Chronic obstructive pulmonary disease (COPD) is a progressive inflammatory process characterised by airflow limitation, resulting in distressing symptoms and frequent exacerbations.1 Given the high prevalence of COPD and its effect on physical functioning, the societal burden of this disease is very high, and with an aging population, disease burden will likely rise in the future.2 In Canada, the prevalence of COPD is estimated at around 4% of the population, with a lifetime prevalence of 23% in those over 40 years of age.3 The burden of COPD is significant, contributing to a higher rate of hospitalisation and mortality.4

There are a variety of treatment modalities for COPD that depend on the patient’s level of severity, including short and long acting anti-cholinergics, short and long acting β agonists, oral or inhaled corticosteroids, theophylline and oxygen.5,6 Several clinical trials have evaluated the efficacy of individual treatments compared with placebo or to each other.6-16 In addition, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommendations suggest that physicians consider adding a second bronchodilator treatment rather than prescribing high dose bronchodilator monotherapy to mitigate adverse effects.4 However, little is known about the combination of different classes of drugs to improve treatment of COPD. It is hypothesised that as different classes of drugs have different mechanisms of action, their combined usage might have additive or even synergistic effects7. The Optimal Therapy of COPD trial17-19 was a multicentre randomised, double blind, controlled clinical trial designed to compare the effect of 1 year of treatment of COPD with three treatment regimens: (1) tiotropium 18 μg once daily + placebo twice daily (TP group); (2) tiotropium 18 μg once daily + salmeterol 25 μg/puff, 2 puffs twice daily (TS group); and (3) tiotropium 18 μg once daily + fluticasone/salmeterol 250/25 μg/puff, 2 puffs twice daily (TFS group). The primary outcome of the study, the proportion of exacerbation free patients at the end of 1 year of follow-up, did not differ among the three treatment groups. However, there was a statistically significant difference in lung function, number of exacerbations requiring hospitalisations, total hospitalisations and quality of life in favour of the TFS group. As exacerbations and hospitalisations are an important source of resource utilisation and costs in COPD,2 these results suggest that combination therapy with tiotropium–fluticasone/salmeterol might be a favourable treatment alternative compared with tiotropium alone.

**Methods**

The present economic evaluation is based on an intention to treat analysis of the OPTIMAL trial from the perspective of the Canadian healthcare system. The main analysis focuses on the cost effectiveness of the combination therapy with tiotropium–fluticasone/salmeterol versus tiotropium or tiotropium–salmeterol.
incremental cost per exacerbation avoided. The other outcome
studied was the incremental cost per quality adjusted life year
(QALY) gained. The time horizon of the analysis was 1 year,
in line with the follow-up duration of the OPTIMAL study.

The design, patient recruitment, methods and results of the
OPTIMAL trial have been described elsewhere.18 19 The study
included 449 patients with moderate to severe COPD from 27
Canadian academic and community medical centres. To be
enrolled, patients had to have experienced at least one
exacerbation prompting medical intervention in the year
preceding randomisation, have had a history of 10 pack-years
of cigarette smoking and moderate or severe airflow
obstruction defined as post-bronchodilator forced expiratory
volume in 1 s (FEV₁) <65% predicted. The primary outcome
measure was the proportion of patients who experienced a
respiratory exacerbation within 52 weeks of randomisation.
Respiratory exacerbations were defined as a sustained worsen-
ing of patient’s respiratory condition, from the stable state and
beyond normal day to day variations, necessitating use of oral or
intravenous corticosteroids or antibiotics. The study was
designed to detect an 18% risk difference with alpha = 0.05,
and 80% power, and with the provision of 5% dropouts. Quality
of life was assessed by SGRQ at baseline and at four follow-up
visits, 4, 20, 36 and 52 weeks after randomisation.

Handling missing data
An important aspect of economic evaluations conducted along-
side a clinical trial is how to deal with missing data due to
attrition. In the OPTIMAL trial, 13.4% of patients had
incomplete follow-up (excluding patients who died). Partially
observed longitudinal data may introduce bias into the
estimation of the costs and effectiveness20 and several rigorous
approaches to rectify this issue have been described.21 22 We
followed recommendations by Oostenbrink22 and Briggs
and colleagues,23 and the International Society for
Pharmacoeconomics and Outcomes Research,24 in dealing with
missing cost and effectiveness data. We divided the whole
follow-up period into discrete time intervals and used a
combination of imputation and bootstrapping to quantify
uncertainty caused by missing values and the finite study
sample size. For each patient, the last period in which the
patient had been followed was determined separately for costs
and effectiveness outcomes. We used propensity scores,
stratified by treatment group, for imputing the missing costs
and effectiveness data caused by attrition.22 Covariates used
to calculate the propensity scores were age, gender, study site,
number of exacerbations in the preceding year, baseline FEV₁
and the value of the missing variable in the preceding period.

