

A systematic review of economic evaluations of therapy in asthma

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Background: Asthma's cost-effectiveness is a major consideration in the evaluation of its treatment options. Our objective was to perform a systematic review of the cost-effectiveness of asthma medications.

Methods: We performed a systematic search of MEDLINE, EMBASE, CINAHL, Cochrane Database of Systematic Reviews, OHE-HEED, Database of Abstracts of Reviews of Effects, Cochrane Central Register of Controlled Trials, Health Technology Assessments Database, NHS Economic Evaluation Database, and Web of Science and reviewed references from key articles between 1990 and Jan 2008.

Results: A total of 49 RCTs met the inclusion criteria. Maintenance therapy with inhaled corticosteroids was found to be very cost-effective and in uncontrolled asthmatics patients currently being treated with ICS, the combination of an ICS/LABA represents a safe, cost-effective treatment. The simplified strategy using budesonide and formoterol for maintenance and reliever therapy was also found to be as cost-effective as salmeterol/fluticasone plus salbutamol. Omalizumab was found to be cost-effective. An important caveat with regard to the published literature is the relatively high proportion of economic evaluations which are funded by the manufacturers of specific drug treatments.

Conclusion: Future studies should be completed independent of industry support and ensure that the comparator arms within studies should include dosages of drugs that are equivalent.

Keywords: asthma, medication, cost-effectiveness, cost of illness, economic costs

Asthma is a chronic disease manifested by variable airflow obstruction and airway inflammation.¹ There has been a significant increase in the global prevalence, morbidity, mortality, and economic burden associated with asthma over the last 40 years.²

The appropriate choice of asthma medication is important in achieving asthma control. There are two major classes of asthma medications – controllers or preventers which reduce inflammation in the airway, and symptom relievers which give symptomatic relief. Inhaled corticosteroids (ICS) are the mainstay of anti-inflammatory therapy and for more severe asthma are usually combined with a long-acting β_2 -agonist (LABA). Oral corticosteroids are generally reserved for the treatment of acute asthma exacerbations, although some patients with severe asthma are steroid dependent. Leukotriene modifiers are one of the newer classes of drugs which are available in an oral form and act as anti-inflammatory therapy. Bronchodilators relieve the symptoms of asthma by relaxing airway smooth muscles and are divided into short-acting β_2 -agonists (SABA) and LABA.

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Asthma is responsible for significant medical resource utilization and given that it is a chronic condition, cost-effectiveness is a major consideration in the evaluation of treatment options.³ The costs of asthma medication have increased dramatically since 1985 and this is especially true with the availability of more expensive combination inhalers as well as newer biological drugs such as omalizumab.

To our knowledge, there has been no systematic review evaluating the cost-effectiveness of asthma medications. Our goal in conducting this systematic review is to evaluate the literature with respect to this question.

Method

Literature review

A systematic review was conducted to identify English language articles published between 1990 and Jan 2008 that provided data on the cost of asthma medications. The following electronic databases were searched: MEDLINE, EMBASE, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Cochrane Database of Systematic Reviews (CDSR), Health Economic Evaluation Database (OHE-HEED), Database of Abstracts of Reviews of Effects, Cochrane Central Register of Controlled Trials, Health Technology Assessments Database (Technology Assessments), NHS Economic Evaluation Database (Economic Evaluations), and Web of Science and references were reviewed from key articles. Duplicate citations were identified and removed using RefWorks bibliographic management software.

Study selection

A total of 177 titles and abstracts of all publications identified by the primary literature search were reviewed by two investigators (K.B. and B.Q.), independently. The inclusion and exclusion criteria used for study selection are outlined in Table 1. The full text of the 80 potentially eligible papers,

determined after the first level of screening, were reviewed to assure that each paper met the inclusion criteria for population and outcomes of interest.

