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ORIGINAL RESEARCH

Economic analyses comparing tiotropium with ipratropium or salmeterol in UK patients with COPD

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Abstract

Aims: This study presents a cost-effectiveness and budget impact analysis comparing cost and outcomes for UK patients with COPD treated with either tiotropium, ipratropium or salmeterol.

Methods: A previously-published COPD cost-effectiveness model was adapted for the UK, then used to estimate the cost-effectiveness of tiotropium compared to salmeterol and ipratropium. Additional epidemiological data were used to estimate the budget impact of switching patients from ipratropium or salmeterol to tiotropium.

Results: In England, the estimated annual cost per patient on tiotropium was £1350, on salmeterol was £1404, and on ipratropium was £1427; in Scotland/Wales/Northern Ireland (S/W/NI) these costs were £1439, £1565, and £1631, respectively. Tiotropium patients experienced better quality-adjusted life-years (QALYs) across all comparisons, and this option was therefore dominant compared to salmeterol and ipratropium. The probability of tiotropium being dominant ranged from 72% to 87% across comparisons. At a willingness-to-pay threshold of £20,000 per QALY, tiotropium had at least a 97% chance of being cost-effective. The estimated annual saving per primary care trust (PCT) of switching patients from salmeterol and ipratropium to tiotropium in England was £230,000 and in S/W/NI was £160,000.

Conclusions: Tiotropium is a cost-effective alternative to ipratropium and salmeterol, and switching COPD patients from ipratropium and salmeterol to tiotropium could result in considerable cost savings for PCTs along with improvements in quality-of-life.

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Introduction

Chronic obstructive pulmonary disease (COPD) is characterised by chronic airflow limitation that is not fully reversible and usually progressive.[1] Characteristic symptoms include chronic and progressive dyspnoea, cough, and sputum production, which result in significant impairments in exercise capacity and quality of life.[1] Worsening lung function is also associated with exacerbations that tend to become more frequent with increasing disease severity.[2] This contributes to a more rapid decline in lung function,[3] increased mortality, and further reductions in quality of life.[4]

COPD is estimated to kill over 30,000 people in the UK each year. Following a national COPD audit in 2003 by the British Thoracic Society and the Royal College of Physicians, it was found that an average of 15% of patients died within three months of being admitted to hospital with acute exacerbations of COPD.[5] In the UK in 2004, the total annual cost of COPD to the National Health Service (NHS) was estimated by the National Institute of Clinical Excellence (NICE) to be £500m in direct costs, and £1 billion when including indirect costs.[6] Currently an estimated 1.4% of the population in England has a clinical diagnosis of COPD,[7] though the prevalence rate in adults over the age of 15 has been estimated to be 3.1%,[8] with rates expected to rise over

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the next decade.[9] However, COPD is both preventable and treatable, with treatment used to control symptoms and reduce disability associated with the disease.[1,5]

COPD treatment goals embrace smoking cessation, improving lung function, increasing exercise capacity, preventing exacerbations and optimising nutrition. However, bronchodilation and pharmacotherapy for exacerbations remains of particular importance in the treatment of COPD. NICE recommends that patients with breathlessness and exercise limitation should use a short-acting bronchodilator as needed (either a β2-agonist or an anticholinergic). If this treatment becomes ineffective, NICE recommends that patients should be switched to either combination therapy with a short-acting anticholinergic (SAAC) and a short-acting β2-agonist (SABA), or a long-acting anticholinergic (LAAC), or a long-acting β2-agonist (LABA).[10]

To date, no cost-effectiveness analysis has been published in the UK comparing these COPD treatments. Here, from an NHS cost perspective, we present a cost-effectiveness analysis comparing combined SAAC/SABA therapy, a LAAC, and a LABA, in patients with COPD. We also present a budget impact analysis to compare the relative costs of switching between treatments.

