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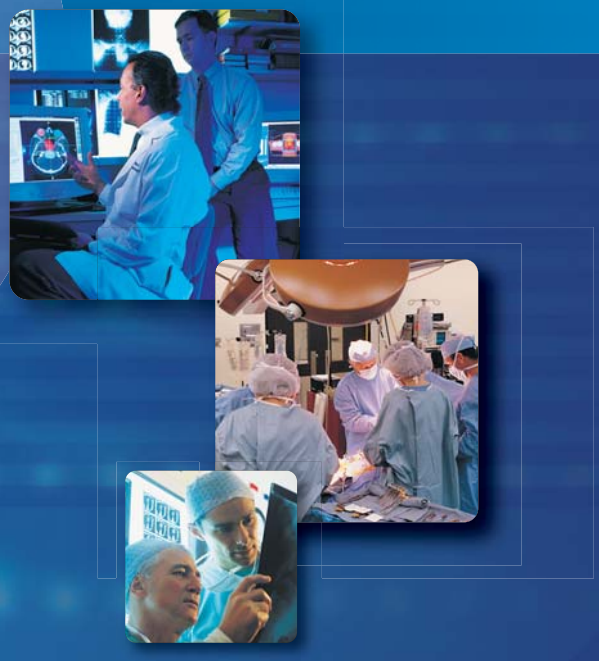
Long-acting ß2-agonists (LABA) plus Corticosteroids versus LABA Alone for Chronic Obstructive Pulmonary Disease



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Canadian Agency for Drugs and Technologies in Health

Long-acting ß$_2$-agonists (LABA) plus Corticosteroids versus LABA Alone for Chronic Obstructive Pulmonary Disease

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March 2007

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Authorship

Irvin Mayers was involved in project design, literature review, and write-up. Philip Jacobs was involved in the project design, literature search, modelling, and write-up. Darcy D. Marciniuk was involved in project design, literature review, and write-up. Anderson Chuck was involved in project management, literature search, and modelling. Janice Varney was involved in the literature search.

Conflicts of Interest

Dr. McIvor has received research grants and honoraria from pharmaceutical companies related to research, education, and advisory boards on obstructive lung disease, including but not limited to GlaxoSmithKline, AstraZeneca, Boehringer Ingelheim, Pfizer, Altana.

REPORT *IN BRIEF*

March 2007

Long-acting ß$_2$-agonists (LABA) plus Corticosteroids versus LABA Alone for Chronic Obstructive Pulmonary Disease

Technology and Condition

Combination therapy (CT) of an inhaled long-acting β_2-agonist (LABA) with an inhaled corticosteroid (ICS) in patients diagnosed with chronic obstructive pulmonary disease (COPD).

Issue

COPD affects at least 3.2% of the adult population and leads to significant associated health care costs. CT has been recommended in clinical practice, yet there is uncertainty about the cost-effectiveness of this approach and its potential budgetary impact.

Methods and Results

Three relevant randomized controlled trials were identified through a systematic literature review. Estimates of changes in exacerbation, serious adverse events, and mortality rates were then derived. Using a Markov model, the three-year and lifetime cost-effectiveness of CT compared with LABA alone was estimated for four disease-management strategies. With Strategy 1 (base case), all patients were treated with LABA. With Strategy 2, in addition to the base case, ICS was given to patients with Stage-3 disease only. With Strategy 3, in addition to the base case, ICS was given to patients with Stage-2 and Stage-3 disease only. With Strategy 4, in addition to the base case, ICS was given to all patients. The budget impact of switching patients from LABA to CT was conducted based on Alberta utilization data.

Implications for Decision Making

- **CT in all COPD stages is more effective than LABA alone**. Available evidence suggests that CT results in fewer overall exacerbations and improved quality of life measures, compared with treatment by LABA alone. There is no evidence to suggest that mortality differs with different strategies.

- **Different treatment strategies will vary in cost-effectiveness.** The lifetime cost of using a LABA (discounted at 5%) is C$9,636 per COPD patient. Adding an ICS for the most severe patients (strategy 2) results in an increase of C$93 per patient; strategy 3 increases costs by an additional C$321; and strategy 4 increases costs by C$3,120. Each strategy is associated with an additional increase of 0.01 quality-adjusted life year (QALY) per patient. Strategies 2 and 3 may be perceived as cost-effective by those who are prepared to pay up to C$50,000 for a QALY.

- **CT requires additional resources.** Switching all patients who are >65 years old and only receive a LABA without an ICS to CT treatment would require, by extrapolation, an additional C$3.3 million in Alberta, and C$43.7 million nationally.

This summary is based on a comprehensive health technology assessment available from CADTH's web site (www.cadth.ca): Mayers I, Jacobs P, Marciniuk DD, Chuck A, Varney J. *Long-acting β_2-agonists (LABA) plus corticosteroids versus LABA alone for chronic obstructive pulmonary disease.*

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EXECUTIVE SUMMARY

The Issue

Chronic obstructive pulmonary disease (COPD) is a respiratory disorder largely caused by smoking. It is marked by progressive, partially reversible airway obstruction, systemic manifestations, and increasing frequency and severity of exacerbations. Patients with COPD are characteristically short of breath (dyspnea), and cannot tolerate physical activity. The symptoms are usually insidious, but patients need increasing care as the disease progresses.

COPD is a major cause of morbidity and mortality throughout the world; it is the fourth leading cause of death. The prevalence of the disease and the associated mortality are estimated to increase significantly in the coming decades, because of the aging population worldwide.

Guidelines from the Canadian Thoracic Society (CTS) for the management of COPD outline several pharmacologic and non-pharmacologic therapies to optimize the care of patients. One of these recommendations involves combination therapy (CT) incorporating a long-acting B_2-agonist (LABA) and an inhaled corticosteroid (ICS) for patients with a forced expiratory volume (FEV_1) of <50% predicted, and ≥3 exacerbations per year. These clinical guidelines do not give an assessment of the cost effectiveness or the cost implications of this recommendation. Given that the cost of this CT is almost double that of LABA therapy alone ($1,011 per year compared with $587 annually for LABA alone), it would be prudent to assess the economic impact of each alternative, taking into account the cost of the medications, and their impact on health care resources.

Objectives

We conducted an economic analysis to determine the cost effectiveness and the budgetary impact, in a Canadian context, of CT versus LABA alone. Using the clinical guidelines and present management of COPD as the basis for our analysis, we examined the following interventions:

- maintenance therapy for all patients with COPD using LABA alone
- CT for severe cases (FEV_1 <35% predicted) only, and LABA for the remainder of patients with moderate or mild disease
- CT for severe or moderate COPD cases (FEV_1 <50% predicted), and LABA for the remainder of COPD patients with mild disease
- CT for all patients with COPD, regardless of severity.

