Cost-effectiveness of inhaled corticosteroids for chronic obstructive pulmonary disease according to disease severity

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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 investigated the use (and no use) of inhaled corticosteroids in patients with varying severity of chronic obstructive pulmonary disease (COPD). The effects of inhaled corticosteroids were evaluated using four strategies:

- none of the patients were treated during the follow-up period;
- all patients regardless of disease severity were treated;
- inhaled corticosteroids were given only to patients with Stage 2 or 3 disease; and
- inhaled corticosteroids were given only to those with Stage 3 disease.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis and cost-utility analysis.

Study population
The study population comprised a hypothetical cohort of patients with COPD. The patients were divided into three mutually exclusive groups:

- Stage 1 disease, defined as a forced expiratory volume in 1 second (FEV1) of greater than 50% of predicted;
- Stage 2 disease, defined as an FEV1 of 35% to less than 50% of predicted; and
- Stage 3 disease, defined as an FEV1 of less than 35% of predicted.

Setting
The study setting was primary care. The economic study was carried out in the University of Alberta, Canada.

Dates to which data relate
The effectiveness data were derived from studies published between 1986 and 2003. The price year was 1999/2000.

Source of effectiveness data
The effectiveness data were derived from a review and synthesis of published studies, supplemented with authors' assumptions.
Modelling
A Markov model was used to estimate the effects of inhaled corticosteroids. All the patients were followed for 3 years in 3-month blocks. For each 3-month period, the probabilities of death and exacerbation were assessed for each patient within each disease category. In moving from one 3-month cycle to the next, a small proportion of patients progressed to a higher disease severity category, based on the expected declines in FEV1 for each severity group. Patients who died during the 3-month cycle were censored from further analysis. Survivors of each cycle were passed through another 3-month cycle.

Outcomes assessed in the review
The outcomes assessed in the review were:

- the proportions of COPD patients with disease Stage 1, 2 or 3;
- the mean rate of FEV1 decline in each severity group;
- the monthly rate of exacerbations (including mild, moderate and severe);
- the percentage of COPD patients with Stage 3 disease requiring hospitalisation after an exacerbation;
- the rate by which inhaled corticosteroids reduced all types of exacerbations;
- all-cause mortality by disease severity;
- the rate by which inhaled corticosteroids reduced all-cause mortality;
- the health-related quality of life (HRQL) for COPD patients by disease severity; and
- the reduction in HRQL associated with exacerbations related to COPD.

Study designs and other criteria for inclusion in the review
Not reported.

Sources searched to identify primary studies
Not reported.

Criteria used to ensure the validity of primary studies
Not reported.

Methods used to judge relevance and validity, and for extracting data
Not reported.

Number of primary studies included
Approximately 14 primary studies were included in the review, of which at least one was a review itself.

Methods of combining primary studies
Not reported.

Investigation of differences between primary studies
Results of the review
The proportions of COPD patients with Stage 1, 2 or 3 of the disease, were 93% (Stage 1), 4% (Stage 2) and 3% (Stage 3), respectively.

The mean rate of FEV1 decline in each severity group was 47 mL per patient per year.

The monthly rates of exacerbations (mild, moderate, severe) were:

4.66% (mild), 0.19% (moderate) and 0.13% (severe), respectively, for Stage 1 patients;
3.80% (mild), 9.05% (moderate) and 1.76% (severe), respectively, for Stage 2 patients; and
0% (mild), 10.16% (moderate) and 4.42% (severe), respectively, for Stage 3 patients.

The percentage of COPD patients with Stage 3 disease requiring hospitalisation after an exacerbation was 30%.

The rate by which inhaled corticosteroids reduced all types of exacerbations was 30% (relative risk, RR=0.70, 95% confidence interval, CI: 0.58 - 0.84).

The all-cause 3-month mortality rate was 1.2% in patients with Stage 1 disease, 1.8% in those with Stage 2 disease, and 2.8% in those with Stage 3 disease.

The rate by which inhaled corticosteroids reduced all-cause mortality was 16% lower in patients treated with inhaled corticosteroids than in the control group (RR=0.84).

The HRQL for COPD patients was 0.84 for a stable patient with Stage 3 disease, 0.92 for a patient with Stage 2 disease, and 1.0 for a patient with Stage 1 disease.