Methods

Interventions

Three interventions were included in the cost-effectiveness and budget impact analyses. These were: the SAAC ipratropium; the LABA salmeterol; and the LAAC tiotropium. Each of these treatments were given alongside usual care, which included SABAs but excluded anticholinergics and (with the exception of the salmeterol intervention) any LABAs.

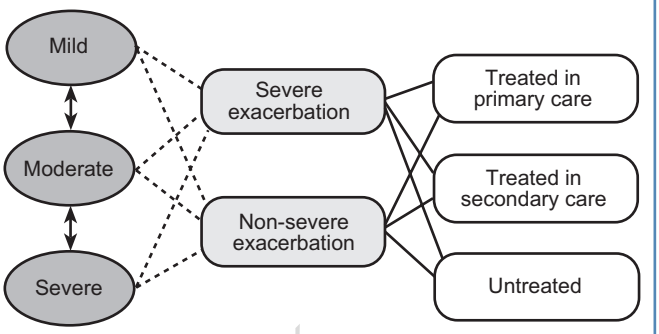
Patients treated with salmeterol received 50mcg twice-daily via a metered dose inhaler (MDI).[11] Patients treated with ipratropium received 40mcg four-times daily via a metered-dose inhaler (MDI),[12] and patients treated with tiotropium received 18mcg once-daily via a HandiHaler®.[11-13]

Model structure

The model used in this analysis is based on a previously published COPD model[14] which is adapted for the UK. It is a three-state Markov model, where the states represent patients with mild, moderate or severe disease (see Figure 1). These severity groups are in accordance with NICE COPD guidelines.[10] Thus, mild disease is defined by a forced expiratory volume in one second (FEV_1) of 50%-80% predicted, moderate disease an FEV_1 of 30%-49% predicted, and severe disease an FEV_1 < 30% predicted. Deaths were excluded in the model since the number of deaths recorded in the clinical trials was low.[14]

Patients within each disease state had a probability of experiencing either a severe exacerbation (SE) or non-severe exacerbation (NSE). This probability varied by disease state and treatment. An exacerbation was defined as a complex of respiratory symptoms lasting for at least three days. Exacerbation severity was based on physicians' assessments of the intensity of the adverse event. An NSE was defined as 'an awareness of a sign or symptom which was easily tolerated' or as 'discomfort enough to cause interference with usual activity'. An SE was defined as 'incapacitating or inability to do work or usual activity.'[14]

Figure 1. Three-state COPD health economic Markov model, with probabilities of severe and non-severe exacerbations treated within primary care, secondary care or outside the NHS.



To model the improvement in pulmonary function that was observed across treatment groups during the first few days of the clinical trial, the length of the first cycle was eight days; the second cycle was 22 days and subsequent cycles were one month. A one-month period was selected to incorporate the full effect of an exacerbation in terms of resource use and quality of life, and to minimise the risk of experiencing more than one exacerbation in any one cycle. Transitions between states were considered to occur halfway through the cycle. The model ran for 13 cycles, corresponding to one year of therapy.

Efficacy data

The efficacies for the three interventions were based on the results from six multi-centre, randomised, double-blind, double-dummy, parallel-group trials comparing tiotropium 18mcg once-daily with ipratropium 40mcg four-times daily,[12] tiotropium 18mcg once-daily with salmeterol 50mcg twice-daily,[11] and tiotropium 18mcg daily with placebo.[13] In all trials patients were allowed their usual care which included SABAs but excluded anticholinergics and LABAs. The one-year ipratropium-controlled trials were conducted in the Netherlands and Belgium,[12] the six-month salmeterol-controlled trials in North America, Europe, Australia and South Africa,[11] and the one-year placebo-controlled studies in the US.[13] Inclusion criteria included patients with COPD who were required to be relatively stable, to have moderate to

severe airflow obstruction with an $FEV_1 \leq 65\%$ predicted (salmeterol controlled trials ≤60%) and an FEV_1/forced vital capacity (FVC) ratio ≤ 0.7. These clinical trials and their outcomes have been extensively reported elsewhere.[11-13] Transition rates between disease severity states and exacerbation rates by disease severity were derived from the clinical trial data[11-13] and are published and extensively described elsewhere.[14]

