Economic evaluation of treating chronic obstructive pulmonary disease with inhaled corticosteroids and long-acting beta 2-agonists in a health maintenance organization


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 four treatment options for patients with chronic obstructive pulmonary disease (COPD). The options were:

- long-acting beta2-antagonists (LABA) alone (e.g. salmeterol);
- inhaled corticosteroids (ICS; e.g. fluticasone propionate);
- a combination of ICS and LABA (ICS+LABA); and
- a "comparison" treatment that excluded the administration of ICS and LABA but included other COPD drugs, namely short-acting beta-agonists, xanthine, anticholinergic or combined bronchodilators.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population was derived from an observational cohort study. It comprised patients with COPD at a 200,000-member HMO in New Mexico, USA, who were aged 40 years or older and who were treated with ICS alone, LABA alone, ICS+LABA, or with different drugs that did not include either LABA or ICS. The inclusion criteria were:

- patients had to be enrolled in the HMO between the study period (between 1 January 1995 and 31 December 2000);
- eligible patients had to have made at least two outpatient visits, or alternatively one hospital admission, that was coded as chronic bronchitis, emphysema or COPD within the study period; and
- patients had to have a first enrolment at the HMO at least 12 months before enrolment to the study.

Patients with signs of cystic fibrosis, bronchiectasis or lung cancer were excluded from the study. In addition, all patients enrolled into the study were assumed to be regular medication users.

Setting
The setting was an HMO in New Mexico, USA (i.e. the Lovelace Health Plan). The economic study was carried out in the USA.

Dates to which data relate
The effectiveness and resource use data were collected between January 1st 1995 and 31st December 2000. All costs were reported for the price year 2001.

Source of effectiveness data
The current study was a modelling study (survival analysis). The effectiveness data were derived from a parent observational cohort study and from administrative records from the database of the Lovelace Patient HMO.

Link between effectiveness and cost data
Although not explicitly stated, the costing appears to have been carried out retrospectively on the same sample of patients as that used in the effectiveness study.

Study sample
The sample size was not determined in the planning phase of the study. In addition, power calculations were not performed retrospectively. Patients at the Lovelace HMO who met the inclusion criteria were included in the study sample. No patients were reported to have refused to participate. Overall, 1,154 patients with a mean age of 66 years and roughly equal proportions of men and women were recruited into the study. Of those, 274 patients comprised the "comparison" treatment group, 538 the ICS alone group, 130 the LABA alone group, and 212 the ICS+LABA group.

Study design
The analysis was based on an observational single-centre cohort study. Data were collected from records from 1st January 1995 until 31st December 2000. For each patient, data were collected from the first day after a 90-day drug treatment course until 31 December 2000, unless the patient died.

Analysis of effectiveness
It was not stated whether the analysis was conducted on an intention to treat basis. The authors reported that differences between treatment groups were observed in relation to demographic and disease severity characteristics. The primary health outcomes were survival at 36 months and survival over the patients’ lifetime. A Cox proportional hazards model was used for the former and a parametric proportional hazards regression model, based on a Gompertz distribution, for the latter. The authors constructed a random-effects model with generalised least-squares estimator to adjust for prognostic factors. Life expectancy was discounted at a rate of 5%.

Effectiveness results
In the within-study analysis (survival at 36 months), the discounted life expectancy was 2.41 years (95% confidence interval, CI: 2.30 to 2.55) in the "comparison" treatment group, 2.60 years (95% CI: 2.56 to 2.68) in the ICS alone group, 2.63 years (95% CI: 2.53 to 2.74) in the LABA alone group, and 2.70 years (95% CI: 2.64 to 2.78) in the ICS+LABA group.

In the lifetime analysis, discounted life expectancy was estimated to be 3.88 years (95% CI: 3.25 to 5.02) in the "comparison" treatment group, 5.06 years (95% CI: 4.34 to 6.6) in the ICS alone group, 5.27 years (95% CI: 4.19 to 7.21) in the LABA alone group, and 6.14 years (95% CI: 4.89 to 8.63) in the ICS+LABA group.