### Table 1 Unit costs (2006 CAN$) for each component of resource utilisation

<table>
<thead>
<tr>
<th>Item</th>
<th>Value (2006 CAN$)</th>
<th>Unit</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Telephone to MD/healthcare professional</td>
<td>14.6</td>
<td>Per call</td>
<td>MSP</td>
</tr>
<tr>
<td>Urgent respiratory care visit in home</td>
<td>67.4</td>
<td>Per visit</td>
<td>MSP</td>
</tr>
<tr>
<td>Urgent MD visit</td>
<td>85.1</td>
<td>Per visit</td>
<td>MSP</td>
</tr>
<tr>
<td>Urgent ED visit</td>
<td>255.8</td>
<td>Per visit</td>
<td>Chapman</td>
</tr>
<tr>
<td>Hospitalisation</td>
<td>593.2</td>
<td>Per day</td>
<td>VGH fully allocated cost model</td>
</tr>
<tr>
<td>ICU admission</td>
<td>2337.3</td>
<td>Per day</td>
<td>VGH fully allocated cost model</td>
</tr>
<tr>
<td>Tiotropium 18 µg</td>
<td>2.25</td>
<td>Per capsule</td>
<td>Pharmanet Drug Master List</td>
</tr>
<tr>
<td>Salmeterol 25 µg</td>
<td>0.44</td>
<td>Per puff</td>
<td>Pharmanet Drug Master List</td>
</tr>
<tr>
<td>Fluticasone/salmeterol 250/25 µg</td>
<td>1.16</td>
<td>Per puff</td>
<td>Pharmanet Drug Master List</td>
</tr>
</tbody>
</table>

Costs of more than 40 different medications administered during exacerbations were all taken from the British Columbia Pharmanet database.26 ED, emergency department; ICU, intensive care unit; VGH, Vancouver General Hospital.

### Table 2 Results of the base case analysis (with 95% CI)

<table>
<thead>
<tr>
<th>Cost (2006 CAN$)</th>
<th>TP</th>
<th>TS</th>
<th>TFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exacerbations per year</td>
<td>1.56 (1.34 to 1.81)</td>
<td>1.69 (1.47 to 1.94)</td>
<td>1.35 (1.16 to 1.55)</td>
</tr>
<tr>
<td>QALY</td>
<td>0.7092 (0.6953 to 0.7228)</td>
<td>0.7124 (0.6931 to 0.7310)</td>
<td>0.7217 (0.7034 to 0.7389)</td>
</tr>
<tr>
<td>Adjusted incremental QALY*</td>
<td>0 (reference)</td>
<td>-0.0052 (-0.0088 to 0.0032)</td>
<td>-0.0056 (-0.0142 to 0.0251)</td>
</tr>
<tr>
<td>Incremental cost per exacerbation avoided</td>
<td>Reference</td>
<td>Dominated</td>
<td>6510</td>
</tr>
<tr>
<td>Incremental cost per QALY</td>
<td>Reference</td>
<td>Dominated</td>
<td>243180</td>
</tr>
</tbody>
</table>

*Incremental QALYs are adjusted for the baseline utility using a linear regression model.

CAN$, Canadian dollars; TFS, tiotropium+fluticasone/salmeterol; TP, tiotropium+placebo; TS, tiotropium+salmeterol; QALY, quality adjusted life years.

Costs
Healthcare utilisation was systematically collected for each
patient according to the study protocol. The major resource
categories were the study drugs, exacerbation related medica-
tions, nursing and respiratory care visits at home, physician and
emergency room visits, and hospital or ICU admissions. Among
non-COPD related resource utilisation, only the number of
hospitalisations for each patient was recorded. The base case
analysis therefore considered only COPD related costs. Non-
COPD related hospitalisation costs were included in the
sensitivity analysis. Protocol driven costs such as the costs of
prescheduled follow-up visits were excluded from the analysis.

