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Original article

Systematic review of models used in economic analyses in moderate-to-severe asthma and COPD

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t.einarson@rogers.com**Keywords:**

Asthma – COPD – Economic evaluations – Validation

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Citation: J Med Econ 2016; 19:319–55**Abstract****Background:**

Respiratory diseases exert a substantial burden on society, with newer drugs increasingly adding to the burden. Economic models are often used, but seldom reviewed.

Purpose:

To summarize economic models used in economic analyses of drugs treating moderate-to-severe/very severe asthma or chronic obstructive pulmonary disease (COPD).

Methods:

This study searched Medline and Embase from inception to the end of February 2015 for cost-effectiveness/utility analyses that examined at least one drug against placebo, another drug, or other standard therapy in asthma or COPD. Two reviewers independently searched and extracted data with differences adjudicated via consensus discussion. Data extracted included model used and its qualities, validation methods, treatments compared, disease severity, analytic perspective, time horizon, data collection (pro- or retrospective), input rates and sources, costs and sources, planned sensitivity analyses, criteria for cost-effectiveness, reported outcomes, and sponsor.

Results:

This study analyzed 53 articles; 14 (25%) on asthma and 39 (75%) COPD. Markov models were commonly used for both asthma and COPD-related economic evaluations. Relatively few studies validated their model. For asthma-related studies, 10 examined inhaled corticosteroids and nine studied omalizumab. Placebo or standard therapy was the comparison in 11 studies and active drugs in the remainder.

Conclusions:

Few studies include validation of their models. Furthermore, controversy concerning some results was uncovered in this study, which needs to be avoided in the future.

IntroductionRespiratory diseases such as chronic obstructive pulmonary disease (COPD) and asthma are persistent, with little chance of complete remission. As well, both diseases are widespread, occurring throughout the world. The 2010 Global Burden of Disease study undertaken by the World Health Organization estimated that more than 9.6% of the world's population have either COPD or asthma, affecting about 329 million and 334 million people, respectively¹.Both COPD and asthma negatively impact patients in terms of health status, duration, and quality-of-life, as well as costs². These ailments also substantially

impact society with respect to resource utilization (e.g., medical care, hospitalization, drugs and other treatments), and associated costs. A recent study from France estimated it cost €9382 (57% direct costs) for each patient with COPD³. In the US, Ford *et al.*⁴ predicted that the burden of COPD in that country would rise to \$49 billion by 2020. O'Neill *et al.*⁵ estimated that the cost of treating refractory asthma in the UK was between £2912 and £4217 per annum per patient. Thus, the costs are very large and increasing, which causes concern amongst payers and formulary managers.

Novel therapies are costly to develop. Estimates of the cost for the development and launching of a new drug run as high as USD \$1.8 billion^{6,7}. At the same time, success rates for new drugs have been declining and, thereby, returns on investment have been negatively impacted^{6,8}. In order to recoup development expenses, the costs of developing novel therapeutics (both successful and unsuccessful) are usually passed onto the consumer. At the point of purchase, the consumer determines whether there is value for money in purchasing the novel therapeutics.

Consequently, there has been an emphasis on economics, which assesses value for money⁹. Pharmacoeconomic analyses apply the concepts of economics to the comparison of drugs¹⁰. Interest in this area is high, as evidenced by recent reviews of the pharmacoeconomics of both asthma^{11,12} and COPD¹³. However, these reviews have focused mainly on either the results of the analyses¹¹ or the quality of the reporting^{12,14}. A review focusing on the models used to arrive at the pharmacoeconomic outcomes has not been undertaken to date.

There are three basic models for assessing the pharmacoeconomics of drugs; prospective, predictive and retrospective¹⁵. Prospective models are often associated with clinical trials comparing drugs or treatments, which allows the prospective gathering of data. The predictive model is usually referred to as a decision analytic analysis, but also includes Markov models and discrete event simulations. These types predict the average outcome, given a set of inputs. The retrospective model uses patient charts or databases, using data that have already been collected. In general, prospective models focus on short-term acute treatments and usually cannot be extrapolated to long-term therapy¹⁵.

Despite reviews of the economics of drugs in asthma or COPD, the models used have seldom been their focus, as evidenced by a search of the literature. While there was one recent review identified by Kirsch¹³ that examined only Markov models in COPD, that study reviewed only smoking cessation interventions, rather than drugs to treat asthma or COPD. We, therefore, undertook the present research to review the types of models that have been utilized in cost-effectiveness analyses of drugs used to treat asthma and COPD since the introduction of biologic treatment.

Methods

This research was guided by the PRISMA statement for reviews¹⁶. Criteria for acceptable studies were developed *a priori*, as was the search strategy. All steps of the process were done in duplicate by independent reviewers.

Eligibility criteria

Studies eligible for inclusion in this study were economic evaluations related to pharmacotherapy interventions for at least moderate-to-severe asthma or chronic obstructive pulmonary disease or both. The target population consisted of patients having severe disease (or worse); however, patient samples often presented mixed severities. We, therefore, allowed patients having moderate-to-severe disease or perhaps a small proportion with milder forms. For this analysis, only the severity of the disease itself was considered; treatments exclusively used for acute exacerbations, whether severe or not, were not accepted. Asthma was considered sufficiently severe if identified as such by the authors or if patients were symptomatic on >800 µg/day of corticosteroids or if their average peak expiratory volume (PEV) was <70% (i.e., below the midpoint of the range for the moderate disease). COPD was considered sufficiently severe if the majority of patients were classified as having GOLD-3 or GOLD-4 disease or if the average forced expiratory volume (FEV) was <65% (i.e., below the midpoint of the range for moderate disease). We accepted studies dealing with either adults or pediatrics. Patients could not be immunocompromised or have any other concomitant respiratory diseases. Either inpatient or outpatient populations or both could be examined. We also accepted dynamic progression models of COPD that included disease severity that ranged from mild-to-severe or very severe disease as well as death, such as Markov models or discrete event simulations.

There must have been two or more therapeutic options compared, at least one of which was a drug. Acceptable types of analyses were those that combined both costs and outcomes into an incremental cost-effectiveness ratio (ICER). That is, we included cost-effectiveness and cost-utility analyses, but excluded cost-minimization and cost-consequence analyses.

The first biologic to be licensed (for any indication) was infliximab, in 1998¹⁷. Its original indication was Crohn's disease, but the potential for using biologics in treating respiratory diseases was quickly recognized¹⁸. Trials were soon undertaken in patients with COPD¹⁹. It may be postulated that the era of biologic treatment for asthma began with the Australian approval of omalizumab in 2002¹⁷. However, the process began in the year 2000²⁰. The authors assumed that economic analyses of biologic treatment related to asthma would not have been published

prior to the year 2000. As such, only full text, peer-reviewed articles published between 2000–2015 were considered.

Information sources

The search engines used to identify relevant articles were: Embase 1980–2015 week 7, and Medline 1946 to February week 2, 2015. Within these databases, searches were limited to the above-mentioned dates. Retrieved articles were hand searched for relevant studies not identified by search engines. Furthermore, PubMed was searched for more recent studies not yet included in the other search engines used.

Search and study selection

Two reviewers independently searched the databases using key words ‘cost effectiveness.mp OR exp cost-benefit analysis’, ‘costs and cost analysis OR cost utility.mp’, ‘willingness to pay.mp’, ‘asthma OR COPD’, and ‘full text’. Results were compared first after examining the titles and abstracts (first filtration) and again after retrieving full text articles (second filtration). At each stage, discrepancies were adjudicated via consensus discussion.

Data items

Data collected included author names, year of publication, country, sponsor, model type and structure, validation of the model, disease and its severity, patients examined, data collection (i.e., prospective vs retrospective), treatments compared, time horizon(s), analytic perspective(s), clinical rates used and their sources, resources costed and sources of utilization rates, currency and year of costing, discount rate for costs and outcomes, criterion used to determine cost-effectiveness, outcomes examined, sensitivity analyses planned, reported costs for each treatment, reported outcomes, incremental cost-effectiveness ratios (ICERs), sensitivity analyses reported, and conclusions made by the authors. Items were recorded in a spreadsheet and results were then compared between data extractors. All cases of difference were settled through discussion.

Data analysis

Models were defined in three broad categories: trial based (prospective), decision models (predictive), and models based on patient data records (retrospective). Three types of trial models were possible, including (1) the dedicated economic RCT which was designed specifically for an economic analysis, (2) the piggyback trial, where an economic arm was added to the clinical protocol of the RCT and all data were collected prospectively, and (3) the retrospective RCT, where an existing RCT was used and

economic data were fitted post-hoc. Four types of decision models were considered. They included (1) the classical decision tree, (2) the Markov model (and all of its variants), (3) patient level simulations (e.g., discrete event simulations), and (4) spreadsheet models where calculations were done on a spreadsheet as opposed to dedicated software-based models. Finally, patient data based models comprised three types: (1) administrative databases, which were designed for other purposes such as the payment of claims for healthcare services, (2) patient registries designed to prospectively collect patient data for specific diseases, and (3) patient charts, which could be either paper or electronic. Data were tabulated and analyzed descriptively.

Results

The search process is depicted in Figure 1. We were able to use data from 53 articles, including 14 (25%) in patients with asthma^{12,21–33} and 39 (75%) in patients with COPD^{33–71}. No papers were found that examined patients having both diseases concomitantly.

Among the 14 papers on asthma, eight were from Europe, five (36%) from North America, and one (7%) from South America. Nine (64%) were sponsored by the pharmaceutical industry, two (14%) by non-government foundations, and three (21%) did not mention funding. Table 1 summarizes the models that have been used. In asthma patients, one was trial based (retrospectively modeled an existing RCT), 11 were decision models (10 Markov and one spreadsheet decision analysis), and two were based on electronic patient data records.

Table 2 provides details of the models, describing their structures and characteristics. Among the Markov models used in asthma, only three reported validation of some sort, but most often providing few details. All of the studies collected data retrospectively. Ten of the studies examined inhaled corticosteroids and nine studies omalizumab. Placebo or standard therapy was the comparison in 11 studies and active drugs in the remainder. Six focused on adults only, seven included adolescents as well as adults, and one was restricted to children <18. The perspective of the analysis was societal in three, the healthcare system in nine, and third party payer in two. Two studies used a time horizon of 12 weeks, seven used 1 year, one used 10 years and six examined over a lifetime. Two studies employed two different time horizons.

