

Drug Class Review on Inhaled Corticosteroids

Update #3: Preliminary Scan Report

April 2007

The purpose of this report is to make available information regarding the comparative effectiveness and safety profiles of different drugs within pharmaceutical classes. Reports are not usage guidelines, nor should they be read as an endorsement of, or recommendation for, any particular drug, use or approach. Oregon Health & Science University and RTI-UNC Evidence-based Practice Center do not recommend or endorse any guideline or recommendation developed by users of these reports.

Produced by
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

CECIL G.
sheps
CENTER

FOR HEALTH SERVICES RESEARCH
UNIVERSITY OF NORTH CAROLINA AT CHAPEL HILL

Oregon Evidence-based Practice Center
Mark Helfand, MD, MPH, Director

Copyright © 2006 by Oregon Health & Science University
Portland, Oregon 97201. All rights reserved.



OBJECTIVE

The purpose of this preliminary updated literature scan process is to provide the Participating Organizations with a preview of the volume and nature of new research that has emerged subsequent to the previous full review process. Provision of the new research presented in this report is meant only to assist with Participating Organizations' consideration of allocating resources toward a full update of this topic. Comprehensive review, quality assessment and synthesis of evidence from the full publications of the new research presented in this report would follow only under the condition that the Participating Organizations ruled in favor of a full update. The literature search for this report focuses only on new randomized controlled trials, and actions taken by the FDA or Health Canada since the last report. Other important studies could exist.

Date of Last Update

April 2005 (searches through March 2005)

Scope and Key Questions

The Oregon Evidence-based Practice Center wrote preliminary key questions, identifying the populations, interventions, and outcomes of interest, and based on these, the eligibility criteria for studies. These key questions were reviewed and revised by representatives of organizations participating in the Drug Effectiveness Review Project (DERP). The participating organizations of DERP are responsible for ensuring that the scope of the review reflects the populations, drugs, and outcome measures of interest to both clinicians and patients. The participating organizations approved the following key questions to guide this review:

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?

Inclusion criteria

Populations

- Study participants include adult or pediatric outpatients with asthma and adult outpatients with COPD

Interventions

Six different ICSs currently are available in the United States:

- beclomethasone dipropionate (beclomethasone)
- budesonide
- flunisolide
- fluticasone propionate (fluticasone)
- mometasone furoate (mometasone)
- triamcinolone acetonide (triamcinolone)

Effectiveness outcomes

- 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)

Safety outcomes

- 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

METHODS**Literature Search**

To identify relevant citations, we searched Ovid MEDLINE, Ovid MEDLINE Daily Update, and Ovid MEDLINE In-Process & Other Non-Indexed Citations from January 2004 through December 21, 2006 using terms for included drugs and indications, and limits for humans, English language, and randomized controlled trials or controlled clinical trials. We also searched FDA (<http://www.fda.gov/medwatch/safety.htm>) and Health Canada (<http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories->

[avis/prof/2006/index_e.html](#)) web sites for identification of new drugs, indications, and safety alerts. All citations were imported into an electronic database (EndNote 8.0) and duplicate citations were removed.

Study Selection

One reviewer assessed abstracts of citations identified from literature searches for inclusion, using the criteria described above.

RESULTS

Overview

Searches resulted in 244 citations. Of those, there are 21 new potentially relevant trials (see Appendix A, attached).

New Drugs

None at this time, however ciclesonide appears to be in the process of applying for FDA approval for an asthma indication.

New Safety Alerts

None.

Appendix A. Abstracts of potentially relevant new trials of ICS

1. Acun, C., N. Tomac, et al. (2005). "Effects of inhaled corticosteroids on growth in asthmatic children: a comparison of fluticasone propionate with budesonide." *Allergy Asthma Proc* 26(3): 204-6.

In asthmatic children inhaled corticosteroids are widely used. However, there are some concerns about the systemic adverse effects of these drugs, especially in the growing child. We performed this prospective study in order to compare the effects of 400 microg/day of budesonide (BUD) and 250 microg/day of fluticasone propionate (FP) on growth in prepubertal (aged 4-11.5 years), moderate persisting asthmatic children. One hundred patients (51 boys and 49 girls), who were randomized into two groups, were recruited for the study. The first group was treated with BUD, 2X 200 microg/day, and the second group was treated with FP, 2X 125 microg/day, by using a medium-size volume-spacer metered-dose inhaler. Growth in children with asthma who were treated by inhaled corticosteroids was calculated by growth velocity over a 12-month period. Comparisons between treatment groups were calculated by t-test and chi-square test. There were no significant differences between BUD and FP groups for sex, age, first height, and growth velocity. Moderate persisting, prepubertal asthmatic children treated with 250 microg/day of FP appeared to have no different linear growth than those children who received 400 microg/day of BUD.

2. Adams, N., J. M. Bestall, et al. (2005). "Inhaled fluticasone versus inhaled beclomethasone or inhaled budesonide for chronic asthma in adults and children." *Cochrane Database Syst Rev*(2): CD002310.

