albuterol use, and patient diary evaluations of symptoms were evaluated. The treatment groups were similar in mean age (63.3 and 63.9 years) and screening pulmonary function (44.1 and 43.2 percent of

predicted FEV_1). Both fluticasone/salmeterol and ipratropium/albuterol improved lung function, symptoms, and supplemental albuterol use compared with baseline. Fluticasone/salmeterol was more effective than ipratropium/albuterol for improvement in morning pre-dose FEV_1, morning PEF, six-hour FEV_1 AUC, Transition Dyspnea Index (TDI) focal score, daytime symptom score, night-time awakenings, sleep symptoms, and albuterol-free nights (p=0.013). Compared with day one, at week eight, the FEV_1 and the six-hour FEV_1 AUC significantly increased with fluticasone/salmeterol and significantly decreased with ipratropium/albuterol (p=0.003). The incidence of adverse events was similar between treatment groups, except for a higher incidence of oral candidiasis with fluticasone/salmeterol.

An eight-week, multicenter, randomized, double-blind, double-dummy, parallel-group study of subjects with moderate to severe COPD was conducted to compare fluticasone propionate/salmeterol 250/50 mcg twice daily with ipratropium/albuterol 36/206 mcg four times daily.[68] The primary measure of efficacy was morning preadministration FEV_1, with secondary measures being morning PEF, six-hour FEV_1 AUC, percentage of symptom-free nights, Transition Dyspnea Index (TDI) score, and overall daytime symptom score. The results of the study showed that the therapeutic regimen of fluticasone propionate/salmeterol resulted in greater improvements in morning preadministration FEV_1, morning PEF, and six-hour FEV_1 AUC (all, p<0.001), TDI score (p=0.026), overall daytime symptom score (p=0.024), percentage of symptom-free nights (p=0.010), nighttime awakenings due to respiratory symptoms (p=0.002), sleep symptom score (p=0.003), and percentage of days and nights without rescue albuterol use compared with the ipratropium/albuterol therapeutic regimen (p=0.021 and p<0.001, respectively). The type and incidence of adverse events experienced from each therapeutic regimen were also similar between the two groups. The study concluded that subjects with moderate to severe COPD experienced greater improvements in lung function and symptom measures with fluticasone propionate/salmeterol than with ipratropium/albuterol.

fluticasone/salmeterol (Advair) DPI versus budesonide/formoterol (Symbicort) DPI

A double-blind, double-dummy study compared the efficacy of stable versus adjusted doses of inhaled corticosteroid plus long-acting beta agonists. The study was conducted in 688 adult patients with persistent asthma and an FEV_1 of 81 percent.[69] Initially, patients were randomized to receive either fluticasone/salmeterol 250 mcg/50 mcg one inhalation twice daily or budesonide/formoterol 200 mcg/6 mcg two inhalations twice daily. After four weeks of this stable dosing, 581 patients (about 15 percent discontinuation rate) in both groups continued for an additional forty-eight weeks on either as stable dose of fluticasone/salmeterol or an adjustable dosing regimen of budesonide/formoterol that required either halving the dose and stepping up or down as indicated by presence or absence of nocturnal awakenings due to asthma, frequency of rescue medication use, and changes in morning peak expiratory flow (PEF). The primary endpoint was the percentage of symptom free days. Patients receiving stable dosed fluticasone/salmeterol had a significantly greater percentage of symptom-free days compared to those receiving adjustable budesonide/formoterol (58.8 versus 52.1 percent; p=0.034) and experienced fewer emergency room visits/hospitalizations (0.18 versus 0.33; p=0.008). Patients in the adjustable budesonide/formoterol group used an average of 1.8 inhalations daily with nearly 83 percent (n=235) stepping down to one inhalation daily. The results suggest that there is minimum daily amount of maintenance therapy necessary to prevent exacerbations in adults with persistent asthma.