For cost data from the United States (US) figures were converted to 2008 US dollars using the medical care component of the consumer price index from the US Bureau of Labor Statistics. For cost data from other countries, costs were first converted to 2008 currency values using the health or equivalent component of that country's consumer price index. Figures were then converted to 2008 US dollars, using currency exchange rates of AUD\$1.00 = USD\$0.888, CAD\$1.00 = USD\$0.998, EUR€1.00 = USD\$1.477, GBP£1.00 = USD\$1.986. If the year of the cost data was not reported, it was assumed to be the year of article publication. In all cases, both the original cost figures provided in the publications as well as the equivalent costs in 2008 US dollars are reported. Neither intangible costs nor disability adjusted life-years (DALYs) were evaluated in this systematic review.

Data abstraction

The following information was abstracted from all publications: authors, year of publication, primary country of origin, study design and duration, whether the study was placebo controlled, patient characteristics (population, age, and gender), number of patients enrolled in each treatment arm, types of analysis, cost measurements, and comparative medications.

Methodological quality assessment

The methodological quality assessment in this review was divided into two parts. First, the quality of the economic evaluations was assessed using the checklist for assessing economic evaluations published by Drummond and Jefferson⁴ (see Table 2). Secondly, the quality of the clinical effectiveness studies was assessed using modified criteria based on CRD Report No. 4.⁵ Study qualities were assessed and data were extracted by one reviewer and confirmed by a second reviewer. Items were scored as positive, negative, or unclear. Randomized controlled trials (RCTs) that fulfilled 50% or more of the internal validity items were considered of high methodological quality. Any disagreements between the reviewers were resolved through consensus.

Statistical analysis

Due to the heterogeneity between studies in terms of the variety of medications and unit cost data the results of the

Table 1 Inclusion and exclusion criteria

Inclusion	Exclusion
<ul style="list-style-type: none"> English language Studies that consider the costs of asthma medications Studies from 1990 onwards 	<ul style="list-style-type: none"> Conference abstracts, case reports, letters, comments, editorials, and review papers Studies that consider asthma with other comorbidities (such as allergies, COPD) Studies that didn't quote costs in the results section Non-RCT trials Animal or <i>in vitro</i> studies

Abbreviations: COPD, chronic obstructive pulmonary disease; RCT, randomized controlled trials.

Table 2 Criteria for evaluating an economic analysis based Drummond and Jefferson assessment method*⁴

1. Was a well-defined question asked in an answerable form?
2. Was a comprehensive description of the competing alternatives provided?
3. Was there evidence that the program's effectiveness was established?
4. Were all the important and relevant costs and consequences identified?
5. Were costs and consequences measured accurately with appropriate physical units?
6. Were costs and consequences credibly valued?
7. Were costs and consequences adjusted for differential timing?
8. Was an incremental analysis of costs and consequences of alternatives performed?
9. Was a sensitivity analysis performed?
10. Did the presentation and discussion of the study results include all issues of concern to users?

*Note: All items have three possible responses, Yes (+), Cannot tell (N/A), and No (-).

economic evaluations did not allow a quantitative meta-analysis to be completed.

Results

Literature search

The primary literature search identified 2,976 citations. After removing duplicate citations there were 2,073 unique citations. Manual screening of all titles and abstracts identified 307 articles that contained primary clinical data evaluating the cost of asthma treatment. Of the 307 full text articles retrieved and reviewed by the investigators, 49 RCT met the inclusion criteria (see Figure 1).

Quality assessment

Most of the authors of our sample studies clearly described their inclusion and exclusion criteria and the population as well as specifying the primary outcome measures. Eighty-nine percent of studies were rated as being of high-quality. The quality of 65% of these studies was more than 7/10.

Characteristics of the selected studies

Of the 49 identified studies, 12 were based in the US, 16 in mainland Europe (mainly Sweden), 10 in the United Kingdom (UK), and two in Canada. Ten of the reviewed studies were multinational. Forty-seven studies involved the evaluation of both the cost and efficacy of the study medication. In each study, comparative effects of different medications on asthma-related health care utilization and costs were reported. Study funding sources according to the articles are reported in Table 3.