BACKGROUND: Beclomethasone dipropionate (BDP) and budesonide (BUD) are commonly prescribed inhaled corticosteroids for the treatment of asthma. Fluticasone propionate (FP) is newer agent with greater potency in in-vitro assays. **OBJECTIVES:** To compare the efficacy and safety of Fluticasone to Beclomethasone or Budesonide in the treatment of chronic asthma. **SEARCH STRATEGY:** We searched the Cochrane Airways Group trial register (January 2004) and reference lists of articles. We contacted trialists and pharmaceutical companies for additional studies and searched abstracts of major respiratory society meetings (1997 to 2003). **SELECTION CRITERIA:** Randomised trials in children and adults comparing Fluticasone to either Beclomethasone or Budesonide in the treatment of chronic asthma. **DATA COLLECTION AND ANALYSIS:** Two reviewers independently assessed articles for inclusion and methodological quality. One reviewer extracted data. Quantitative analyses were undertaken using RevMan analyses 1.0.1. **MAIN RESULTS:** Fifty six studies (12, 119 participants) met the inclusion criteria. Methodological quality was variable. Dose ratio 1:2: FP produced a significantly greater FEV1 (0.14 litres, 95% Confidence Interval (CI) 0.06 to 0.22), morning PEF (11.10 L/min, 95%CI 3.12 to 19.09 L/min) and evening PEF (9.31 L/min, 95%CI 5.12 to 13.5 L/min). This applied to all drug doses, age groups, and delivery devices. No difference between FP and BDP/BUD were seen for trial withdrawals. Symptoms and rescue medication use were widely reported but few trials provided sufficient data for analysis. When given at half the dose of BDP/BUD, FP led to a greater likelihood of pharyngitis. There was no difference in the likelihood of oral candidiasis. Plasma cortisol and 24 hour urinary cortisol was measured frequently but

data presentation was limited. Dose ratio 1:1: FP produced a statistically significant difference in am PEF (9.58 L/min (95% CI 5.20 to 13.97)), pm PEF (7.41 L/min (95% CI 2.61 to 12.22)), and FEV1 (0.09 L (0.02 to 0.17)). The effects on exacerbations were mixed. There was an increase in the incidence of hoarseness, but no significant difference in pharyngitis, candidiasis, or cough. **AUTHORS' CONCLUSIONS:** Fluticasone given at half the daily dose of beclomethasone or budesonide leads to small improvements in measures of airway calibre, but it appears to have a higher risk of causing hoarseness when given at the same daily dose. Future studies should attempt to establish the relative efficacy of inhaled steroids delivered with CFC-free propellants.

3. Adams, N. P., J. B. Bestall, et al. (2005). "Inhaled beclomethasone versus placebo for chronic asthma." *Cochrane Database Syst Rev*(1): CD002738.

BACKGROUND: Inhaled beclomethasone dipropionate (BDP) has been, together with inhaled budesonide, the mainstay of anti-inflammatory therapy for asthma for many years. A range of new prophylactic therapies for asthma is becoming available and BDP has been reformulated using a hydrofluoroalkane-134a (HFA) propellant which is free from chlorofluorocarbon (CFC). **OBJECTIVES:** The objectives of this review were to: (1) Compare the efficacy of BDP with placebo with both CFC and HFA propellants in the treatment of chronic asthma. (2) Explore the possibility that a dose response relationship exists for BDP in the treatment of chronic asthma. (3) To provide the best estimate of the efficacy of BDP as a benchmark for evaluation of newer asthma therapies.

SEARCH STRATEGY: Electronic searches were current as of January 2003.

SELECTION CRITERIA: Randomised parallel group design trials for a minimum period of four weeks, in children and adults comparing CFC-BDP or HFA-BDP with placebo in the treatment of chronic asthma. Two reviewers independently assessed articles for inclusion and methodological quality. **DATA COLLECTION AND ANALYSIS:** One reviewer extracted data; authors were contacted to clarify missing information. We analysed data with RevMan Analyses 1.0.2. **MAIN RESULTS:** 60 studies recruiting 6542 participants met the inclusion criteria. **CFC-BDP (57 studies):** In non-oral steroid treated patients, at doses of 400 mcg/day or less CFC-BDP produced significant improvements from baseline in a number of efficacy measures compared with placebo, including forced expiratory volume in one second (FEV1) 360 ml (95% CI 260 to 460); FEV1 (% predicted) WMD 12.41% (95% CI 8.18 to 16.64) and morning peak expiratory flow rate (am PEF) WMD 35.95 L/min (95% CI 27.85 to 44.04). BDP also led to reductions in rescue beta-2 agonist use compared with placebo of -2.32 puffs/d (95% CI -2.55 to -2.09) and reduced the relative risk (RR) of trial withdrawal due to an asthma exacerbation 0.25 (95% CI 0.12 to 0.51). Subgroup analyses based on treatment duration provide support to the proposal that a treatment period of greater than four weeks is required to realise a fuller treatment effect. In oral steroid treated patients BDP led to significantly greater reductions in oral prednisolone use WMD -4.91 mg/d (95% CI -5.88 to -3.94 mg/d) and greater likelihood of withdrawing oral steroid treatment RR 8.02 (95% CI 3.23 to 19.92). **HFA-BDP (3 studies):** In non-oral steroid-treated patients, HFA-BDP was significantly more effective than placebo in improving FEV1, morning and evening PEF, FEF25 to 75%, reduced asthma symptoms and beta2-agonists daily consumption. Significant effects for such outcomes were apparent after six weeks of treatment. In oral steroid treated patients, HFA-BDP improved significantly FEV1 and am PEF. The summary

estimates for these outcomes suggested a high level of heterogeneity, and divergent aims of the studies may contribute to the variation we observed. Limited data on adverse events were reported. **AUTHORS' CONCLUSIONS:** This review has quantified the efficacy of CFC-BDP and HFA-BDP in the treatment of chronic asthma and strongly supports its use. Current asthma guidelines recommend titration of dose to individual patient response, but the published data provide little support for dose titration above 400 mcg/d in patients with mild to moderate asthma. There are insufficient data to draw any conclusions concerning dose-response in people with severe asthma.

