Cost effectiveness of inhaled steroid withdrawal in outpatients with chronic obstructive pulmonary disease

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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 compared the continued use of inhaled corticosteroids (ICS) versus placebo treatment (withdrawal or disruption of ICS), in patients with chronic obstructive pulmonary disease (COPD) who had been treated with ICS for 4 months. Patients on ICS treatment were prescribed fluticasone propionate (FP) via Diskus 500 microg twice daily.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised patients with COPD on ICS treatment (i.e. receiving 1,000 microg/day FP for 4 months). Further inclusion criteria were not reported in the current study, but elsewhere (van der Valk et al. 2002, see 'Other Publications of Related Interest' below for bibliographic details).

Setting
The setting was secondary care and the community. The economic study was carried out in the Netherlands.

Dates to which data relate
The effectiveness data were derived from a completed study that had been published in 2002. The cost data were derived from official sources, while the costs of the pharmaceuticals were based on market prices. All costs were reported for the price year 2002.

Source of effectiveness data
The effectiveness evidence was derived from a single study, the COPE study (van der Valk et al. 2002).

Link between effectiveness and cost data
The costing was carried out prospectively on the same sample of patients as that used in the effectiveness study (i.e. the COPE study).

Study sample
It was not reported in the current study whether the sample size was determined in the planning phase, or whether power calculations were conducted retrospectively based on the existing sample. In addition, the method of sample selection was not reported. The authors reported that details of the study had been published elsewhere (van der Valk et
al 2002.). Overall, after 4 months of ICS treatment, 244 patients were randomised to either continue FP or to receive placebo for a 6-month period. The number of patients in each of the two groups (FP and placebo) was not reported.

**Study design**

The analysis was based on a randomised, double-blind, parallel-group study that was conducted in a single centre. Patients had a 4-month run-in period, and were followed up at 3 and 6 months. The methods of randomisation, blinding, and any losses to follow-up were not reported in the current study. Relevant details are given elsewhere (van der Valk et al. 2002).

**Analysis of effectiveness**

It was not reported whether the analysis was conducted on an intention to treat basis or on treatment completers only. In addition, it was not reported whether the patient groups were comparable at analysis. The primary health outcomes used were the number of hospital admissions and number of exacerbations. Based on the clinical evidence of the COPE study, the following input parameters were assessed (and used in the decision analytic model):

- the probability of rapid recurrent exacerbations;
- the probability of further exacerbations when returned to open FP;
- the probability of at least one hospital admission in patients who continue to experience exacerbations following the use of open FP;
- the probability of at least one hospital admission during the 6-month trial period in patients free of exacerbations following the use of open FP;
- the probability of at least one exacerbation in patients not experiencing recurrent exacerbations; and
- the probability of at least one hospital admission in patients not experiencing recurrent exacerbations.

**Effectiveness results**

The effectiveness results were reported per patient. In the FP strategy group, the number of exacerbations was 0.87 per patient and the number of hospital admissions 0.073. In the placebo group, the number of exacerbations was 1.37 per patient and the number of hospital admissions 0.116.

It was reported that during the study, 21.5% of patients in the placebo group had recurrent exacerbations and recommenced open FP treatment for the rest of the follow-up study period. These patients used, on average, FP for 50% (91 days) of the 6-month period.

The base-case values of the input parameters used in the model were as follows.

- The probability of rapid recurrent exacerbations was 0.049 (95% confidence interval, CI: 0.023 to 0.102) in the FP group and 0.215 (95% CI: 0.151 to 0.296) in the placebo group.
- The probability of further exacerbations when returned to open FP was 0.833 (95% CI: 0.436 to 0.970) in the FP group and 0.385 (95% CI: 0.224 to 0.575) in the placebo group.
- The probability of at least one hospital admission in patients who continue to experience exacerbations following the use of open FP was 0.400 (95% CI: 0.118 to 0.769) in the FP group and 0.300 (95% CI: 0.108 to 0.603) in the placebo group.
- The probability of at least one hospital admission during the 6-month trial period in patients free of exacerbations following the use of open FP was 0.000 (95% CI: 0.000 to 0.793) in the FP group and 0.063 (95% CI: 0.011 to 0.283) in the placebo group.
The probability of at least one exacerbation in patients not experiencing recurrent exacerbations was 0.445 (95% CI: 0.358 to 0.535) in the FP group and 0.453 (95% CI: 0.356 to 0.553) in the placebo group.