mometasone furoate (Asmanex) DPI versus placebo

A twelve week, multicenter, double-blind, parallel-group, placebo-controlled study evaluating two dosing regimens of mometasone (100 mcg every evening and 100 mcg twice daily) in 296

children ages four to eleven years of age with asthma and prior use of ICS.[70] The primary efficacy variable was the change in FEV_1 from baseline to endpoint. The average changes for the daily dose was 4.73 points while the twice daily dose was 5.52 points (p=0.002). The active treatments did not differ from placebo in adverse event reporting. In conclusion, both doses of mometasone were well tolerated, significantly improved lung function, maintained effective asthma control and improved quality of life in children with asthma.

mometasone furoate (Asmanex) DPI versus budesonide DPI (Pulmicort) versus placebo

An eight-week, multicenter, placebo-controlled, double-blind, double-dummy study was conducted in 262 patients (12 years of age or older) with moderate persistent asthma to compare the safety and efficacy of once daily mometasone DPI (Asmanex) to budesonide DPI (Pulmicort) and placebo.[71] Patients were randomized to once-daily morning treatment with mometasone 440 mcg, low-dose budesonide 400 mcg, or placebo. The primary efficacy endpoint was percent change in FEV_1 from baseline to final evaluable visit. At endpoint, the FEV_1 was significantly greater ($p<0.01$) in the mometasone DPI group (8.9 percent) than both the budesonide DPI group (2.1 percent) and placebo group (-3.9 percent). Secondary efficacy variables including morning and evening peak expiratory flow rates, albuterol use, percentage of asthma symptom-free days and physician-evaluated response to therapy were also significantly improved at endpoint in the mometasone DPI group compared with both the placebo and budesonide DPI groups ($p<0.05$). Both active treatments were well tolerated.

Clinical Trials: Safety

There is concern that prolonged treatment with high doses of inhaled corticosteroids may have a detrimental effect on bone mineral density, cause ocular toxicity, suppress the adrenal/pituitary axis and inhibit vertical growth.

budesonide (Pulmicort)

Pooled safety data from budesonide inhalation suspension studies (n=2,356) found there were small differences in short-term growth velocity between children who received budesonide inhalation suspension and those who received reference treatment in two of five trials that evaluated this variable.[72] No posterior subcapsular cataracts were reported in any study. The frequencies of oropharyngeal events and infection with budesonide inhalation suspension were comparable with those of reference treatments. No increased risk of varicella or upper respiratory tract infection was apparent, and budesonide inhalation suspension did not cause significant adrenal suppression in studies assessing this variable.

There are also data from the inhaled Steroid Treatment as Regular Therapy in Early Asthma (START) study that evaluated the safety of once-daily budesonide use over three years in patients aged five to 66 years with mild, persistent asthma (n=7,221).[73] The most commonly reported events included respiratory infections, rhinitis, pharyngitis, bronchitis, viral infections, and sinusitis. Fewer asthma-related, serious adverse events were reported with budesonide (2.2 percent) compared with placebo (3.8 percent). Oral candidiasis was reported more frequently with budesonide (1.2 percent) than with placebo (0.5 percent).

fluticasone (Flovent)

A randomized, double-blind, placebo-controlled study of 160 patients with asthma who had minimal previous exposure to corticosteroids was performed to evaluate the effects of treatment with fluticasone versus placebo on bone, hypothalamic-pituitary-adrenal (HPA) axis function, and

the eyes in patients with asthma.[74] Patients received low-dose fluticasone at 88 mcg twice daily, high-dose fluticasone at 440 mcg twice daily or placebo twice daily for two years. Long-term treatment with 88 mcg of fluticasone twice daily was comparable to placebo in all skeletal, ophthalmic, and HPA axis function assessments. Treatment with fluticasone at 440 mcg twice daily resulted in no significant effects on bone mineral density and a statistically significant, but not clinically important, temporary reduction in cortisol production.

fluticasone (Flovent) versus budesonide (Pulmicort)