A unit cost was assigned for each component of resource
utilisation (table 1). The price of medications, including the
study drugs and medications used to treat exacerbations, were
based on the prices the provincial government reimburses
under the drug coverage programme.26 All medications for
exacerbations were recorded by drug name and duration,
allowing the accurate calculation of costs for each patient. The
daily cost of hospitalisation for COPD patients was taken from
the fully allocated cost model of a tertiary care hospital in
Vancouver. The cost of an emergency room visit for a COPD
exacerbation was based on the report by Chapman and
colleagues.27 All other unit costs were based on the fee-for-
service rates of the British Columbia Medical Services Plan.26
All costs were inflated to 2006 Canadian dollars using the
consumer price index reported by Statistics Canada.29
Because the period of data collection covered only 1 year, no
discounting was necessary. The analysis was performed from the third
party payer perspective, and no indirect medical costs or out-
of-pocket costs were included.
Cost effectiveness analysis

The incremental cost effectiveness ratio (ICER) was calculated for each effectiveness outcome, for TS and TFS versus TP and also for TFS versus TS groups. Uncertainty in the estimation of the costs and effectiveness were modelled by nested imputation and bootstrapping. In each cycle, the missing values were imputed and the complete dataset was bootstrapped within each treatment group. This method accounts for the uncertainty due to both the missing values and the finite study sample size. For each run of imputation and bootstrapping, we calculated (for each patient) the total cost, QALY and number of exacerbations. These outcomes were then averaged for patients within each treatment arm. The contribution of different cost components (MD/emergency department visits, hospital/ICU admission, study treatments and exacerbation medications) to total costs was also evaluated. Expected value (mean) of the cost and effectiveness outcomes along with their confidence intervals, plots on the cost effectiveness plane and cost effectiveness acceptability curves were generated based on 10 000 iterations of nested imputation/bootstrapping. Fieller’s method was used to generate 95% confidence ellipses for the joint distribution of cost and effectiveness outcomes.

Sensitivity analysis

Various assumptions and scenarios were evaluated in the one way sensitivity analyses. Firstly, we restricted the dataset to patients for whom all data on costs and effectiveness were available (complete case scenario). This would eliminate the uncertainty caused by missing values. However, as patients who do not complete their follow-up are often those with more severe disease, it was expected that the complete case analysis would underestimate costs and overestimate effectiveness outcomes. Another sensitivity analysis included non-COPD related hospitalisation costs. Daily costs of non-COPD related hospitalisation was modelled as equal to the average daily cost of hospital stay for surgery and medicine wards. Sensitivity analysis also included the calculation of outcomes in subgroups of patients defined by COPD severity (according to the GOLD criteria). As the administration of SGRQ was performed on predetermined visits and often not during patients’ exacerbations, we felt that it might have failed to capture the effect of exacerbations in quality of life. Therefore, in another analysis, utility loss during exacerbations was modelled by lowering patients’ utilities by 15% and 50% during mild/moderate and severe exacerbations, respectively. Severe exacerbation was defined as one that requires hospitalisation. Finally, two alternative approaches in estimating exacerbations in those who died were evaluated in sensitivity analysis. In the first approach, it was assumed that if patients had survived, they would have no more exacerbations during the follow-up period. In the second approach, it was assumed that patients would have no more exacerbation free periods had they survived to the end of the follow-up.

RESULTS

Total costs, rate of exacerbation and QALYs stratified by each of the treatment arms, and the ICERs comparing non-dominated strategies with each other, are reported in table 2. When the exacerbation rate was the effectiveness outcome, the TS strategy was dominated by TP as it resulted in higher costs and a higher rate of exacerbations. The ICER for avoiding one exacerbation was $6510 for TFS compared with TP.

After adjusting QALYs for the baseline utilities in each group, the incremental QALYs of TS and TFS versus TP decreased from 0.0052 to −0.0052 and from 0.0125 to 0.0056, respectively, reflecting the lower utility at the start of the trial for the TP group. The 95% confidence intervals of the adjusted incremental QALYs for both TFS versus TP and TS versus TP crossed zero, indicating that the observed QALYs were not significantly different from that of the TP strategy for both alternative treatments. When the adjusted QALY was the health outcome, the TS was dominated compared with TP because of its higher costs and lower effectiveness. The ICER for avoiding one exacerbation was $243 180 per one QALY gained.

The cost components contributing to the overall COPD related costs in each group are shown in fig 1. Overall, the higher cost of study drugs in the TFS and TS groups was only partially offset by the lower costs in some other components (mainly ICU admissions and MD visits) compared with the TP.
Despite the fact that patients in the TFS group had significantly lower probability of hospitalisation, the total hospitalisation cost was higher in the TFS group. This was because of an extraordinary long length of stay for one patient in the TFS group who was hospitalised from day 36 until his death at day 251 (215 days of hospitalisation). When this patient was removed from the analysis, the COPD related hospitalisation costs reduced by $568 (to $1256) for the TFS group, and the ICER of TFS versus TP decreased to $3876 per one exacerbation avoided and $145 756 per QALY gained.

