Comparative cost-effectiveness of a fluticasone-propionate/salmeterol combination versus anticholinergics as initial maintenance therapy for 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.

CRD summary
This study assessed the cost-effectiveness of initial maintenance therapy with fluticasone propionate and salmeterol combined, compared with anticholinergics, for patients with chronic obstructive pulmonary disease. The authors concluded that the combination could have clinical benefits, at a lower cost than the anticholinergics. There were some limitations to the study, particularly a risk of selection bias, and the reliability of the results is unclear. The authors' conclusions should be treated with caution.

Type of economic evaluation
Cost-effectiveness analysis

Study objective
The objective was to assess the cost-effectiveness of initial maintenance therapy with fluticasone propionate and salmeterol combined, compared with anticholinergics, for patients with chronic obstructive pulmonary disease (COPD).

Interventions
The intervention was fluticasone propionate 250 micrograms (µg) plus salmeterol 50µg, as an initial maintenance combination, for patients aged 40 years or older. This was compared with ipratropium, alone or as a fixed-dose combination with albuterol, and compared with tiotropium.

Location/setting
USA/secondary care.

Methods
Analytical approach:
A retrospective observational cohort study was conducted, using health care claims data, from 2002 to 2009, stored on the IMS LifeLink Health Plan Claims Database. Patients were followed up for three to 12 months. The authors stated that they took a health plan perspective.

Effectiveness data:
The effectiveness data were from a retrospective observational cohort study. The health care events included COPD-related out-patient visits and antibiotic or oral corticosteroid prescription within 10 days of a visit, emergency department visits, hospitalisations, and emergency department visits or hospitalisations (combined endpoint). Events were measured from 30 days after therapy initiation for patients with three to 12 months of follow-up data; 16,684 patients on the combination, 14,449 patients on ipratropium, and 12,659 patients on tiotropium. Hazard ratios for the time to first COPD-related event (relative to the fluticasone-salmeterol combination) were estimated using Cox proportional hazard models that controlled for age, gender, treatment, comorbidities, and COPD-related health care use at baseline. The key effectiveness outcome was the risk of COPD exacerbations, measured by the time to the first COPD-related health care event.

Monetary benefit and utility valuations:
Not applicable.

Measure of benefit:
The health benefit was measured using the hazard ratios for the time to the first COPD-related health care event.

**Cost data:**
The total annual mean COPD-related health care costs were calculated for patients with 12 months of follow-up data (12,595 patients for the combination, 10,617 for ipratropium, and 9,126 for tiotropium). This included medical (out-patient, emergency department, and in-patient care) and pharmacy costs (out-patient prescriptions). The predicted (adjusted) annual costs were estimated, using generalised linear models to control for differences in age, gender, treatment, comorbidities, and COPD-related health care use at baseline. Baseline use was based on database records for the six months before each patient's maintenance therapy started. Costs were reported in 2009 US $ and inflated, where necessary, using the medical care component of the consumer price index.

**Analysis of uncertainty:**
Confidence intervals for the mean adjusted cost differences were estimated using bootstrapping methods (1,000 random samples from the study population) to estimate the cost variance. Standard deviations were reported for the total cost outcomes, with 95% confidence intervals for the hazard ratios. Sensitivity analyses were conducted to assess the impact of assumptions on the date from which the outcomes were assessed and censoring of patient data.

**Results**
Using the salmeterol combination cohort as the reference, the hazard ratios, for an out-patient visit, with oral corticosteroid, were 1.65 (95% CI 1.41 to 1.94) for ipratropium and 1.49 (95% CI 1.26 to 1.76) for tiotropium. For an out-patient visit, with antibiotic, the ratios were 1.39 (95% CI 1.23 to 1.57) for ipratropium and 1.33 (95% CI 1.17 to 1.51) for tiotropium. For an emergency department visit, the ratios were 1.78 (95% CI 1.59 to 2.00) for ipratropium and 1.33 (95% CI 1.17 to 1.51) for tiotropium. For a hospitalisation or emergency department visit, the hazard ratios were 1.64 (95% CI 1.50 to 1.79) for ipratropium and 1.29 (95% CI 1.17 to 1.41) for tiotropium.