Forty children (ages one to three years) with mild asthma were studied in a three-way crossover, randomized, placebo-controlled, double-blind trial.[75] Treatment with medium-dose fluticasone MDI 200 mcg twice daily was compared with low-dose budesonide MDI 200 mcg twice daily and placebo, all given via a spacer device. Systemic steroid activity was assessed after one and four weeks of treatment by measured increase in lower-leg length. The increases in lower-leg length during placebo, budesonide, and fluticasone treatments were 85, 45, and 34 µm/day, respectively. Compared to placebo, the growth in lower-leg length was significantly reduced from both corticosteroid treatments. The differences between budesonide and placebo (40 µm/day) and between fluticasone and placebo (51 µm/day) were statistically significant. The difference between the two active treatment groups, fluticasone and budesonide, was not statistically significant.

fluticasone/salmeterol (Advair) DPI and fluticasone (Flovent) DPI

A randomized, multicenter, double-blind, active-controlled, parallel-group study in 203 children with persistent asthma who were symptomatic during inhaled corticosteroid therapy were examined to compare the safety of twice-daily treatment of inhaled fluticasone plus salmeterol with that of fluticasone alone.[76] The subjects received either fluticasone/salmeterol (100/50 mcg) or low-dose fluticasone (100 mcg) alone twice daily for 12 weeks. The results of the study showed that the safety profile of fluticasone/salmeterol was comparable to that of fluticasone alone with the overall incidence of adverse events being 59 percent for fluticasone/salmeterol and 57 percent for fluticasone. The changes in heart rate, blood pressure, and laboratory variables were infrequent and similar between both groups, and no patients had clinically significant abnormal electrocardiographic findings during treatment. The incidence of withdrawals within the study due to asthma exacerbations was two percent in the fluticasone/salmeterol group and five percent in the fluticasone group. Therefore, the study concluded that in children with persistent asthma, fluticasone/salmeterol twice daily was well tolerated, with a safety profile similar to that of fluticasone used alone.

budesonide (Pulmicort) DPI versus fluticasone (Flovent) DPI

The systemic effects of high-dose budesonide 1,600 mcg/day and high-dose fluticasone 1,500 mcg/day were compared in a randomized, double-blind, cross-over study of 60 adult patients with moderate to severe asthma not controlled on high dose beclomethasone or budesonide.[77] HPA axis suppression of the two treatment groups was assessed by morning serum cortisol and 12-hour nocturnal urinary cortisol excretion measured at the end of each treatment period. Neither treatment produced significant suppression of either parameter compared to baselines. The ratio between the AUC serum cortisol measured after fluticasone treatment and after budesonide treatment was 0.99, indicating equivalent effects on the HPA axis. Two exacerbations of acute asthma occurred during budesonide treatment and none during fluticasone treatment. Both treatments were well tolerated.

Bone Mineral Density and Fracture

Several studies have been performed to evaluate the relative effects of the various agents on bone mass and metabolism.

A multicenter, double-blind, parallel-group study randomized 69 mild to moderate asthmatic adults to treatment with medium or high doses of fluticasone or beclomethasone.[78] After one year, there was no loss of trabecular or integral bone in the distal radius or tibia in any of the patients.

In a randomized, double-blind, placebo-controlled trial, the authors recruited 412 current smokers or recent quitters with mild to moderate COPD.[79] They used inhaled triamcinolone 600 mcg or placebo twice daily. Femoral neck and lumbar spine BMD were measured at baseline and again after one and three years. Serum osteocalcin was measured at baseline, three months, one year, and three years. After three years, BMD at the femoral neck decreased 1.78 percent more with inhaled corticosteroid than with placebo ($p<0.001$). More participants in the inhaled corticosteroid group experienced six percent or more loss of femoral neck BMD ($p=0.002$). Lumbar spine BMD increased in the placebo group by 0.98 percent but decreased by 0.35 percent in the inhaled corticosteroid group (a difference of -1.33 percent, $p=0.007$). Changes in osteocalcin did not correlate with changes in BMD. Fractures, lost height, or osteoporosis diagnoses were not increased among inhaled corticosteroid users compared with placebo users.

