Maintenance plus reliever budesonide/formoterol compared with a higher maintenance dose of budesonide/formoterol plus formoterol as reliever in asthma: an efficacy and cost-effectiveness study

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 study examined three strategies for the treatment of asthma:

- budesonide/formoterol 160/4.5 microgram once daily plus additional doses as needed (1xSMART);
- budesonide/formoterol 160/4.5 microgram twice daily plus additional doses as needed (2xSMART);
- budesonide/formoterol two doses of 160/4.5 microgram twice daily plus formoterol 4.5 microgram as needed (2x2FIX+F).

Children aged 6 to 11 years old used the 80/4.5 microgram formulation of budesonide/formoterol with the same number of doses in each treatment strategy as the older patients.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised patients from the age of 6 years with asthma. The article stipulated that the patients should be not well-controlled on maintenance therapy with inhaled corticosteroids (ICS) or should be well-controlled on a combination of ICS and long-acting inhaled beta2-antagonist. Patients should present a forced expiratory volume in 1 second of at least 60% of predicted normal after inhalation of a short-acting inhaled beta2-antagonist. Patients with a smoking history of more than 10 pack-years were excluded.

Setting
The setting was primary or secondary care in an outpatient context. The economic study was carried out in Sweden.

Dates to which data relate
The dates when the effectiveness and resource use data were gathered were not reported. The price year was 2004.

Link between effectiveness and cost data
The costing was carried out prospectively on the same sample of patients that provided the effectiveness data.
Study sample
Power calculations were performed in the preliminary phase of the study on the basis of one of the primary clinical outcomes, the Asthma Control Questionnaire (ACQ). The calculations suggested that, assuming a specific change in ACQ and an expected drop-out rate, a sample size of 465 patients would provide a power of 80% at a 5% significance level. A total of 590 patients were initially identified according to specific inclusion criteria and were considered for a 2-week run-in period. However, 64 discontinued and a further 35 did not fulfill eligibility criteria for the run-in phase (prior use of medications or symptoms). Therefore, a sample of 491 patients was finally allocated to the three treatment arms. There were 164 patients (49% men) in the 2x2FIX+F group, 165 (49% men) in the 2xSMART group, and 162 (43% men) in the 1xSMART group. The mean age was 40.8 (+/- 19.9) years (age range: 6 to 82) in the 2x2FIX+F group, 38.2 (+/- 20.6) years (age range: 6 to 79) in the 2xSMART group, and 39.7 (+/- 19.6) years (age range: 7 to 78) in the 1xSMART group. However, data post-randomisation were not available for 2 patients, thus the analysis of effectiveness was based on 489 patients. No patients changed their maintenance medication during the study-period.

Study design
This was a prospective, open-label, randomised, parallel-group clinical trial, which was carried out at 53 primary health care centres or hospitals in Sweden. Each participating centre had two randomised lists, one for patients aged 12 years or older and another for children aged 6 to 11 years. Random allocation was based on a computer-generated programme. The length of follow-up was 6 months. The number of patients who discontinued was 21 in the 2x2FIX+F group, 14 in the 2xSMART group, and 26 in the 1xSMART group. Reasons for discontinuations were multiple, such as loss to follow-up (only 2 patients in each treatment group), adverse events, or eligibility criteria not fulfilled.

Analysis of effectiveness
The primary clinical end points were the change in ACQ from baseline to the last visit and the change in morning peak expiratory flow (PEF) from baseline to treatment. The former (change in ACQ) included 5 of the 7 questions in the original questionnaire and was self-administered at the clinic visits. The latter (change in PEF) was measured using a Mini Wright PEF Meter for 4 weeks and then for 14 days prior to the clinic visits after 12 and 24 weeks. Several secondary efficacy variables were also used in the analysis, such as:

- the change in the overall and domain scores of the Standardized Asthma Quality of Life Questionnaire from baseline to the last visit;
- the change in the overall and domain scores of the Standardized Pediatric Asthma Quality of Life Questionnaire from baseline to last visit;
- the change in the overall and domain scores of the Satisfaction of Asthma Treatment Questionnaire from baseline to the last visit;
- the rating of asthma status;
- the number of inhalations of maintenance and as-needed medication in diary card data;
- the percentage of asthma controlled days; and
- the time to first asthma exacerbation and the rate of exacerbation per 6 months.

Asthma- and non asthma-related serious adverse events were finally collected. The analysis appears to have been conducted on an intention to treat basis. At baseline, the study groups were well matched with respect to their demographics and disease characteristics.

Effectiveness results
No statistically significant differences between groups were observed in terms of the ACQ, although clinically important improvements were observed in all groups.
The mean morning PEF values increased (from baseline to treatment) from 418 to 434 L/minute in the 2x2DIX+F group, from 429 to 435 L/minute in the 2xSMART group, and from 412 to 415 L/minute in the 1xSMART group.

There were statistically significantly greater increases with the 2x2DIX+F group of 9 L/minute versus the 2xSMART group, (p=0.006) and of 12 L/minute versus the 1xSMART group, (p<0.001).

The difference between the two SMART groups did not reach statistical significance.

Time to first exacerbation and number of exacerbations were comparable between groups. Similarly, no differences in asthma quality of life were observed.

An increase in asthma controlled days from run-in to treatment was observed in the 2x2DIX+F group (from 65 to 72%) and in the 2xSMART group (from 73 to 76%), but a decrease was seen in the 1xSMART group (from 73 to 65%).