Methods

We used a model where patients were followed in three-month cycles over three years, and over the patient's lifetime. Patient cohorts were 60-year-old current or former smokers with COPD. Preliminary and background data were obtained from published literature, with efficacy data being obtained from a systematic review that was conducted for this study. We used a health systems perspective, with cost data based on current Alberta health care costs. Outcomes were measured using health utilities. The budget impact of switching patients from LABA to CT based on Alberta utilization data was also estimated.

Results

The results of the model indicate that CT for moderate or severe patients (versus LABA alone) would result in an extra cost of $321 per person for an incremental utility of 0.01 quality- adjusted life year (QALY). This represents $26,357 per additional QALY (discounted at 5%) over an individual's lifetime versus using LABA alone. The model tested well for sensitivity, except for the mortality variable. There is no evidence to indicate that mortality differs with the various strategies, but if such differences were to be found, the model results would likely be affected. The additional cost, nationally, of switching from LABA to CT for those currently taking LABA would be approximately $43.7 million.

Conclusions

Our results indicate that CT administered to moderate or severe COPD patients may be perceived as cost effective, if the health system is prepared to pay up to $50,000 for a QALY. Our budget impact analysis indicates that additional resources would be required. A reduction in the use of other health care resources, however, could compensate for some of the difference.

ABBREVIATIONS

ATS	American Thoracic Society
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CT	combination therapy
CTS	Canadian Thoracic Society
DALY	disability-adjusted life year
ERS	European Respiratory Society
FEV_1	forced expiratory volume
HRQL	health-related quality of life
ICER	incremental cost-effectiveness ratio
ICS	inhaled corticosteroids
LABA	long-acting $beta_2$-agonists
QALY	quality-adjusted life year
RR	relative risk
SMART	the Salmeterol Multi-center Asthma Research Trial

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APPENDICES - available from CADTH's web site www.cadth.ca

1 INTRODUCTION

1.1 Background

1.1.1 Disease

"Chronic obstructive pulmonary disease (COPD) is a respiratory disorder that is characterized by progressive, partially reversible airway obstruction, systemic manifestations and increasing frequency and severity of exacerbations."[1] The limitation in airflow is commonly associated with an abnormal inflammatory response. Disease symptoms—shortness of breath (dyspnea) and intolerance to physical activity—are usually insidious in onset, but ultimately result in patients requiring medical intervention.

COPD is a major cause of morbidity and mortality throughout the world; it is the fourth leading cause of death.[2] Significant increases in the prevalence and mortality of the disease are predicted in the coming decades. With the reduction in patients' quality of life, there will be increasing demands on health care.

Smoking is the most important risk factor for the development of COPD, although other agents such as work-related dusts, noxious fumes, and gas also pose risk factors.[1] COPD should be suspected in patients with observable dyspnea, cough, or sputum production, and in patients with a significant smoking history.[1]

Many methods are used to classify disease severity in COPD patients, often using the degree of pulmonary function impairment,[2,3] or the magnitude of symptoms.[1] In general, and regardless of the classification system used, the severity of symptoms, the frequency of exacerbations, the risk of lung cancer, and the mortality rate increase as the disease becomes more severe.[1]

Acute exacerbations are the most frequent cause of medical visits, hospital admissions, and death among patients with COPD.[4] Acute exacerbations are defined as a sustained worsening of dyspnea, cough, or sputum production, leading to an increased use of maintenance medications, or supplementation with additional medications.[1] Exacerbations accelerate the rate of decline in patients' lung functions, and are an important measure of their quality of life.[1]

Exacerbations can vary in severity. A mild exacerbation might be a slight increase in shortness of breath, which can be successfully treated with minor changes to a patient's pharmacologic therapy. In advanced stages of the disease, exacerbations increase, with symptoms becoming more severe, so that patients usually require emergency room or hospital assessment and treatment. A severe exacerbation would include marked shortness of breath, and the inability to perform basic daily activities. Hospital care, including expensive pharmacologic treatment, intensive care support, and mechanical ventilation may be required. Significant mortality is associated with frequent, severe exacerbations. Interventions are effective in preventing the occurrence, and reducing the severity of exacerbations experienced by patients.

1.1.2 Interventions

The goals of COPD management include preventing disease progression, alleviating breathlessness and other respiratory symptoms, improving exercise tolerance, preventing and treating exacerbations, improving health status, and reducing mortality.[1] All these goals are achievable, even in advanced

stages of the disease, with integrated modern management.[1] This involves pharmacologic and non-pharmacologic interventions that are customized to suit the needs of an individual patient.[1] Pharmacologic therapies that are often used in managing stable outpatients include bronchodilators (short- and long-acting), inhaled corticosteroids, and oxygen. Two primary pharmacological interventions for the continuous treatment of COPD are long-acting beta$_2$-agonists (LABA) and inhaled corticosteroids (ICS). The other commonly used pharmacological intervention, short- or long-acting anti-cholinergic medications, will not be addressed in this analysis.

There is evidence that LABA and ICS can improve lung function for patients with COPD. LABAs are potent bronchodilators,[5] while ICS can help prevent airway inflammation.[6] A new class of drugs, which is a combination of LABA and ICS, is often called combination therapy (CT). LABAs by themselves may have weak anti-inflammatory effects, but the combination of LABA and ICS has an added synergistic effect on airway inflammation.[7-10]

Although CT has been shown to be superior to LABA alone, it is more expensive. According to the Alberta Health and Wellness Drug Benefit List and formulary (2005),[11] an average daily dose of a LABA and ICS combination costs about $2.80, while one dose of LABA costs about $1.61 (Table 1).

The Canadian Thoracic Society (CTS) provides the following recommendations for maintenance therapy using long-acting inhaled bronchodilators and ICS in stable COPD patients.[1]

- For patients whose symptoms persist despite reasonable short-acting bronchodilator therapy, a long-acting bronchodilator should be used. Those recommended include the anti-cholinergic preparation tiotropium (18 µg once daily), or a LABA (formoterol 12 µg twice daily or salmeterol 50 µg twice daily). Short-acting β_2-agonists may be used as needed for immediate symptom relief.
- For patients with moderate to severe persistent symptoms and exercise intolerance, a combination of tiotropium 18 µg once daily and LABA (i.e., formoterol 12 µg twice daily or salmeterol 50 µg twice daily) is recommended to maximize bronchodilation. It should be noted, however, that studies are ongoing on the effect of this combination on various health outcomes and results are not yet available. Short-acting β2-agonists can be used as needed for immediate symptom relief.
- Regular use of high dosage ICS alone should only be considered in patients with moderate to severe COPD who have recurrent, acute exacerbations (i.e., ≥3 exacerbations per year, especially for those requiring the use of oral corticosteroids). These recommendations may be overly stringent, and they may be modified to suggest earlier initiation after one acute exacerbation.

While the CTS does recommend CT for a specific group of COPD patients (those with an FEV_1 <50% predicted and ≥3 exacerbations per year), their guidelines also state that "…information directly comparing long-acting bronchodilator therapy with combination long-acting bronchodilator therapy and inhaled corticosteroid therapy is required for any definitive recommendation with respect to the role of ICS and LABA products for the enhanced control of dyspnea."[1] Since the release of the guidelines in 2003,[1] however, no additional studies have been published examining the role of combination inhaled long-acting bronchodilators and ICS in COPD.