Linear Growth

Evidence on growth velocity and height over an extended time period is available from the Childhood Asthma Management Program (CAMP) trial that compared budesonide with nedocromil and placebo in 1,041 children followed for four to six years.[80] A difference consistent with the above magnitude occurred during the first year of the study. However, in long-term follow up, the difference in growth velocity was not maintained, and all groups had similar growth velocity at the end of treatment. There was still a one centimeter difference between the study groups at the end of treatment. A slight difference in bone age suggests the potential for catch up for the inhaled corticosteroid group. An ancillary study of the CAMP trial demonstrated that low-dose budesonide 400 mcg/day over a three year period had no effects on HPA axis function in children with mild to moderate asthma.[81] Growth in children taking corticosteroids by any route should be carefully monitored.

Special Populations

Pediatrics

The safety and effectiveness of the inhaled corticosteroids has been established in various pediatric age groups as listed on the indications chart.

Drug Interactions

The main route of metabolism for many corticosteroids is via the cytochrome P450 isoenzyme 3A4. Inhibitors of CYP3A4 (ritonivir, ketoconazole, itraconazole, clarithromycin, erythromycin) may increase the plasma concentration of inhaled corticosteroids. Fluticasone use in combination with ritonavir has been associated with systemic corticosteroid effects such as Cushing's syndrome and adrenal suppression.

Adverse Effects

Drug	Cough	Headache	Nausea	Oral candidiasis	Pharyngitis	URI
Corticosteroids						
beclomethasone MDI (QVAR)[82]	1-3	12	1	0	8	9
budesonide DPI (Pulmicort Flexhaler)[83]	--	--	1.8	1.3	2.7	2.2
budesonide DPI (Pulmicort Turbuhaler)[84]	*	13-14	1-3	2-4	5-10	19-24
budesonide suspension (Pulmicort Respules)[85]	5-9	≥3	--	--	≥3	34-38
flunisolide MDI (Aerobid, Aerobid-M)[87]	3-9	25	25	3-9	1-3	25
fluticasone MDI (Flovent)[88, 89]	*	17-22	1-3	2-5	10-14	15-22
fluticasone MDI (Flovent HFA)[90]	4-6	5-11	*	2-5	1-3	16-18
mometasone DPI (Asmanex)[93]	--	20-22	1-3	4-6	8-13	8-15
triamcinolone MDI (Azmacort)[94]	*	7-21	--	*	7-25	--
Corticosteroid/Bronchodilator Combinations						
budesonide/ formoterol (Symbicort)[95]	=3	6.5	1.4	1.4	=1 - < 3	7.6
fluticasone/ salmeterol DPI (Advair)[96]	3-6	12-13	4-6	1-4	10-13	21-27
fluticasone/ salmeterol (Advair HFA)[97]	--	21	5	1-3	--	16

* Reported

Adverse effects are indicated as percentage occurrence. These data are compiled from different clinical trials and cannot be considered comparative.

Warnings

In 2006, the FDA updated the safety information for products containing salmeterol, including Advair and Advair HFA. Product safety information for Foradil was updated in June 2006. The

new labeling for these products contains a boxed warning about a small, but significant, increased risk of life-threatening asthma episodes or asthma related deaths observed in patients taking salmeterol in the recently completed Salmeterol Multi-center Asthma Research Trial (SMART). In this prematurely stopped study, only the single component agent, Serevent®, was administered. Post-hoc analysis indicates that the risk of these serious reactions was significantly higher in African-Americans. The FDA does note that the benefits of salmeterol in patients with COPD or asthma outweigh the risks.[98]

Dosages (FDA approved)