Resource use and costs

1. Maintenance costs

Maintenance costs were calculated for each patient by disease severity. Estimated resource use was based on responses to a survey by a Delphi Panel that comprised eight clinicians (four general practitioners (GPs) and four secondary care consultants) practising in different areas of the UK. Using UK reference prices inflated to 2009,[15-20] the average annual cost of a patient with mild COPD was estimated to be £226, the cost of a patient with moderate COPD £514, and for a patient with severe COPD £1026 per year. A breakdown into prescription and non-prescription costs is shown in Table 1.

2. Exacerbation Costs

Exacerbation costs were calculated separately for England and Scotland/Wales/NI (S/W/NI), since English hospital costs are based on national tariffs only applicable in England.

S/W/NI exacerbation costs were calculated separately for SEs and NSEs. The Delphi Panel estimated that 66% of SEs and 9% of NSEs required hospitalisation, and that 29% of SEs and 62% of NSEs were treated in primary care. The remainder were assumed to incur no NHS costs. Therefore, the costs of treating an SE and NSE that required hospitalisation (SERH and NSERH, respectively), and the cost of treating an SE and NSE in primary care (SEPC and NSEPC) were calculated to estimate the average costs of an SE and an NSE.

The resource use for each of these exacerbations was estimated by the Delphi Panel with UK reference prices inflated to 2009[16-22] to estimate the total costs. The estimated cost of a SERH was £3564, NSERH was £1347, SEPC was £566, and NSEPC was £202. From these, the estimated cost of an SE in Scotland was £2516 and NSE was £246.

The primary care costs in England associated with exacerbation were assumed to be the same in S/W/NI, as were the proportions of SERH, NSERH, SEPC, and NSEPC. However, hospital costs differed due to the use of tariff charges for hospital admissions, and these depended on whether the admission was elective or non-elective. The proportion of hospitalisations that were elective and non-elective was estimated using data provided by UK NHS Trusts and sourced from the Clinical Hospital Knowledge System (CHKS) database. This database represents over 70% of UK hospital activity. An estimated 99.5% of admissions were non-elective and 0.5% were elective. For hospitalisations for "COPD with an acute exacerbation", the CHKS database was used to estimate the proportions of hospitalisations that were assigned to different Health Resource Groups (HRG3.5). These were converted into HRG4 codes[23] and total costs estimated using reference prices.[21] The estimated cost of an elective admission was £3372 and non-elective admission was £2323, giving an average admission cost of £2328. Following an admission, primary care follow-up costs and other hospitalisation costs were estimated by the Delphi Panel. These were costed using UK reference prices inflated to 2009[16-22] and estimates were £589 for a NSE and £1748 for a SE. Therefore the total average cost of a SE in England was £2854 and of a NSE was £388.

Table 1. Estimated average annual maintenance cost excluding cost of intervention drug.

	Mild	Moderate	Severe
Prescription cost	£96	£138	£257
Non-prescription costs	£130	£376	£769
Total cost	£226	£514	£1,026

3. Intervention costs

The average daily cost for tiotropium was estimated to be £1.11 (based on one HandiHaler combo pack plus refills), the average daily cost of ipratropium was estimated to be £0.20 (based on two puffs of 20mcg four-times daily), and the average daily cost of salmeterol was estimated to be £0.98, based on two puffs of 25mcg twice-daily.[19]

Utility scores

Utility scores by disease severity were estimated using the EQ-5D questionnaire. The estimated utility of patients with mild COPD was 0.787 (95% CI=0.771-0.802), of patients with moderate COPD was 0.750 (95% CI=0.731-0.768), and of patients with severe COPD was 0.647 (95% CI=0.598-0.695).[24] These values were estimated from a sample of 1,235 patients from 13 countries with a mean post-bronchodilator FEV_1 of 48.8% predicted. Estimated disutility due to non-severe exacerbations was 15% of current utility over a month, and for severe exacerbations was 50% of current utility over a month.[14]