Sensitivity analysis
Since for both outcomes TS was dominated by TP, the TS strategy was dropped from further cost effectiveness analyses. Results of the bootstrap/imputation sensitivity analysis are shown in fig 2 (cost effectiveness plane) and fig 3 (cost effectiveness acceptability curve). For the willingness to pay of $6000 per exacerbation or less, treatment with tiotropium alone had the highest probability of being the most cost effective option. When QALYs were the effectiveness outcome, treatment with tiotropium alone had a higher probability of being the best option compared with the other treatments over the whole range of the willingness to pay values analysed ($Can 0–400 000). At the conventional value of $50 000 per QALY, monotherapy with tiotropium had an 80% probability of being the most cost effective strategy compared with the alternatives.

Results of one way sensitivity analyses are presented in table 3. Results were generally robust to the different assumptions explored in the one way sensitivity analysis. Costs in the TS group fell slightly below the costs of the TP group when the data were limited to the complete cases, when non-COPD hospitalisations were included in the costs and in patients with severe COPD. The ICER per exacerbation avoided of TFS versus TP varied from a minimum of $3332 in complete case analysis to more than $47 000 when one exacerbation was assigned to each period after death.

DISCUSSION
Using data from a relatively large, multicentre clinical trial, this study showed that a combination of salmeterol or fluticasone/salmeterol with tiotropium did not seem to be cost effective. The incremental cost effectiveness ratio was more than $6000 for one exacerbation avoided when fluticasone/salmeterol was added to monotherapy with tiotropium. Similarly, the incremental cost effectiveness ratio was more than $200 000 per QALY gained when fluticasone/salmeterol was added to monotherapy with tiotropium. This is despite the fact that exacerbation rates were somewhat lower, and quality of life was significantly higher in the TSF group compared with the two other groups.

There is uncertainty in the findings. For instance, considering the QALY as the effectiveness outcome, and using the conventional effectiveness value of $50 000 per QALY, the
probability that monotherapy with tiotropium is the most cost effective choice is 80%. As no other clinical trial has examined similar combinations of medications, we believe this is the only information available to the decision maker on choosing among the treatments examined here. This signifies the need for more studies evaluating the effectiveness of these treatment regimens in patients with COPD. It is also noteworthy that subgroup analyses revealed that treatment with TS was cost effective in patients with severe COPD. However, patients in this group had an equal rate of exacerbations with only slightly lower costs compared with patients in the TP group, causing considerable uncertainty in this finding.

An incremental cost per exacerbations avoided is somewhat more difficult to interpret than the incremental cost per QALY. In the absence of any studies that measure the willingness of society to pay for each exacerbation avoided, such ICERs can only be compared with similar figures in other cost effectiveness studies. Oostenbrink et al estimated the ICER of tiotropium over ipratropium to be €667 per exacerbation avoided, which is significantly lower than the ICERs for the same outcome in our study. In a 5 year decision analytic model of COPD, Rutten-van Molken et al estimated the ICER of an exacerbation free month for tiotropium versus salmeterol and salmeterol versus ipratropium to be €360 and €1711, respectively. This value is also remarkably lower than the ICER for an exacerbation free period in our study.

The strength of this analysis includes prospective collection of data on both resource use and effectiveness outcomes, which should have minimised the bias that would result in retrospective data collection. The nested imputation and bootstrapping used in this analysis enabled full incorporation of the uncertainty resulting from missing values and limited sample size of the study.

There are some limitations of our analysis. Estimation of utility values was based on a disease specific questionnaire using a newly developed algorithm, which has not been independently validated. As the indirect costs (eg, productivity loss) were not systematically gathered in the OPTIMAL study, the cost effectiveness analysis could not be performed from a societal perspective, as recommended by several authorities. However, productivity losses are likely to be minimal in this elderly population with advanced COPD, as the vast majority of these patients are no longer working. Among the non-COPD related resource utilisation, only hospitalisations were recorded. Deciding whether a particular event with its associated costs is COPD related or not could be difficult at times and the decision will inevitably be subjective to some extent, although such discretion was made by a physician blinded to the treatments.