The joint American Thoracic Society and European Respiratory Society (ATS-ERS) standards for the diagnosis and treatment of patients with COPD[3] state that "data from trials combining long-acting inhaled β_2-agonists and inhaled corticosteroids show a significant additional effect on pulmonary function and a reduction in symptoms in those receiving CT compared with its components. The largest effects in terms of exacerbations and health status are seen in patients with an FEV_1<50% predicted where combining treatment is clearly better than either component used alone." The Global

Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease (2005)[2] concludes that "inhaled glucocorticosteroid combined with a long-acting β_2-agonist is more effective than the individual components."

Table 1: List of assumptions

Model Inputs	Stage 1 FEV_1 >50% Predicted	Stage2 FEV_1 35% to 50% Predicted	Stage 3 FEV_1 <35% Predicted	Sensitivity Analysis Distribution (Range)	Sources
Baseline distribution of patients	93%	4%	3%	N/A	12
Progression to next stage	2.97% (2.87% to 3.07%)	9.94% (9.84% to 10.04%)	N/A	triangular (±0.1)	12
Number of exacerbations with LABA per person per year	0.17 (0.153 to 0.187)	0.59 (0.531 to 0.649)	0.83 (0.747 to 0.913)	triangular (±10%)	13
Mild	93.7%	26.0%	0%		12
Moderate	3.8%	61.9%	69.8%		12
Severe	2.5%	12.0%	30.2%		12
Relative risk reduction of exacerbation with combination therapy versus LABA alone	0.752 (0.742 to 0.762)	0.752 (0.742 to 0.762)	0.752 (0.742 to 0.762)	triangular (±0.1)	14-16
All cause mortality rates for patients in class (events per 100 person-years)	3.92 (3.72 to 4.12)	6.16 (5.85 to 6.47)	9.24 (8.78 to 9.71)	triangular (±5%)	17
QALY (utility) in state	0.897 (0.807-0.987)	0.750 (0.675-0.825)	0.549 (0.494-0.604)	triangular (±10%)	18-19
Mild exacerbation (QALY reduction)	−0.17 (0.15 to 0.19)	−0.17 (0.15 to 0.19)	−0.17 (0.15 to 0.19)		20
Moderate exacerbation (QALY reduction)	−0.47 (0.42 to 0.52)	−0.47 (0.42 to 0.52)	−0.47 (0.42 to 0.52)		21
Severe exacerbation (QALY reduction)	−0.47 (0.42 to 0.52)	−0.47 (0.42 to 0.52)	−0.47 (0.42 to 0.52)		21
Cost excluding therapies under study, per year, no exacerbation	$687 (618 to 756)	$658 (752 to 724)	$1,752 (1,576 to 1,927)	triangular (±10%)	12 (adjusted for Consumer Price Index to 2004)
Mild exacerbation	$59.82 (53.84 to 65.80)	$59.82 (53.84 to 65.80)	$59.82 (53.84 to 65.80)		
Moderate exacerbation	$270.12 (243.11-297.13)	$270.12 (243.11-297.13)	$270.12 (243.11-297.13)		
Severe exacerbation	$4,826.6 (4343.9-5309.3)	$4,826.6 (4343.9-5309.3)	$4,826.6 (4343.9-5309.3)		
Daily cost of treatment				triangular (minimum to maximum)	Alberta Health and Wellness, Drug Benefit List 2005[11]
Average LABA*	$1.61 (1.47 to 1.75)	$1.61 (1.47 to 1.75)	$1.61 (1.47 to 1.75)		
Average ICC*	$2.77 (2.60 to 4.18)	$2.77 (2.60 to 4.18)	$2.77 (2.60 to 4.18)		

* Oxeze=12 µg/dose taken twice; Serevent=50 µg taken twice; Advair (usual dose)=50 µg/250 µg dose taken twice; Advair (high dose)=50 µg/500 µg/2 doses taken twice; Symbicort=200 µg/dose taken twice; N/A=not applicable.

2 THE ISSUE

In 1998 to 1999, roughly half a million people in Canada (3.2% of the adult population) reported that they had the disease, and hospitalization and mortality rates for COPD have continued to rise. For the first time, more females than males in Canada are diagnosed with it.[22]

While studies have examined a potential clinical benefit of CT with inhaled β_2-agonists and ICS in COPD, the cost effectiveness of such therapy has not been evaluated. Information about costs, resource use, and cost effectiveness of using CT is necessary for decision makers, especially formulary managers, to recommend CT to none, all, or a select group of COPD patients.

3 OBJECTIVES

The objectives of this report are to:

- determine the cost effectiveness of inhaled LABA combined with ICS (both medications co-administered individually, or combined in one inhaler device), known as CT, versus administration of a LABA alone as a first-line agent in COPD, using available clinical and Canadian economic evidence
- measure the global economic impact of introducing CT versus LABA in Canada.

4 METHODS

We developed a cost-utility model (Markov) (Appendix 5) to evaluate and compare the use of CT with the use of LABA alone. This analytic approach was written a priori. We obtained model probabilities and the economic characteristics of health states regarding the efficacy of LABA and combination therapies from the available literature.

4.1 Literature Search and Review Strategy (Clinical Efficacy)

We searched selected databases on March 8 and 9, 2005, to find published research that investigated the use of LABA and ICS for patients with COPD (Appendix 1). Systematic reviews and original studies (randomized clinical trials) were identified. PubMed, Medline®, EMBASE®, and HealthSTAR® were searched using MeSH terminology, descriptors, and text words for the disease and drugs (i.e., LABA and ICS) including generic and trade names. Using the same search headings and keywords, we searched Web of Science, International Pharmaceutical Abstracts, and the Centre for Reviews and Dissemination [and its databases including Database of Abstracts of Reviews of Effects (DARE), NHS Economic Evaluation Database (NHS EED), and Heath Technology Assessment (HTA)], Evidence Based Medicine Reviews: Database of Abstracts of Reviews of Effects (DARE), and the Cochrane Register of Controlled Trials.

4.1.1 Inclusion criteria

We searched the systematic reviews and original articles (included and excluded from the reviews) for studies based on the following criteria.

- The trial is prospective and randomized controlled.
- Patients only have COPD.
- The interventional arms include LABA and CT (LABA plus ICS).
- The number of exacerbations is indicated.
- The mortality rates are indicated.

4.1.2 Selection process

Two reviewers (IM and DM) independently reviewed citations, and discarded extraneous studies based on their titles or abstracts. They made the final selection of relevant studies to be included and retrieved. Disagreement regarding the inclusion or exclusion of any report was resolved by discussion and consensus.

4.1.3 Assessment of quality

Two reviewers (IM and PJ) assessed the quality of each included trial using the Jadad quality scoring form (Appendix 2).