Scenarios modelled

1. Base-case scenario

The base-case scenario estimated the incremental cost-effectiveness ratios (ICERs) in patients with COPD between patients treated with tiotropium and ipratropium or salmeterol. The base-case initial distribution of COPD patients by disease severity was based on the distribution of ipratropium and salmeterol patients in Table 2 (derivation provided below). Other health-related outcomes such as numbers of exacerbations are not included as these have been reported elsewhere.[14]

2. Budget impact model

The total budget impact of patients switching to tiotropium from ipratropium and salmeterol was estimated using data from a variety of sources, and was calculated by disease severity for a typical primary care trust (PCT). The average population coverage of a PCT in England was estimated to be 340,000.[25,26] Estimates for the number of patients using salmeterol or ipratropium by severity were derived from CDS patient data.[27] Additional information from the Delphi panel was used to estimate the numbers of patients using both salmeterol and ipratropium. The potential number of patients by disease severity per PCT that could switch to tiotropium is shown in Table 2.

Sensitivity analysis

A multivariate probability sensitivity analysis (PSA) was conducted to estimate the uncertainty around the ICERs calculated for the base-case. The costs (prescribing and non-prescribing maintenance costs by severity; SEPC and NSEPC costs; SERT and NSERT for S/W/NI; elective, non-elective and follow-up costs for SE and NSE in England) were varied using a log-normal distribution with 10% standard error, based on the assumption that as costs tend to be skewed[28] the mean was approximately equal to the standard deviation, and the sample size was approximated at 100. Utilities and the probability of exacerbation were varied using beta distributions, with the parameters for these distributions derived from the confidence intervals of the mean values.[14,24] The probabilities of transition between disease states were varied using a Dirichlet distribution based on the standard errors of the disease transition probabilities.[14] Estimated mean incremental costs and QALYs for each of the base-case comparisons were also calculated from the PSA simulations.

An additional univariate subgroup analysis was conducted to examine the cost-effectiveness of tiotropium vs salmeterol or ipratropium in cohorts composed entirely of either mild, moderate or severe patients.

Table 2. Estimated number of patients for an average primary care trust that could potentially switch from salmeterol or ipratropium to tiotropium.

Disease severity	Number of patients taking ipratropium	Number of patients taking salmeterol
Mild	351	372
Moderate	256	252
Severe	130	112

Results

The model was used to calculate the costs and utilities for patients with COPD treated with either tiotropium, salmeterol or ipratropium in England or S/W/NI. These values are shown in Table 3. In all cases tiotropium was dominant over both ipratropium and salmeterol, since the tiotropium quality-adjusted life-years (QALYs) were greater and the costs lower.

The PSA was conducted to estimate the probability of tiotropium being cost-effective at different willingness-to-pay thresholds. These results are shown in Table 4, along with the mean incremental costs and QALYs for each base-case comparison calculated from the PSA simulations. We see that there is a high probability of cost-effectiveness when the willingness-to-pay threshold is £0 per QALY (i.e. the incremental cost is negative and the incremental QALY is positive), and very high probabilities (≥97%) of cost-effectiveness at willingness-to-pay thresholds used by NICE of £20,000 to £30,000 per QALY.

The model was used to assess cost-effectiveness by

Table 3. Base case costs and QALYs per patient. Tiotropium was dominant when compared to salmeterol and ipratropium in both England and S/W/NI.