4. Altintas, D. U., G. B. Karakoc, et al. (2005). "The effects of long term use of inhaled corticosteroids on linear growth, adrenal function and bone mineral density in children." *Allergol Immunopathol (Madr)* 33(4): 204-9.

In this study we aimed to investigate the long term effects of inhaled steroids on linear growth, adrenal function and bone mineral density. Thirty children with moderate asthma were randomly divided into two groups. Fifteen children (8 boys, 7 girls mean age; 10.6 +/- 2.1) were treated with budesonide (group 1), and 15 (9 boys, 6 girls, mean age; 9.6 +/- 2.4). with fluticasone propionate (group 2). Control group included 30 children. Anthropometric assessment, symptom and medication scores, pulmonary functions, bone mineral density, serum and urine cortisol levels and ACTH stimulation test were evaluated at the beginning of the study and after one year period. Symptom and medication scores, pulmonary functions improved significantly in both groups ($p < 0.05$). The mean annual growth was similar in group 1 and 2 and control group. Bone mineral density was comparable with control group at the beginning of the study and after one year. Mean serum cortisol level diminished at the end of the therapy but no significant differences were found between the initial and end values in respect to urine cortisol levels and cortisol/creatinine ratio. Of three groups ACTH stimulation test revealed that there were no significant difference between study and control groups. In conclusion, although we did not observed any side effects of inhaled corticosteroids we suggest that children treated with inhaled corticosteroids for a long time should be followed closely with respect to side effects.

5. Becker, A. B., O. Kuznetsova, et al. (2006). "Linear growth in prepubertal asthmatic children treated with montelukast, beclomethasone, or placebo: a 56-week randomized double-blind study." *Ann Allergy Asthma Immunol* 96(6): 800-7.

BACKGROUND: Antileukotrienes and inhaled corticosteroids are asthma controller agents widely used in the treatment of pediatric asthma. **OBJECTIVE:** To evaluate the effects of montelukast and beclomethasone on linear growth in prepubertal asthmatic children for 1 year. **METHODS:** This was a 30-center study of boys (6.4-9.4 years old) and girls (6.4-8.4 years old) at Tanner stage I with mild, persistent asthma. After a placebo run-in period, 360 patients were randomized in equal ratios to double-blind, double-dummy treatment with 5 mg of montelukast, 200 microg of beclomethasone twice daily (positive control), or placebo for 56 weeks; 90% of the patients completed the study. The primary end point was linear growth velocity, measured using a stadiometer. **RESULTS:** Linear growth rates were similar between the montelukast and placebo groups; the mean difference for the year was 0.03 cm. The mean growth rate with beclomethasone was significantly less than with placebo (-0.78 cm) or montelukast (0.81

cm) ($P < .001$ for both). Median percentage of days with beta-agonist use was greater with placebo (14.58%) vs montelukast (10.55%) or beclomethasone (6.65%) ($P < .05$ for all). More patients used oral corticosteroid rescue with placebo (34.7%) than with montelukast (25.0%) or beclomethasone (23.5%). An imbalance in bone marker levels was seen with beclomethasone but not with montelukast. **CONCLUSION:** In prepubertal asthmatic children, montelukast did not affect linear growth, whereas the growth rate with beclomethasone was significantly decreased during 1 year of treatment.

6. Bensch, G. W., B. Prenner, et al. (2006). "Once-daily evening administration of mometasone furoate in asthma treatment initiation." *Ann Allergy Asthma Immunol* 96(4): 533-40.

BACKGROUND: In a previous study, a 200-microg once-daily evening dose of mometasone furoate dry powder inhaler (DPI) was effective in patients with asthma previously taking inhaled corticosteroids. No studies have been conducted to test the effect of a once-daily evening dose in patients previously using only short-acting beta₂-adrenergic agonists (SABAs) for symptom relief. **OBJECTIVE:** To evaluate the effectiveness of mometasone furoate DPI administered once daily in the evening as initial controller therapy in patients previously using SABAs alone for asthma. **METHODS:** Patients with mild-to-moderate persistent asthma from 18 US centers participated in a 12-week, randomized, double-blind, placebo-controlled study. Patients received either mometasone furoate DPI, 200 microg, or placebo once daily in the evening. The primary efficacy variable was the change in forced expiratory volume in 1 second from baseline to the end point (last evaluable visit). Other measurements included forced vital capacity, forced expiratory flow between 25% and 75%, morning and evening peak expiratory flow, asthma symptoms, use of albuterol, nocturnal awakenings, physicians' evaluation of response to therapy, and time to asthma worsening. **RESULTS:** At the end point, the mean increase in forced expiratory volume in 1 second relative to baseline for the mometasone furoate DPI group of 0.43 L (16.8%) was significantly greater than that for the placebo group of 0.16 L (6.0%) ($P < .01$). Morning peak expiratory flow, forced vital capacity, and forced expiratory flow between 25% and 75% also significantly improved with mometasone furoate DPI treatment relative to placebo ($P < .01$). Once-daily dosing with mometasone furoate DPI was well tolerated. **CONCLUSION:** Mometasone furoate DPI (200 microg) administered once daily in the evening significantly improves pulmonary function in patients previously using SABAs alone for asthma control.

7. Carlsen, K. C., S. Stick, et al. (2005). "The efficacy and safety of fluticasone propionate in very young children with persistent asthma symptoms." *Respir Med* 99(11): 1393-402.