4.1.4 Data extraction

Two reviewers (IM and DM) independently extracted data on the intervention details and efficacy of LABA and ICS in reducing exacerbations and mortality (Appendix 3). These data were used to estimate model parameters for the economic analysis.

4.1.5 Disagreement

Disagreement between reviewers during quality assessment and data extraction was resolved by discussion and consensus.

4.2 Literature Search (Clinical Safety)

The search strategy for the safety of the drugs is shown in Appendix 4. The titles and abstracts were reviewed for evidence of safety by one reviewer (IM).

4.3 Literature Search Update (Clinical Efficacy and Safety)

At the end of March 2006, we updated the literature search. The new search replicated the original one, and resulted in 111 new references. These were abstracted by PJ and AC. We did not identify any additional clinical trials. One new economic study from Sweden[23] was published. This study compared costs and outcomes, or number of exacerbations, for CT versus LABA alone, but only for higher severity cases of COPD—our two higher severity levels. The results showed that CT was cost effective, which is consistent with our results.

4.4 Economics

4.4.1 Economic modelling

The economic framework was designed to estimate the costs and clinical outcomes, or utility, of providing LABA or CT for COPD patients modelled over the natural history of COPD. We used a Markov model similar to that used by Sin *et al*. (Appendix 5).[12] In this model, a cohort with COPD was followed over several cycles. We assumed an initial cohort of patients distributed over three levels of severity. The cohort progressed through successive cycles at a given rate, or died. In each state, a proportion of those in the cohort had exacerbations of varying severities. Costs and utilities were assigned to disease stages and to exacerbations. Parameters for the model were derived from the literature.

4.4.2 Disease history and severity

The initial cohort in the model was a composite of males (79%) and females (21%) aged 61 years. Most (97%) were current or former smokers.[12] To model the natural history of COPD, all patients were divided into three disease severity strata based on the criteria of the American Thoracic Society.[24]

- Stage 1 disease was defined as forced expiratory volume in one second (FEV_1) ≥50.0% of predicted.
- Stage 2 disease was defined as FEV_1 of 35.0% to 49.9% of predicted.
- Stage 3 disease was defined as FEV_1 <35.0% of predicted.

All modelling assumptions are shown in Table 1. Based on the Third National Health and Nutrition Examination Survey,[25] it was estimated that 93% of the total pool of patients had stage 1 disease, 4% had stage 2 disease, and 3% had stage 3 disease.

The model assumed that FEV_1 declined over time. Based on data from Anthonisen,[26] we assumed that the mean rate of FEV_1 reduction for each severity group was 47 mL per patient per year (11.75 mL over three months). Using this assumption, the estimated probability for a person in stage 1 moving into stage 2 was 0.74% over a three-month period, while the estimated probability for a person in stage 2 moving into stage 3 was 2.48%. Furthermore, we assumed that the risk of mortality, and the frequency and severity of exacerbations increased with declining FEV_1.

For analytic purposes, we classified COPD exacerbations into three categories.[24]

- Mild exacerbations were defined as worsening of symptoms requiring outpatient physician services, and institution of medications or antimicrobials (i.e., exacerbation therapy).
- Moderate exacerbations were defined as clinical episodes requiring emergency department services, or urgent visits to a physician's office (including institution of exacerbation therapy).
- Severe exacerbations were defined as requiring in-patient care (including institution of exacerbation therapy).

The total expected number of exacerbations per person for all severities annually, per health state, was 0.17 for stage 1, 0.59 for stage 2, and 0.83 for stage 3.[13] In stage 1, 93.7% of exacerbations were assumed to be mild, while in stage 2, 74% of clinically apparent exacerbations were assumed to be moderate or severe. For patients in stage 3, we assumed that 30% of exacerbations would require hospitalization (Table 1).[12]

All-cause mortality rates for COPD were estimated to be 3.92% for stage 1, 6.16% for stage 2, and 9.24 % for stage 3 disease (Table 1).[27] All-cause mortality was chosen, because COPD patients may die from complications of COPD and from other causes, but the distinction may be unclear.

4.4.3 Modelling strategies

The model was developed using an analytic horizon of three years divided into three-month increments. This timeframe allowed maximal flexibility for patients to move across disease severity categories.

We evaluated the effects of CTs using four strategies in a Markov model. With strategy 1 (base case), all patients were treated with LABA. With strategy 2, in addition to the base case, ICS are given to patients with stage 3 disease only. With strategy 3, in addition to the base case, ICS are given to patients with stage 2 or stage 3 disease only. With strategy 4, in addition to the base case, ICS are given to all patients.

For each strategy, all patients were followed for three years in three-month periods. For each three-month period, the probabilities of death and exacerbation were applied for each cohort in each disease category. From one three-month cycle to the next, a small proportion of patients moved into a higher disease severity category based on the expected declines in FEV_1. Patients who died during the three-month period were excluded from further analysis.

Survivors of each three-month cycle continued through another cycle, wherein a similar set of probabilities (survival, exacerbation, and disease progression) was applied. A total of 12 cycles translated into 36 months of follow-up. All analyses were conducted using TreeAge Pro Suite (TreeAge Software Inc; Williamstown, MA).

4.4.4 LABA and ICS

Mortality rates varied by the stage of disease. We used the baseline mortality rates for ICS,[17] because these were the only ones available by stage of disease. There was no evidence to indicate that mortality would differ by intervention. Therefore, we assumed, in the base case, that mortality rates were the same for LABA and combined therapies.

The total exacerbation rates by COPD severity level after using LABA (Table 1) were obtained. The exacerbation rates were ranked by severity, and were allocated by applying the distribution of cases according to severity levels, to the overall LABA exacerbation rates. There were nine exacerbation rates in total, based on three COPD levels, and three exacerbation severity levels. To estimate the exacerbation rates for CT, a single relative risk reduction, obtained from the retained articles (Table 1), was applied to each of the nine LABA exacerbation rates.

4.4.5 Calculation of costs

We obtained costs for each of the three COPD stages, and for each of the three exacerbation levels—mild, moderate, and severe (Table 2). The Alberta Health and Wellness Drug Benefit List formulary[11] (Table 1) provided costs for LABA and CTs, based on Alberta prices (Table 2) applied to Canadian recommended doses.[28] Maintenance (routine care) costs by COPD stage occurred over a three-month cycle (Table 1). In addition, if a person had an exacerbation, we added its cost to the maintenance cost (Table 1) of that particular stage. All costs were re-valued as of 2004, using Alberta levels. We alternatively discounted the costs at annual rates of 5% and 3%.