	Intervention Drug	Maintenance Costs		Exacerbations		Total	QALY
		Non-prescribing	Prescribing	Non-Severe	Severe		
England							
Tiotropium	£407	£320	£136	£270	£307	£1439	0.744
Salmeterol	£356	£375	£150	£326	£358	£1565	0.730
Ipratropium	£74	£398	£154	£345	£661	£1631	0.723
S/W/NI							
Tiotropium	£407	£320	£136	£172	£271	£1305	0.744
Salmeterol	£356	£375	£150	£207	£316	£1404	0.730
Ipratropium	£74	£398	£154	£219	£582	£1427	0.723

Table 4. Probability of being cost-effective at different willingness-to-pay thresholds with mean incremental costs and QALYs calculated as part of the probability sensitivity analysis.

		Mean Incremental Cost	Mean Incremental QALY	Willingness-to-pay threshold £0 per QALY	£20k per QALY	£30k per QALY
Tiotropium vs Salmeterol	England	-£169	0.014	86%	97%	98%
	S/W/NI	-£136	0.014	84%	97%	98%
Tiotropium vs Ipratropium	England	-£348	0.021	87%	99%	100%
	S/W/NI	-£272	0.021	72%	98%	99%

Table 5. Outcomes by disease severity. Tiotropium was dominant when compared to salmeterol and ipratropium in both England and S/W/NI across severity groups except when compared to ipratropium in severe patients, where the ICER was £1,600 per QALY in England and £3,450 per QALY in S/W/NI.

	Disease severity	Inc. QALY	England Inc. Cost	Scotland Inc. Cost
Tiotropium vs salmeterol	Mild	0.012	-£70	-£49
	Moderate	0.018	-£190	-£157
	Severe	0.012	-£155	-£127
Tiotropium vs ipratropium	Mild	0.022	-£291	-£208
	Moderate	0.022	-£158	-£93
	Severe	0.020	£32	£69

disease severity. These results are shown in Table 5. In all cases the incremental QALY was positive in favour of tiotropium, and in all comparisons the incremental cost was negative and therefore dominant, except in the severe group for tiotropium vs ipratropium. In this exception, the ICER in England was £1,600 per QALY and in S/W/NI was £3,450 per QALY.

The results from the budget impact analysis are shown in Table 6. Expected savings per PCT for England were £230,000 per year and in S/W/NI were £160,000 per year. The cost of tiotropium was more than offset by savings made in other cost categories, with the major saving resulting from a reduction in severe exacerbations. In particular, the breakdown by disease severity shows that the greatest savings result from switching mild patients to tiotropium.

Discussion

The economic model that forms the basis for this analysis has previously been published and validated elsewhere.[14] That study showed that tiotropium was associated with a reduction in disease severity compared with other bronchodilators, and reductions in the numbers of exacerbations per patient per year compared with salmeterol and ipratropium. This study has adapted that model so that it can be applied to disease severity classifications defined by NICE, includes UK patterns of resource use and UK unit costs, and uses updated utility values. The result is a model applicable to the UK which is able to compare COPD treatments recommended by NICE.

The QALY values calculated for tiotropium patients were consistently higher than for salmeterol and ipratropium patients. The utility values were derived independently from the efficacy data; however, they do reflect the efficacies observed in the clinical trial data.[11-13] These also reflect the differences in quality of life shown using the St Georges Respiratory Questionnaire[29] during the clinical trials.[11-13] These improvements in utility result from tiotropium patients experiencing delayed progression and reduced exacerbation rates, as observed in the clinical trial data.

The Oostenbrink study[14] compared costs in the Netherlands and Canada, and found that in the Netherlands tiotropium was the least expensive treatment, followed by salmeterol then ipratropium. In Canada the costs were lower than in the Netherlands but similar across treatments. Here we find the costs are similar between England and S/W/NI, though consistently higher in England. This is as a direct result of the Payment by Results cost tariffs leading to higher hospital-associated care costs. When costs are calculated by

Table 6. Incremental costs/savings per PCT of switching from ipratropium and salmeterol to tiotropium.