The reduction in HRQL associated with exacerbations related to COPD was 0.32 for each episode.

Methods used to derive estimates of effectiveness
The authors made assumptions to supplement the effectiveness data derived from the literature. These assumptions were based on the literature.

Estimates of effectiveness and key assumptions
Based on a mean rate of FEV1 decline in each severity group of 47 mL per patient per year, the authors calculated a probability of 0.74% for a person with Stage 1 disease progressing to Stage 2 during a 3-month period, and of 2.48% for progression from Stage 2 to 3 disease.

The authors assumed that, because there was little evidence that inhaled corticosteroids had a substantial effect on the rate of decline in FEV1, the same transitional probability values would apply to patients who did or did not use inhaled corticosteroids after the first year of treatment.

The authors assumed that the average duration of exacerbations was 1 week for mild exacerbations, 2 weeks for moderate exacerbations, and 4 weeks for severe exacerbations.

Measure of benefits used in the economic analysis
The measures of benefits used were the quality-adjusted life-years (QALYs) gained and the exacerbations reduced. HRQL was derived from the literature, as was the reduction in HRQL due to exacerbations.
Direct costs
The costs and the quantities were not reported separately. The direct costs of the health care provider were included in the analysis. These covered direct costs pertaining to office, emergency and hospital visits, and medication costs. The direct hospital costs were calculated using the 1999 to 2000 fee schedules from Alberta Health and Wellness. The medication costs were derived from the Alberta Health and Wellness drug list. Since the costs could be incurred up to 3 years, all future costs were appropriately discounted at an annual rate of 5%. Only the marginal costs (i.e. the costs above and beyond routine care with no corticosteroids) were considered in the analysis.

Statistical analysis of costs
The costs were treated as point estimates (i.e. the data were deterministic).

Indirect Costs
The indirect costs included in the analysis were those associated with work loss during exacerbations for those aged younger than 65 years. With 55% of all COPD patients being under 65 years, and only 65% of those younger than 65 years being employed, the authors estimated that 36% of all persons in the COPD age range were employed. It was assumed that persons with moderate exacerbations lost 1 day of work, while those with severe exacerbations lost 7 days. The workdays lost were then multiplied by the Canadian average daily wage. Since the costs could be incurred up to 3 years, all future costs were discounted at an annual rate of 5%. Only the marginal costs (i.e. the costs above and beyond routine care with no corticosteroids) were considered in the analysis.

Currency
US dollars ($). The exchange rate was Canadian $1 = US $0.72.

Sensitivity analysis
To determine the robustness of the data to a different range of assumptions, the authors performed multivariate sensitivity analyses in which the effects of the relevant covariates were adjusted simultaneously for each of the strategies. Using Monte Carlo simulation, the authors randomly sampled all variables and produced 100,000 sample sets. The authors also undertook the analysis using a lifetime horizon and evaluated the cost-effectiveness of inhaled corticosteroids, assuming that they had no effect on all-cause mortality. The authors also evaluated the approach of treating patients with Stage 2 or 3 disease for 6 months and then discontinuing treatment for nonresponders.

Estimated benefits used in the economic analysis
In the base-case strategy (i.e. patients not receiving inhaled corticosteroids) 2.71 QALYs were gained. The QALYs gained with the other strategies were 2.72 when inhaled corticosteroids were administered to patients with Stage 3 disease, 2.72 when corticosteroids were given with those with Stage 2 or 3 disease, and 2.74 when corticosteroids were given to all patients regardless of disease severity.

Cost results
The total marginal costs (i.e. the costs above and beyond treatment with no corticosteroids) were $922 per patient when treating patients with Stage 2 or 3 disease.

If all COPD patients were to be treated with corticosteroids, the marginal cost would be $3,612 per patient.

The total marginal costs would be $774 if only Stage 3 patients were given corticosteroids.

Synthesis of costs and benefits
The costs and benefits were combined using an incremental cost-utility ratio (i.e. the cost per extra QALY gained) and using an incremental cost-effectiveness ratio (i.e. the cost per extra exacerbation reduced). Strategies involving
treatment with corticosteroids were compared with the strategy without corticosteroid treatment.