Table 2: Unit costs			
Item	**Cost**	**Units**	**Source**
Routine items			
Outpatient visit internist	$35.68	visits	AHCIP code 0303A INMD
Outpatient visit GP	$28.97	visits	AHCIP code 0303A
Spirometry	$99.56	procedures	AHCIP codes 0338C ($39.68), 0338A ($9.40), 0338N ($25.74), 0338H ($24.74)
Beta-adrenergics	$4.72	days	general salbutomol, DIN 00002232987, $0.59/puff, 8 per day
Theophylline	$0.50	days	400 mg per day, oral, $0.5036
Inhaled steroids	$1.26	days	Flovent, 500 mg per day, 250 mg aerosol $0.6302
Oxygen therapy	N/A	days	
Exacerbation items			
ICU days	$2,916	days	3 x daily ward rate
Ward days	$972	days	AHW
ER visits	$461.42	visits	ACCS code 863 ($418) AHCIP code 0303A E/M ($43.42)
Antibiotics	$6.28	days	clarithromycin, 1,000 mg, 500 mg oral ($3.1442)
Systemic steroids	$0.13	days	prednisone, 30 mg per day, 5 mg $0.022

AHCIP=Alberta Health Care Insurance Plan, Schedule of Medical Benefits, 2005;[29] AHW=Alberta Health and Wellness;[30] ACCS=Ambulatory Case Classification System, in Health Costing in Alberta, 2004;[30] GP=general practitioner; ICU=intensive care unit; ER=emergency room; N/A=not applicable.

4.4.6 Health outcomes

The health outcome that we considered was health-related quality of life (HRQL). A quality-adjusted life year (QALY) value was obtained for the duration of each of the three stages (Table 1). Each time that a person had an exacerbation, the patient's utility was reduced by a specified amount for that three-month cycle (Table 1).

We assumed, in the base case, that there was no mortality reduction in CT versus LABA. Over the 12-month period of their study, Calverley *et al.* noted that the mortality was five, 13, and five cases in the CT budesonide-formoterol, the LABA formoterol alone, and the placebo groups respectively.[14] The authors stated that most of the deaths were related to COPD, and not to cardiovascular events. The same agents were studied in a population that included more severe COPD.[15] These authors noted a mortality of six, six, and nine patients in the budesonide-formoterol, formoterol alone, and placebo groups respectively. The authors stated that there did not seem to be any treatment-related mortality effect. Finally, a study using salmeterol rather than formoterol as the LABA did not specify mortality rates, but commented that there were no unanticipated cardiac events in the groups receiving salmeterol.[16]

4.4.7 Sensitivity analysis

We conducted probabilistic analyses of all key variables (Table 1). In cases where variances were not found in the literature, we used −10% and +10% of the base values as our upper and lower limits. The results were reported as an acceptability curve.[31] An acceptability curve shows the probability that an intervention is cost effective at any given threshold (e.g., $50,000 per QALY).

A separate sensitivity analysis was conducted on the QALY decrement associated with a moderate and a severe exacerbation (5% discount rate using the three-year model). The QALY decrement associated with a moderate exacerbation was 0.42 (0.47−10%), and 0.52 (0.47+10%) for a severe exacerbation.

4.4.8 Budget impact

We assessed the impact of replacing LABA with CT, or adopting CT for those who use neither, on health services in Alberta. We made the assumption that those who are >65 years old, and have been prescribed ipratropium have COPD. This is the only way to identify current drug use among COPD patients on a population basis. We excluded those with COPD who were not prescribed ipratropium, CT, ICS, or LABA, and those who had asthma and not COPD, but were prescribed tiotropium. This latter number is likely to be small.

We obtained data (year-end March, 2003), from Alberta Health and Wellness,[32] on the number of persons >65 years old in Alberta, using the provincial drug plan—this includes virtually the entire population >65 years old—who had prescriptions that were indicative of COPD (as specified).

For these individuals, we derived a utilization analysis for the following therapeutic alternatives:
- situation as of year-end 2003, described by Alberta Health and Wellness
- use of CT instead of LABA (for those who had used LABA)
- use of CT for those who used LABA, and might switch to CT, and for those who previously used neither CT nor LABA, but might add CT.

The third option would provide an overestimate of the use of CT, because the Canadian guidelines would recommend first to include a short- or longer-acting β_2-agonist, rather than a direct switch to CT.

We developed an estimate of the cost of each alternative assuming an annual (365-day) provincial cost of $587 for LABA, and $1,011 for CT (Table 1). All users of ipratropium would continue using this drug.

5 RESULTS

5.1 Clinical

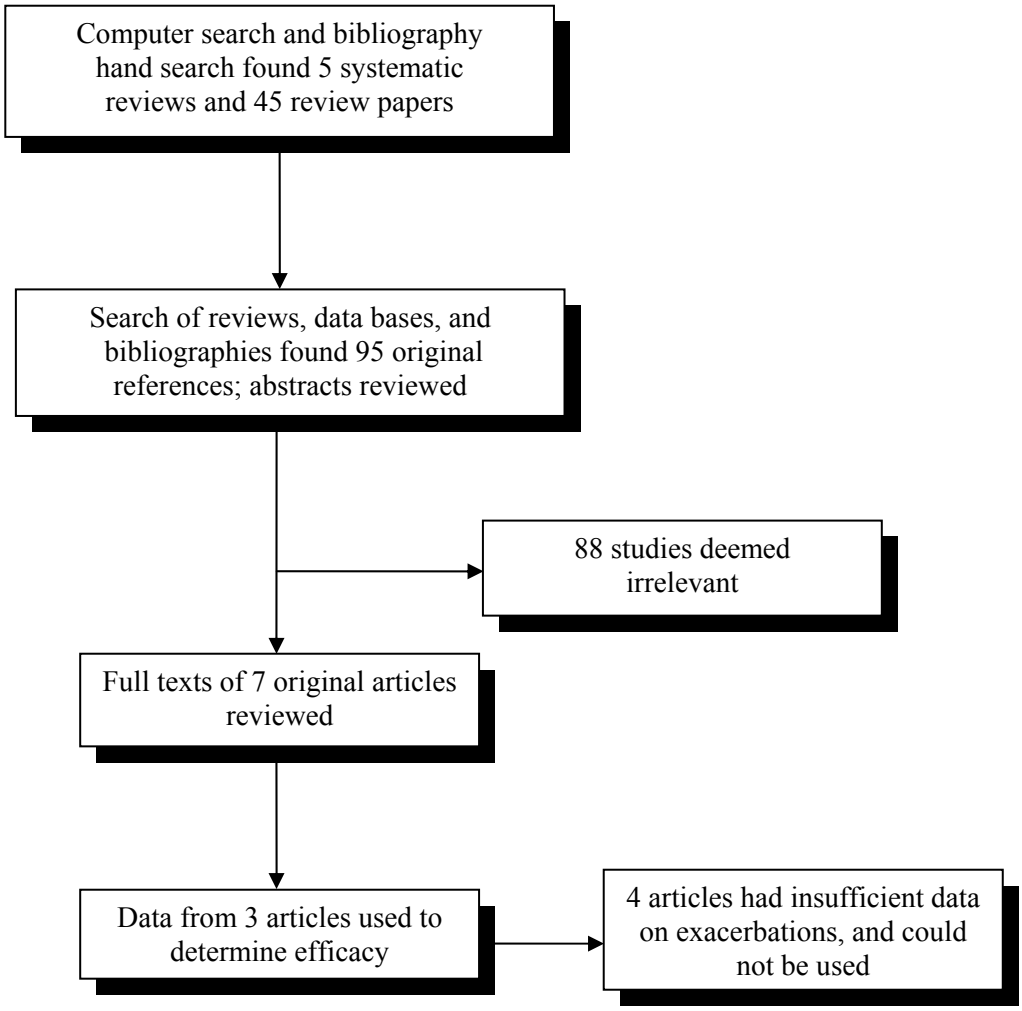
5.1.1 Quantity and quality of selected reports