Table 3 summarizes the inputs into the models and their sources for asthma-related pharmacoeconomic studies. Eleven studies used RCTs as their primary source for clinical data and three used patient data. In seven analyses, discounting was not done because the time horizon did not exceed 1 year. In all of the others, discounting was done for both costs and outcomes. Cost were discounted from 3–5%

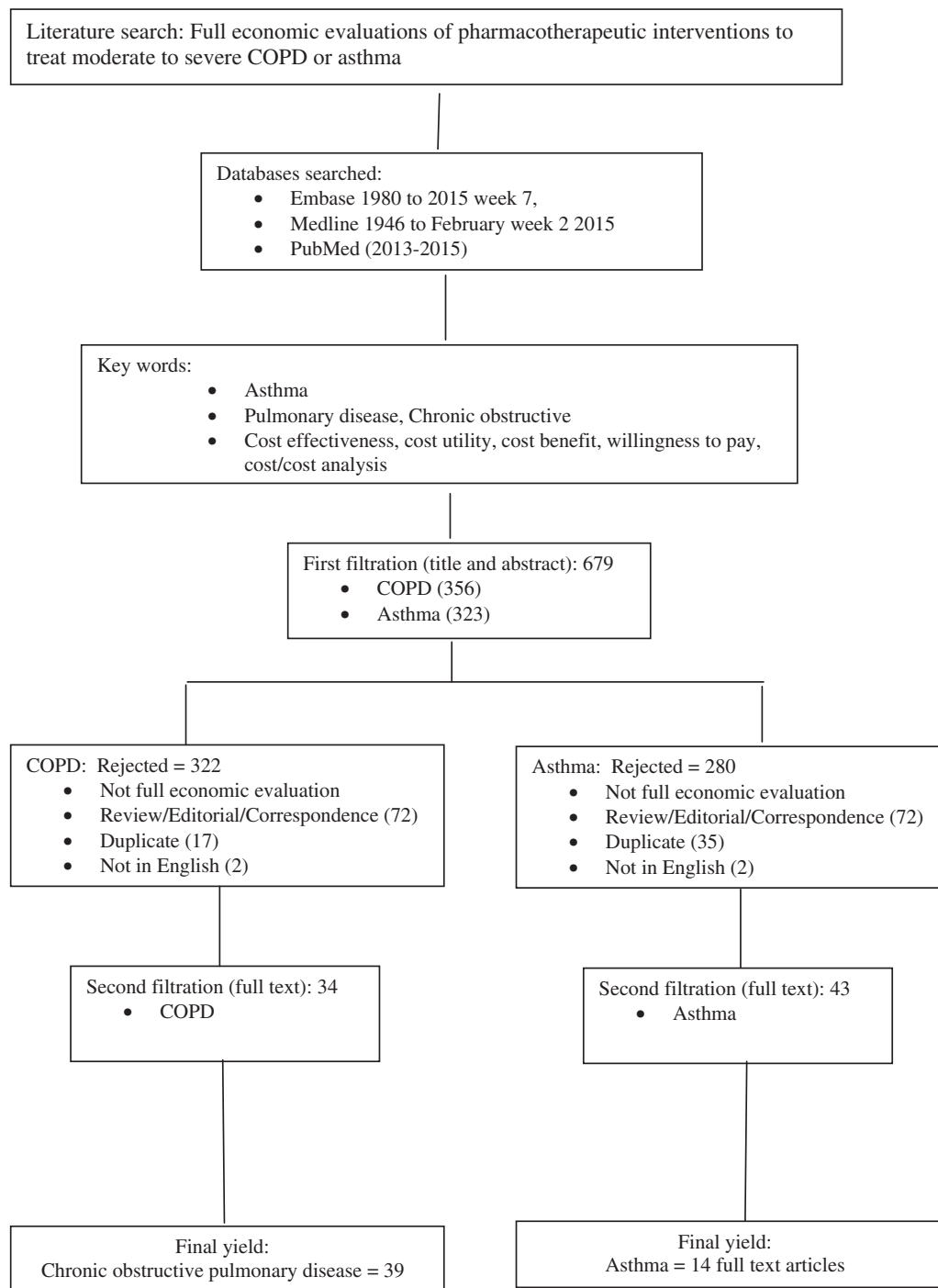


Figure 1. Literature search tree.

and outcomes from 1–3.5%. Ten included only direct costs and four included both direct and indirect costs. Ten out of 12 reported sensitivity analyses, and two did not perform any.

Results of the models used in the economic analysis of drugs used for severe asthma appear in Table 4. Costs were reported in either US dollars, Canadian dollars, British

pounds or Euros. Results varied widely; for example Brown *et al.*²¹ and Dal Negro *et al.*¹¹³ concluded that omalizumab compared to standard care was cost-effective, while Campbell *et al.*²² reported that omalizumab was not cost-effective compared to standard care.

There were 39 studies that employed economic models to assess drugs used in severe COPD. Table 5 describes

Table 1. Models used in economic analyses of severe asthma and COPD.

Model type	Sub-type	Disease examined		
		Asthma	COPD	Total
Trial based	Prospective economic trial	0	0	0
	RCT with economic data collection (piggyback)	0	6	6
	Existing RCT	1	1	2
	Sub-total	1	7	8
Decision model	Markov	10	10	22
	Decision tree	0	1	1
	Patient level simulation	0	1	1
	Spreadsheet	1	2	3
	Sub-total	11	16	27
Patient data records	Administrative database	0	0	0
	Patient/disease registry	0	0	0
	Chart review/electronic medical records	2	1	3
	Sub-total	2	0	2
Total		14	39	53

model characteristics in economic analysis of severe COPD. Economic analyses were carried out in Australia (1), Belgium (3), Canada (7), Denmark (1), Finland (1), Germany (1), Greece (1), Italy (1), the Netherlands (3), Norway (1), Singapore (1), Spain (1), Sweden (3), Switzerland (1), the UK (9), and the US (7). Most of the studies (30/39, 77%) were sponsored by pharmaceutical companies. The remainder of the studies did not explicitly state source of funding, but did not include authors who were affiliated with either a pharmaceutical or contract research firm. Approximately half of the articles (19/39, 49%) did not mention any validation process. The shortest time period used to analyze data was 16 weeks and the longest was a lifetime. Thirteen of the 39 studies used a time horizon of between 3–5 years, and 10 used a time horizon of 1 year. Few studies (five) approached their analysis from a societal perspective, while most used a third party payer perspective. Most studies (67%) collected data retrospectively, with 13 of the 39 (33%) studies collecting data prospectively. A Markov structured model was used in 19 studies. There were eight studies that were based on randomized controlled trials.

Table 6 details the inputs into economic models in severe COPD. Most (29/39, 74%) studies calculated direct costs only. Where applicable (i.e., in studies where the time horizon was more than 1 year), costs and outcomes were discounted between 3–5%, depending on local pharmacoeconomic requirements. Willingness-to-pay thresholds used for interpretation of results varied widely, between £20,000/QALY and \$100,000/QALY.

Table 7 presents the results from the economic models used in severe COPD. Agents or comparators used in analysis include: aclidinium, betamethasone, fluticasone propionate, formoterol, indacaterol, indacaterol/glycopyrronium, ipratropium, long-acting beta-agonists, OM-85

BV (immunostimulating agent), placebo, roflumilast, salmeterol, tiotropium, and usual care.

Discussion

In this review, we were able to use data from 14 studies that examined patients with asthma and 39 that researched patients with COPD. Our search did not find studies that examined patients who suffered from both asthma and COPD simultaneously. Furthermore, with the exception of a few studies, our search did not locate studies that took into account the severity of the diseases. One reason could be the difficulty in defining the different levels of severity. Furthermore, few drugs are expressly indicated for severe cases of either COPD or asthma and, as such, economic evaluations with this perspective have not been undertaken.

In both asthma and COPD-related economic evaluations, predictive decision-analytic type models were predominant, with Markov models being most commonly used. Given the chronic nature of either asthma or COPD, use of Markov and discrete event simulation models may be most appropriate.

However, study parameters, for the most part, were not validated. Validation of models may include face validation, where experts would confirm the model structure used, data sources cited, and assumptions made. Other types of validation such as internal, external, or predictive validity were also largely absent from the studies included in this review. The joint task force of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) and the Society for Medical Decision Making (SMDM) recommend use of validation in their Good Practices Research report³⁴.

Table 2. Model structure and characteristics in economic analyses of severe asthma.

Reference (Year)	Country	Sponsor	Model structure	Validation	Patients/severity	Data collection	Treatments compared	Time horizon	Perspective
Brown <i>et al.</i> ²¹ 2007	Canada	Novartis	Markov model ²⁵ with five states: (1) day-to-day asthma (no exacerbations), (2) clinically significant non-severe exacerbations, (3) clinically significant severe exacerbations, (4) all cause death, (5) asthma related death Cycle length = 2 weeks	not reported	adolescents and adults (12–73) severe persistent allergic asthma despite ICS + LABA	retrospective	omalizumab add-on for 5 years standard therapy	Lifetime	Canadian health-care system
Campbell <i>et al.</i> ²² 2010	USA	Novartis	Markov model with 6 states: (1) chronic asthma, (2) exacerbation (oral steroids), (3) exacerbation (emergency room), (4) exacerbation (hospitalization), (5) asthma mortality, (6) other mortality 2 week transitions	not reported	average age = 40, 60% females moderate-to-severe persistent asthma inadequate control with ICS	retrospective	omalizumab add-on for 5 years standard therapy	1 year lifetime	US payer
Dal Negro <i>et al.</i> ²³ 2011	Italy	not stated	Pre-post comparison using data from a patient database	not reported	23 patients aged 26–45 with adequate data persistent atopic asthma resistant to common therapies	retrospective	12 months pre-omalizumab 12 months with omalizumab	1 year	Regional Health System
Dal Negro <i>et al.</i> ²⁴ 2012	Italy	Novartis	Pre-post comparison using data from a patient database	not reported	16 patients >12 years old, 50% females persistent atopic asthma severe, difficult to treat	retrospective	12 months pre-omalizumab 36 months with omalizumab	1 year	Regional Health System
Dewilde <i>et al.</i> ²⁵ 2006	Sweden	Novartis	Markov model with five states: (1) daily symptoms, (2) clinically significant non-severe exacerbations, (3) clinically significant severe exacerbations, (4) all cause death, (5) asthma related death Cycle length = 2 weeks	not reported	average age = 40, 67% female severe persistent asthma	retrospective	omalizumab add-on for 5 years standard therapy	lifetime	Societal (Sweden)

Gerzeji <i>et al.</i> ²⁶ 2012	Italy	Chiesi Farmaceutici	Markov model with five states: (1) successful control, (2) sub-optimal control, (3) outpatient managed exacerbation, (4) inpatient managed exacerbation, (5) death Cycle length = 1 week	not reported	Adults aged 16–65 moderate-to-severe persistent asthma	retrospective	betamethasone/for-moterol fluticasone propionate/salmeterol	12 weeks 1 year	Italian National Health Service
Miller <i>et al.</i> ²⁷ 2007	Canada	AstraZeneca	Spreadsheet model	not reported	patients aged 45 (range 12–84), 59% female moderate-to-severe asthma	retrospective	betamethasone/for-moterol fluticasone propionate/salmeterol	1 year	Health Care System societal (Canada)
Norman <i>et al.</i> ¹² 2013	UK	NICE	Markov model with five states: (1) day-to-day symptoms, (2) clinically significant non-severe exacerbations, (3) clinically significant severe exacerbations, (4) all cause death, (5) asthma related death Cycle length: first = 16 weeks, others = 3 months	developed by one analyst checked by another internal validation	adults + adolescents ≥ 12 and children 6–11 years old Severe exacerbations despite daily ICS + LABA Step 4 or 5 treatment	retrospective	omalizumab add-on for 5 years standard therapy	lifetime	UK National Health Service
Novartis ²⁸ 2007	UK	Novartis	Markov model with five states: (1) day-to-day symptoms, (2) clinically significant non-severe exacerbations, (3) clinically significant severe exacerbations, (4) all cause death, (5) asthma related death Cycle length: first = 16 weeks, others = 3 months	not reported	adults + adolescents ≥ 12 years old severe persistent IgE mediated allergic asthma	retrospective	omalizumab add-on for 5 years standard therapy	lifetime (40 years)	UK National Health Service

(continued)

Table 2. Continued.

