Effect of fluticasone propionate and salmeterol in a single device, fluticasone propionate, and montelukast on overall asthma control, exacerbations, and costs


Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The use of three alternative first-line maintenance treatments for asthma control:

- fluticasone propionate (100 microg) and salmeterol (50 microg) administered twice daily from a single discus (FP-S);
- fluticasone propionate (FP; 100 microg); and
- montelukast (MO; 10 mg).

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised patients aged 15 years or older with a diagnosis of asthma, as defined by the American Thoracic Society, for at least 6 months. Patients were required to demonstrate a pre-dose forced expiratory volume in one second (FEV1) of 50 to 80% of predicted and an increase in FEV1 of 15% or more after 2 inhalations (180 microg) of albuterol. All patients had used only an inhaled or oral short-acting beta2-agonist on a regular or as-needed basis during the 3 months. Exclusion criteria included the use of ICSs within 2 months of screening, pregnancy, use of tobacco products in the previous year, a smoking history of 10 packs or more, and hospitalisation for asthma within 3 months of screening. A further exclusion criterion was hypersensitivity to any beta2-agonist, sympathomimetic drug, leukotriene antagonist, or corticosteroid.

Setting
The setting was primary care. The economic study was carried out in the USA.

Dates to which data relate
The effectiveness and resource use data were gathered from studies published in 2001 and 2002. The price year was 2002.

Source of effectiveness data
The effectiveness evidence was derived from a synthesis of published studies.

Outcomes assessed in the review
The outcomes estimated were:

- the changes in FEV1 and FEV1 (percentage of predicted),
- morning and evening peak expiratory flow rate (PEFR),
- the total symptom score,
- the percentage of symptom-free days (SFDs),
- albuterol use,
- the proportion of rescue-free days,
- night-time awakenings,
- the proportion of awakening-free nights, and
- the risk of exacerbations (which were defined as an event that required an emergency department visit or hospitalisation, an unscheduled physician visit, or treatment with oral or parenteral corticosteroids).

**Study designs and other criteria for inclusion in the review**

It was unclear whether a systematic review of the literature was undertaken to identify primary studies. Only randomised clinical trials (RCTs) were included in the review. The characteristics of the patients were similar among the 4 trials selected and details for each study were provided. However, the 4 trials presented different comparisons of the three strategies investigated (FP-S, FP and MO) and different lengths of follow-up. All trials were based on an intention to treat analysis.

**Sources searched to identify primary studies**

Not stated.

**Criteria used to ensure the validity of primary studies**

The validity of the primary studies was ensured by selecting only RCTs.

**Methods used to judge relevance and validity, and for extracting data**

Not stated.

**Number of primary studies included**

Four primary studies were included in the review.

**Methods of combining primary studies**

Groups of patients receiving the same treatment were pooled. The effectiveness results were analysed using covariance models that adjusted for study, investigative site and baseline value. Pooling together the 4 trials led to a total of 427 patients in the FP-S group, 529 patients in the FP group, and 954 patients in the MO group. The patients’ characteristics were similar among the three groups.

**Investigation of differences between primary studies**

The authors stated that similar inclusion and exclusion criteria were used in the 4 trials. In addition, follow-up data were examined at 12 weeks in order to make the results of the studies comparable.
Results of the review
The change in FEV1 was 24.2% in the FP-S group, 22% in the FP group, and 13.4% in the MO group, (p<0.05 for FP-S versus FP and MO).

The change in FEV1 (percentage of predicted) was 15.5% in the FP-S group, 13.6% in the FP group, and 8.4% in the MO group, (p<0.05 for FP-S versus FP and MO).

The change in morning PEFR (L/minute) was 84.9 in the FP-S group, 56 in the FP group, and 36.1 in the MO group, (p<0.05 for FP-S versus FP and MO).

The change in evening PEFR (L/minute) was 65.9 in the FP-S group, 44.7 in the FP group, and 29.6 in the MO group, (p<0.05 for FP-S versus FP and MO).

The change in total symptom score was -1 in the FP-S group, -0.8 in the FP group, and -0.6 in the MO group, (p<0.01 for FP-S versus MO).

The change in percentage of SFDs was 43.6% in the FP-S group, 28.4% in the FP group, and 20.2% in the MO group, (p<0.001 for FP-S versus FP and MO).

The change in albuterol use (puffs/24 hour) was -3.4 in the FP-S group, -2.9 in the FP group, and -2.1 in the MO group, (p<0.05 for FP-S versus FP and MO).

The change in the proportion of rescue-free days was 52.2% in the FP-S group, 40.5% in the FP group, and 27.1% in the MO group, (p<0.05 for FP-S versus FP and MO).

The change in the number of night-time awakenings was -0.8 in the FP-S group, -0.6 in the FP group, and -0.5 in the MO group, (p<0.001 for FP-S versus MO).