Our search revealed 145 reports, consisting of five systematic reviews,[17,33-37] 45 review papers, and 95 articles (Figure 1). We reviewed abstracts for all relevant original articles—those identified in the systematic reviews, original reports, and other reviews. Seven original studies were identified as meeting the initial selection criteria. The reviewers read the entire manuscripts, and eliminated four, because they contained insufficient information on exacerbations. The three remaining articles, which the reviewers would abstract, were Calverley (TRISTAN),[16] Calverley,[14] and Szafranski.[15]

The quality of the three retained articles was:
- for Calverley (TRISTAN), five points out of a possible five, adequate allocation concealment
- for Calverley, four points out of a possible five, adequate concealment
- for Szafranski, four points out of a possible five, inconclusive information to rate concealment.

Characteristics of the three studies are presented in Table 3. All three studies were judged to be of sufficiently high (e.g., >2) quality to create estimates of effectiveness.

Figure 1: Progress through selection of potentially relevant studies



5.1.2 Efficacy

The outcomes of the three studies are presented in an evidence table (Appendix 6). Effectiveness is expressed in terms of the number of exacerbations and their severities. Our analysis indicates that mortality rates were similar for both interventions, and therefore mortality does not enter into our results. The combined relative risk in the base case analysis is the weighted average of the three studies, summarized in Appendix 6. This weighted average relative risk of an exacerbation for combined therapy compared to LABA is 0.752. This risk reduction is uniformly applied to the frequencies of exacerbations in all stages, and applied to the severity of exacerbations at each stage.

Table 3: Characteristics of included studies			
Study	Calverly[16]	Calverly[14]	Szafranski[15]
Industry sponsored	yes	yes	yes
Study design	randomized, double-blind, parallel	randomized, double-blind, parallel	randomized, double-blind, parallel
Quality assessment score	5	4	4
Subject inclusion criteria	COPD FEV_1 25% to 70%	COPD FEV_1 ,<50%	COPD FEV_1 <50%
Interventions	placebo, salmeterol 50 mg twice daily; fluticasone 500 mg twice daily; salmeterol-fluticasone (500 µg/50 µg twice daily)	placebo, budesonide 400 µg twice daily; formoterol 9 µg twice daily; budesonide-formoterol (400 µg/9 µg twice daily)	placebo; budesonide 320 µg twice daily; formoterol 9 µg twice daily; budesonide-formoterol (320 µg/9 µg twice daily)
Other COPD medications allowed	salbutamol, mucolytics, theophyline, anticholinergics	short-acting rescue, oral steroids, antibiotics, anticholinergics, theophylline	none except short-acting rescue
Study duration	12 months	12 months	12 months
Length of run-in period	2 weeks	2 weeks	2 weeks
HRQL assessment	yes, SGRQ	yes, SGRQ	yes, SGRQ

COPD=chronic obstructive pulmonary disease; HRQL=health-related quality of life; FEV_1= forced expiratory volume; SGRQ=St George's Respiratory Questionnaire

5.1.3 Safety

No differences were noted in the serious adverse events between groups in the three studies[14-16] that we included in our analysis, although there were differences in minor side effects. Oropharyngeal candidiasis tended to be higher in the group receiving combination LABA with ICS when compared to the placebo or LABA alone groups (6%, 1%, and 1% respectively).[16] The overall frequency of recorded adverse events was similar between the LABA group and the combined LABA with ICS group (19% and 17% respectively), and these both tended to be lower than the placebo group (26%)[14]. Calverley *et al*.[14,16] found an overall lower incidence of adverse events (0.5%, 0.6%, and 0.5% respectively).

On September 7, 2005, GlaxoSmithKline sent an advisory note to Canadian physicians[37] about potential safety concerns with salmeterol (Serevent®), a LABA used to treat asthma in conjunction with an ICS, or COPD independently or as part of a salmeterol-fluticasone combination inhaler (Advair®). The Salmeterol Multi-Center Asthma Research Trial (SMART)[38] studied 26,355 subjects with asthma. Their primary endpoint (combined respiratory-related death and life-threatening experience) tended to be higher in the group treated with salmeterol than with placebo (RR=1.4, 95% CI=0.91 to 2.14), but the results were not significant. The risk of asthma-related death also increased in the salmeterol group compared with the placebo group (RR=4.37, 95% CI=1.25 to 15.34). The increase in mortality was greatest in those patients taking salmeterol who did not report taking concomitant ICS as part of their usual asthma therapy at study entry. The numbers of deaths were similar in the placebo group (three of 6,138) and salmeterol group (four of 6,127) if they were also taking ICS.