The cost-effectiveness of the different asthma medications evaluated are summarized below:

Inhaled corticosteroids

The impacts of ICSs on asthma patients as well as their cost-effectiveness were evaluated in 18 studies.^{6–23} In three of the studies it was reported that there was a cost-benefit to the introduction of ICS therapy and that this therapy brought about significant decreases in health care utilization and asthma-related cost.^{8,11,21}

Budesonide (with or without other asthma medications)

In fourteen studies the results of a cost-effectiveness analysis of the ICS budesonide versus placebo or in comparison with other asthma medications were reported.^{6,9–16,18–22} Of these, in five studies it was found that treatment using budesonide, over the long term, was more cost-effective than placebo or other usual asthma therapy, with a substantial reduction in hospitalizations, emergency department visits, and school or caregiver work days missed (see Table 4).^{9,11,18,21,22} It was also shown that the additional drug costs were substantially offset by reduced use of health care services and indirect costs. In a 3-year study evaluating the early use of ICS conducted in eight different countries (Australia, Canada, China, France, Spain, Sweden, UK, and US), treatment with budesonide was also found to be cost-saving in Australia, Canada, and Sweden from both a health care payer and societal perspectives.⁹ Another study randomized patients to receive budesonide with three different doses or placebo.¹⁸ The investigators found the number of emergency department visits, days lost from work, and days of hospitalization all to be lower in the budesonide groups, leading to significantly reduced total healthcare costs and increased productivity compared to placebo ($P < 0.05$). The average cost in the placebo group was found to be \$37 per day compared with \$11, \$9, and \$18 in budesonide 200 µg, 400 µg, and 800 µg daily dosing groups, respectively. In another high quality study, the cost-effectiveness ratio of budesonide relative to placebo was found to be decreased to \$3.70 (95% CI, \$0.10–\$8.00).²¹

Comparing the cost-effectiveness ratio of different ICSs

Fluticasone propionate (FP) versus BUD

In five studies the cost differences between FP and BUD was explored. Although FP was found to be more expensive than BUD in all studies, when the impact on outcomes was assessed, FP proved to be the most cost-effective