Reference (Year)	Country	Sponsor	Model structure	Validation	Patients/severity	Data collection	Treatments compared	Time horizon	Perspective
Obaand Salzman ²⁹ 2004	USA	none stated	modeled existing RCTs	not reported	males or females 12–75 years old patients with allergic asthma symptomatic despite inhaled corticosteroids	retrospective	omalizumab SC for 7 months placebo	52 weeks	Third party payer
Price and Briggs ³¹ 2002	UK	GlaxoSmithKline	Markov model with five states: (1) successful control, (2) hospital-managed exacerbation, (3) primary-care managed exacerbation, (4) sub-optimal control, and (5) treatment failure Cycle length: 1 week	not reported	adults and children >12 years old moderate-to-severe asthma treated with inhaled drugs	retrospective	fluticasone propionate/salmeterol fluticasone propionate	12 weeks	UK National Health Service
Rodríguez-Martínez et al. ³⁰ 2013	Colombia	none stated	Markov model with three states: (1) no symptoms, (2) sub-optimal control, (3) asthma exacerbation Cycle length: 1 week	not reported	children <18 years old persistent asthma	retrospective	beclomethasone budesonide fluticasone ciclesonide	12 months	Compulsory Insurance Plan of Colombia
van Nooten et al. ³² 2013	Netherlands	Novartis	Markov model with five states: (1) daily symptoms, (2) clinically significant non-severe exacerbations, (3) clinically significant severe exacerbations, (4) all cause death, (5) asthma related death Cycle length = 2 weeks	validated by Brown et al. ²¹ and Dewilde et al. ²⁵	adults aged 40 uncontrolled allergic asthma	retrospective	omalizumab add-on for up to 5 years standard therapy	lifetime	societal
Wu et al. ³³ 2007	USA	National Heart, Blood and Lung Institute	Markov model with six states: (1) chronic, (2) acute, (3) urgent care visits, (4) emergency room visits, (5) hospitalization, and (6) death Cycle length = monthly	used in at least two previous analyses	adults >18 years persistent asthma	retrospective	omalizumab add-on standard therapy	10 years	Societal (all direct costs)

ACT, Asthma Control Test; ICS, inhaled corticosteroids; LABA, long-acting beta-agonists.

Table 3. Model inputs in economic analyses of severe asthma.

Reference (Year)	Costs	Currency and year	Discounting	Input rates	Data source	Items costed	Data sources	Criterion	Planned sensitivity analyses
Brown <i>et al.</i> ²¹ 2007	Direct	CAD converted to euros (year not stated)	Costs: 5% QALYs: 5%	exacerbation rates resource use utilities death rates	ETOPA ³⁹ INNOVATE ⁴⁰ ETOPA ³⁹ Price <i>et al.</i> ⁴¹ Lowhagen <i>et al.</i> ⁴² , Statistics Canada ⁴³	exacerbations drugs physician visits hospitalization omitted omalizumab administration costs	not stated Ontario Drug Benefit Ontario Schedule of Benefits CIHI	ICER = €35,000/ QALY (CAD \$50,000)	probabilistic, 1-way: (a) no discounting, (b) 3% discount on costs + outcomes, (c) 5-year time horizon, (d) including administration costs, (e) mortality 0%, (f) mortality 2.48%
Campbell <i>et al.</i> ²² 2010	Direct	USD, 2008	Costs: 3% QALYs: 3%	exacerbation rates utilities death rates	Bousquet <i>et al.</i> ⁴⁴ Humbert <i>et al.</i> ⁴⁰ Humbert <i>et al.</i> ⁴⁰ , Tsuchiya <i>et al.</i> ⁴⁶ , Price <i>et al.</i> ⁴¹ , Sullivan <i>et al.</i> ⁴⁷	care drugs hospitalization	Ayres <i>et al.</i> ⁴⁵ Bousquet <i>et al.</i> ⁴⁴ MarketScan database	not stated	probabilistic (5000 iterations), 1-way on all inputs using 95% confidence limits 1-way analyses on costs, all rates, response definition
Dal Negro <i>et al.</i> ²³ 2011	Direct	euros, 2008	not applicable	hospitalizations drug use physician visits	patients charts patients charts patients charts	hospitalizations drugs physician visits	DRG (Regional Tariff), National Hospital Discharge Database Italian Drugs Formulary, Off-Patent Drugs Reference Price System Regional Tariffs, DYSCO ⁴⁸	\$27,000–\$165,000/ QALY	not stated
Dal Negro <i>et al.</i> ²⁴ 2012	Direct	euros, 2011	not applicable	hospitalizations drug use physician visits utilities	patients charts patients charts patients charts	hospitalizations drugs physician visits	DRG (Regional Tariff), National Hospital Discharge Database Italian Drugs Formulary, Off-Patent Drugs Reference Price System Regional Tariffs, DYSCO ⁴⁸	\$27,000–\$165,000/ QALY	not stated

(continued)

Table 3. Continued.

Reference (Year)	Costs	Currency and year	Discounting	Input rates	Data source	Items costed	Data sources	Criterion	Planned sensitivity analyses
Dewilde <i>et al.</i> ²⁵ 2006	Direct Indirect	Swedish kronor converted to euros, 2006	Costs: 3% Outcomes: 3%	exacerbation rates utilities death rates	INNOVATE ⁴⁰ , Price <i>et al.</i> ⁴¹ Lohagen <i>et al.</i> ⁴² , Swedish life tables (No reference provided)	exacerbations hospital costs drugs time lost	Swedish Association of Local Authorities Swedish Association of Local Authorities Pharmaceutical Benefits Board Statistics Sweden	€53,384 (500,000 SEK)	Probabilistic sensitivity analyses (5000 simulations) 12 1-way sensitivity analyses varying rates for mortality, discount, utilities, time horizon, healthcare costs, costs for extra life years gained
Gerzeli <i>et al.</i> ²⁶ 2012	Direct	euros, 2010	not applicable	transition rates resource use hospitalization mortality utilities	ICAT SE ⁴⁹ Priceand Briggs ³¹ , GOAL ⁵⁰ , experts Ministry of Health de Marco <i>et al.</i> ³¹ literature (average from 5 studies)	resource use hospitalization	Ministry of Health DRG (Regional Tariff)	not stated	Probabilistic sensitivity analyses (100,000 simulations) 1-way and bivariate on costs, transition probabilities (minimum/maximum values, threshold analysis)
Miller <i>et al.</i> ²⁷ 2007	Direct Indirect	CAD, 2005	not applicable	clinical rates resource use	Vogelmeier <i>et al.</i> ⁵² Vogelmeier <i>et al.</i> ⁵² , expert panel	drugs medical nursing care hospitalizations lost wages	Ontario Drug Benefit Ontario Schedule of Benefits Nursing Services Study Alberta Health Costing Statistics Canada	not stated	1-way on exacerbation rate, drugs costs, wages, hospitalization cost
Norman <i>et al.</i> ¹² 2013	Direct	UK pounds, 2010	Costs: 3.5% Outcomes: 3.5%	exacerbation rates resource use utilities death rates	INNOVATE ⁴⁰ , Lanier and Marshall ⁵³ INNOVATE ⁴⁰ , Lanier and Marshall ⁵³ Bousquet <i>et al.</i> ⁴⁴ , Lloyd <i>et al.</i> ⁵⁴ , de Vries ⁵⁵ , UK Life Tables	resource use	Humbert <i>et al.</i> ⁴⁰ , Lanier and Marshall ⁵³ , NHS Reference Costs	£30,000	3 scenarios: patients hospitalized, patients on maintenance oral steroids, patients with ≥3 exacerbations, rates of exacerbation, effectiveness, mortality, utilities, horizon, dosing, costs
Novartis ²⁸ 2007	Direct	UK pounds, 2006	Costs: 3.5% Outcomes: 3.5%	exacerbation rates resource use	INNOVATE ⁴⁰ ETOPA ³⁹ , INNOVATE ⁴⁰ , ETOPA ³⁹	resource use	Humbert <i>et al.</i> ⁴⁰ , Lanier and Marshall ⁵³ , NHS Reference Costs	£30,000	1-way on rates, time horizon, treatment duration
Oba and Salzman ²⁹ 2004	Direct	USD, 2003	not applicable	clinical rates utilities	Busse <i>et al.</i> ⁵⁶ , Soler <i>et al.</i> ³⁷ Busse <i>et al.</i> ⁵⁶ , Soler <i>et al.</i> ⁵⁷	drugs hospitalization	Drug Topics published studies	not stated	best/worst case for costs, for each outcome

Price and Briggs ³¹ 2002	Direct	UK pounds, 2000	not applicable	clinical rates resource use	Kavuru <i>et al.</i> ⁵⁸ Kavuru <i>et al.</i> ⁵⁸	drugs attacks	MIMS Hoskins <i>et al.</i> ⁵⁹	not stated	Probabilistic (1000 simulations)
Rodríguez-Martínez <i>et al.</i> ³⁰ 2013	Direct	UK pounds, 2007	not applicable	clinical rates resource use utilities	24 published papers asthma guidelines, local experts' survey of patients' parents	drugs hospital care	National manual of drug prices Hospital records	£9803.96/QALY (3× GDP in 2008)	Probabilistic (10,000 simulations), 1-way, 2-way, and multi-way analyses
van Noften <i>et al.</i> ³² 2013	Direct Indirect	euros, 2010	Costs: 4% Outcomes: 1.5%	clinical rates resource use	observational registry observational registry	care and drugs	Dutch cost lists, published studies	not stated	rates of exacerbation, death; cost of drug, exacerbations time horizon, workdays lost, retaining non-responders
Wu <i>et al.</i> ³³ 2007	Direct Indirect	USD, 2005	Costs: 3% Outcomes: 3%	clinical rates hospitalization utilities resource use	Paltiel <i>et al.</i> ⁶⁰ , Walker <i>et al.</i> ⁶¹ Busse <i>et al.</i> ⁵⁶ , Corren <i>et al.</i> ⁶² Niebauer <i>et al.</i> ⁶³ Eight published studies	drugs care productivity	Drug Topics Red Book eight published studies US Bureau of Labor	no consensus	1-way analyses on costs and rates

CAD, Canadian dollars; CHI, Canadian Institute for Health Information; DRG, Diagnosis Related Group; SEK, Swedish kronor; USD, United States dollars.

Table 4. Model outputs from economic analyses of severe asthma.

	Treatments compared	Outcomes Cost	Clinical	Amount	ICER	Sensitivity analyses	Conclusions
Brown <i>et al.</i> ²¹ 2007	lifetime omalizumab* standard care	€61,257 €27,403	QALYs QALYs	7.57 6.49	€31,209	CI: €27,739–€40,840 69.7% of ICERS <€35,000 Range of 1-way results: €23,762–€66,443	omalizumab is cost-effective
Campbell <i>et al.</i> ²² 2010	1 year lifetime omalizumab standard care omalizumab* standard care	USD \$23,000 USD \$3600 USD \$174,500 USD \$83,400	QALYs hospitalizations ER visits steroid exacerbations QALYs hospitalizations ER visits corticosteroid bursts QALYs QALYs	0.72 0.03 0.03 0.83 0.66 0.06 0.06 1.30 14.19 13.87	USD \$306,200 \$646,667 \$646,667 \$41,277 USD \$287,200	1-way analyses: sensitive to changes in utilities, exacerbation mortality, omali- zumab price, exacerbation rates, response definition none <\$200,000/QALY	adding omalizu- mab to usual care improves QALYs at an increase in direct medical costs not cost-effective
Dal Negro <i>et al.</i> ²³ 2011	1 year (pre/post) omalizumab standard care	€586.71/month €241.49/month	QALYs FEV ACT QALYs FEV ACT	0.53 57.61 11.87 0.70 75.46 19.4	€25,983 €21.9/FEV% €57.3/ACT point	not done	cost-effective
Dal Negro <i>et al.</i> ²⁴ 2012	1 year (pre/post) (averaged over 3 years post) omalizumab standard care	€8038 €2869	QALYs hospitalizations ER visits QALYs hospitalizations ER visits QALYs	0.78 0 0.25 0.56 0.94 0.69	€23,880 €5499 €11,748	not done	cost-effective
Dewilde <i>et al.</i> ²⁵ 2006	lifetime omalizumab* standard care	€95,456 €52,702	QALYs QALYs	12.357 11.595	€56,091	Probabilistic ICER = €57,961 (€31,328–€120,552) 1-way: sensitive to exacerbation mortality rate, time horizon, discount rate 1-way ICERS: €39,675– €131,130	omalizumab pro- vides cost off- sets, improves quality-of-life and may have an attractive ICER in treating severe allergic asthma cost-effective
Gerzeli <i>et al.</i> ²⁶ 2012	12 weeks 1 year B/F FP/S B/F FP/S	€175.03 €188.70 €745.48 €804.60	QALW WSC QALW WSC QALW WSC QALW WSC	9.737 6.381 9.696 6.015 42.448 42.279 31.152 29.628	dominant dominant dominated dominated dominant dominated dominated	68% of simulations for QALW favoured B/F (dominated 63%) 64% of simulations for WSC favoured B/F (dominated 59%) minor changes in sensitivity analyses not reported	cost-effective