	Intervention Costs	Maintenance Costs		Exacerbations		Total*
		Non-prescribing	Prescribing	Non-severe	Severe	
England	£283,000	-£99,000	-£24,000	-£96,000	-£294,000	-£230,000
S/W/NI	£283,000	-£99,000	-£24,000	-£61,000	-£259,000	-£160,000

*Negative sign indicates net savings

severity, the additional cost of tiotropium is always offset by savings made through reduced progression and exacerbations. The only exceptions are when compared to ipratropium in patients with severe COPD where the ICER is £1,600 per QALY in England and £3,450 per QALY in S/W/NI. However, this is well below the threshold of £30,000 per QALY commonly used by NICE in England and Wales, and the SMC (Scottish Medicines Consortium) in Scotland, to assess whether or not alternative treatments are cost-effective.

Savings made by switching patients from ipratropium to tiotropium are highest in patients with mild COPD, and are driven by a large difference in the probabilities of experiencing an exacerbation, especially a severe exacerbation. It is also driven by a relatively large reduction in the probability of transition to moderate COPD. Savings and QALYs gains made by switching patients from salmeterol to tiotropium are highest in moderate COPD, and primarily driven by a large difference in the probability of patients with moderate COPD developing severe COPD. Differences between the COPD severity states are surrounded by considerable uncertainty, which has been explored elsewhere.[14]

Limitations of this model are that the resource use was based on estimates from a Delphi Panel rather than actual recorded resource use. However, the data on resource use for exacerbations in England were derived using HRG level data from the NHS CHKS hospital database, which may be considered more robust than estimates from the Delphi Panel. Here we find that the costs for S/W/NI and England are remarkably similar given the differences in the methods by which they were calculated which provide confidence in these estimates. An additional limitation is the uncertainty associated with the costs. Due to multiple sources being used to calculate the costs, it was not possible to estimate the uncertainty directly from the data, and therefore assumptions around the shape of the distribution were required in order to undertake the PSA. As a result of this uncertainty, the base-case results were based on deterministic results shown in Table 3. Using deterministic parameters can result in a bias in non-linear models.[30] However, the results in Table 4 show that correcting for this bias improves the estimated cost-effectiveness of tiotropium. This is due to the costs being skewed in the PSA, meaning that the average costs for the outcomes (e.g. exacerbation costs and maintenance cost) are greater than the deterministic mean costs. Since patients given tiotropium have fewer exacerbations and maintenance costs, the savings in the PSA will be greater than in the deterministic model. However, this does not change the results, as tiotropium is dominant – using the values from the PSA will mean tiotropium is still dominant.

A characteristic of the model is that all model inputs related to the effectiveness of treatment are based on patient-level trial data from the tiotropium clinical trial programme. This minimises the effects of different inclusion and exclusion criteria, and trial designs that often complicate comparisons between trials. In addition, this approach provided the opportunity to test the internal consistency of the model by comparing the model outcomes with the results of the clinical trials. The differences in exacerbation rates were similar between the model and those found in the clinical trials. The ability to compare the model outcomes with the results of the clinical trials on tiotropium provides the model with transparency, which facilitates understanding of the effects of changing model inputs and may increase its acceptance by local authorities involved in the decision-making process. A limitation of this characteristic is that data from other clinical trials on the efficacy of salmeterol and ipratropium, and the design of these studies, are not considered in the model inputs and outputs. Meta-analyses are often used to overcome this; however, in this case, variation in baseline characteristics and study protocols precluded this.[31]

Given the chronic nature of COPD, the time horizon over which costs and benefits are calculated is relatively short. The one-year time horizon was chosen as this was the duration of the clinical trials. The salmeterol trial was only six months, and in this case alone data was extrapolated to 12 months. Longer-term trial data would be desirable in order to estimate the long-term cost-effectiveness of tiotropium.

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Conflict of interest declarations

Jane Griffin and Ray Gani are employees of Boehringer Ingelheim who manufacture and co-promote tiotropium. Steve Kelly is an employee of Pfizer who co-promote tiotropium. Maureen Rutten-van Mölken is a consultant who has received fees for work carried out for Boehringer Ingelheim and Pfizer.

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