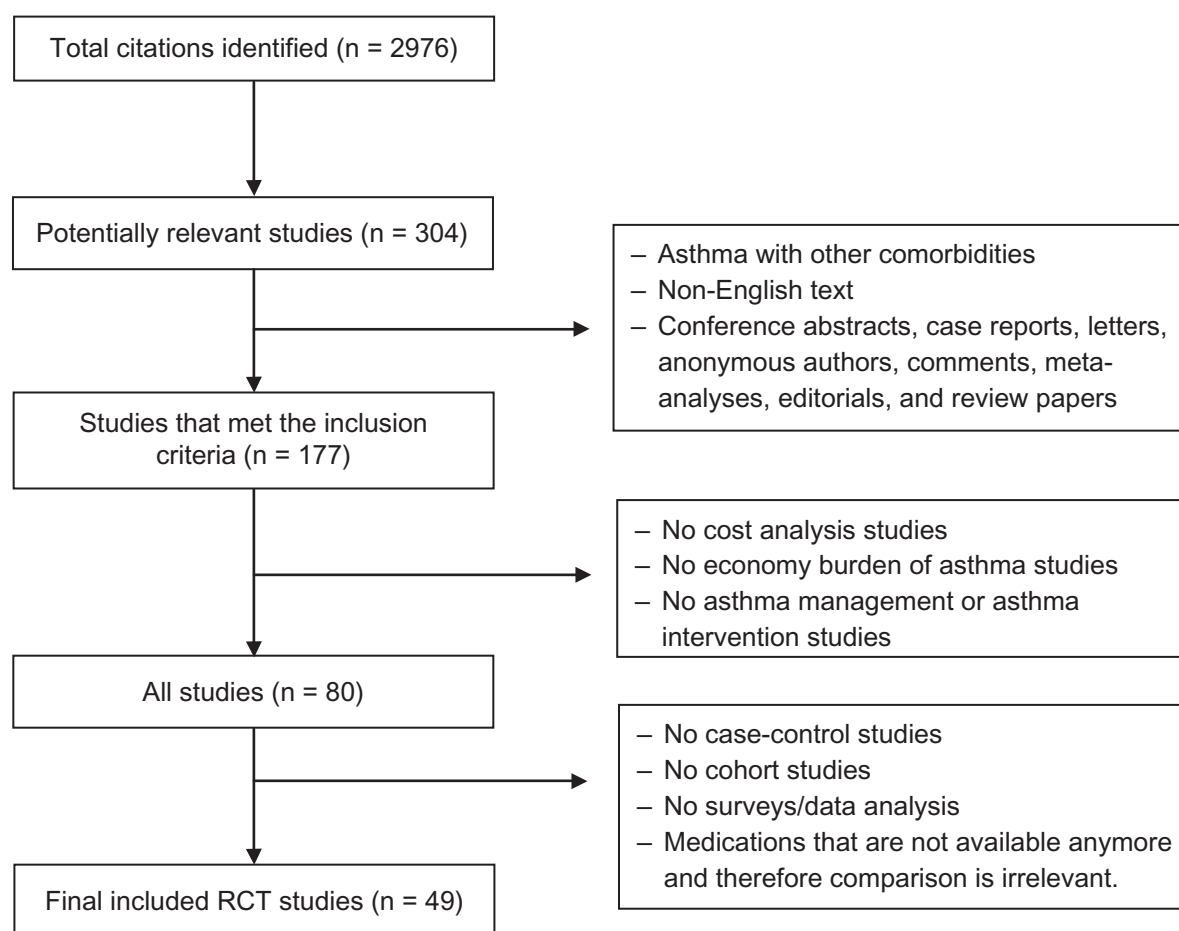


Figure 1 Results of a systematic literature search.

Abbreviations: RCT, randomized controlled trials.

option (Table 5).^{24–28} Delivery of the medications by different devices was found to have no effect on the results in three of the studies.^{24,26,28} In another study, the efficacy and tolerability of FP via a metered-dose inhaler and Volumatic spacer device was compared with nebulized budesonide (nBUD).²⁵ Although the study didn't involve an evaluation the cost-effectiveness of the medications, the cost per patient analysis for nebulized budesonide was found to be 1.7 to 3.5 times more expensive than FP. Given the expense of nebulized therapy this result would not be unexpected. In contrast to the above studies, in a clinical trial conducted in UK, it was reported that budesonide, whether administered once or twice daily, was a more cost-effective treatment option than fluticasone dry-powder disk inhaler.²⁷

FP versus flunisolide (FL)

In a cost-effectiveness analysis conducted in Germany, in a comparison of two ICS (FP and FL), the average daily treatment in the FP groups was found to be higher than in the FL groups, however, all cost-effectiveness ratios favoured

FP. An incremental cost-effectiveness ratio (ICER) analysis revealed that when switching from FL to FP, there were additional costs of \$5.86 and \$6.03 per additional symptom-free day (SFD), and of \$2.82 and \$2.61 for each additional successfully treated patient per day, would be incurred. In these patients, management with FP was found to be more cost-effective than with FL.²⁹

FP versus triamcinolone acetonide (TA)

In a further study, FP 250 µg twice daily was compared with TA 200 µg in patients with persistent asthma. It was found that the daily cost per successfully treated patient based upon a $\geq 12\%$ increase in forced expiratory volume in one second (FEV_1) was \$6.15 for the FP treated group and \$9.60 for the TA-treated group. In addition, the cost for improvement in symptoms was determined to be \$18.11 per additional SFD for FP and \$23.40 per additional SFD for TA. The ICER that would be incurred if patients were switched from the less effective treatment, TA, to FP was \$0.88 per day for an additional patient to achieve a 12% improvement in FEV_1 .³⁰

Table 3 Study funding sources according to the articles

Reference	Year of publication	Country/ies	Sponsoring companies
13	2006	Multicountry	AstraZeneca
16	2006	Sweden	AstraZeneca Sweden
21	2003	US	AstraZeneca Sweden
25	1998	UK	Glaxo Wellcome, UK Ltd.
26	1998	Germany	Glaxo Wellcome
27	1996	UK	Astra Pharmaceuticals Ltd.
29	1999	Germany	Glaxo Wellcome
30	2000	US	Glaxo Wellcome, Inc.
31	2000	UK	AstraZeneca Pharmaceuticals UK Ltd.
32	2005	Multicountry	AstraZeneca R&D; Lund
36	1998	Multicountry	Novartis
37	1993	Netherlands	Netherlands Health Research Promotion Program (SGO), Glaxo, Astra Pharmaceuticals and Boehringer Ingelheim
41	2002	UK	GlaxoSmithKline Inc.
42	2004	US	GlaxoSmithKline Inc.
43	2005	Multicountry	GlaxoSmithKline Inc.
45	2001	US	GlaxoSmithKline Inc.
47	2002	US	GlaxoSmithKline Inc.
48	2007	Sweden	Novartis Pharma AG
49	2006	Multicountry	Novartis
50	1996	UK	Glaxo Wellcome resource