The change in the proportion of awakening-free nights was 27.4% in the FP-S group, 27.4% in the FP group, and 18.1% in the MO group, (p<0.001 for FP-S versus MO).

Compared with FP-S patients, FP patients had a 2.6 (95% confidence interval, CI: 1.04 - 6.61) times greater risk of exacerbations, while MO patients had a 3.6 (95% CI: 1.54 - 8.57) times greater risk of exacerbations within 12 weeks of starting therapy. Further, the regression analysis showed that more patients were withdrawn from the studies because of asthma exacerbations with the use of MO and FP than with the use of FP-S, (p<0.04).

Measure of benefits used in the economic analysis
The health outcomes were left disaggregated and no summary benefit measure was used in the economic evaluation. In effect, a cost-consequences analysis was carried out.

Direct costs
Discounting was not relevant because of the short timeframe of the analysis (12 weeks). The unit costs were presented but the quantities of resources used were not. The economic evaluation considered only the costs of the medications under examination and the costs associated with an asthma exacerbation, such as physician office visit, emergency department visit and hospitalisation. The cost/resource boundary of the study was not explicitly reported. Resource use was estimated from a retrospective review of resource consumption for the patients included in the 4 trials that provided the clinical evidence. The costs were estimated from a published study and from average wholesale prices. The analysis assumed 100% compliance with therapy. The price year was 2002.

Statistical analysis of costs
The costs were treated deterministically.
**Indirect Costs**
The indirect costs were not considered in the economic evaluation.

**Currency**
US dollars ($).

**Sensitivity analysis**
Sensitivity analyses were not carried out.

**Estimated benefits used in the economic analysis**
See the 'Effectiveness Results' section.

**Cost results**
The mean daily wholesale price of maintenance drug therapy was $3.72 for FP-S, $2.91 for MO and $1.78 for FP.

The mean daily exacerbation costs for all patients in the 4 studies were $0.41 for FP-S, $4.60 for FP and $7.57 for MO.

In addition, the mean daily exacerbation costs for only those patients who experienced an exacerbation were $29 for FP-S, $128 for FP and $154 for MO.

**Synthesis of costs and benefits**
A synthesis of costs and benefits was not relevant since a cost-consequences analysis was carried out.

**Authors' conclusions**
The combination of fluticasone propionate plus salmeterol (FP-S) as first-line maintenance therapy for asthma control in patients previously symptomatic while taking beta2-agonists was more effective than fluticasone propionate (FP) or montelukast (MO). In addition, it was associated with lower exacerbation-related costs, owing to fewer and less severe exacerbation episodes.

**CRD COMMENTARY - Selection of comparators**
The selection of the comparators was appropriate as all of them reflected actual maintenance treatment strategies for patients with persistent asthma. The dosages used were clearly reported. You should decide whether they are valid comparators in your own setting.

**Validity of estimate of measure of effectiveness**
The effectiveness evidence came from a combination of data extracted from 4 clinical trials. The authors did not state whether a systematic review of the literature had been undertaken to identify the studies. The results of the studies were pooled depending on the treatment received, and appropriate regression models were used to adjust for differences among the 4 trials. The authors stated that the designs and methodological characteristics of the primary studies were comparable. The validity of the primary studies was ensured by the use of RCTs. Characteristics of each study (i.e. study samples and patient details) were provided. The authors pointed out a potential limitation of their analysis in that there was a lack of head-to-head comparisons of the three treatment groups.

**Validity of estimate of measure of benefit**
No summary benefit measure was used in the analysis because a cost-consequences analysis was conducted. Please refer to the comments in the 'Validity of estimate of measure of effectiveness' field (above).
Validity of estimate of costs
The perspective of the study was unclear and only the direct medical costs associated with maintenance therapy were considered in the study. The unit costs were presented but there were no details on the quantities of resources used. This reduces the possibility of replicating the study in other settings. The source of the economic data was reported. Resource use was based on patient-level data. The price year was reported, which aids reflation exercises in other settings. The cost estimates were treated deterministically and were specific to the study setting. In effect, no sensitivity analyses were carried out.

Other issues
The authors reported the results from two published studies and stated that their findings were consistent with previous investigations. The issue of the generalisability of the study results to other settings was not addressed and sensitivity analyses were not carried out. Thus, the external validity of the study was limited. The authors stated that the superior efficacy of FP-S was probably because the combined strategy treated both of the main components of asthma (inflammation and smooth muscle dysfunction). The study referred to patients with persistent asthma and this was reflected in the authors’ conclusions.

Implications of the study
The study results supported the use of FP-S as first-line maintenance therapy for asthma control in patients previously using beta2-agonists.

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Funded by grants from GlaxoSmithKline.

Bibliographic details

Other publications of related interest


Indexing Status
Subject indexing assigned by NLM

MeSH
Acetates /administration & dosage /economics; Administration, Inhalation; Adolescent; Adrenal Cortex Hormones