We aimed to evaluate the efficacy and safety of fluticasone propionate (FP) in children aged 12-47 months with recurrent/persistent asthma symptoms. One hundred and sixty children (12-47 months) were randomised into this multicentre, double-blind, placebo-controlled, parallel-group study, and treated with either FP (100 microg bd) or placebo (2 puffs bd), both administered by metered-dose-inhaler and Babyhaler for 12 weeks. The primary endpoint was percentage of symptom-free 24h periods. Over weeks 1-12, FP-treated patients had significantly more percentage symptom-free 24-h periods compared with placebo (odds ratio 0.53; 95% CI 0.29-0.95; $P = 0.035$). Relative to baseline, where

all patients were symptomatic for at least 21/28 days of the run-in, the improvement equated to one additional symptom-free 24 h period per week. FP patients also had a significantly higher percentage of 24 h periods with no wheeze or cough, the odds ratio for treatment difference corresponding to two additional wheeze-free and one additional cough-free periods per week. FP was well-tolerated, with similar reported adverse events in both groups. Urinary cortisol-creatinine ratio was slightly decreased among FP patients after 12 weeks, but with no clinical correlates. FP is effective for the treatment of chronic persistent asthma symptoms in very young children.

8. Calverley, P. M., J. A. Anderson, et al. (2007). "Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease." *N Engl J Med* 356(8): 775-89.

BACKGROUND: Long-acting beta-agonists and inhaled corticosteroids are used to treat chronic obstructive pulmonary disease (COPD), but their effect on survival is unknown. **METHODS:** We conducted a randomized, double-blind trial comparing salmeterol at a dose of 50 microg plus fluticasone propionate at a dose of 500 microg twice daily (combination regimen), administered with a single inhaler, with placebo, salmeterol alone, or fluticasone propionate alone for a period of 3 years. The primary outcome was death from any cause for the comparison between the combination regimen and placebo; the frequency of exacerbations, health status, and spirometric values were also assessed. **RESULTS:** Of 6112 patients in the efficacy population, 875 died within 3 years after the start of the study treatment. All-cause mortality rates were 12.6% in the combination-therapy group, 15.2% in the placebo group, 13.5% in the salmeterol group, and 16.0% in the fluticasone group. The hazard ratio for death in the combination-therapy group, as compared with the placebo group, was 0.825 (95% confidence interval [CI], 0.681 to 1.002; $P=0.052$, adjusted for the interim analyses), corresponding to a difference of 2.6 percentage points or a reduction in the risk of death of 17.5%. The mortality rate for salmeterol alone or fluticasone propionate alone did not differ significantly from that for placebo. As compared with placebo, the combination regimen reduced the annual rate of exacerbations from 1.13 to 0.85 and improved health status and spirometric values ($P<0.001$ for all comparisons with placebo). There was no difference in the incidence of ocular or bone side effects. The probability of having pneumonia reported as an adverse event was higher among patients receiving medications containing fluticasone propionate (19.6% in the combination-therapy group and 18.3% in the fluticasone group) than in the placebo group (12.3%, $P<0.001$ for comparisons between these treatments and placebo). **CONCLUSIONS:** The reduction in death from all causes among patients with COPD in the combination-therapy group did not reach the predetermined level of statistical significance. There were significant benefits in all other outcomes among these patients. (ClinicalTrials.gov number, NCT00268216 [ClinicalTrials.gov]).

9. D'Urzo, A., J. P. Karpel, et al. (2005). "Efficacy and safety of mometasone furoate administered once-daily in the evening in patients with persistent asthma dependent on inhaled corticosteroids." *Curr Med Res Opin* 21(8): 1281-9.

BACKGROUND: Once-daily dosing with an inhaled corticosteroid (ICS) may simplify asthma management and improve patient compliance. Since asthma is frequently worse at night, evening dosing appears to be a more obvious choice to accommodate the

chronobiology of asthma than morning dosing. **OBJECTIVE:** The primary study objective was to compare the efficacy and safety of mometasone furoate (MF) dry powder inhaler (MF-DPI) 400 microg qd PM (one 400 microg inhalation) with placebo for the treatment of asthma in patients previously dependent on twice a day (bid, bis in die) ICS therapy. We also compared different regimens of MF-DPI with each other and with placebo. **METHODS:** This 12-week, multicenter, double-blind, placebo-controlled study evaluated lung function and asthma symptoms in 400 subjects with persistent asthma randomized to MF-DPI 200 microg qd (once a day, quaque die) PM, 400 microg qd PM as one inhalation from a 400 microg device, 400 microg qd PM as two inhalations from a 200 microg device, 200 microg twice daily (bid), or placebo. Evening doses were to be taken in the late afternoon or early evening, preferably before dinner time. **RESULTS:** Mean changes from baseline at endpoint in FEV₁ (forced expiratory volume in 1 s) were similar for MF-DPI 400 microg qd PM (one inhalation; 0.41 L), MF-DPI 400 microg qd PM (2 inhalations; 0.49 L), MF-DPI 200 microg qd PM (0.41 L), and MF-DPI 200 microg bid (0.51 L); and all were significantly improved compared with placebo (0.16 L; $p < 0.001$). Secondary efficacy variables, including nocturnal awakenings and use of rescue albuterol, were also significantly improved with MF-DPI treatment compared with placebo. All treatments were generally safe and well tolerated, with adverse events of mild to moderate severity. **CONCLUSIONS:** Once-daily evening dosing of MF-DPI at doses of 400 and 200 microg restored lung function and improved nocturnal and daytime symptom control in subjects with asthma previously dependent on bid ICS therapy. Comparable effectiveness of a total daily dose of 400 microg was demonstrated between once daily in the evening and twice-daily administration. The results also confirm the effectiveness of MF-DPI 200 microg qd PM, the lowest dose studied.

10. Gartlehner, G., R. A. Hansen, et al. (2006). "Efficacy and safety of inhaled corticosteroids in patients with COPD: a systematic review and meta-analysis of health outcomes." *Ann Fam Med* 4(3): 253-62.