The probability of at least one hospital admission in patients not experiencing recurrent exacerbations was 0.135 (95% CI: 0.067 to 0.253) in the FP group and 0.116 (95% CI: 0.051 to 0.245) in the placebo group.

**Clinical conclusions**
The authors concluded that discontinuation of FP treatment in patients with COPD resulted in a greater number of hospital admissions and exacerbations in comparison with patients who continued FP treatment.

**Modelling**
The authors constructed a decision analytic model to evaluate the incremental cost-effectiveness of the ICS versus ICS withdrawal policy. The time horizon of the model was 6 months.

**Measure of benefits used in the economic analysis**
Exacerbations averted and hospital admissions averted were the outcome measures in the economic analysis.

**Direct costs**
From the perspective of the health care payer, the direct costs included in the analysis were the hospitalisation costs, the cost of an emergency room visit, the cost of scheduled and emergency outpatient visits, and exacerbation costs. The hospital costs covered the salaries of the pulmonary physician and lung function technician, and the cost of treatment with oral steroids. The medication costs of FP (500 microg daily), prednisolone, amoxicillin-clavulanate included a dispensing fee which equalled the pharmacy cost per prescription. The costs and the quantities of resources used were not reported separately. The costs were derived from official published sources, while the costs of medications were based on market prices. The quantities of resources used were based on actual data and were derived from the patients' records. Discounting was not relevant as the costs were incurred during less than 2 years. All the costs were reported for the year 2002.

**Statistical analysis of costs**
The costs were treated deterministically.

**Indirect Costs**
The indirect costs were not included in the analysis.

**Currency**
Dutch guilders (Dfl) converted to Euros (EUR). Conversion rate EUR 1 = Dfl 2.20.

**Sensitivity analysis**
The authors conducted a one-way sensitivity analysis to assess the robustness of the results to variability in the data. All costs, apart from hospitalisation costs, were varied over a range of 50% to 150%. The probabilities of experiencing exacerbations and of hospital admission, and the costs associated with hospital admissions, were varied between the lower and upper 95% CI.

A Monte Carlo simulation with 1,000 interactions was also conducted to investigate the impact on the total costs and cost per exacerbation and per hospital admission prevented when the cost parameters and probabilities were varied simultaneously over their ranges and 95% CIs.
For the cost of exacerbations and FP, the authors followed triangular distributions. FP costs were varied in the model in order to investigate generalisability of the results to other settings with cheaper or more expensive drug costs. The cost of hospital admissions followed a normal distribution and all probabilities a logistic normal distribution.

**Estimated benefits used in the economic analysis**
See the 'Effectiveness Results' section. The authors estimated the incremental benefits. They reported that when the FP strategy was compared with placebo, the number-needed-to-treat (NNT) to prevent one exacerbation was 2 while the NNT to prevent one hospital admission was 24.

**Cost results**
The total direct costs were reported per patient over the 6-month period. The total costs were EUR 511 (including EUR 238 for FP) in the FP group and EUR 456 in the placebo group.

**Synthesis of costs and benefits**
An incremental cost-effectiveness analysis was performed. The incremental cost-effectiveness of the FP strategy compared with the placebo strategy was EUR 110 per exacerbation prevented and EUR 1,286 per hospital admission prevented.