Miller <i>et al.</i> ²⁷ 2007	1 year	B/F FP/S	HS: CAD \$1315 Soc: CAD \$1538 HS: CAD \$1541 Soc: CAD \$1854	serious exacerbations serious exacerbations serious exacerbations serious exacerbations	0.24 0.24 0.31 0.31	dominant dominant	B/F dominated in all but 1 sensitivity analysis where it was equivalent	cost-effective
Norman <i>et al.</i> ¹² 2013	lifetime lifetime	omalizumab (≥ 12 years)* standard care omalizumab (6–11 years)* standard care	£72,938 £33,218 £92,497 £40,218	QALYs QALYs QALYs QALYs	14.13 13.66 17.39 16.72	£83,822 £78,009	Price = patient access scheme discount ICER = £83,822 with omalizu- mab list price aged ≥ 12 ICER = £78,009 with omalizu- mab list price aged 6–11 1-way ICERs: £46,029– £112,033 Hospital group ≥ 12 years: ICER = £31,782 Hospital group 6–11 years: ICER = £30,109 Oral steroid group ≥ 12 years: ICER = £34,386 ≥ 3 exacerbation group ≥ 12 years: ICER = £53,087 ≥ 3 exacerbation group 6–11 years: ICER = £48,537 1-way ICERs: £50,319– £98,688	not cost-effective not cost-effective
Novartis ²⁸ 2007	lifetime (40 years)	omalizumab (≥ 12 years)* standard care				£30,600	£26,500 for the high-risk hospitalization group £21,700 using data from ETOPA study Sensitivity analyses: average ICER: £31,700 (£23,200– £48,200) Sensitivity using 0% mortality ICER: £73,200 NICE estimate: £38,900; 23.6% probability of being cost-effective	cost-effective not cost-effective
Oba and Salzman ²⁹ 2004	52 weeks	omalizumab for 7 months placebo omalizumab for 7 months placebo omalizumab for 7 months placebo		patients with 0.5 point decrease in AQLQ patients with 1.5 point decrease in AQLQ SCD		\$378 \$517 \$388–\$523	CI: \$146–\$919 Best case: \$280 (\$107–\$684) CI: \$200–\$1259 Best case: \$383 (\$146–\$937) Sensitivity: \$148–\$1273	incremental cost far exceeds cost/SCD with other drugs Should restrict to very specific groups with severe asthma

(continued)

Table 4. Continued.

	Treatments compared	Outcomes Cost	Clinical	Amount	ICER	Sensitivity analyses	Conclusions
Price and Briggs ³¹ 2002	12 weeks FP fluticasone propionate	£15.77 £11.83	SCW	66% 47%	£20.83/SCW	95% CI for ICER: –£64.94 (dominant) to £112.66 Sensitivity: FP/S has 10–6% more SFWs	cost-effective at a willingness-to-pay of £45/SFW 80% of the time
Rodríguez-Martínez <i>et al.</i> ³⁰ 2013	12 months beclomethasone fluticasone ciclesonide budesonide	£106.16 £231.19 £270.15 £309.27	QALY QALY QALY QALY	0.9262 0.9325 0.9051 0.8999	£19,835.28 dominated dominated	exacerbation costs most influential	beclomethasone is cost-effective when WTP <£21,129
van Nooten <i>et al.</i> ³² 2013	lifetime omalizumab* omalizumab (undiscounted) standard care standard care undiscounted	€151,619 €227,688 €95,754 €161,499	QALY QALY	25.74 22.93	€38,371 €38,528	Probabilistic: 75% of ICERs <€44,000/QALY 1-way sensitivity analyses (14 reported): all but one ICER €32,375–€80,332	cost-effective for this country
Wu <i>et al.</i> ³³ 2007	10 years omalizumab standard care	\$131,000 \$16,000	QALM	80.01 78.33	\$821,000	Also reported an ICER of \$120/SFD. Sensitivity: changing exacerbation rates, ICERS = \$727,000–\$853,000/QALY changing event rates, ICERS = \$207,000–\$1.42 million/QALY changing costs: ICER = \$100,000/QALY	not cost-effective

B/F, beclomethasone + formoterol; CI, 95% confidence interval; ER, emergency room; FP, fluticasone propionate; FP/S, fluticasone propionate + salmeterol; HS, Healthcare System perspective; QALW, quality adjusted life week; QALM, quality adjusted life month; QALY, quality adjusted life year; SCD, symptom controlled day; SCW, symptom controlled week; SFD, symptom free day; Soc, societal perspective; WSC, weeks with symptom control.

*Omalizumab given for the first 5 years only.

Table 5. Model structure and characteristics in economic analyses of severe COPD.

Reference (Year)	Country	Sponsor	Model structure	Validation	Patients/severity	Data collection	Treatments compared	Time horizon	Perspective
Ayres <i>et al.</i> ⁴⁵ 2003	UK	GlaxoSmithKline	economic RCT based on ISOLDE ⁶⁴	not needed	adults aged 49–75 moderate-to-severe COPD	prospective	(1) FP (2) placebo	6 months	UK National Health Service
Briggs <i>et al.</i> ⁶⁵ 2006	UK	GlaxoSmithKline	Modeled ISOLDE Trial ⁶⁴	not needed	adults aged 64, 75% males moderate-to-severe COPD	prospective	(1) FP (2) placebo	3 years	UK National Health Service
Briggs <i>et al.</i> ⁶⁶ 2010	UK	GlaxoSmithKline	economic RCT based on TORCH ⁶⁷	not needed	adults average age 65, 76% males moderate-to-severe COPD FEV1 <60%	prospective	(1) FP/S (2) FP (3) S (4) placebo	3 years	Health Service/Third party payer
Chuck <i>et al.</i> ⁶⁸ 2008	Canada	GlaxoSmithKline	Regression model using TORCH ⁶⁷ data Markov model with 3 states: Stage 1 (FEV1 ≥50%), Stage 2 (FEV 35–49.9%, Stage 3(FEV <35%)); also exacerbations (mild, moderate, severe) Cycle length: 3 months economic RCT (piggylback)	not stated	mostly severe COPD (FEV1 <60%)	retrospective	(1) LABA + IC (all stages) (2) LABA + IC (Stages 2–3) (3) LABA + IC (Stage 3 only) (4) IC only	3 years lifetime	Health System
Collet <i>et al.</i> ⁶⁹ 2001	Canada	Jouveinal Inc.	peer reviewed by FRSQ (a Government Agency) not stated	adults aged 70, 66% males mostly severe COPD	prospective	(1) OM-85 BV (immunostimu-lating agent) (2) placebo	6 months	Health System	
Dalal <i>et al.</i> ⁷⁰ 2010	USA	GlaxoSmithKline	spreadsheet model based on pooled data from 2 RCTs	comparison with another similar study in Italy	adults >40, FEV <50% severe COPD	retrospective	(1) FP/S (2) S	1 year	Third party payer
Dal Negro <i>et al.</i> ³⁵ 2007	Italy	GlaxoSmithKline	Markov chain with 5 states: COPD Stages 1–4 and death Cycle length: 1 year	comparison with another similar study in Italy	adults severe (Stage 3) and very severe (Stage 4)	retrospective	(1) FP/S (2) B/F (3) FP (4) S (5) control (standard therapy)	lifetime	National Health Service
Earnshaw <i>et al.</i> ³⁶ 2009	USA	GlaxoSmithKline	Markov model with 4 states: (1) moderate, (2) severe, (3) very severe, (4) death Also mild, moderate, severe exacerbations within states. Markov model 3 states: (1) Mild, (2) moderate, (3) severe	not stated	adults 40–80, FEV <60%	retrospective		lifetime	Third party payer
Gani <i>et al.</i> ⁷¹ 2010	UK	Boehringer Ingelheim & Pfizer	Markov model 3 states: (1) Mild, (2) moderate, (3) severe	Oostenbrink <i>et al.</i> ⁷²	Age not specified: Mild-to-severe COPD	retrospective	(1) tiotropium (2) ipratropium (3) salmeterol (4) placebo (1) tiotropium + usual care (2) tiotropium	1 year	National Health Service
Hettie <i>et al.</i> ⁷³ 2012	UK and Belgium	Boehringer Ingelheim	Markov model (1) moderate, (2) severe, (3) very severe, (4) death	Oostenbrink <i>et al.</i> ⁷⁴	75.4% male, 64.5 age moderate-to-very severe	prospective		4 years	Health care payer
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Table 5. Continued.

Reference (Year)	Country	Sponsor	Model structure	Validation	Patients/severity	Data collection	Treatments compared	Time horizon	Perspective
Hogan <i>et al.</i> ⁷⁵ 2010	USA	Novartis	Not stated	Not specified	Not stated	Prospective	(1) formoterol (2) ipratropium (3) placebo	12 weeks	Not stated
Hoogendorn <i>et al.</i> ⁷⁶ 2013	The Netherlands	Boehringer Ingelheim	Markov model (1) moderate, (2) severe, (3) very severe, (4) death	Oostenbrink <i>et al.</i> ⁷⁴	74% male; mean age 62.9	Prospective	(1) tiotropium (2) salmeterol	1 and 5 years	German statutory health insurance Societal
Jones <i>et al.</i> ⁷⁷ 2003	UK	GlaxoSmithKline	Not specified	Not specified	83% male; mean age 62	Prospective	(1) salmeterol 50 mg (2) salmeterol 100 mg	16 weeks	Healthcare provider
Karabis <i>et al.</i> ⁷⁸ 2014	USA	Mapi HEOR and Forest research	Markov model (1) moderate, (2) severe, (3) very severe, (4) death	Not specified	53% male Mean age 64.3%	Retrospective	(1) acilidinium (2) tiotropium	5 years	Healthcare payer
Lee <i>et al.</i> ⁷⁹ 2006	Singapore	Department of Medicine, National University Hospital	Not stated	Not specified	Not specified	Retrospective	Addition of tiotropium to usual care	Not specified	Not specified
Lofthall <i>et al.</i> ⁸⁰ 2005	Sweden	AstraZeneca	Not stated	Not specified	Patients at least 40 years of age	Prospective	B/F combined inhaler B/F each as monocomponent	Not specified	Healthcare provider
Maniadakis <i>et al.</i> ⁸¹ 2006	Greece	Boehringer Ingelheim	Markov 3 states: Moderate, severe, very severe	Oostenbrink <i>et al.</i> ⁷²	Not specified	Retrospective	Tiotropium salmeterol	1 year	Greek National Health Service
Mittmann <i>et al.</i> ⁸² 2011	Australia, Canada	AstraZeneca	Not specified	CLIMB ⁸²	Not specified	Retrospective	(1) B/F + tiotropium (2) placebo + tiotropium	12 weeks	Healthcare provider
Naik <i>et al.</i> ⁸³ 2010	US	Duquesne University School of Pharmacy, Pittsburgh, PA, USA	Markov: 2 states on treatment and maintenance therapy	Not specified	Not specified	Retrospective	tiotropium salmeterol	1 year	Third party payer
Najafzadeh <i>et al.</i> ⁸⁴ 2008	Canada	Faculties of medicine and pharmacy across Canada	Decision analytic	Not specified	Not specified	Prospective	S, F/S, tiotropium	5 year	Canadian healthcare system
Neyt <i>et al.</i> ⁸⁵ 2010	Belgium	Belgian Health Care Knowledge Centre Academic Centre for Primary Care, AstraZeneca	Decision analytic	Not specified	Not specified	Prospective	tiotropium No tiotropium	1 year	Healthcare payer
Nielsen <i>et al.</i> ⁸⁶ 2013	Denmark Finland, Norway, Sweden		modelled CLIMB trial ⁸²	not stated	adults (average age = 62) moderate-to-severe COPD FEV1 = 38%) adults (average age = 66) moderate-to-severe COPD FEV1 = 44%)	Retrospective	(1) B/F tiotropium (2) placebo + tiotropium	3 months	Societal Healthcare provider
Obat ⁸⁷ 2007	USA	not stated	spreadsheet model	not stated		Retrospective	(1) tiotropium placebo (2) S placebo (3) tiotropium salmeterol	1 year	Third party payer