PURPOSE: We wanted to review systematically the efficacy, effectiveness, and safety of inhaled corticosteroids with respect to health outcomes in patients with chronic obstructive pulmonary disease (COPD). **METHODS:** We searched MEDLINE, EMBASE, The Cochrane Library, and the International Pharmaceutical Abstracts to identify relevant articles. We limited evidence to double-blinded randomized controlled trials (RCTs) for efficacy, but we also reviewed observational evidence for safety. Outcomes of interest were overall mortality, exacerbations, quality of life, functional capacity, and respiratory tract symptoms. When possible, we pooled data to estimate summary effects for each outcome. **RESULTS:** Thirteen double-blinded RCTs determined the efficacy of an inhaled corticosteroid compared with placebo; 11 additional studies assessed the safety of inhaled corticosteroid treatment in patients with asthma or COPD. Overall, COPD patients treated with inhaled corticosteroids experienced significantly fewer exacerbations than patients taking placebo (relative risk [RR] = 0.67; 95% CI, 0.59-0.77). No significant difference could be detected for overall mortality (RR = 0.81; 95% CI, 0.60-1.08). Evidence on quality of life, functional capacity, and respiratory tract symptoms is mixed. Adverse events were generally tolerable; pooled discontinuation rates did not differ significantly between inhaled

corticosteroid and placebo treatment groups (RR = 0.92; 95% CI, 0.74-1.14). Observational evidence, however, indicates a dose-related risk of cataract and open-angle glaucoma. Severe adverse events, such as osteoporotic fractures, are rare; the clinical importance of the additional risk is questionable. **CONCLUSIONS:** Overall, the risk-benefit ratio appears to favor inhaled corticosteroid treatment in patients with moderate to severe COPD. Existing evidence does not indicate a treatment benefit for patients with mild COPD.

11. Gluck, P. A. and J. C. Gluck (2005). "A review of pregnancy outcomes after exposure to orally inhaled or intranasal budesonide." *Curr Med Res Opin* 21(7): 1075-84.

BACKGROUND: Inadequately controlled rhinitis is associated with worsening asthma, one of the most common potentially serious causes of pregnancy complications. Recent evidence-based guidelines now stress the importance of inhaled corticosteroids as first-line therapy in controlling asthma during pregnancy, with preference given to budesonide. Both inhaled and intranasal budesonide formulations are rated Pregnancy Category B; all other inhaled and intranasal corticosteroids are rated Pregnancy Category C. **OBJECTIVE:** To review data from clinical and epidemiological studies investigating the effects of orally inhaled or intranasal budesonide on pregnancy outcomes.

METHODS: Clinical and epidemiological studies on the effects of maternal exposure to orally inhaled or intranasal budesonide were identified through searches of the literature indexed on Medline or the Developmental and Reproductive Toxicology (DART) database through January 2005. The search terms used were: 'budesonide' and 'pregnancy'; 'pregnancy complications'; 'teratogens'; 'fetus'; 'embryo'; or 'toxicology'. The search was limited to English-language articles and those evaluating humans. Pertinent abstracts were identified from recent US asthma and allergy meetings. **RESULTS:** A total of five articles and three abstracts meeting the search criteria were identified.

Retrospective epidemiological studies and a randomized, placebo-controlled, multicenter trial found no clinically or statistically significant effects on fetal outcomes among more than 6600 infants whose mothers were exposed to orally inhaled budesonide during pregnancy. Women who reported use of orally inhaled budesonide either during early pregnancy only or throughout pregnancy gave birth to infants of normal gestational age, birth weight, and length, with no increased rate of stillbirths, multiple births, or congenital malformations. In a retrospective case-control analysis, no association was found between inhaled budesonide or intranasal budesonide and the overall rate of infant cardiovascular defects. However, a marginally increased risk of less severe cardiovascular defects (odds ratio = 1.58, 95% confidence interval 1.02 to 2.46) was observed with intranasal budesonide in one analysis, possibly the result of a random association due to multiple testing or an unidentified confounder. **CONCLUSION:**

Maternal exposure to orally inhaled budesonide during pregnancy is not associated with an increased risk of congenital malformations or other adverse fetal outcomes in studies of more than 6600 infants. Data on pregnancy outcomes after maternal exposure to intranasal budesonide are limited, but the totality of evidence, including pharmacological studies showing a much lower systemic exposure after intranasal administration, indicates its safety profile is at least comparable with that of orally inhaled budesonide.

12. Guilbert, T. W., W. J. Morgan, et al. (2006). "Long-term inhaled corticosteroids in preschool children at high risk for asthma." *N Engl J Med* 354(19): 1985-97.

BACKGROUND: It is unknown whether inhaled corticosteroids can modify the subsequent development of asthma in preschool children at high risk for asthma.

METHODS: We randomly assigned 285 participants two or three years of age with a positive asthma predictive index to treatment with fluticasone propionate (at a dose of 88 mug twice daily) or masked placebo for two years, followed by a one-year period without study medication. The primary outcome was the proportion of episode-free days during the observation year. **RESULTS:** During the observation year, no significant differences were seen between the two groups in the proportion of episode-free days, the number of exacerbations, or lung function. During the treatment period, as compared with placebo use, use of the inhaled corticosteroid was associated with a greater proportion of episode-free days ($P=0.006$) and a lower rate of exacerbations ($P<0.001$) and of supplementary use of controller medication ($P<0.001$). In the inhaled-corticosteroid group, as compared with the placebo group, the mean increase in height was 1.1 cm less at 24 months ($P<0.001$), but by the end of the trial, the height increase was 0.7 cm less ($P=0.008$). During treatment, the inhaled corticosteroid reduced symptoms and exacerbations but slowed growth, albeit temporarily and not progressively. **CONCLUSIONS:** In preschool children at high risk for asthma, two years of inhaled-corticosteroid therapy did not change the development of asthma symptoms or lung function during a third, treatment-free year. These findings do not provide support for a subsequent disease-modifying effect of inhaled corticosteroids after the treatment is discontinued. (ClinicalTrials.gov number, NCT00272441.).