Long-acting β_2 agonists

In a further study, patients with mild to moderate asthma were randomized to eformoterol 12 μg bid and salmeterol 50 μg bid via either a pressurised metered dose inhaler (pMDI) or metered dose powder inhaler (DPI) to determine the cost-effectiveness of each long-acting bronchodilator in

the treatment of asthma. Patients had been receiving at least 200 $\mu\text{g}/\text{day}$ inhaled corticosteroid at a constant dose for at least 4 weeks prior to study entry. Findings in the study indicated that the total medical costs of treating patients with eformoterol were significantly lower than the costs of treating a similar population with salmeterol via either DPI or pMDI (\$141 versus \$146 or \$150, respectively). The mean cost of achieving a SFD on salmeterol was estimated to be between 25% (pMDI) and 41% (DPI) more than achieving the same result using eformoterol Turbuhaler.³¹

LABA versus SABA

In five studies the use of LABA or SABA medications in the treatment of asthma were compared.^{32–36} Overall, the mean cost-effectiveness ratios of formoterol were found to be higher than those for SABA. The results of three studies indicated that LABA (particularly formoterol) achieved significant improvements in effectiveness, less use of reliever and maintenance medication, and reduced resource utilization, with no increase or only a limited increase in health care cost compared with SABA.^{32,33,35} The first study was based on the Real-Life Effectiveness of Oxis Turbuhaler as needed in asthmatic patients (RELIEF), and evaluated the cost-effectiveness of formoterol 4.5 μg and salbutamol 200 μg in Sweden and Spain. At study entry, 76% of patients were being treated with ICS and 31% with long-acting bronchodilators. Compared to salbutamol, the authors found formoterol to be associated with statistically significant improvements in effectiveness, reduced health care resource utilization, and with lower health care costs in the patients with severe disease.³² In a further study, formoterol was compared to terbutaline in combination with inhaled steroids in patients with moderate to severe asthma. In this study lower costs of treatment with for-

Table 4 Studies in which budesonide was found to be more cost-effective than placebo or other usual asthma therapy

Ref. #	Study duration	Country	Budesonide versus placebo		Budesonide	Placebo
			Health care cost reduction (patient/yr)	P value	Total costs (patient/yr)	Total costs (patient/yr)
9	3 yrs	Australia	\$21	<0.05	NA	NA
		Sweden	\$48	0.01		
		Canada	\$44	<0.1		
11	6 m	US	NA	NA	\$3,828	\$5,180
18	6 m	US	NA	NA	BT 200 μg , n = 53, \$11	\$37
					BT 400 μg , n = 55, \$9	
					BT 800 μg , n = 57, \$18	
21	3 yrs	US	\$11.30, Health care perspective \$3.70, Societal perspective	NA	NA	NA
22	3 yrs	US	192/3 yr	NA	NA	NA

Notes: All currencies have been converted and inflated to year 2008. Yr = year(s).

Table 5 Cost comparison of fluticasone and budesonide

Ref. #	Medication and delivery	Dose		Cost per successfully treated patient	
		FP	BUD	FP	BUD
24	FP diskhaler versus BUD reservoir dry powder device	200	400	\$22.77/w	\$24.41/w
25	FP via MDI and Volumatic spacer versus BUD nebulizer	1 mg	2 and 4 mg	\$158.04	\$273.75, 2 mg \$554.29, 4 mg
26	FP MDI versus BUD Turbuhaler	250	600	\$3.97/d	\$4.87/d
27	FP dry powder disk inhaler device or BUD Turbuhaler	200	200 400	\$4.12/d	\$2.85/d, BUD 200 \$2.37/d, BUD 400
28	FP Accuhaler versus. BUD Turbuhaler	200	400	\$56.84/w	\$93.01/w

Note: All currencies have been converted and inflated to year 2008.