Oha ³⁷ 2009	USA	none stated	Markov model with 4 states: (1) stable, (2) exacerbation requiring a physician visit, (3) exacerbation requiring hospitalization, (4) death Cycle length: 3 months	not stated	adults (average age = 65)	retrospective	(1) FP/S (2) FP (3) S (4) placebo	3 years	Third party payer
Onukwuoha <i>et al.</i> ³⁸ 2008	USA	PHRMA Foundation	medical records	A pulmonologist validated diagnosis and severity levels	adults (average age = 68.9) >92% moderate, severe, or very severe COPD	retrospective	(1) tiotropium (2) ipratropium	1 year	Veterans Affairs Health Care System
Oostenbrink <i>et al.</i> ³⁰ 2004	Netherlands Belgium	Boehringer Ingelheim GmbH	RCT (piggyback) by Vincken <i>et al.</i> ³¹	not applicable	average FEV1 = 51% Adults >40 years old moderate-to-severe COPD (FEV1 ≤ 65%)	prospective	(1) tiotropium (2) ipratropium	1 year	Societal (direct costs only)
Oostenbrink <i>et al.</i> ³² 2005	Netherlands Canada	Boehringer Ingelheim GmbH	Markov model with three states: moderate, severe, very severe. Each state can have non-severe or severe exacerbations	Model outputs compared with 2 clinical trials	adults (average age 64) moderate-to-severe COPD	retrospective	(1) tiotropium (2) salmeterol (3) ipratropium	1 year	
Price <i>et al.</i> ³³ 2011	Germany	Novartis	Markov model with four health states (mild, moderate, severe, very severe) and death. States also had 2 sub-states with exacerbations: (1) severe (managed as outpatients) and (2) very severe (managed in hospital) Cycle length: 3 months using a cohort of 1000 patients	Clinical rates and resource use validated by a clinician Model structure validated by an external economist Model outputs compared with other models and published clinical rates/mortality previously validated by Price <i>et al.</i> ³³ Experts validated inputs Data outputs validated against epidemiologic studies and other economic analyses	adults (average age 64) moderate-to-severe COPD	retrospective	(1) indacaterol (2) tiotropium	3 years	German Healthcare provider
Price <i>et al.</i> ³⁴ 2013	UK	Novartis UK	Markov model with four health states (mild, moderate, severe, very severe) and death. States also had 2 sub-states with exacerbations: 1) severe (managed as outpatients) and 2) very severe (managed in hospital) Cycle length: 3 months		Adults (average age = 63.6) moderate-to-severe COPD	retrospective	(1) indacaterol (2) tiotropium (3) salmeterol	3 years	UK National Health Service

(continued)

Table 5. Continued.

Reference (Year)	Country	Sponsor	Model structure	Validation	Patients/severity	Data collection	Treatments compared	Time horizon	Perspective
Price <i>et al.</i> ⁹⁵ 2014	Sweden	Novartis	patient level simulation model Cycle length: 6 months	previously done by Asukai <i>et al.</i> ⁹⁶	adults (average age = 63) moderate-to-severe COPD with a low risk of exacerbations	retrospective	(1) indacaterol/glycopyrronium (2) indacaterol + glycopyrronium (3) FP/S	1, 3, 5, 10 years; lifetime	Swedish societal
Rutten-van Molken <i>et al.</i> ⁹⁷ 2007	Spain	Boehringer Ingelheim Pfizer Global	Markov model with 4 states: moderate, severe, very severe, death Cycle length: 8 days for the first; others = 1 month	not stated	moderate, severe, or very severe COPD	retrospective	(1) tiotropium (2) salmeterol (3) ipratropium	5 years	Societal (Spain) Spanish National Healthcare System
Rutten-van Molken <i>et al.</i> ⁹⁸ 2007	UK	ALTANA Pharma	RCT piggyback trial	not applicable	Adults ≥ 40 years old severe-to-very severe COPD	prospective	roflumilast placebo	1 year	UK society UK National Health Service
Samyshtkin <i>et al.</i> ⁹⁹ 2013	Switzerland	Takeda Pharma	Markov model with 3 states: severe, very severe, and dead Cycle length: 1 month	not stated	severe-to-very severe COPD associated with bronchitis; aged >40 years old	retrospective	(1) roflumilast + LAMA (2) roflumilast + LABA/ICS (3) roflumilast + LABA/ICS + LAMA LABA/ICS + LAMA roflumilast + LABA LABA	lifetime	Swiss payer UK National Health Service
Samyshtkin <i>et al.</i> ⁵⁰ 2014	UK	Takeda Pharmaceuticals	Markov model with 3 states: severe, very severe, and dead Cycle length: 1 month	not stated	severe-to-very severe COPD associated with bronchitis; aged 64 years old	retrospective	ICS in all patients ICS for Stage 2 + 3 ICS for Stage 3 only none	3 years, lifetime	Societal
Sin <i>et al.</i> ¹⁰⁰ 2004	Canada	Institute of Health Economics	Markov model; states included three disease stages as well as death Cycle length: 3 months	not stated	Stage 1: FEV1 $\geq 50\%$ Stage 2: FEV1 35%–50% Stage 3: FEV1 $<35\%$	retrospective	FP/S usual care	25 years	Canadian healthcare payer
Spencer <i>et al.</i> ¹⁰¹ 2005	Canada	GlaxoSmithKline	Markov model with 4 states: (1) mild, (2) moderate, (3) severe, (4) death Cycle length: 3 months	One author provided 'validation' of the model assumptions and costing estimates' not stated	Adults aged 63 $\pm$ 8.6 years old FEV1 = 25–70%	retrospective	FP placebo (FP withdrawn)	6 months	Healthcare system
van der Palen <i>et al.</i> ¹⁰² 2006	Netherlands	Netherlands Asthma Foundation Amicon Insurance GlaxoSmithKline Boehringer Ingelheim			adults aged 40–75 moderate-to-severe (FEV1 20–80%)	retrospective			

CAD, Canadian dollars; CHF, Swiss francs; DKK, Danish kroner; NOK, Norwegian kroner; OECD, Organization for Economic Cooperation and Development; RAMO, Régie de l'Assurance Maladie du Québec; RCT, randomized controlled trial; SEK, Swedish kronor; USD, United States dollars.

Table 6. Model inputs in economic analyses of severe COPD.

Reference (Year)	Costs	Currency and year	Discounting	Input rates	Data source	Items costed	Data sources	Criterion	Planned sensitivity analyses
Ayres <i>et al.</i> ⁴⁵ 2003	Direct, indirect (days lost)	UK pounds, 1998	not applicable	clinical resources	ISOLDE ⁶⁴ ISOLDE ⁶⁴	drugs hospitalization medical care days lost	Published costs (University of Kent) Published costs (University of Kent) Published costs (University of Kent) UK Department of Transport British National Formulary Published costs (University of Kent) Published costs (University of Kent)	not stated (willingness-to-pay)	Rates of FEV ₁ exacerbations with/without indirect costs
Briggs <i>et al.</i> ⁶⁵ 2006	Direct	UK pounds 1998–1999	Costs: 3.5% Outcomes: 3.5%	clinical resources utilities	ISOLDE ⁶⁴ ISOLDE ⁶⁴ ISOLDE ⁶⁴	drugs hospitalization medical care	Alberta Health Costing Alberta Health Costing Alberta Health Costing	£20,000/QALY	Best/worst case on imputed data
Briggs <i>et al.</i> ⁶⁶ 2010	Direct only	USD, 2007	Costs: 3% QALYs: 3%	clinical resources utilities	TORCH ⁶⁷ TORCH ⁶⁷ TORCH ⁶⁷ , Dolan ¹⁰³	drugs	IMS	\$100,000/QALY	not done
Chuck <i>et al.</i> ⁶⁸ 2008	Direct only	CAD, 2006	Costs: 3% and 5%	clinical resources utilities	10 published studies 4 published RCTs Oosterbrink <i>et al.</i> ⁹⁰ Borg <i>et al.</i> ¹⁰⁴	drugs hospitalization medical care	Alberta Health Costing Alberta Health Costing Alberta Health Costing	\$50,000/QALY	Probabilistic (100,000 simulations) 1-way sensitivity analyses: Rates of disease progression, exacerbation, mortality, discount rate, QALY value, costs
Collet <i>et al.</i> ⁶⁹ 2001	(days lost, need for help, caregiver burden)	CAD, 1995	not applicable	clinical resources	Collet <i>et al.</i> ¹⁰⁵ Collet <i>et al.</i> ¹⁰⁵	drugs medical care days lost	RAMQ RAMQ Average wage in Quebec	not stated	Also, excluded TORCH Trial (milder disease) [Calverley] Probabilistic (1000 simulations), cost and clinical rates
Dalal <i>et al.</i> ⁷⁰ 2010	Direct only	USD, 2007	not applicable	clinical	Anzueto <i>et al.</i> ¹⁰⁶ Ferguson <i>et al.</i> ⁸⁸	drugs hospital costs medical care	Drug Topics Redbook Stanford <i>et al.</i> ¹⁰⁷ Nurmamambetov <i>et al.</i> ¹⁰⁸	not stated	not stated

(continued)

Table 6. Continued.

Reference (Year)	Costs	Currency and year	Discounting	Input rates	Data source	Items costed	Data sources	Criterion	Planned sensitivity analyses
Dal Negro <i>et al.</i> ³⁵ 2007	Direct only	euros, year not stated	not stated	clinical exacerbations	ISOLDE ⁶⁴ , Calverley <i>et al.</i> ^{109,110} , Szafranski <i>et al.</i> ¹¹¹ , ISOLDE ⁶⁴ , Price <i>et al.</i> ⁴¹ , TORCH ⁶⁷	drugs Care	National Health Service Luccioni <i>et al.</i> ¹¹² , Dal Negro <i>et al.</i> ¹¹³		1-way analyses on input rates, costs
Earnshaw <i>et al.</i> ³⁶ 2009		USD, 2006	Costs: 3% Outcomes: 3%					\$50,000/QALY	Probabilistic (10,000 simulations) 1-way on rates of exacerbation, mortality, duration of exacerbations, utility weights, transition probabilities Probabilistic sensitivity analysis
Gani <i>et al.</i> ⁷¹ 2010	Direct	£, 2009	Not applicable	Clinical resources	Brusasco <i>et al.</i> ¹¹⁴ , Vincken <i>et al.</i> ⁹¹ , Casaburi <i>et al.</i> ¹¹⁵	Drugs hospitalization	Britton ¹¹⁶ , Department of Health NHS reference costs, Griffiths <i>et al.</i> ¹¹⁷ , Curtis, MIMS online, personal communication	£20,000/QALY	Probabilistic sensitivity analysis
Hertel <i>et al.</i> ¹¹⁸ 2012	Direct	£, otherwise not stated	3.5% (costs and outcomes)	Clinical Utilities Resources	Mills <i>et al.</i> ¹¹⁹ , Calverley <i>et al.</i> ⁶⁷ , British National Formulary	Drugs Maintenance Community treated exacerbation	British National Formulary	£20,000–30,000/QALY	Probabilistic sensitivity analysis
Hettie <i>et al.</i> ⁷³ 2012	Drug costs	£, euro 2011	UK Costs/ Benefits 3.5% Belgium costs 3% and benefits 1.5% Not applicable	Utilities resource	Rutten van Mölken <i>et al.</i> ⁵⁷	Drugs Maintenance Hospitalization	Cleemput <i>et al.</i> ¹²⁰ 2008	£30,000/QALY	Deterministic and probabilistic sensitivity analysis
Hogan <i>et al.</i> ⁷⁵ 2010	Direct	Not stated		Clinical Resources Utilities	Dahl <i>et al.</i> ¹²¹	Study drugs; rescue medication	Dahl <i>et al.</i> ¹²¹ 2001	Not stated	1-way sensitivity analysis
Hoogendorn <i>et al.</i> ⁷⁶ 2013	Direct, Out of pocket, Productivity loss	€, 2010	3%	Clinical	POET-COPD ¹²²	hospitalizations, days at intensive care unit, ambulance transportations, emergency room visits and contact with five types of healthcare providers	Koopmanschap <i>et al.</i> ¹²³	Not stated	One way and probabilistic sensitivity analysis