If corticosteroids were given only to patients with Stage 3 disease, the cost per QALY gained would be $11,100 and the cost per exacerbation reduced would be $600. By giving corticosteroids to patients with Stage 2 or 3 disease, the cost increased to $17,000 per QALY gained and $1,000 per exacerbation reduced. Giving corticosteroids to patients regardless of disease severity was associated with a cost of $46,200 per QALY gained and $10,000 per exacerbation reduced.

If inhaled corticosteroids had no effect on mortality, the cost-effectiveness values became less favourable. For example, providing these drugs to patients with Stage 3 disease resulted in a cost per QALY gained of $34,100.

Using a lifetime model produced more favourable cost-effectiveness values. Even when corticosteroids were given to all patients, the cost per QALY gained was only $4,600. The results from the multivariate sensitivity analysis showed that, using a $50,000 per QALY gained threshold, there was a 57% probability that the strategy of providing inhaled corticosteroids to all patients regardless of severity would be cost-effective. The probability increased to 95% if inhaled corticosteroids were given to only Stage 2 or 3 patients, and to 84% if corticosteroids were provided to only patients with Stage 3 disease. If 25% of patients were nonresponders, the overall cost per QALY gained would be $18,100. If 50% were nonresponders, the cost per QALY gained would be $19,200.

Authors' conclusions
In patients with chronic obstructive pulmonary disease (COPD), the use of inhaled corticosteroids in those with Stage 2 or 3 disease for 3 years resulted in improved quality-adjusted life expectancy at a cost that was similar to that of other therapies commonly used in clinical practice.

CRD COMMENTARY - Selection of comparators
Although no explicit justification was given for using treatment with no corticosteroids as the comparator, it would appear to represent current practice in the authors' setting. You should decide if the comparator represents current practice in your own setting.

Validity of estimate of measure of effectiveness
The authors did not report that a systematic review of the literature had been undertaken. It was unclear whether this review was conducted systematically to identify relevant research and minimise biases, as the authors did not report the sources searched to identify research nor the methodology of the review. The authors did not report how the results from the primary studies were combined to derive several measures of effectiveness (such as exacerbation rates in Stage 1 disease). The authors made assumptions, based on the literature, to supplement the results of the review. It was sometimes unclear when the authors had made an assumption or an estimate to populate the model, whether this had been derived from the literature. However, the authors did undertake appropriate sensitivity analysis to test the robustness of their results. They also estimated cost-effectiveness ratios assuming no mortality benefits of corticosteroids, as the 95% CIs of the effectiveness of corticosteroids contained a value of 1.

Validity of estimate of measure of benefit
The estimation of benefits was modelled using a Markov model, which was appropriate. However, discounting would have been relevant as the benefits were incurred during more than 2 years, but it does not appear to have been performed.

Validity of estimate of costs
All the categories of cost relevant to the perspective adopted appear to have been included in the analysis. However, it was unclear whether all the direct costs were included in the analysis, as the authors did not provide sufficient details of all the costs incurred by the health service. Also, it would appear that several indirect costs were omitted, such as those due to productivity losses arising from premature death from COPD. It would appear that these omissions would bias in
favour of no corticosteroid treatment. The costs and the quantities were not reported separately, which will limit the generalisability of the authors' results. The costs were derived using schedules from Alberta Health and Wellness. Appropriate multivariate sensitivity analyses were undertaken. The authors performed appropriate currency conversions. Since the costs were incurred during 3 years, the future costs were discounted at an annual rate of 5%.

Other issues
The authors did not make appropriate comparisons of their findings with those from other studies. However, the issue of generalisability to other settings was partly addressed in the sensitivity analysis. The authors do not appear to have presented their results selectively and their conclusions reflected the scope of the analysis. The authors reported a number of further limitations to their study. First, there were a few variables for which the authors did not have high-quality estimates, for example, the authors could not find a standard agreement on how best to classify exacerbations. Second, there was limited information on the rates of exacerbation within each stage of disease, especially for Stage 1 disease. Third, the model was limited to a 3-year time horizon because of a paucity of clinical efficacy data on corticosteroids beyond that period. Finally, the authors did not include the costs of potential side effects of corticosteroids, such as osteoporosis, because, as they stated, these costs were unlikely to occur during a 3-year timeframe.

Implications of the study
The authors reported that certain sub-groups of patients with Stage 2 or 3 disease (i.e. those with increased disease severity) could benefit from corticosteroid therapy.

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