Drug	Adult		Pediatric	
	Initial	**Maximum**	**Initial**	**Maximum**
Corticosteroids				
beclomethasone MDI (QVAR)[99]	40-160 mcg BID	320 mcg BID	40 mcg BID	80 mcg BID
budesonide DPI (Pulmicort Flexhaler)[100]	360 mcg BID	720 mcg BID	180 mcg BID	360 mcg BID
budesonide DPI (Pulmicort Turbuhaler)[101]	200-400 mcg BID	800 mcg BID	200 mcg BID	400 mcg BID
budesonide suspension (Pulmicort Respules)[102]	--	--	250-500 mcg BID or 250-1,000 mcg once daily	250-500 mcg BID or 500-1,000 mcg once daily
flunisolide MDI (Aerobid, Aerobid-M)[104]	500 mcg BID	1,000 mcg BID	500 mcg BID	500 mcg BID
fluticasone MDI (Flovent, HFA)[105, 106]	88-880 mcg BID	880 mcg BID	4-11years (HFA) 88 mcg BID	4-11years(HFA) 88 mcg BID
mometasone DPI (Asmanex)[107]	220 mcg daily PM (if on bronchodilators alone or inhaled steroids) or 440 mcg BID (if on oral corticosteroids)	440 mcg daily (single or divided doses) or 880 mcg daily	<u>12 years and older</u> 220 mcg daily in PM (if on bronchodilators alone or inhaled steroids) or 440 mcg BID (if on oral corticosteroids)	<u>12 years and older</u> 440 mcg daily (single or divided doses) or 880 mcg daily
triamcinolone MDI (Azmacort)[108]	200 mcg TID-QID or 400 mcg BID	1,600 mcg daily	100-200 mcg TID-QID or 200-400 mcg BID	1,200 mcg daily

Dosages (FDA approved - continued)

Drug	Adult		Pediatric	
	Initial	Maximum	Initial	Maximum
Corticosteroid/Bronchodilator Combinations				
budesonide/formoterol (Symbicort) [111]	80mcg/4.5mcg BID – 160mcg/4.5mcg BID	160mcg/4.5 mcg BID	12 years and older 80mcg/4.5mcg BID – 160mcg/4.5mcg BID	12yrs and older 160mcg/4.5mcg BID
fluticasone/salmeterol DPI (Advair)[112]	100 mcg/50 mcg BID – 500 mcg/50 mcg BID	500 mcg/50 mcg BID	4-11 years 100 mcg/50 mcg BID	--
fluticasone/salmeterol MDI (Advair HFA)[113]	45mcg/21mcg BID 115mcg/21mcg BID 230mcg/21mcg BID	230mcg/21 mcg BID	12 years and older 45mcg/21mcg BID 115mcg/21mcg BID 230mcg/21mcg BID	12 yrs and older 230mcg/21mcg BID

Summary

In 2004, a meta-analysis of randomized trials in children and adults was completed comparing fluticasone to either beclomethasone or budesonide in the treatment of chronic asthma.[116] Two reviewers independently assessed articles for inclusion and methodological quality. Forty-eight studies (11,479 participants) met the inclusion criteria. When compared at a fluticasone to budesonide/beclomethasone dose ratio of 1:2, fluticasone produced a significantly greater FEV_1 morning PEF and evening PEF. This applied to all drug doses, age groups, and delivery devices, although subgroup analyses suggested that the relative benefit of fluticasone might be greater in more severe patients treated with higher doses of inhaled corticosteroid.

When used in equivalent dosages, efficacy among all inhaled corticosteroids is similar. There are differences between the agents in dosage frequency and the number of puffs needed for each dose. All of the inhaled corticosteroids are effective when given twice daily although, most often, triamcinolone must be administered three or four times a day.

A meta-analysis of published and unpublished literature evaluated the impact of long-term inhaled corticosteroid use on bone density in adult patients with asthma or COPD.[117] The authors found that long-term use was not associated with significant changes in bone density.

Data from the United Kingdom based General Practice Research Database have been evaluated to determine whether children or adolescents exposed to inhaled corticosteroids are at a higher risk of having bone fractures compared with non-exposed individuals.[118] The authors concluded that they were not.

When selecting an agent for an individual patient, consideration must be given to the characteristics of the particular delivery device. This is particularly important for the very young

and the very old. For children under five years, a MDI with a spacer and, when needed, a face mask may be preferable. If this is not effective, consideration could be given towards nebulizer therapy or, for children between three and five years, a DPI. For children five years and older, an MDI with a spacer is usually effective.

The newest agent, mometasone furoate (Asmanex), represents an additional option in the inhaled corticosteroid arsenal. There are no comparative efficacy trials available to date that compare mometasone to other inhaled corticosteroids. The combination product, fluticasone/salmeterol (Advair), may increase compliance for patients requiring both products. It is a NAEPP Step Three treatment for moderate, persistent asthma and is appropriate only after patients have been stabilized on their corticosteroid dose.

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