Clinical conclusions
The analysis demonstrated that, compared with other drug treatments, ICS, LABA or their combination result in greater life expectancy for patients with COPD.

Modelling
The authors used a Cox proportional hazards model to compare the likelihood of survival between treatment groups at
36 months. In addition, a parametric proportional hazards regression model based on a Gompertz distribution was used to estimate life expectancy and poor long-term prognostic of individuals with COPD. The covariates included in the models were reported in another study (Mapel 2003, see Other Publications of Related Interest- below for bibliographic details).

**Measure of benefits used in the economic analysis**
The authors used life-years gained as the measure of benefit in the economic analysis. The benefits were derived from the models and were discounted at a rate of 5%.

**Direct costs**
The health care costs included in the analysis were for outpatient medication, hospitalisation and ambulatory care. The authors reported that the costs of ambulatory care included physician visits, radiology, laboratory testing, rehabilitation and further outpatient services that were not described in detail. The costs and the quantities were not reported separately. The costs and resources used were derived from administrative records from the patient database in the authors' setting (Lovelace HMO). Since the costs were incurred for longer than 2 years they were appropriately discounted.

**Statistical analysis of costs**
The cost data were incomplete due to the fact that some patients were excluded. In each treatment group, the monthly probability of remaining in the group analysis was estimated using the Kaplan-Meier survivor function for time-to-censoring. The authors divided the initial time interval of the cost dataset into smaller sub-periods and applied weights to reflect the censoring samples over time. The result was to create a costing dataset where the costs were assigned to the equivalent month during which they were accumulated. Secondly, the inverse probability weighted method was used to adjust for censored individuals. According to this analysis, the covariate-adjusted monthly costs were multiplied by the inverse monthly probability of being observed. In addition, a random-effects model with generalised least square estimator was constructed in order to adjust for prognostic factors. The covariates of the model were equivalent to the survival analysis. The results of the model were used to generate fitted values of monthly costs. All statistical analyses were carried out using statistical software (SAS 8.0 for Windows, STAT 7.0 for Windows).

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

**Currency**
US dollars ($).

**Sensitivity analysis**
The authors used a non-parametric bootstrapping technique, based on 1,000 re-samples, to test the robustness of the results and to estimate 95% CIs around the estimates of cumulative costs and life expectancy. A bootstrapping analysis was used to plot cost-effectiveness planes. In addition, cost-effectiveness acceptability curves were plotted for each treatment option in order to determine the preferable treatment option over a range of willingness-to-pay (WTP) values. The cost-effectiveness acceptability curves were constructed using Excel for Windows.

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

**Cost results**
In the within-study analysis (i.e. 36 months), the cumulative discounted costs for the 1,154 patients enrolled were
$28,030 (95% CI: 23,400 to 33,750) in the comparison group, $35,170 (95% CI: 29,970 to 40,620) in the ICS alone group, $27,380 (95% CI: 21,780 to 32,510) in the LABA group, and $33,780 (95% CI: 28,700 to 39,440) in the ICS+LABA group.

When a lifetime analysis was conducted, the total discounted cumulative costs were $48,950 (95% CI: 31,800 to 72,500) in the comparison group, $71,860 (95% CI: 50,900 to 103,180) in the ICS group, $57,500 (95% CI: 32,380 to 91,720) in the LABA group, and $79,560 (95% CI: 50,020 to 122,070) in the ICS+LABA group.

**Synthesis of costs and benefits**

An incremental cost-effectiveness analysis was performed. The incremental cost-effectiveness ratio between pairs of treatment options was estimated by dividing the difference in expected costs by the differences in life expectancy.

It was reported that in the within-study analysis (i.e. 36 months), the comparison group and the ICS alone group resulted in higher costs and less effectiveness than LABA alone (these options were dominated). The ICS+LABA treatment option resulted in an incremental cost of $91,430 per additional life-year gained in comparison with LABA alone.

In the lifetime analysis, the ICS alone group resulted in higher costs and less effectiveness than LABA alone (this option was dominated). When the LABA alone treatment option was compared with the comparison option (i.e. no ICS or LABA), it resulted in an incremental cost of $6,110 per additional life-year gained. When the ICS+LABA treatment was compared with LABA alone, it resulted in an incremental cost of $27,570 per additional life-year gained.