The mean 12-month (unadjusted) COPD-related total health care costs were $2,018 (SD 7,658) for the combination, $2,809 (SD 12,219) for ipratropium, and $2,453 (SD 9,588) for tiotropium. The predicted adjusted costs were $2,068 for the combination, $2,841 for ipratropium, and $2,408 for tiotropium. The adjusted differences in 12-month COPD-related costs, compared with the combination were $773 (95% CI 716 to 829) for ipratropium and 339 (95% CI 287 to 395) for tiotropium. The greater costs of ipratropium were mainly driven by increased in-patient and emergency department medical costs.

In the sensitivity analyses, the ipratropium and tiotropium cohorts maintained higher risks of events than the combination.

**Authors’ conclusions**
The authors concluded that starting treatment with the salmeterol combination could have clinical benefits, at a lower cost than anticholinergic treatment.

**CRD commentary**

**Interventions:**
The intervention and comparators were clearly reported, but the dosage was only given for the intervention. It was not clear if any of the comparators was the usual care, which is most relevant for cost-effectiveness. The authors indicated that other treatments were available, but were not included. The exclusion of a relevant option could change the cost-effectiveness results.

**Effectiveness/benefits:**
The demographic and clinical characteristics of the population were clearly reported. The effectiveness outcomes and methods used to derive them were clearly reported. Different samples were used to measure the effectiveness and the costs, depending on the length of follow-up data available. The authors stated that the demographic, clinical and other baseline characteristics of the cost sample were similar to those of the effectiveness sample.

**Costs:**
The cost and usage categories and results were clearly reported. The price year and adjustment methods were clearly reported. Specific details of how the costs were valued were not reported (whether or not the unit costs were from the NHS Economic Evaluation Database (NHS EED) Produced by the Centre for Reviews and Dissemination Copyright © 2019 University of York
database, as well as the resource use). It is difficult, therefore, to assess the appropriateness or generalisability of the costs.

Analysis and results:
The results of the main analysis were clearly reported. The sensitivity analysis was limited and no methods and no specific results were reported, making it difficult to assess the variation in the results. A potential limitation was the observational study design. As participants were not randomised to treatment, there was a risk of selection bias (outcome differences caused by systematic differences between the cohorts, rather than the treatment itself). An attempt was made to reduce this bias by controlling for key baseline characteristics. The authors noted some differences between the cohorts, which could have affected the outcomes, despite trying to control for key variables. The risk of selection bias is therefore likely to be significant. Other limitations include the lack of an incremental cost-effectiveness analysis, and the short time horizon. The authors noted the key strengths of their study, which were the large sample size and the intention-to-treat analysis.

Concluding remarks:
There were some limitations to the study, particularly the risk of selection bias, and the robustness of the results is unclear. The authors' conclusions should be treated with caution.

Funding
Funded by GlaxoSmithKline, marketers of the fluticasone-salmeterol combination.

Bibliographic details

PubMedID
21311689

DOI
10.2147/COPD.S15455

Indexing Status
Subject indexing assigned by NLM

MeSH
Aged; Albuterol /analogs & derivatives /economics /therapeutic use; Ambulatory Care /economics; Androstadienes /economics /therapeutic use; Cholinergic Antagonists /economics /therapeutic use; Cost-Benefit Analysis; Drug Combinations; Drug Costs; Drug Prescriptions /economics; Emergency Medical Services /economics; Female; Fluticasone Propionate, Salmeterol Xinafoate Drug Combination; Glucocorticoids /economics /therapeutic use; Hospital Costs; Hospitalization /economics; Humans; Insurance, Pharmaceutical Services /economics; Ipratropium /economics /therapeutic use; Kaplan-Meier Estimate; Male; Middle Aged; Models, Economic; Proportional Hazards Models; Pulmonary Disease, Chronic Obstructive /drug therapy /economics; Retrospective Studies; Risk Assessment; Risk Factors; Scopolamine Derivatives /economics /therapeutic use; Time Factors; Tiotropium Bromide; Treatment Outcome; United States

AccessionNumber
22011000389

Date bibliographic record published
13/04/2011

Date abstract record published
06/06/2013