13. Hampel, F. C., Jr., M. Sugar, et al. (2004). "Once-daily budesonide inhalation powder (Pulmicort Turbuhaler) improves health-related quality of life in adults previously receiving inhaled corticosteroids." *Adv Ther* 21(1): 27-38.

In the treatment of asthma, the conventional measures used to monitor a patient's progress and health status do not address the impact of functional impairments associated with the disease that may affect the patient's daily life. Unlike those measures, health-related quality of life (HRQL) reflects the physical, psychological, and social difficulties a patient perceives on a day-to-day basis. This study was conducted to determine the effects of once-daily budesonide inhalation powder via the Pulmicort Turbuhaler on the HRQL in adult patients with asthma previously treated with other inhaled corticosteroids. A total of 184 patients 18 to 70 years of age who previously received inhaled corticosteroids were enrolled in this double-blind, placebo-controlled, parallel-group, multicenter study. Patients were randomly assigned to budesonide 400 microg once daily or to placebo for 12 weeks. Each patient's HRQL was assessed at randomization and at weeks 4 and 12 with the Asthma Quality of Life Questionnaire (AQLQ). More patients receiving budesonide than those receiving placebo reported statistically significant ($P < \text{or} = .05$) improvements in HRQL at weeks 4 and 12. With the exception of the domain pertaining to exposure to environmental stimuli, differences from placebo in overall AQLQ scores and individual domain scores were clinically important ($> \text{or} = 0.5$ units). In addition, 2.4 patients needed to be treated with once-daily budesonide for 1 patient to demonstrate clinically important improvement. Budesonide 400 microg administered once daily via the Pulmicort Turbuhaler provides statistically significant and clinically

important HRQL benefit in adult patients with asthma previously receiving inhaled corticosteroids.

14. Karpel, J. P., W. W. Busse, et al. (2005). "Effects of mometasone furoate given once daily in the evening on lung function and symptom control in persistent asthma." *Ann Pharmacother* 39(12): 1977-83.

BACKGROUND: The chronobiology of asthma suggests that, for once-daily dosing, an evening dose may be the most effective treatment paradigm. **OBJECTIVE:** To evaluate the efficacy and safety of mometasone furoate dry powder inhaler (MF-DPI) administered once daily in the evening or twice daily in patients with asthma previously maintained on twice-daily regimens of inhaled corticosteroids. **METHODS:** In this 12-week, multicenter, placebo-controlled trial, 268 subjects \geq 12 years of age with inhaled corticosteroid-dependent asthma and baseline forced expiratory volume in 1 second (FEV(1)) between 50% and 85% of predicted were randomized to receive treatment with MF-DPI 400 mug once daily in the evening, MF-DPI 200 mug twice daily, or placebo. The primary efficacy variable was mean change in FEV(1) from baseline to endpoint. Other lung function measures, asthma symptoms, quality of life, and rescue medication use also were assessed. **RESULTS:** At endpoint, mean FEV(1) was significantly improved with both MF-DPI doses compared with placebo ($p < 0.001$). The 2 active treatment groups were statistically indistinguishable from each other. Secondary efficacy variables, including nocturnal awakenings, asthma worsenings, quality of life, and rescue medication use, were also significantly improved for both MF-DPI treatments compared with placebo. Both dosages were well tolerated; no clinically meaningful changes in laboratory values or vital signs were observed. **CONCLUSIONS:** MF-DPI 400 mug once daily in the evening was as effective as MF-DPI 200 mug twice daily in improving pulmonary function, asthma symptoms, and quality of life compared with placebo in subjects previously using twice-daily regimens of an inhaled corticosteroid.

15. Lasserson, T. J., C. K. Cates, et al. (2006). "Fluticasone versus HFA-beclomethasone dipropionate for chronic asthma in adults and children." *Cochrane Database Syst Rev*(2): CD005309.

BACKGROUND: The relative efficacy of fluticasone (FP) and beclomethasone (BDP) propelled with CFCs has been well established. The potency of HFA-BDP is thought to have been improved with new propellant and some studies suggest that it may equipotent at half the dose of CFC propelled-BDP. There is a need to revisit this question in the light of a potentially more potent new non-CFC propellant. **OBJECTIVES:** To determine the relative efficacy of FP and HFA-propelled BDP in chronic asthma. **SEARCH STRATEGY:** The Cochrane Airways Group Specialised Register was searched using pre-specified terms. Searches were current as of January 2006. **SELECTION CRITERIA:** Randomised controlled trials were eligible for inclusion in the review. We compared either CFC or HFA-propelled FP with HFA-propelled BDP. We made a distinction between HFA-BDP and HFA-BDP extra fine, which dispenses smaller particles of drug, leading to different, usually more peripheral distribution in the airways. Any inhaler device was considered, and there was no restriction on studies with or without spacers. We included studies which assessed HFA-BDP given via either pMDI, breath-actuated MDI, or DPI. **DATA COLLECTION AND ANALYSIS:** Two reviewers independently