The sensitivity analysis demonstrated that higher uncertainty was observed for the results of the within-study analysis, as demonstrated through the wider CIs around the costs and effects and through the broader dispersion of the bootstrap replicates.

The cost-effectiveness acceptability curves verified that the LABA treatment option was the preferred option for WTP values of less than $91,000 per year of life gained. For values of WTP higher than $91,000, ICS+LABA was the most cost-effective treatment option.

On the other hand, the lifetime analysis demonstrated that the "comparison" treatment option (i.e. no ICS or LABA) was the preferred option for a WTP of less than $6,100. LABA alone became the preferred option for a WTP of between $6,100 and $27,500, while for a WTP of greater than $27,500, the ICS+LABA treatment option demonstrated the best value for money.

**Authors’ conclusions**

Given the survival estimates derived from observational studies, long-acting beta2-agonists (LABA) and the combination of inhaled corticosteroid (ICS) plus LABA (ICS+LABA) are likely to be cost-effective treatment options in the USA.

**CRD COMMENTARY - Selection of comparators**

The choice of the comparators was explicitly justified. LABA and/or ICS are regarded as relatively new treatment options and were still being tested in randomised trials during the course of the current study. You should decide if they represent widely used technologies in your own setting.

**Validity of estimate of measure of effectiveness**

The analysis was based on an observational single-centre cohort study. The study sample was representative of the study population. Although the patient groups were shown to differ at baseline and in demographic characteristics, a statistical analysis was not undertaken to adjust for possible bias and confounding factors. However, it was not possible to comment on the internal validity of the study since the authors referred to a separate paper for details of the clinical study.
Validity of estimate of measure of benefit
The authors used life-years gained as the measure of benefit in the economic analysis. These were appropriately derived directly from the models.

Validity of estimate of costs
The perspective of the third-party payer was adopted in the economic analysis. It appears that all the relevant categories of costs have been included in the analysis. Summary costs were reported but the costs and the quantities were not reported separately, thus limiting the reproducibility of the results to other settings. The costs and resources used were based on actual data and were derived from administrative records from the patient database in the authors setting (Lovelace HMO). As only charges were available, the authors estimated the costs using an appropriate cost-to-charge ratio. The costs were treated stochastically and a sensitivity analysis was conducted to test the robustness of the results. Discounting was appropriately conducted and the price year was reported, which will aid any future reflation exercises.

Other issues
The authors did not compare the results of their study with those from other studies. This was due to a lack of published literature in this specific area. However, they reported that published literature suggest that ICS and LABA are effective in mitigating symptoms of COPD and have a clear impact on quality of life. The issue of generalisability of the results to other settings was directly addressed.

The authors reported a number of limitations to their study. For example, disease severity estimates were based on proxy information derived from health care use. In addition, the covariates used to estimate survival were used to adjust for costs, introducing bias into the cost estimates used in the analysis. The authors suspected that “immortal time bias” might have been introduced because different groups of patients were included in the study cohort at different dates. In case patients do not survive for adequate time and are characterised as unexposed, it is possible that treatment benefits are overestimated. The indirect costs were not included in the economic analysis to take account of the impact of the disease on lost productivity. Survival estimates pertaining to patients’ lifetime were based on the extrapolation of survival trends during 36 months.

Implications of the study
The authors did not make explicit recommendations for changes in policy or practice. However, they suggested various areas where future research and more information are needed. First, they recommended that in future studies survival of disease estimates should be based on spirometric measurements. In addition, covariates should be adjusted to avoid biased cost estimates. Future economic evaluations should incorporate the indirect costs and account for productivity losses. A cost-utility model including estimates of quality of life, differentiating among patients with diverse severity of COPD disease, was also recommended.

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Other publications of related interest
Mapel DW. The USA Lovelace experience: examining systematic biases that affect the relationship between inhaled corticosteroids and survival in COPD. Eur Resp J 2003;22 Suppl 43:26s-32s.


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Subject indexing assigned by NLM

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