Another shortcoming of this analysis, like the majority of economic evaluations conducted alongside clinical trials, is the difference in the management of patients in reality and in the carefully controlled setting of a clinical trial. For instance, patients in the OPTIMAL study received a specific recommendation on the usage of other COPD related medications and received regular follow-up visits. Such protocol specific management options might have had an impact on the observed ICERs for the same outcome in other cost effectiveness studies. Oostenbrink et al estimated the ICER of over ipratropium to be J 0.00312 0.0096. This value is also remarkably lower than the ICER for an exacerbation free period in our study.

There are some limitations of our analysis. Estimation of utility values was based on a disease specific questionnaire using a newly developed algorithm, which has not been independently validated. As the indirect costs (eg, productivity loss) were not systematically gathered in the OPTIMAL study, the cost effectiveness analysis could not be performed from a societal perspective, as recommended by several authorities. However, productivity losses are likely to be minimal in this elderly population with advanced COPD, as the vast majority of these patients are no longer working. Among the non-COPD related resource utilisation, only hospitalisations were recorded. Deciding whether a particular event with its associated costs is COPD related or not could be difficult at times and the decision will inevitably be subjective to some extent, although such discretion was made by a physician blinded to the treatments. Another shortcoming of this analysis, like the majority of economic evaluations conducted alongside clinical trials, is the difference in the management of patients in reality and in the carefully controlled setting of a clinical trial. For instance, patients in the OPTIMAL study received a specific recommendation on the usage of other COPD related medications and received regular follow-up visits. Such protocol specific management options might have had an impact on the observed ICERs for the same outcome in other cost effectiveness studies. Oostenbrink et al estimated the ICER of over ipratropium to be J 0.00312 0.0096.
resource utilisation and effectiveness outcomes. A good example, as discussed by Oostenbrink and colleagues, is the possibility that patients following prescheduled follow-up visits during a clinical trial might prefer not to initiate an unscheduled visit to another physician or healthcare facility for their complaints, and instead might seek treatment during their protocol driven visit. Therefore, the resource utilisation when protocol driven visits are excluded may underestimate the cost of physician visits that would have occurred in real life settings.

The 1 year time horizon of this study is in line with many other clinical trials and cost effectiveness studies in this field but decision makers might be interested in results over a longer time horizon. We chose not to extrapolate the results of this study beyond 1 year as there is little reason to believe that long term usage of these medications would change the order of their cost effectiveness as observed. There are some instances in which the cost effectiveness is strongly affected by the choice of the time horizon. For example, the ICER of lung volume reduction surgery versus medical therapy in the US was found to change from $190 000 to $55 000 per QALY at 3 and 10 years, respectively. Such dependency on the time horizon, in our belief, is mainly due to the difference in the pattern of costs over time between the two arms. In the lung reduction surgery arm, a significant portion of costs accumulates at the beginning and is diluted over time while costs of medical therapy tend to be constant throughout. Here, costs and effectiveness outcomes in all three arms were accumulated at relatively steady rates and hence it is unlikely that the extrapolation of outcomes beyond the time horizon of the study will have any asymmetric effects on the treatment strategies.

In summary, although the OPTIMAL clinical trial demonstrated that patients treated with tiotropium plus fluticasone/salmeterol had significantly better disease specific quality of life and fewer hospitalisations than patients treated with tiotropium plus placebo, these improvements in health outcomes were associated with increased costs. Increased costs associated with the medication more than offset the reduction in the costs of other healthcare resources. The results of this study suggest that among the three treatment options evaluated here, monotherapy with tiotropium appears to be the most economically attractive.

Funding: This study was funded, in part, by the National Sanitarium Association, Ontario, Canada and the Canadian Institutes of Health Research (CIHR) through an operating grant for the clinical trial. CAM is funded by a Canada Research Chair in effectiveness analysis alongside clinical trials: the ISPOR RCT-CEA Task Force report. Value Health 2003;13:548–65.

REFERENCES


Cost effectiveness of therapy with combinations of long acting bronchodilators and inhaled steroids for treatment of COPD

M Najafzadeh, C A Marra, M Sadatsafavi, S D Aaron, S D Sullivan, K L Vandemheen, P W Jones and J M Fitzgerald

Thorax 2008 63: 962-967 originally published online July 11, 2008
doi: 10.1136/thx.2007.089557

Updated information and services can be found at:
http://thorax.bmj.com/content/63/11/962

These include:

References
This article cites 32 articles, 7 of which you can access for free at:
http://thorax.bmj.com/content/63/11/962#BIBL

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Topic Collections
Articles on similar topics can be found in the following collections

- Health policy (183)
- Health service research (169)
- Drugs: respiratory system (526)

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/