The differences between the 1xSMART group and the 2x2DIX+F group and the 2xSMART group were both statistically significant. However, the difference between the 2x2DIX+F group and the 2xSMART group did not reach statistical significance.

Asthma status improved in all groups. Similar safety profiles were seen.

**Clinical conclusions**

The effectiveness analysis showed that, except for minor differences in morning PEF, similar clinical end points were observed with the three treatments.

**Measure of benefits used in the economic analysis**

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

**Direct costs**

The analysis of the costs was carried out from a societal perspective. The direct costs included were medications (both maintenance and as-needed), visits to physician or nurse, telephone contacts with physician or nurse, days in hospital, and emergency room visits. The unit costs were presented separately from the quantities of resources used. Resource use was estimated from the sample of patients included in the effectiveness study. The costs were derived from two published studies and from average wholesale prices. Discounting was not relevant as the costs were incurred during a 6-month period. The price year was 2004.

**Statistical analysis of costs**

The analysis of variance model was used to assess whether differences in resource consumption and costs were statistically significant.

**Indirect Costs**

As a societal perspective was adopted, the productivity costs associated with absence from work were included in the analysis. The unit costs and the quantities of resources used were reported. The number of days off work was derived directly from the sample of patients included in the effectiveness study. The source of the unit costs was not explicitly stated. Discounting was not relevant as the costs were incurred during a 6-month period. The price year was 2004.

**Currency**

Swedish kronor (SEK). The exchange rate to US dollars ($) and UK pounds sterling () was SEK 1 = $0.13 = 0.07.
Sensitivity analysis
The issue of uncertainty was not addressed.

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

Cost results
The total costs per patient were:

- SEK 3,447 with 2x2FIX+F (direct costs SEK 3,183, indirect costs SEK 264),
- SEK 2,711 with 2xSMART (direct costs SEK 2,577, indirect costs SEK 134), and
- SEK 1,683 with 1xSMART (all direct costs).

Differences between 2x2FIX+F and 2xSMART or 1xSMART were statistically significant (p=0.023 and p<0.001, respectively).

Synthesis of costs and benefits
The costs and benefits were not combined.

Authors' conclusions
Compared with the 2x2FIX+F treatment (budesonide/formoterol plus additional formoterol as needed), the use of budesonide/formoterol was 30 to 40% lower in both SMART (Symbicort Maintenance and Reliever Therapy) groups while maintaining asthma control. The one dose once-daily maintenance treatment (1xSMART) resulted in a low level of treatment failure but led to more days with symptoms. Consequently, a daily dose of two inhalations (2xSMART) appears to be the most effective and efficient strategy for patients with moderate, persistent asthma.

CRD COMMENTARY - Selection of comparators
The authors provided a clear justification for the choice of the comparators. Specifically, the two SMART approaches were compared in order to evaluate the validity of the adjustable therapy. The inclusion of the fixed treatment as a third comparator ensured that the "best possible" treatment option for patients with persistent asthma was considered. Dosages were clearly reported as they were the key element of the analysis. You should consider whether they are valid comparators in your own setting.

Validity of estimate of measure of effectiveness
The analysis was based on a randomised controlled trial. This was appropriate for the study question as the three treatment groups were evaluated simultaneously and in parallel. The authors provided some information on the randomisation procedure. Blinding of the patients and physicians was not performed due to the nature of the intervention. However, the blinding of researchers who collected the outcome information should have been possible and would have reduced the potential impact of assessment bias. The authors stated that the study design was chosen to reflect a real-life situation. Power calculations were appropriately performed to ensure that the size of the study sample was adequate. Extensive information on patient follow-up was provided. The characteristics of the patient sample were reported. The fact that the study groups were comparable at baseline strengthens the robustness of the analysis. Further, the evidence came from a great number of centres, which makes the study sample likely to be representative of the patient population. These issues tend to enhance the internal validity of the analysis.

Validity of estimate of measure of benefit
No summary benefit measure was used in the analysis because a cost-consequences analysis was conducted.

**Validity of estimate of costs**
The use of a broad perspective represented a strength of the analysis. The authors provided extensive information on the unit costs, quantities of resources used and the price year, which will help when replicating the analysis in other time periods and other settings. However, the cost estimates were specific to the Swedish setting and the use of alternative cost data was not investigated. Caution will therefore be required if assessing the relevance of the cost estimates in other countries. Statistical analyses were carried out only to assess the significance of cost-differences.

**Other issues**
The authors did not make extensive comparisons of their findings with those from other studies. They also did not explicitly address the issue of the generalisability of the study results to other settings. Sensitivity analyses were not carried out, which limits the external validity of the analysis. In general, the study results should be considered specific to Sweden. The study results were reported in full and the conclusions of the study were consistent with the objective of the analysis.

**Implications of the study**
The study results support the use of the 2xSMART regimen in treating patients with moderate, persistent asthma.

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**Indexing Status**
Subject indexing assigned by NLM

MeSH
Administration, Inhalation; Adolescent; Adult; Asthma /drug therapy /economics; Bronchodilator Agents /administration & dosage /economics /therapeutic use; Budesonide /administration & dosage /economics /therapeutic use; Child; Cost-Benefit Analysis; Dose-Response Relationship, Drug; Drug Therapy, Combination; Ethanolamines /administration & dosage /economics /therapeutic use; Formoterol Fumarate; Health Care Costs /statistics & numerical data; Humans; Quality of Life; Surveys and Questionnaires

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