Cost-effectiveness of available treatment options for patients suffering from severe COPD in the UK: a fully incremental analysis

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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 objective was to assess the cost-effectiveness of different treatments for patients with severe or very severe chronic obstructive pulmonary disease. The authors concluded that the UK clinical practice was cost-effective, and roflumilast was a cost-effective addition, for patients who continued to exacerbate. The methods were good and generally well reported, but the clinical evidence was highly uncertain and its validity cannot be fully assessed from this paper. The results should be considered to be uncertain.

Type of economic evaluation
Cost-utility analysis

Study objective
The objective was to assess the cost-effectiveness of different treatments for patients with severe or very severe chronic obstructive pulmonary disease (COPD).

Interventions
Various first and second-line treatments were assessed, as combinations of four options. The four options were a long-acting muscarinic antagonist (LAMA); a long-acting beta agonist (LABA); an inhaled corticosteroid; and roflumilast, an oral, once-daily selective phosphodiesterase-4 inhibitor, used in addition to bronchodilators.

Location/setting
UK/out-patient care.

Methods
Analytical approach:
A cohort Markov model was developed to estimate the costs and outcomes of the alternative treatments, over 30 years. This model was based on a published COPD model. Two separate analyses were completed: one for patients who were tolerant of inhaled corticosteroids, and the other for those who were not, including those who declined them. All patients were assumed to have severe COPD associated with chronic bronchitis, at the start. Their lung function was in the middle of the range of forced expiratory volume in one second (FEV1) for severe COPD, as a percentage of that predicted for the general population (40%), and they continued to exacerbate on treatment so far. The authors stated that the perspective was that of the UK NHS.

Effectiveness data:
The key efficacy outcome was the rate of COPD exacerbation, characterised by an increase in the frequency and intensity of symptoms, such as dyspnoea, cough and sputum production. The relative rate ratios of exacerbation for each regimen were calculated, based on a published mixed-treatment comparison. The transition from first- to second-line treatment was determined by the average time on a first-line regimen, which was assumed to be one year. Mortality was modelled using data from UK life tables, adjusted to the standardised mortality for COPD, and mortality due to hospital-treated exacerbations. The hospital case fatality rate was from a UK National Chronic Obstructive Pulmonary Disease Audit in 2008. The characteristics of the model cohort, including initial exacerbation rates, were based on a pooled analysis of two clinical trials of roflumilast (M2-124 and M2-125).

Monetary benefit and utility valuations:
The utility values were derived for two COPD health states, severe and very severe. These were based on EQ-5D data from a pooled analysis of the M2-124 and M2-125 clinical trials of roflumilast. Utility decrements, from another published source, were applied for patients who were treated for an exacerbation.

**Measure of benefit:**
The measure of benefit was quality-adjusted life-years (QALYs). A discount rate of 3.5% per annum was applied.

**Cost data:**
Only the direct medical costs were included in the model. These were the costs of maintenance for patients in the severe and very severe COPD states, COPD drugs, and community or hospital treatment for exacerbations. Monthly maintenance costs were from the NHS National Schedule of Reference Costs for 2009 to 2010, or published literature. Drug costs were from the 2011 British National Formulary (BNF). The costs of community treatment for exacerbations were based on resource use from a GOLD Strategy Group report, and NHS Reference Costs, the Personal Social Services Research Unit 2010 and the 2011 BNF. The costs of hospital treatment were derived using data from health care resource groups, and NHS Reference Costs, with authors' assumptions for the number of patients arriving at hospital by ambulance. The costs were in UK £ and were discounted at a rate of 3.5% per annum.

**Analysis of uncertainty:**
The parameter uncertainty was explored using one-way deterministic sensitivity analyses and probabilistic sensitivity analysis. Scenario analyses were conducted to investigate the effects of uncertainties in the assumptions on the model results. The results of the deterministic analyses were presented in a tornado diagram; and the results of the probabilistic analysis were presented as a scatter plot, on the cost-effectiveness plane, and as a cost-effectiveness acceptability curve of the probability of cost-effectiveness across a range of willingness-to-pay thresholds.

**Results**
The results, for all strategies, for patients who were tolerant and those who were intolerant of inhaled corticosteroids, were presented.

For patients who were tolerant, the costs ranged from £22,342 to £23,230 by regimen; and the QALYS ranged from 5.39 to 5.51. The cost-effectiveness frontier analysis suggested initial treatment with a LABA or LAMA, then LAMA plus LABA or inhaled corticosteroid, if initial treatment failed, was the most cost-effective regimen, with LAMA plus LABA or inhaled corticosteroid plus roflumilast, as the next option.

For the intolerant patients, the costs ranged from £21,477 to £22,222 by regimen; and the QALYS ranged from 5.13 to 5.22. The cost-effectiveness frontier suggested that initial treatment with a LABA or LAMA, then a LAMA plus a LABA was the most cost-effective alternative, followed by a LAMA plus a LABA plus roflumilast.

The cost-effectiveness acceptability curve for patients who were tolerant, indicated that a LAMA plus a LABA or inhaled corticosteroid plus roflumilast was cost-effective versus a LAMA plus a LABA or inhaled corticosteroid in over 80% of simulations, at a willingness-to-pay threshold of £30,000 per QALY gained. Similar results were found for intolerant patients.

In the deterministic sensitivity analysis, the key drivers of cost-effectiveness, for both cohorts, were the relative rates of exacerbations for the treatment alternatives.

**Authors' conclusions**
The authors concluded that the UK clinical practice was cost-effective for the management of COPD, and the addition of roflumilast was a cost-effective alternative, for patients who continued to exacerbate.

**CRD commentary**
**Interventions:**
The authors stated that a LAMA, a LABA and an inhaled corticosteroid were included in the treatment options, as they were recommended by the UK National Institute for Health and Clinical Excellence (NICE) guidelines. Roflumilast was included due to its approval from the European Medicines Agency (EMEA), after the NICE guidelines were developed. No other treatments were discussed.
Effectiveness/benefits:
The effectiveness estimates and their sources were clearly reported. Only limited details of the mixed-treatment comparison and pooled analysis of the roflumilast trials, used for the relative rate ratios and initial characteristics, were reported. The appropriateness of these sources is therefore unclear. The authors stated that the mixed-treatment comparison assessed the breadth of available evidence, suggesting that any relevant trials should have been identified. These trials are likely to have been heterogeneous, particularly in their populations, and the issues and uncertainty that pooling may cause cannot be ignored.

Costs:
The costs were clearly reported and relevant to the perspective adopted. The sources used to derive the costs were clearly reported, and were specific to the UK. An appropriate discount factor was applied. It was unclear if the costs were adjusted to a price year.

Analysis and results:
The model was clearly described, with a diagram provided. The results were clearly reported and appropriate diagrams were used. A range of appropriate sensitivity analyses was conducted to assess uncertainty, but the full details, such as the parameter distributions and the ranges used for the deterministic analysis, were not presented. The authors stated that the key limitation to their study was a lack of published data, with no head-to-head clinical trial evidence being available for certain treatment regimens. They suggested that further research should aim to address this lack of data.

Concluding remarks:
The methods were good and generally well reported, but without a full discussion and assessment of the pooled clinical evidence, and with the uncertainty that this creates, the results should be considered to be uncertain.

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