Jones <i>et al.</i> ⁷⁷ 2003	Direct costs	Not stated	Not applicable	Clinical Resources Utilities	Boyd <i>et al.</i> ¹²⁴ Boyd <i>et al.</i> ¹²⁴ patient diary	ER visits Outpatient hospital visits Inpatient hospital visits GP visits study drugs rescue medication concurrent medication	Patient diary cards	Not stated	Carried out but not reported - Not specified
Karabis <i>et al.</i> ⁷⁸ 2014	Direct costs	USD 2012	3% Costs and benefits	Clinical Resources Utilities	Kenwin <i>et al.</i> ¹²⁵ Quanjier <i>et al.</i> ¹²⁶ Rutten-van Molken and Lee ¹²⁷	Drug COPD management Exacerbations	Not specified Yu <i>et al.</i> ¹²⁸	\$50,000/QALY	Probabilistic
Lee <i>et al.</i> ⁷⁹ 2006	Direct costs	Singapore dollars	Not specified	Clinical Resources	Casaburi <i>et al.</i> ¹¹⁵ , Brusasco <i>et al.</i> ¹¹⁴ , Niewoehner <i>et al.</i> ¹²⁹	Drug exacerbation hospitalization	Not specified Not specified Ministry of Health; national healthcare group data	Not specified	1-way sensitivity
Lofdahl <i>et al.</i> ⁸⁰ 2005	Direct costs	Swedish kroner (converted to euros)	Not applicable	Clinical Resources	Calverley <i>et al.</i> ⁶⁷	Total healthcare costs	Calverley <i>et al.</i> ⁶⁷	Not specified	1 way sensitivity
Maniadakis <i>et al.</i> ⁸¹ 2006	Direct costs	2005 euros	Not applicable	Resources utility	Not specified Oostenbrink <i>et al.</i> ⁷²	Study medication	General hospital Heraklion	Not specified	1-way sensitivity
Mittmann <i>et al.</i> ⁸² 2011	Direct costs	2009, Canadian, Australian dollars; Swedish kroner	Not applicable	Resources Clinical	CLIMB ⁸²	Hospital and other exacerbation Study drugs Healthcare utilization	CLIMB ⁸²	Not specified	1 way sensitivity analysis
Naik <i>et al.</i> ⁸³ 2010	Direct costs	Not stated	Not applicable	Clinical Resources	Casaburi <i>et al.</i> ¹¹⁵ Vincen <i>et al.</i> ⁹¹ Donohue <i>et al.</i> ¹³⁰	Drug costs, hospi- talization costs, monitoring costs, and physician visit costs	Red book Medical Insurance Reimbursement- based Maximum Allowable Charges	Not specified	1 way sensitivity analysis
Najafzadeh <i>et al.</i> ⁸⁴ 2008	Direct costs	2006 Canadian dollars	Not applicable	Clinical Resources Utility	OPTIMAL ^{131,132}	Drug Medical resource utilization	Pharmanet Drug Master List Medical Services Commission. Payment Schedule.	Not specified	1 way sensitivity analysis

(continued)

Table 6. Continued.

Reference (Year)	Costs	Currency and year	Discounting	Input rates	Data source	Items costed	Data sources	Criterion	Planned sensitivity analyses
Neyt <i>et al.</i> ⁸⁵ 2010	Direct costs	Not stated	Not applicable	Clinical Resources Utility	O'Reilly <i>et al.</i> ¹³³ Roede <i>et al.</i> ¹³⁴ Belgian database	Drug Hospital related exacerbation Other exacerbations drugs hospital care medical care sick leave	O'Reilly <i>et al.</i> ¹³³ Roede <i>et al.</i> ¹³⁴ Belgian database	Not specified	1 way sensitivity analysis
Nielsen <i>et al.</i> ⁸⁶ 2013	Direct and indirect	DKK, 2011 euros, 2011 (Finland) NOK, 2011 SEK, 2011	not applicable	clinical resources	CLIMB ⁸² CLIMB ⁸²		national medicines agencies national Ministry of Health national Ministry of Health OECD Labour costs Drug Topics Red Book Nieuwenier <i>et al.</i> ¹²⁹ , Pennachio ¹³⁵ , DRG Code 99214 for COPD		
Oba ⁸⁷ 2007	Direct only	USD, 2005	not applicable	clinical utilities	6 published trials (meta-analyzed) Nieuwenier <i>et al.</i> ¹²⁹	drugs Hospital medical	Drug Topics Red Book Pennachio ¹³⁵ , Thompson Healthcare 5 published studies, Thompson Healthcare	not stated	1-way on costs, unscheduled visits, incremental QALYs
Oba ³⁷ 2009	Direct only	USD, 2006	Costs: 3% Outcomes: 3%	clinical utility	TORCH ⁶⁷ TORCH ⁶⁷	drugs medical hospital	Drug Topics Red Book Pennachio ¹³⁵ , Thompson Healthcare Veterans Affairs Veterans Affairs Maryland Health Consortium list	not stated	Probabilistic (10,000 simulations) 1-way on clinical rates, discount rate, costs, hospitalizations, mortality and utilities
Onukwughu <i>et al.</i> ⁸⁹ 2008	Direct only	USD, 2004	not applicable	clinical medical hospital	patient records patient records patient records	drugs hospitalization emergency room		cost savings was preferred outcome	Probabilistic (1000 draws) 1-way on rates of exacerbation and adherence, costs
Oostenbrink <i>et al.</i> ⁹⁰ 2004	Direct only	euros, 2001	not applicable	clinical rates resources quality-of-life	Vincken <i>et al.</i> ⁹¹ Vincken <i>et al.</i> ⁹¹ Vincken <i>et al.</i> ⁹¹	drugs laboratory medical care hospital care	List prices List prices average physician fees in the trial Oostenbrink <i>et al.</i> ¹³⁶ Oostenbrink <i>et al.</i> ^{90,137} (2 studies in 2004) Ontario Drug Benefit Formulary Oostenbrink <i>et al.</i> ^{90,137} , Ontario Schedule of Benefits	willingness-to-pay	1-way on costs, resource use, threshold values for improvement and quality of life Probabilistic (5000 simulations) 1-way on rates of transition, exacerbation, baseline disease severity, utility weights, costs
Oostenbrink <i>et al.</i> ⁹² 2005	Direct only	euros, 2001	not applicable	clinical utilities	Brusasco <i>et al.</i> ¹¹⁴ Casaburi <i>et al.</i> ¹¹⁵ , Vincken <i>et al.</i> ⁹¹ , Borg <i>et al.</i> ¹⁰⁴ , Paterson <i>et al.</i> ¹³⁸ , Spencer and Jones ¹³⁹	drugs clinical		willingness-to-pay	

Price <i>et al.</i> ⁹³ 2011	Direct only	euros, 2010	Costs: 3% Outcomes: 3%	clinical utilities mortality	INHANCE ¹⁴⁰ INLIGHT-2 ¹⁴¹ , UPLIFT ¹⁴² Ståhl <i>et al.</i> ¹⁴³ Rutten-van Mölken <i>et al.</i> ⁹⁷	drugs clinical	German Drug Index (Lauer Taxe) Uniform Value Scale	not stated	Probabilistic (1000 simulations) Univariate on clinical rates, time hori- zon, mortality and costs
Price <i>et al.</i> ⁹⁴ 2013	Direct only	UK pounds, 2011	Costs: 3.5% Outcomes: 3.5%	clinical utility values mortality	Donohue <i>et al.</i> ¹⁴⁰ , Kormann <i>et al.</i> ¹⁴⁴ , Price <i>et al.</i> ⁹³ Rutten-van Mölken <i>et al.</i> ¹⁴⁵ Rutten-van Mölken <i>et al.</i> ⁹⁷	clinical drugs	National Health Service British National Formulary	£20,000/QALY	Probabilistic (1000 simulations) 1-way on clinical rates, mortality, discount rate
Price <i>et al.</i> ⁹⁵ 2014	Direct, indirect (productivity)	SEK, 2013	Costs: 3% Outcomes: 3%	clinical resources mortality utilities	Dahl <i>et al.</i> ¹⁴⁶ , Vogelmeier <i>et al.</i> ¹⁴⁷ , Mahler <i>et al.</i> ¹⁴⁸ Jansson <i>et al.</i> ¹⁴⁹ , Jansson <i>et al.</i> ¹⁵⁰ , Lindberg <i>et al.</i> ¹⁵¹ Rutten-van Mölken <i>et al.</i> ¹⁵²	drug costs clinical care productivity	FASS 2013 drug prices Jansson <i>et al.</i> ¹⁴⁹ Jansson <i>et al.</i> ¹⁵⁰ Jansson <i>et al.</i> ¹⁵⁰	not stated	Probabilistic (1000 cohorts with 10,000 patients) 1-way on rates of improvement and exacerbation, baseline severity
Rutten-van Mölken <i>et al.</i> ⁹⁷ 2007	Direct and indir- ect (sick leave)	euros, 2005	Costs: 6% Outcomes: 6%	clinical resources mortality utilities	Oostenbrink <i>et al.</i> ⁷² , Miravittles <i>et al.</i> ¹⁵³ Miravittles <i>et al.</i> ¹⁵³ Miravittles <i>et al.</i> ¹⁵⁴ Badia <i>et al.</i> ¹⁵⁵ , Spencer <i>et al.</i> ¹⁰¹	clinical hospital drugs sick leave	SOIKOS database SOIKOS database SOIKOS database National Health Service	willingness-to- pay	Probabilistic (5000 simulations) 1-way on disease severity, Discount rate
Rutten-van Mölken <i>et al.</i> ⁹⁸ 2007	Direct, indirect (work/leisure days lost, impairment)	euros, 2004	not applicable	clinical hospital work lost/impairment	directly observed directly observed patient questionnaire	drugs, care workdays lost	National Health Service, Published costs (University of Kent)	willingness-to- pay	Imputation method, method of calcu- lating productivity costs, unit costs for hospitalization
Samyshkin <i>et al.</i> ⁹⁹ 2013	Direct only	CHF, 2011	Costs: 2.5% Outcomes: 2.5%	clinical resources utilities mortality	Bateman <i>et al.</i> ¹⁵⁶ Mills <i>et al.</i> ¹¹⁹ , Calverley <i>et al.</i> ¹⁵⁷ , Oostenbrink <i>et al.</i> ⁷² Rutten-van Mölken <i>et al.</i> ¹⁵⁸ Spencer <i>et al.</i> ¹⁰¹	drugs clinical	Swiss Medicines Compendium Schramm(2005), TARMED Suisse	CHF 72,000/ QALY (€60,000/QALY)	Probabilistic 1-way on clinical rates, costs, dis- count rate

(continued)

Table 6. Continued.

