Cost-effectiveness of salmeterol, fluticasone, and combination therapy for COPD

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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.

CRD summary
The aim was to assess whether maintenance inhaled medication was cost-effective for patients with moderate-to-severe chronic obstructive pulmonary disease. The author concluded that, at willingness-to-pay thresholds over 52,800 US dollars per quality-adjusted life-year, combined fluticasone and salmeterol propionate therapy was most cost-effective, below this threshold no maintenance therapy, with bronchodilator use as needed, was most cost-effective. The author's conclusions are consistent with the results, but uncertainties that warrant further consideration remain.

Type of economic evaluation
Cost-utility analysis

Study objective
The aim was to evaluate the cost-effectiveness of three inhaled medications, salmeterol, fluticasone, and combination therapy, to determine their cost-effectiveness as maintenance therapy for patients with moderate-to-severe chronic obstructive pulmonary disease (COPD).

Interventions
The interventions were twice daily treatment with a combination of salmeterol (50μg) and fluticasone propionate (500μg), fluticasone propionate (500μg) alone, salmeterol (50μg) alone, and placebo (no maintenance therapy), with short-acting bronchodilator use as needed.

Location/setting
USA/primary care.

Methods
Analytical approach:
The author used a Markov model to capture the progressive nature of the disease and estimate the clinical and economic impact of the four treatment options. The model had four disease states: stable, exacerbation requiring a physician visit, severe exacerbation requiring hospitalisation, and death. Movement between states could occur every three months, to fully capture the impact of exacerbations on quality of life. The time horizon was three years and the author stated that the perspective was that of a third-party payer.

Effectiveness data:
The clinical data were from the Towards a Revolution in COPD Health (TORCH) trial (Calverley, et al. 2007, see 'Other Publications of Related Interest' below for bibliographic details). This was a large multicentre, randomised, double-blind, parallel-group, placebo-controlled trial. The quarterly mortality was calculated, using an exponential approximation. Those who died within each three month period were excluded from further analysis. Physician visits and hospitalisation rates were adjusted to the three-month cycle and incorporated in the model. These event rates for death, hospitalisation, and exacerbation were used as a proxy for the event rates between the two exacerbation states, as this information was not collected during the TORCH trial. The key clinical parameters were the exacerbations of COPD requiring physician visits, the hospitalisation rates, the all-cause mortality, and changes in health status.

Monetary benefit and utility valuations:
The utility estimates were based on a conversion of data from the St George's Respiratory Questionnaire (SGRQ) to the European Quality of life (EQ-5D) questionnaire, using a published algorithm (Stahl, et al. 2005, see 'Other Publications of Related Interest' below for bibliographic details). This was a large multicentre, randomised, double-blind, parallel-group, placebo-controlled trial. The quarterly mortality was calculated, using an exponential approximation. Those who died within each three month period were excluded from further analysis. Physician visits and hospitalisation rates were adjusted to the three-month cycle and incorporated in the model. These event rates for death, hospitalisation, and exacerbation were used as a proxy for the event rates between the two exacerbation states, as this information was not collected during the TORCH trial. The key clinical parameters were the exacerbations of COPD requiring physician visits, the hospitalisation rates, the all-cause mortality, and changes in health status.
of Related Interest' below for bibliographic details). The SGRQ data were from the TORCH trial.

Measure of benefit:
The measure of benefit was quality-adjusted life-years (QALYs) gained.

Cost data:
The analysis included the direct medical costs of the acquisition and administration of drugs and the treatment of COPD exacerbations. The drug costs and dispensing costs were from the 2006 Red Book and were discounted by 15% to reflect the typical retail acquisition costs. The costs of hospital visits were diagnosis-related group data from Thomson Healthcare. The costs of treatment exacerbations needed some assumptions, which were reported. All costs were presented in US dollars ($), at 2006 values, and were discounted at a rate of 3%.

Analysis of uncertainty:
Multiple one-way and probabilistic sensitivity analyses were performed to assess the impact on the results of variations in the key inputs.

Results
The total costs were $2,780 for placebo, $5,832 for salmeterol propionate, $6,927 for fluticasone, and $9,598 for combination therapy. The QALYs gained were 1.444 with placebo, 1.498 with salmeterol propionate, 1.510 with fluticasone, and 1.575 with combination therapy.