assessed studies for inclusion in the review. Data were extracted and entered in to RevMan 4.2 using standard meta-analytical techniques with predefined criteria for exploring statistical heterogeneity. **MAIN RESULTS:** Eight studies (1260 participants) met the inclusion criteria of the review. One study was conducted in children. Study reporting quality was fair, but all studies were of short duration (three to twelve weeks). Only studies assessing HFA-BDP extra fine in comparison with FP were identified. Lung function was not significantly different between extra fine BDP and FP when compared at the same dose in parallel studies, change in FEV1: 0.04 litres (95% CI -0.03 to 0.11 litres; three studies, 659 adults); change in am PEF: -0.69 litres (95% CI -11.21 to 9.83 litres; two studies, 364 adults). Individual studies reported non-significant findings in symptom scores and quality of life questionnaires. There was no significant difference between FP and HFA-BDP in the risk of study withdrawal, dysphonia or when data were reported as any adverse event. **AUTHORS' CONCLUSIONS:** There was no significant difference between FP and extra fine HFA-BDP on FEV(1) or peak flow at a dose ratio of 1:1. However, the number of studies and width of the confidence intervals in the analyses do not exclude a clinically meaningful difference between these two drugs. Difficulty in the successful manipulation of the devices studied may be a barrier to the widespread use of MDIs. One paediatric study was included in the review, so extrapolation of the findings of this review to children is limited. Further longer term studies in adults and children with moderate and severe asthma are required.

16. Lumry, W. R., M. M. Conway, et al. (2006). "Fluticasone propionate hydrofluoroalkane inhalation aerosol in patients receiving inhaled corticosteroids." *Ann Allergy Asthma Immunol* 96(1): 51-9.

BACKGROUND: Inhaled corticosteroids (ICSs) delivered by metered-dose inhalers that contain chlorofluorocarbon propellants are being discontinued because of the harmful effects of chlorofluorocarbon on the ozone layer. Therefore, some metered-dose inhaler products are being reformulated with "ozone-friendly" hydrofluoroalkane propellants.

OBJECTIVE: To evaluate treatment with fluticasone propionate hydrofluoroalkane inhalation aerosol, 88, 220, and 440 microg twice daily, vs placebo in patients with asthma receiving an ICS. **METHODS:** Randomized, double-blind, parallel-group, 12-week study. **RESULTS:** Mean morning predose percent predicted forced expiratory volume in 1 second increased by 2.2%, 3.2%, and 4.6% in the fluticasone propionate, 88-, 220-, and 440-microg twice-daily, groups, respectively, compared with an 8.3% decrease for placebo ($P < .001$ vs placebo for all groups). Secondary pulmonary function end points and asthma symptoms showed similar improvements compared with placebo. Discontinuation from the study due to lack of efficacy was 50% in the placebo group and 11%, 10%, and 6% in the fluticasone propionate, 88-, 220-, and 440-microg twice-daily, groups, respectively. At week 12, the probability of remaining in the study was 0.89, 0.90, and 0.94 for the fluticasone propionate, 88-, 220-, and 440-microg twice-daily, groups, respectively, vs 0.45 for the placebo group ($P < .001$ for all). Changes in 24-hour urinary cortisol excretion rates were similar among treatment groups. **CONCLUSIONS:** Fluticasone propionate hydrofluoroalkane, previously shown to be a clinically suitable alternative to fluticasone propionate chlorofluorocarbon, was effective and well tolerated. The ability to switch from fluticasone propionate chlorofluorocarbon and other chlorofluorocarbon-containing ICSs to fluticasone propionate hydrofluoroalkane without

sacrificing asthma control or tolerability will facilitate a smooth transition to this nonchlorofluorocarbon-containing medicinal.

17. O'Byrne, P. M., S. Pedersen, et al. (2006). "Effects of early intervention with inhaled budesonide on lung function in newly diagnosed asthma." *Chest* 129(6): 1478-85.
STUDY OBJECTIVES: Asthmatic patients lose lung function faster than normal subjects. The effectiveness of early intervention with inhaled corticosteroids on this decline in lung function is not established in recent-onset disease. **DESIGN:** The Inhaled Steroid Treatment as Regular Therapy in Early Asthma study was a randomized, double-blind study in 7,165 patients (5 to 66 years old), with persistent asthma for < 2 years to determine whether early intervention with low-dose inhaled budesonide prevents severe asthma-related events and the decline in lung function. Patients received budesonide (200 mug qd for children < 11 years old and 400 mug qd for others) or placebo for 3 years in addition to usual asthma medications. **RESULTS:** Treatment with budesonide significantly improved prebronchodilator and postbronchodilator FEV(1) percentage of predicted and reduced the mean declines from baseline for postbronchodilator FEV(1) at 1 year and 3 years: - 0.62% and - 1.79% for budesonide and - 2.11% and - 2.68% for placebo, respectively (p < 0.001). The decline was more marked for male patients, active smokers, and patients > 18 years old, and the smallest treatment effects were in adolescents. **CONCLUSIONS:** Long-term, once-daily treatment with low-dose budesonide improved both prebronchodilator and postbronchodilator FEV(1) in patients with recent-onset, persistent asthma, and reduced the loss of lung function over time.

18. Pinna, J. L., M. J. Noonan, et al. (2005). "Fluticasone propionate HFA-134a pressurized metered-dose inhaler in adolescents and adults with moderate to severe asthma." *J Asthma* 42(10): 865-71.
In this randomized, double-blind, placebo-controlled trial, 397 patients with moderate to severe asthma, previously treated with bronchodilators alone, received fluticasone propionate 88, 220, or 440 microg twice daily, or placebo via metered dose inhaler (MDI) for 12 weeks. Mean change from baseline to endpoint in pre-dose percent predicted forced expiratory volume in one second (FEV1) was greater (p < 0.001) in each fluticasone propionate group (9.0%, 88 microg bid; 9.8%, 220 microg bid; 11.2%, 440 microg bid) versus placebo (3.4%). Morning and evening peak expiratory flow (PEF), asthma symptoms, and supplemental albuterol use also improved in all fluticasone propionate groups versus placebo. The incidence of adverse events and 24-hour urine cortisol excretion rates were similar between active treatments and placebo.