Reference (Year)	Costs	Currency and year	Discounting	Input rates	Data source	Items costed	Data sources	Criterion	Planned sensitivity analyses
Samyshkin <i>et al.</i> ¹⁵⁰ 2014	Direct only	UK pounds, year not stated	Costs: 3.5% Outcomes: 3.5%	clinical resources utilities mortality	Rabe ¹⁵⁹ , Bateman <i>et al.</i> ¹⁵⁶ , data on file Calverley <i>et al.</i> ¹⁵⁷ Rutten-van Mölken <i>et al.</i> ¹⁵⁸ Ekberg-Aronsson <i>et al.</i> ¹⁶⁰	drugs exacerbations	British National Formulary NHS lists	£20,000–£30,000/QALY	Probabilistic (2000 simulations) 1-way on clinical rates, discount rate, patient age, disease severity, utility values, costs
Sin <i>et al.</i> ¹⁰⁰ 2004	Direct + indirect (lost wages)	CAD, 2000	Costs: 5%	clinical resources utilities	4 published trials 4 published trials several published articles	exacerbations medical care hospital care lost wages	Alberta Health Care Plan Alberta Health Care Plan Alberta Health Costing Canadian National Population Health Survey	\$50,000/QALY	Probabilistic (100,000 simulations) 1-way on time horizon, response rates
Spencer <i>et al.</i> ¹⁰¹ 2005	Direct only	CAD, 2002	Costs: 5% Outcomes: 5%	clinical resources utilities	TRISTAN ¹¹⁰ , 7 RCTs TRISTAN ¹¹⁰ , 7 RCTs Health Survey for England ¹⁶¹ Brazier <i>et al.</i> ¹⁶¹ Spencerand Jones ¹³⁹ COPE ¹⁰² , patient charts	maintenance therapy exacerbations Hospitalization	Ontario Case Costing Program Ontario Case Costing Program London Health Science Centre	\$100,000/QALY	Probabilistic analyses 1-way on clinical rates, discount rates
van der Palen <i>et al.</i> ¹⁰² 2006	Direct only	euros, 2002	not applicable	clinical resources	COPE ¹⁰² , patient charts	drugs medical care hospital care	Local price list Oostenbrink(2002) Oostenbrink(2002)	not stated	Probabilistic (1000 simulations) 1-way on costs, probabilities

Table 7. Model outputs from economic analyses of severe COPD.

Reference (Year)	Time horizon	Sub-set	Treatment	Outcomes			Conclusions
				Cost	Clinical	Amount	
Ayres <i>et al.</i> ⁴⁵ 2003	6 months	Societal viewpoint NHS viewpoint	FP*	£3.65	patient with 10% improvement in FEV1	—£3.39	cost-effective cost-effective
			placebo*	£4.06	exacerbation-free patient	—£7.19	
			FP (direct cost)*	£2.75	moderate-to-severe exacerbation-free patient	—£3.28	
			placebo (direct cost)*	£2.72	patient with 10% improvement in FEV1	£0.25	
Briggs <i>et al.</i> ⁶⁵ 2006	3 years	Observed cases Full analysis (imputed data)	FP	£2494	exacerbation-free patient	£9500	cost-effective
			placebo	£1341	QALYs	£9282	
			FP	£2530	QALYs		
			placebo	£1509	QALYs		
Briggs <i>et al.</i> ⁶⁶ 2010	3 years	Pooled USA Eastern Europe Western Europe Other	FP/S	\$12,967	QALYs	\$43,346	FP/S is preferred as it had the lowest C/E ratio
			FP	\$11,486	QALYs	dominated	
			S	\$11,035	QALYs	\$77,130	
			placebo	\$9456	QALYs	dominated	
			FP/S	\$24,830	QALYs	dominated	
			FP	\$22,692	QALYs	\$2924	
			S	\$21,717	QALYs	dominated	
			placebo	\$18,891	QALYs	dominated	
			FP/S	\$7710	QALYs	\$24,048	
			FP	\$6437	QALYs	dominated	
			S	\$3815	QALYs	dominated	
			placebo	\$4455	QALYs	\$2100	
			FP/S	\$7619	QALYs	dominated	
			FP	\$6797	QALYs	dominated	
			S	\$6603	QALYs	dominated	
			placebo	\$5623	QALYs		
			FP/S	\$6511	QALYs		
			FP	\$5726	QALYs		
			S	\$5404	QALYs		
			placebo	\$4490	QALYs		

(continued)

Table 7. Continued.

Reference (Year)	Time horizon	Sub-set	Treatment	Outcomes			Conclusions
				Cost	Clinical	Amount	
Chuck <i>et al.</i> ⁶⁸ 2008	3 years lifetime	Base case Base case	IC only	\$3719	QALYs	2,405	FP/S is cost-effective for patients in Stages 2 and 3 FP/S is cost-effective for patients in Stages 2 and 3
			LABA + IC (Stage 3 only)	\$3758	QALYs	2,406	
			LABA + IC (Stages 2–3)	\$3853	QALYs	2,408	
			LABA + IC (all stages)	\$5204	QALYs	2,411	
			IC only	\$9636	QALYs	6,763	
Dal Negro <i>et al.</i> ³⁵ 2007	lifetime	NHS only	LABA + IC (Stage 3 only)	\$9788	QALYs	6,769	Reported: All but S dominated controls; S was slightly more costly ERROR = results not interpreted correctly FP/S is cost effective over salmeterol all others are dominated (B/F extended; F and C strongly dominated)
			LABA + IC (Stages 2–3)	\$10,142	QALYs	6,776	
			LABA + IC (all stages)	\$13,282	QALYs	6,783	
Chuck <i>et al.</i> ⁶⁸ 2008	6 months	Societal viewpoint	OM-85 BV placebo		day of hospitalization for respiratory disease		Cost-effective
			FP/S	\$4842	Annualized exacerbation rate	4.76	
Dal Negro <i>et al.</i> ⁷⁰ 2010	1 year	Base case	S	\$5066		5.67	Cost-effective
Dal Negro <i>et al.</i> ³⁵ 2007	lifetime	NHS only	S	€33,369	Average exacerbations/patient	10.07	Reported: All but S dominated controls; S was slightly more costly ERROR = results not interpreted correctly FP/S is cost effective over salmeterol all others are dominated (B/F extended; F and C strongly dominated)
			B/F	€33,945	Average exacerbations/patient	9.66	
			FP/S	€34,038	Average exacerbations/patient	9.09	
			controls	€34,632	Average exacerbations/patient	12.04	
			F	€34,754	Average exacerbations/patient	10.14	
			S	€33,369	Average exacerbations/patient	55	
			B/F	€33,945	Average exacerbations/patient	220	
			FP/S	€34,038	Average exacerbations/patient	257	
			controls	€34,632	Average exacerbations/patient	0	
			F	€34,754	Average SFDs/patient	37	

Eamshaw ²⁶ 2009	Lifetime	none	Advair® 500/50 Fluticasone propionate Placebo	\$42,019 \$23,727 \$18,986	QALY QALY QALY	7.42 6.58 6.74	33,865/QALY dominated —	77% of simulations resulted in an ICER of less than \$50,000	Advair is cost effective compared to no maintenance treatment
Gani <i>et al.</i> ⁷¹ 2010	1 year	None	Tiotropium Salmeterol Ipratropium	£1439 £1565 £1631	QALY QALY QALY	0.744 0.73 0.723	dominated dominated	WTP threshold 97–98% probability of <£20,000/QALY	Tiotropium is cost effective compared to salmeterol or ipratropium
Hertel <i>et al.</i> ¹¹⁸ 2012	30 years	None	LABA LABA LABA + roflumilast LABA + roflumilast LABA + LABA LABA + LABA + roflu- milast LABA/ICS LABA/ICS + roflumilast LABA + LABA/ICS LABA + LABA/ ICS + roflumilast Usual care	£22,342 £22,370 £22,749 £22,779 £22,687 £23,100 £22,468 £22,878 £22,816 £23,230	QALY QALY QALY QALY QALY QALY QALY QALY QALY QALY	5.39 5.42 5.43 5.46 5.45 5.48 5.43 5.46 5.48 5.51	LAMA + LAB- A + roflu- milast versus LABA + LABA, was £13,764/ QALY	Results robust	addition of roflumilast to the standard of care regimens is cost-effective
Hettle <i>et al.</i> ⁷³ 2012	4 year		Tiotropium Usual care	£6475 £5679	QALY QALY	2.645 2.594	£15,567/ QALY	The probability of cost- effectiveness at a willingness-to-pay threshold of £30,000 was over 60%.	Adding tiotropium to usual care is cost- effective.
Hogan <i>et al.</i> ⁷⁵ 2010	12 weeks		Placebo Ipratropium Formoterol 12 Formoterol 24	\$38.93 \$76.34 \$214.91 \$418.92	QALY QALY QALY QALY	1.50 1.1 6.60 4.8	Dominated 25.20/QoL Dominated		Formoterol 12 provided greater QoL out- come than ipratro- pium bromide at an additional cost of \$554.28 per year. Tiotropium is cost- effective
Hoogendorn <i>et al.</i> ⁷⁶ 2013	1 and 5 year		Tiotropium – 1 year Salmeterol – 1 year Tiotropium – 5 year Salmeterol – 5 year Placebo	1570 1380 7520 6896 £192.37 £102.26	QALY QALY QALY QALY Symptom free night	0.746 0.734 3.26 3.18 60% 48%	Euro8141/ QALY	Results robust	
Jones <i>et al.</i> ⁷⁷ 2003	16 weeks		Acidimium tiotropium	126,274 USD 128,591 USD	QALY QALY	3.50 3.49	£5.67 per symptom free night dominated	Reduction in hospital costs offsets cost of salmeterol	
Karablis <i>et al.</i> ⁷⁸ 2014	5 years		Tiotropium + usual care					Results robust	Single inhaler cost- effective compared to F or placebo
Lee <i>et al.</i> ⁷⁹ 2006	1 year		Usual care B/F Single inhaler B monocomponent F monocomponent Placebo	2518 3194 3653 3213					
Lofdahl <i>et al.</i> ⁸⁰ 2005	1 year		Tiotropium Salmeterol	€2504 €2655	Exacerbation free months	11.15 10.98	dominated	The probability that tiotropium is cost- effective was 65% at a ceiling value of €0 and reached 77% at a ceiling ratio of €1000	
Maniadakis <i>et al.</i> ⁸¹ 2006	1 year								

(continued)

Table 7. Continued.

Reference (Year)	Time horizon	Sub-set	Treatment	Outcomes			Sensitivity analyses	Conclusions
				Cost	Clinical	Amount	ICER†	
Mittmann <i>et al.</i> ⁸² 2011	1 year		Tiotropium Salmeterol No treatment	1408.59 1268.66 392.1	Exacerbation avoided	1.12855 1.05156 0.69443	1817.37 2454.48	tiotropium is more cost-effective than salmeterol and no treatment
Najatzadeh <i>et al.</i> ⁸⁴ 2008	1 year		Tiotropium + placebo Tiotropium + F/S Tiotropium + S	CS2678 CS4042 CS2801	QALY QALY QALY	0.7092 1.35 1.69		Tiotropium is not cost- effective
Neyt <i>et al.</i> ⁸⁵ 2010	1 year		tiotropium real-world tiotropium theoretical salmeterol real world	427.71 621 225.46	Incremental QALY	0.013		
Nielsen <i>et al.</i> ⁸⁶ 2013	3 months 3 months	Denmark: Societal Finland: Societal Norway: Societal Sweden: Societal Denmark: Health system Finland: Health system Norway: Health system Sweden: Health system	B/F + tiotropium placebo + tiotropium B/F + tiotropium placebo + tiotropium B/F + tiotropium placebo + tiotropium B/F + tiotropium placebo + tiotropium B/F + tiotropium placebo + tiotropium B/F + tiotropium placebo + tiotropium placebo + tiotropium	DKK 3713 DKK 3756 467€ 436€ NOK 3313 NOK 3827 SEK 4494 SEK 4575 DKK 3713 DKK 3756 467€ 436€ NOK 3313 NOK 3827 SEK 4494 SEK 4575	exacerbations/patient exacerbations/patient	0.11 0.29 0.11 0.11 0.11 0.29 0.11 0.11 0.11 0.29 0.11 0.11 0.29 0.11 0.29 0.11 0.29	dominant dominated 174 € dominant dominated dominated dominated DKK 1580 307 € dominant dominated SEK 1573	Dominant in 50% of simulations no change if antibiotics are included Dominant in 32% of simulations 149€ if antibiotics are included Dominant in 74% of simulations no change if antibiotics are included Dominant in 52% of simulations no change if antibiotics are included DKK 1449 if antibiotics are included 281€ if antibiotics are included no change if antibiotics are included SEK 1342 if antibiotics are included Range: \$11,780– \$77,214 1-way ICERs: \$5160– \$53,571 Range: \$23,650– \$98,750 1-way ICERs: \$10,825–\$56,000 1-way: could save \$244–\$967 and gain 0.011–0.060 QALYs
Oba ⁸⁷ 2007	1 year		tiotropium placebo salmeterol placebo tiotropium	\$835 (incremental) \$1066 (incremental) \$330 (incremental)	QALYs QALYs QALYs	0.032 (incremental) 0.026 (incremental) 0.036 (incremental)	\$26,094 \$41,000 –\$391	Cost-effective Cost-effective Cost-effective (cost saving)

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(continued)

Table 7. Continued.