The incremental costs, compared with the next best alternative, were $3,052 for salmeterol propionate (compared with placebo), $1,095 for fluticasone (compared with salmeterol propionate), and $2,671 for combination therapy (compared with fluticasone). The incremental QALYs were 0.054 with salmeterol propionate, 0.013 with fluticasone, and 0.065 with combination therapy.

In the base case, salmeterol propionate and fluticasone were both extendedly dominated by combination therapy, as they were more expensive and less cost-effective. The incremental cost-effectiveness ratio (ICER) for combination therapy over fluticasone was $41,092 per QALY. Its ICER compared with placebo was $52,046 per QALY.

The cost-effectiveness acceptability curve of the results of the probabilistic analysis suggested that the ICER for combined therapy over placebo was likely to be $52,800 per QALY. Sensitivity analysis suggested that the ICER was most sensitive to the utility weight, the quarterly mortality, the quarterly cost of salmeterol, and the quarterly hospitalisation rate.

Authors' conclusions
The author concluded that the most cost-effective strategies for patients with moderate-to-severe COPD were placebo, with bronchodilator use as needed, up to a willingness to pay $52,800 for a QALY, and combined fluticasone and salmeterol propionate therapy at higher willingness-to-pay thresholds. When no maintenance therapy was not an acceptable option, salmeterol was the most cost-effective strategy up to a willingness to pay $49,500 per QALY, after which combined therapy was most cost-effective.

CRD commentary
Interventions:
The interventions were well described and appear to have been appropriate; the comparator of no prevention (placebo), with short-acting bronchodilator use as needed, was likely to have been the usual care. These interventions could be applicable to other settings.

Effectiveness/benefits:
The effectiveness data were from one trial, which seems to have been well designed and applicable to the study setting, but no details were provided, making an assessment of its validity and quality difficult. A systematic review of the clinical evidence was available, but the author chose to use the TORCH data. The incremental cost-effectiveness results based on the data from this systematic review were used to assess if the baseline results were robust. These results differed slightly, suggesting that salmeterol was more cost-effective than combined therapy at certain thresholds.
Systematic reviews are widely accepted as the preferred source for effectiveness data, so it is unclear why the author did not present this as the base case. The utility weights were estimated by mapping the trial condition-specific quality of life data to the EQ-5D, using a published algorithm. Mapping is often used to calculate utilities, where the utility data has not been collected or is not otherwise available. Details of the algorithm were presented, but the need for this type of mapping introduced uncertainty around the accuracy of the utility weights obtained. This was acknowledged by the author and a comparison with other utility weights, derived using the same mapping algorithm, was undertaken.

**Costs:**
The perspective was clearly defined and the author appropriately included only the direct costs. The composition of these costs was not provided and the costs were reported as category totals, which may limit their replication for other settings. Details of the resource use assumptions for the costs of exacerbations were presented and the references for the cost data were provided. Actual costs were used rather than reimbursement costs and the rationale for this was given and seems to have been appropriate. The price year, discount rates, and adjustment method were reported and details of some of the baseline cost inputs were available in an online appendix.

**Analysis and results:**
The model structure was described, but no diagram was provided. The incremental approach was appropriate for comparing the cost-effectiveness of the treatments relative to the next best alternative. The results were well presented, but they differed from other studies, suggesting that a lot of uncertainty remained. The results were compared with those of another modelling study which found that a long-acting beta-2 agonist, such as salmeterol, was consistently more cost-effective than combined treatment. It was suggested that this was due to the fact that a greater improvement in quality of life on combination therapy during a stable phase was not included, which led to an underestimation of its ICER. The issue of whether this greater improvement was justified or not was not discussed. The probabilistic sensitivity analysis was appropriate for capturing the full effect of parameter uncertainty, but forms of uncertainty, such as structural uncertainty, might remain. The author discussed numerous strengths and limitations of the study and provided a reasonable discussion about some of the key data uncertainties.

**Concluding remarks:**
Overall, the cost-effectiveness analysis was satisfactory. The results and discussion were well presented, but the rationale for some of the modelling assumptions could have been made clearer. There were some limitations to the study, many of which were highlighted and discussed by the author. The author's conclusions are consistent with the results, but uncertainties that warrant further consideration remain.

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