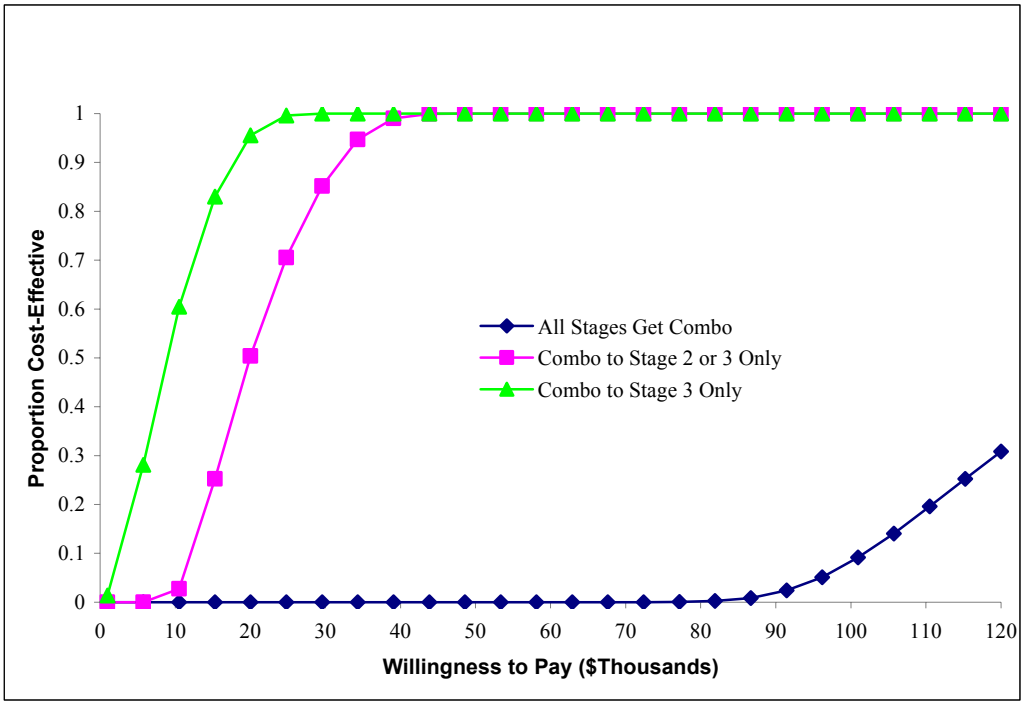
Table 4: Results – base case					
Treatment Scenario	**Cost Per Patient**	**Incremental Cost**	**QALY**	**Incremental QALY**	**Incremental Cost-Effectiveness Ratio**
Three-year time horizon with 5% discount rate					
LABA for all stages	$3,719	—	2.405	—	—
Combination therapy for stage 3 only	$3,743	$24	2.408	0.00248	$9,670 per QALY
Combination therapy for stages 2 and 3	$3,829	$86	2.411	0.00272	$31,606 per QALY
Combination therapy for all stages	$5,173	$1,344	2.416	0.00495	$271,241 per QALY
Three-year time horizon with 3% discount rate					
LABA for all stages	$3,818	—	2.406	—	—
Combination therapy for stage 3 only	$3,843	$25	2.408	0.00248	$10,073 per QALY
Combination therapy for stages 2 and 3	$3,931	$88	2.411	0.00272	$32,341 per QALY
Combination therapy for all stages	$5,310	$1,379	2.416	0.00495	$278,305 per QALY
Lifetime horizon with 5% discount rate					
LABA for all stages	$9,636	—	6.763	—	—
Combination therapy for stage 3 only	$9,729	$93	6.775	0.01187	$7,829 per QALY
Combination therapy for stages 2 and 3	$10,050	$321	6.787	0.01217	$26,357 per QALY
Combination therapy for all stages	$13,170	$3,120	6.800	0.0132	$235,828 per QALY
Lifetime horizon with 3% discount rate					
LABA for all stages	$10,493	—	6.763	—	—
Combination therapy for stage 3 only	$10,597	$104	6.775	0.01187	$8,754 per QALY
Combination therapy for stages 2 and 3	$10,951	$354	6.787	0.01217	$29,066 per QALY
Combination therapy for all stages	$14,329	$3,378	6.800	0.01323	$255,329 per QALY

5.2 Economics

5.2.1 Cost and cost effectiveness

The cost statistics include the cost of drug therapy plus the cost of maintenance (routine care) and treatment of exacerbations. The cost-per-person estimates for the three-year time horizon are shown in Table 4. These statistics are presented for four categories, in increasing order of magnitude, using the method of analysis outlined in Drummond *et al*.[39] Cost per person is lowest when LABA is provided to all persons. In this case, with a 5% discount rate, it is $3,719. The cost increases to $3,743 when CT is given to persons in COPD stage 3. The cost is higher ($3,829) when persons in stages 2 and 3 receive CT, and most expensive when all receive CT. Although LABA therapy costs less than CT, its provision is associated with additional system costs, notably because of more exacerbations.

Figure 2: Acceptability curve for three-year model



Conducted at a 5% discount rate.

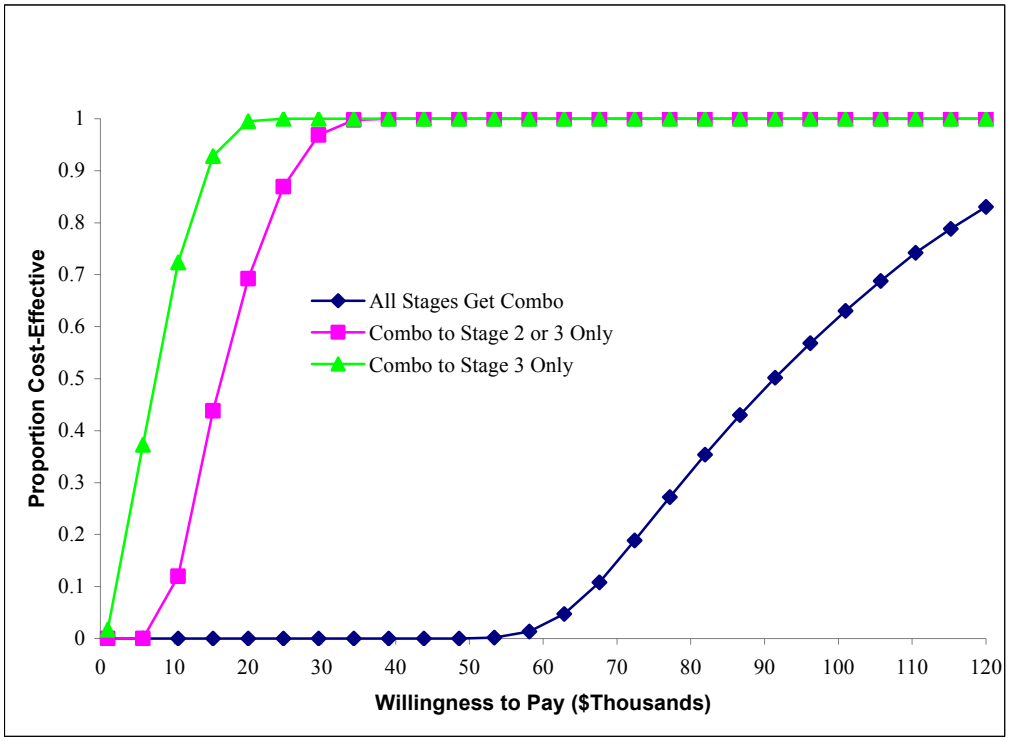
The total number of quality-adjusted life years (QALY) is shown in Table 4. Over a three-year time horizon, the entire cohort generated 2.408 QALYs per person if CT was given only to those with stage 3 COPD. This increased to 2.411 when persons in stages 2 and 3 received CT. The outcome measure for the complete cohort when LABA was given to everyone was lower than for any cohort where CT was provided. There are no mortality effects in this analysis, so that all differences in outcomes are due to health quality changes.

The incremental cost-effectiveness ratio (Table 4) is presented in successive order—starting with the lowest cost interventions, LABA, for all cases—with costs being the focus variable. If we changed the intervention and provided CT for COPD stage 3 cases, the incremental cost-effectiveness ratio (ICER) over a three-year horizon would be $9,670 per QALY. The marginal ICER for providing CT for stages 2 and 3 is $31,606; for all stages, it is $271,241 per QALY. When we choose a lifetime horizon, the results are of a similar magnitude (Table 4).