19. Silverman, M., A. Sheffer, et al. (2005). "Outcome of pregnancy in a randomized controlled study of patients with asthma exposed to budesonide." *Ann Allergy Asthma Immunol* 95(6): 566-70.
BACKGROUND: Budesonide is the only inhaled corticosteroid to be given a category B pregnancy rating by the US Food and Drug Administration, based on observational data from the Swedish Medical Birth Registry. However, data from large randomized controlled trials are lacking. **OBJECTIVE:** To compare pregnancy outcomes among patients with recent-onset mild-to-moderate persistent asthma receiving low-dose budesonide vs placebo. **METHODS:** In a randomized, double-blind, placebo-controlled

trial, 7241 patients aged 5 to 66 years with mild-to-moderate persistent asthma for less than 2 years and no previous regular corticosteroid therapy received once-daily budesonide or placebo via dry powder inhaler in addition to their usual asthma medication for 3 years. This trial was followed by a 2-year open-label treatment period. The daily dose of budesonide was 400 microg for adults. The study included 2473 females aged 15 to 50 years at randomization. Pregnancy was not an exclusion criterion (except for U.S. patients). RESULTS: Of 319 pregnancies reported, 313 were analyzed. Healthy children were delivered in 81% and 77% of all pregnancies in the budesonide and placebo groups, respectively. Of the 196 pregnancies reported by participants taking budesonide, 38 (19%) had adverse outcomes: 23 (12%) had miscarriages, 3 (2%) had congenital malformations, and 12 (6%) had other outcomes. Of the 117 pregnancies reported in the placebo group, 27 (23%) had adverse outcomes: 11 (9%) had miscarriages, 4 (3%) had congenital malformations, and 12 (10%) had other outcomes. CONCLUSIONS: Treatment with low-dose inhaled budesonide in females with mild-to-moderate persistent asthma does not seem to affect the outcome of pregnancy.

20. Sin, D. D., L. Wu, et al. (2005). "Inhaled corticosteroids and mortality in chronic obstructive pulmonary disease." *Thorax* 60(12): 992-7.

BACKGROUND: Clinical studies suggest that inhaled corticosteroids reduce exacerbations and improve health status in chronic obstructive pulmonary disease (COPD). However, their effect on mortality is unknown. METHODS: A pooled analysis, based on intention to treat, of individual patient data from seven randomised trials (involving 5085 patients) was performed in which the effects of inhaled corticosteroids and placebo were compared over at least 12 months in patients with stable COPD. The end point was all-cause mortality. RESULTS: Overall, 4% of the participants died during a mean follow up period of 26 months. Inhaled corticosteroids reduced all-cause mortality by about 25% relative to placebo. Stratification by individual trials and adjustments for age, sex, baseline post-bronchodilator percentage predicted forced expiratory volume in 1 second, smoking status, and body mass index did not materially change the results (adjusted hazard ratio (HR) 0.73; 95% confidence interval (CI) 0.55 to 0.96). Although there was considerable overlap between subgroups in terms of effect sizes, the beneficial effect was especially noticeable in women (adjusted HR 0.46; 95% CI 0.24 to 0.91) and former smokers (adjusted HR 0.60; 95% CI 0.39 to 0.93).

CONCLUSIONS: Inhaled corticosteroids reduce all-cause mortality in COPD. Further studies are required to determine whether the survival benefits persist beyond 2-3 years.

21. Tan, W. C., C. J. Lamm, et al. (2006). "Effectiveness of early budesonide intervention in Caucasian versus Asian patients with asthma: 3-year results of the START study." *Respirology* 11(6): 767-75.

OBJECTIVE AND BACKGROUND: Few studies have assessed the effectiveness of inhaled corticosteroid therapy exclusively in Asian patients with asthma. The present analysis compared the efficacy of early intervention with inhaled budesonide in Caucasian and Asian patients over the first 3 years of the inhaled Steroid Treatment As Regular Therapy in early asthma study. METHODS: Patients aged 5-66 years with mild persistent asthma of <or=2 years' duration were randomized to 3 years of double-blind treatment with once-daily budesonide 200 microg (for patients aged<11 years) or 400

microg administered via Turbuhaler or placebo, plus usual asthma therapy. RESULTS: Budesonide significantly improved asthma outcomes in both Caucasian (n=4661) and Asian (n=1995) patients compared with reference therapy (placebo plus usual asthma therapy). Budesonide reduced the risk of a first severe asthma-related event by 42% and 49% in Caucasian and Asian patients, respectively, over the 3-year treatment period ($P < 0.001$ for both). Moreover, budesonide significantly increased symptom-free days, decreased nights with sleeping problems, improved pre- and postbronchodilator FEV1 and reduced the need for additional asthma medications of particular drug classes compared with reference therapy. Except for differences in the patterns of use of additional asthma medications, outcomes with budesonide and overall adverse events were similar in the Caucasian and Asian patient populations. CONCLUSION: Inhaled budesonide administered once daily in Asian patients with recent-onset, mild persistent asthma significantly improved asthma control and pulmonary function compared with reference therapy. Moreover, this effectiveness paralleled that observed in Caucasian patients.