The one-way sensitivity analyses demonstrated that the costs per exacerbation and per hospital admission prevented were sensitive to the variability of different input parameters. When the relative risk (RR) of recurrent exacerbations following FP withdrawal decreased to the lower limit of the 95% CI (RR 1.9 compared with RR 4.4 in the baseline analysis), the FP strategy incurred a cost of EUR 1,000 per exacerbation prevented. When the RR was 5.4, both strategies had an equal cost. The results were also sensitive to a reduction in FP cost to 75% of the base-case cost. Using a probability of hospital admission of 28% (upper limit of the 95% CI), the FP strategy would save EUR 571 per exacerbation prevented. The results were also sensitive to the probability of a hospital admission in those who develop recurrent exacerbations following FP withdrawal and continue to have subsequent exacerbations following the use of open FP (range of cost per exacerbation prevented from EUR 264 to a saving of EUR 134), in those who only have an occasional exacerbation following FP withdrawal (range of cost per exacerbation prevented from EUR 245 to a saving of EUR 157), and in those who remain on FP and only have an occasional exacerbation (range of cost per exacerbation prevented from EUR 402 to a saving of EUR 57).

The 1,000 simulations of the Monte Carlo analysis demonstrated similar results. The median cost per exacerbation prevented was EUR 127 (interquartile range: -52 to 331) and the median cost per hospital admission prevented was EUR 122 (interquartile range: -1,411 to 3,069).

**Authors' conclusions**
"Over a 6-month period, withdrawing FP (fluticasone propionate) in a pre-selected population of COPD (chronic obstructive pulmonary disease) patients led to absolute cost savings but with a higher rate of exacerbations and hospital admissions."

**CRD COMMENTARY - Selection of comparators**
A justification was given for the comparators used. There is conflicting evidence about the long-term effectiveness of ICS in patients with COPD. The authors chose placebo as a comparator for the intervention drug. This allowed the active value of the treatment to be evaluated, but did not include an active agent as an alternative. If there are any, which is likely, it makes this study only a partial analysis.

**Validity of estimate of measure of effectiveness**
The analysis was based on a randomised, double-blind, parallel-group, single-centre study, which seems to have been appropriate given the study question. The study referred to patients with COPD. However, it was unclear whether the
study sample was representative of the study population because no details of the patients were provided. It is not possible to comment on the internal validity of the effectiveness results since the authors referred to a separate clinical paper for details of the clinical study. In addition, no power calculations were reported. Thus, it was not possible to ascertain whether the results obtained were due to the intervention or to chance.

Validity of estimate of measure of benefit
Exacerbations averted and hospital admissions averted were used as outcome measures in the economic analysis. These were derived from the single study.

Validity of estimate of costs
The analysis of the costs was performed from the perspective of the health care payer. It appears that all the relevant categories of costs have been included in the analysis. The costs and the quantities were not reported separately, which will not enable the analysis to be easily reworked for other settings. The costs were derived from official published sources (drug costs were based on market prices), while the quantities of resources used were derived from actual data (i.e. the patients' records). In addition, an extensive sensitivity analysis was carried out to assess the robustness of the estimates used. Appropriate currency conversions were performed and, since all costs were incurred during 6 months, discounting was not necessary. The price year was reported, which will aid any future reflation exercises.

Other issues
The authors did not compare their results with other economic evaluations. However, this might have been because of a lack of studies in the same area. The issue of generalisability of the results was not directly addressed. The authors appear to have presented their results selectively. The study enrolled patients with COPD already on ICS treatment for a 4-month period and this was reflected in the authors' conclusions. The authors did not report any limitations to their study.

Implications of the study
The authors suggest "treatment with ICS should be resumed in those who have rapid recurrent exacerbations following withdrawal. Pre-screening of patients (for example, those without asthmatic features) is highly recommended, both to prevent unnecessary harm to patients and to prevent an unnecessarily high workload for the physician". In addition, they called for a long-term study, to investigate the effects of withdrawing ICS in all COPD patients and restarting ICS treatment only in those patients who experience rapid recurrent exacerbations.

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