5.2.2 Sensitivity analysis

Figures 2 and 3 show the results of the probabilistic analysis, in which we varied all variables simultaneously. The acceptability curves show that, at a threshold level of $50,000, there is a high probability that providing ICS (instead of LABA) is cost effective for persons with stage 3 alone, or with stages 2 and 3 COPD. This is not true for the provision of ICS for all persons with COPD.

Figure 3: Acceptability curve for lifetime model



Conducted at a 5% discount rate.

The separate sensitivity analysis on the QALY decrement associated with a moderate and severe exacerbation indicates that, starting with LABA for all cases and providing CT for COPD stage 3 cases, the ICER would be $10,071 per QALY. The marginal ICER for providing CT for stages 2 and 3 is $33,620 per QALY; for all stages, it is $272,120 per QALY.

6 HEALTH SERVICES IMPACT

6.1 Budget Impact

The number of persons >65 years old in Alberta in 2003 who used COPD-related drugs is shown in Table 5. The estimated cost of LABA plus combination therapies (but excluding the costs of ipratropium) was $18,017,000 for 20,946 persons. If the 7,449 persons who were taking LABA switched to CT, the total system-wide drug costs for CT would be $21,340,000. This is an increase of about $3.3 million.

If some of these users of LABA were mild cases (in stage 1, for example), then the total number switching to CT would be smaller if our recommendations were accepted. We do not know how many people in the sample were in stage 1, but this number is likely to be small.

Table 5: Results of budget impact analysis, Alberta 2003				
Group	**Number in Province**	**Scenario 1 Cost According to 2003 Alberta Data***	**Scenario 2 All Persons Who Take LABA Switch to CT***	**All Persons Who Take LABA and Ipratropium Alone Start to Take CT***
Persons who were dispensed CT	13,497	$13,645,000	$13,645,000	$13,645,000
Persons who were dispensed LABA but not CT	7,449	$4,372,000	$7,695,000	$7,695,000
Persons who were dispensed ipratropium but not LABA or CT	38,118	N/A	N/A	$38,965,000
Total cost of CT and LABA		**$18,017,000**	**$21,340,000**	**$60,305,000**

*The unit cost of CT was $1,011 per annum, and the unit cost of LABA was $587 per annum (Table 1). N/A=not applicable.

If all the persons who were taking ipratropium (but neither LABA nor CT) also took CT, the total budget for CT drugs would increase to >60 million. We cannot tell how many persons who took ipratropium would be in stages 2 and 3, but the percentage is likely to be considerable. According to the Canadian Respiratory Society COPD guidelines, persons with COPD should be prescribed a short- or longer-acting B2-agonist, rather than switching directly to CT. This would moderate the budget impact, making the $60 million an overestimation. Although the budget impact of moving from LABA to CT is moderate, the impact of providing CT to those additional persons who take neither could be considerable.

The population in Canada who are >65 years old (4.3 million) is 12.5 times that of Alberta (346,000). The budget impact for Canada, therefore, would be in the range of 12.5 times the Alberta impact, and the additional cost, nationally, of switching from LABA to CT for those taking LABA would be approximately $43.7 million.

7 DISCUSSION

Chronic conditions such as COPD are expected to become major contributors to death and disability worldwide by 2020.[40] The onus is on policy makers to respond to the changing face of health care needs by moving away from systems that are focused on episodic care to those of exacerbation prevention. COPD, in particular, is a chronic condition with inexorable but slow progression resulting in opportunities to provide rational and cost-effective treatment. Our analysis offers clear policy choices regarding the provision of LABA alone, and the combination of LABA and ICS for patients with COPD.

To interpret the results of the data from the studies that we reviewed, we must specify a criterion with which to judge the incremental cost-effectiveness ratios (ICERs). Several criteria have been used.[41-43] Laupacis *et al*.[44] used an ICER of $25,000 to indicate strong evidence for adoption of an intervention. More recently, $50,000 is a conventionally quoted reference point.[41] The use of a reference value is a useful interpretative device, but it is an arbitrary one, and is used only as an example. Policy makers, not analysts, are free to accept or reject these values. or to use ICERs as one of several pieces of information in making decisions.

Selecting a cut-off point of $50,000 would imply that CT should be provided for persons in stages 2 and 3 COPD, but not stage 1. The cut-off point would have to be higher for CT to be recommended for everyone. The same conclusions can be drawn when we take a lifetime horizon, but we are less sure of the conclusions that only stages 2 and 3 persons should receive CT.

There are several limitations to this analysis. Only three good quality trials have prospectively examined the effects of CT on exacerbation frequency in COPD.[14-16] None of the trials directly examined the effects in the mildest COPD population. All three trials showed consistent results using two formulations of combination inhalers. Based on the economic model that we used, providing CT for persons with moderate to severe COPD (stage 2 and stage 3) is cost effective at a threshold of $50,000 per QALY gained.

In the relatively small population of patients studied with placebo (n=822), combination inhaler (n=820), or LABA (n=828), there was no clear effect on mortality. The investigators reported that deaths were not related to the medications studied. However, in a large population of subjects with asthma, the use of a LABA in patients who did not report taking concomitant inhaled corticosteroids was associated with a higher death rate. This should be considered in the larger framework of asthma management. The excessive use of short acting β_2-agonists has been associated with increased asthma-related mortality.[45] Conversely, the use of ICS has been shown to protect against asthma-related mortality.[46] Although not statistically significant, Calverly *et al.*[14] found five, five, and 13 deaths in the LABA-ICS, placebo, and LABA alone groups respectively. None of the three COPD trials that we reviewed are powered to see a mortality effect from treatment. It is unclear if the risk of increased mortality with the use of LABA alone is a class effect, or is unique to the agent that was studied (salmeterol). Because there is overlap in the pathophysiology of adult asthma with COPD, and prior studies have suggested a risk with the excessive use of β_2-agonists, it might be prudent to discourage the isolated use of LABAs as maintenance therapy in COPD unless other safety data become available.

The CTS guidelines recommend that combination inhaler therapy be considered for patients with an FEV_1 <50% predicted and with ≥3 exacerbations per year. This analysis suggests that it would be cost effective to start combination inhaler therapy for all stage 2 (FEV_1 <50% predicted) or stage 3 (FEV_1 <35% predicted) patients irrespective of the frequency of exacerbations. This is a small but significant difference in approach. It would, in effect, promote the use of combination inhaler therapy more widely in the more severe COPD population; and the information to family physicians and specialists would be simpler to explain, because CT is a simpler concept to understand than exacerbation criteria. This analysis should also be considered by CTS COPD guideline committee members, and by others who create recommendations for combination inhaler therapy.

8 CONCLUSION

Our results indicate that CT administered to moderate and severe COPD patients may be perceived as cost effective, if the health system is prepared to pay up to $50,000 for a QALY. Our budget impact analysis indicates that additional resources would be required. A reduction in the use of other health care resources could compensate for some of the difference.

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APPENDICES

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