Reference (Year)	Time horizon	Sub-set	Treatment	Outcomes			Conclusions
				Cost	Clinical	Amount	
Price <i>et al.</i> ⁹⁴ 2013	3 years	150 mg 150 mg 300 mg	indacaterol	£4534	QALYs	2.158	indacaterol is cost-effective
			tiotropium	£4781	QALYs	2.150	
			indacaterol	£4583	QALYs	2.158	
			salmeterol	£4692	QALYs	2.149	
			indacaterol	£4501	QALYs	2.162	
Price <i>et al.</i> ⁹⁵ 2014	1 year 3 years 5 years 10 years lifetime		tiotropium	£4760	QALYs	2.151	indacaterol/glycopyrronium is cost-effective
			indacaterol/glycopyrronium	SEK 27,635	QALYs	assumed equal	
			indacaterol + glycopyrronium	SEK 28,403	QALYs	(0.001 more than FP/S)	
			FP/S	SEK 30,379		assumed equal	
			indacaterol/glycopyrronium	SEK 91,788		(0.006 more than FP/S)	
			indacaterol/glycopyrronium	SEK 93,906		assumed equal	indacaterol/glycopyrronium is cost-effective
			indacaterol + glycopyrronium	SEK 100,642		(0.015 more than FP/S)	
			FP/S	SEK 149,464		assumed equal	
			indacaterol + glycopyrronium	SEK 152,772		(0.047 more than FP/S)	
			FP/S	SEK 163,402		assumed equal	
			indacaterol/glycopyrronium	SEK 273,053		(0.200 more than FP/S)	
			indacaterol + glycopyrronium	SEK 278,685		assumed equal	
			FP/S	SEK 300,548		assumed equal	
			indacaterol + glycopyrronium	SEK 500,248		assumed equal	
			FP/S	SEK 508,951		assumed equal	
			indacaterol/glycopyrronium	SEK 543,281		assumed equal	
Rutten-van Malken <i>et al.</i> ⁹⁷ 2007	5 years	societal NHS Base case	tiotropium	€6574	QALYs	3.15	tiotropium had highest net benefit above €7076/QALY, below €11,000/QALY, ipratropium had the highest probability of being cost-effective, above that value, tiotropium had highest probability of being cost-effective
			salmeterol	€6125	QALYs	3.02	
			ipratropium	€5545	QALYs	3.00	
			tiotropium	€6424	QALYs	3.15	
			salmeterol	€5869	QALYs	3.02	
			ipratropium	€5181	QALYs	3.00	
			tiotropium	€3483			
			salmeterol	€35,158			

Rutten-van Möllen <i>et al.</i> ³⁶ 2007	1 year	societal National Health Service	roflumilast placebo roflumilast placebo	€1637 €1401 €1418 €1242	moderate or severe exacerbations relevant improvement in SGRQ moderate or severe exacerbations relevant improvement in SGRQ moderate or severe exacerbations relevant improvement in SGRQ moderate or severe exacerbations relevant improvement in SGRQ	0.96 0.19 1.06 0.14 0.96 0.19 1.06 0.14	€2356 €4712 €1755 €3510	Probability of cost- effectiveness = 10% at a WTP = 0, 70% at €5000, 90% at €50,000 Probability of cost- effectiveness = 10% at a WTP = 0, >70% at €20,000 1-way ICERS: €375– €2817 1-way ICERS: €2363– €5633	Increases costs but lowers healthcare use potential to be cost saving
Samyiskin <i>et al.</i> ³⁵ 2013	lifetime		(1) roflumilast + LAMA LAMA (2) roflumilast + LABA/ ICS LABA/ICS (3) roflumilast + LABA/ ICS + LAMA LABA/ICS + LAMA	CHF 86,754 CHF 83,364 CHF 91,470 CHF 88,161 CHF 99,364 CHF 95,564	QALYs QALYs QALYs QALYs QALYs QALYs	6.466 6.191 6.479 6.191 6.468 6.191	CHF 12,313 CHF 11,456 CHF 13,671	Probabilistic: 79% probability of cost- effectiveness at a WTP of CHF 70,000 Roflumilast + LAMA dominated in 1 case, otherwise ICER = dominant to CHF 17,196 Probabilistic: 96% probability of cost- effectiveness at a WTP of CHF 70,000 Roflumilast + LABA/ ICS dominant to CHF 84,682 Probabilistic: 96% probability of cost- effectiveness at a WTP of CHF 70,000 Roflumilast + LABA/ ICS + LAMA dom- inant to CHF 85,689	Roflumilast cost- effective and reduces burden
Samyiskin <i>et al.</i> ³⁰ 2014	30 years	Base case	roflumilast + LABA LABA	£19,358 £16,161	QALYs QALYs	5.615 5.451	£19,505	CI: £364–£38,646 82% probability of cost-effectiveness at a WTP of £30,000 1-way ICERS: £12,829–£53,435	can be cost-effective ICERS most influenced by exacerbation and mortality rates

(continued)

Table 7. Continued.

Reference (Year)	Time horizon	Sub-set	Treatment	Outcomes			Conclusions
				Cost	Clinical	Amount	
Sin <i>et al.</i> ¹⁰⁰ 2004	3 years 3 years lifetime lifetime	assuming a mortality benefit assuming no mortality benefit assuming a mortality benefit assuming no mortality benefit	no ICs ICs Stage 3 only ICs Stages 2 and 3 ICs all stages no ICs ICs Stage 3 only ICs Stages 2 and 3 ICs all stages no ICs ICs Stage 3 only ICs Stages 2 and 3 ICs all stages	NR NR NR NR NR NR NR NR NR NR NR NR	QALYs QALYs QALYs QALYs QALYs QALYs QALYs QALYs QALYs QALYs QALYs QALYs	2.71 2.72 2.72 2.71 2.72 2.72 2.75 NR NR NR NR NR	Cost-effective Cost-effective
Spencer <i>et al.</i> ¹⁰¹ 2005	25 years	Base case	FP/S	\$25,780 \$6416	QALYs usual care	4.21 4.08	Cost-effective at a WTP of \$100,000/QALY
van der Palen <i>et al.</i> ¹⁰² 2006	6 months	Base case	FP placebo	€511 €456	exacerbations hospital admissions exacerbations hospital admissions	0.87 0.073 1.37 0.116	Overall cost savings but increased exacerbations and hospitalizations Note: ICERs both exceed the average cost to treat the outcome

CI, 95% confidence interval; FP, fluticasone propionate; IC, inhaled corticosteroids; NR, not reported; QALM, quality-adjusted life-month; QALY, quality-adjusted life-year; S, salmeterol; SFD, symptom-free day; SGRQ, St. George's Respiratory Questionnaire; WTP, willingness-to-pay.

*Expressed as cost per day.

†Negative ICER mean cost savings.

Specifically, only Norman *et al.*¹² (who focused on asthma) discussed validation of their model in detail. They did extensive testing to assure the model integrity and that it generated accurate results. Some authors used existing published models, assuming that validation had been done; however, in many cases, the original publications did not discuss validation. For example, van Nooten *et al.*³² indicated that they used ‘the validated and published Markov 5-state omalizumab model’, citing Brown *et al.*²¹ and Dewilde *et al.*²⁵ (the original publication) as references. However, neither the word ‘validate’ nor ‘validation’ appears in the paper by Dewilde *et al.* Since there is overlap in the authorship of those three papers, they would presumably have had access to that information, but failed to include it in their articles. Therefore, there is a need for authors to describe their validation process explicitly and completely.

On the other hand, Hoogedorn *et al.*¹⁶³ identified seven studies and requested that these authors validate their own models using pre-identified criteria. They found a general consistency in structure across models. Outcomes varied somewhat, but the variation could be explained by differences in input values for disease progression and mortality. There was a high probability (90–100% for five models, 70% and 50% for the others) of lifetime cost-effectiveness at a willingness-to-pay of €50,000/QALY. Note that this threshold is quite high compared to those in many jurisdictions. Those authors concluded that mortality was the important factor in determining differences between ICERs.

We identified at least three studies^{35–37} that did not analyze and present their findings according to well-accepted standard procedures^{37,38}. For example, Dal Negro *et al.*³⁵ compared each drug to placebo, which is not appropriate when some alternatives are dominated. According to Drummond *et al.*³⁸, all dominated drugs must first be eliminated from consideration in the analysis and non-dominated alternatives analyzed incrementally, starting with the choice having the lowest cost. Reporting results that include dominated alternatives may affect what is considered to be within accepted threshold parameters. In their analyses, Dal Negro *et al.* failed to eliminate the placebo and fluticasone arms, which were strongly dominated, as well as formoterol/budesonide, which was extendedly dominated. Nevertheless, in the final analysis, their drug was still cost-effective. Earnshaw *et al.*³⁶ also compared each drug to placebo, reporting an ICER for fluticasone/salmeterol vs placebo of \$33,865 per additional QALY gained for which they claimed cost-effectiveness, citing a threshold of \$50,000. However, when calculating incrementally from salmeterol (next in line), the ICER would be ~\$69,889, which far exceeds their limit for cost-effectiveness. A similar situation occurs with the study by Oba³⁷. In his Table 1, he recognized that two drugs were ‘dominated through extended dominance’. Therefore, they should both have been eliminated, but, despite that, Oba

calculated an incremental ICER for fluticasone/salmeterol, comparing it with fluticasone alone (a dominated choice). The reported (incremental) ICER was \$41,092; however, had it been properly compared with the only non-dominated choice (i.e., placebo), the ICER would have been ~\$52,046. If the same criterion used by Earnshaw *et al.* had been used to judge this result (i.e., \$50,000/QALY gained), it would also fail to achieve cost-effectiveness. Thus, there is an apparent need for appropriate reporting of results from economic models.

Conclusions

We have summarized the economic analyses that examined drug use in severe asthma and COPD. Very few biologic drugs have been studied in these patients, and more options are needed. In asthma-related studies, there was not a large number that were found to be cost-effective, and often at a quite high level of willingness-to-pay. Controversy concerning some results was uncovered in this study, which needs to be avoided in the future. More research is needed to fill gaps in knowledge.

As well, there is a need for more complete and accurate reporting of results. The authors should be required to address the issue of model validation and provide adequate documentation of how it was done. Insufficient attention has been placed on the calculation and presentation of results when there are multiple options being compared. Authors, reviewers, and editors need to assure that manuscripts adhere to guidelines for reporting results.

Transparency

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Declaration of financial/other relationships

TRE has received sponsorship from Janssen Pharmaceutica and has declared consultancy/advisory interests from Janssen-Cilag. JVL is an employee of Janssen Pharmaceutica NV and MEHH was an employee at the time of writing. JME peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

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