Abbreviations: W, week; d, day; N/A, not available; FP, fluticasone propionate; BUD, budesonide; MDI, metered-dose inhaler.

moterol (\$495 versus \$542 per patient, respectively) were demonstrated.³³ Everden et al found that in children with symptomatic asthma who were receiving SABA and ICS, treatment with eformoterol was significantly more effective and less expensive than treatment with salmeterol ($P = 0.034$ and $P < 0.001$).³⁵ In contrast to the above studies, in a high quality multinational trial, the cost-effectiveness of formoterol 12 mg metered dose powder inhaler was compared with salmeterol 50 mg inhaled twice daily via Diskhaler in adults with asthma and in which patients were required to keep the dose of ICSs constant throughout the study. In this study no evidence was found to suggest that either treatment was more cost-effective than the other.³⁶

ICSs plus LABA

In eight studies the cost-effectiveness of adding formoterol or salbutamol to BUD in the treatment of moderate, persistent asthma was demonstrated.^{6,8,12–14,16,20,37} In a cost-effectiveness analysis, a combination of inhaled LABA plus ICS therapy was compared with LABA + placebo (PL) in children with asthma aged 7–16 years. It was found that annual drug acquisition costs for the LABA + ICS were \$478 higher than for the LABA + PL group. Annual savings due to reduced health care utilization, excluding the cost of study drugs by the group receiving LABA + ICS compared with LABA + PL, were estimated to be about \$272 per patient. The ICER of LABA + ICS was estimated to be about \$174 per 10% increase in FEV₁, suggesting the combination of LABA + ICS to be a cost-effective treatment option.³⁷

Adding formoterol to budesonide was evaluated in several studies and it was found to be cost-effective in one study,⁶ and less costly in a single inhaler than separate inhalers in two other studies.^{12,20} In another study adjustable maintenance dosing with budesonide/formoterol (one

inhalation twice daily, stepping up to four inhalation twice daily for 1 week if asthma worsened) versus fixed dosing (two inhalation twice daily) was compared for 12 weeks in adults with asthma and significantly lower asthma-related direct costs were found in the adjustable maintenance dosing with budesonide/formoterol in a single inhaler (mean: \$339 versus \$448; $P < 0.001$).⁸ In another study patients were randomized to twice-daily treatment with BUD 100 µg, BUD 100 µg plus formoterol 4.5 µg, BUD 200 µg, or BUD 200 µg plus formoterol 4.5 µg for 12 months and the cost-effectiveness of both treatments was compared.¹⁴ The researchers found that BUD 200 µg plus formoterol 4.5 µg was more cost-effective than BUD 100 µg plus formoterol 4.5 µg. The ICER for this comparison was found to be \$2.99 per SFD gained. Results from an economic analysis comparing the strategy of budesonide/formoterol (Symbicort®) Maintenance and Reliever Therapy (SMART) versus salmeterol/fluticasone (SFC) plus salbutamol demonstrated that the SMART strategy was a cost-effective treatment option from a societal cost perspective, compared with SFC, in Italy, Germany, France, and the UK. The total cost of the SMART strategy was found to be a significantly less costly treatment option than SFC (\$1,416 versus \$1,590; $P = 0.024$).¹³ In another study it was investigated whether the SMART concept could be applied also with only one dose/day as background maintenance therapy. The once daily SMART group (1 × SMART) was compared with a SMART group using twice the maintenance dose (2 × SMART). To make the comparison as strong as possible, a third group was treated with a fixed high maintenance dose budesonide/formoterol (FIX), (4-fold higher than the once-daily SMART group), plus formoterol as needed (2 × 2FIX + Formoterol). Switching patients from 2 × 2FIX + F treatment regimen to 2 × SMART was found to reduce the cost of drugs by \$13,721.¹⁶

SFC vs ICSs

In five studies the cost-effectiveness of SFC 50/100 µg with fluticasone propionate 100 µg was compared.^{15,38–41} Despite the higher drug costs for SFC, the cost per successfully treated week was found to be lower for SFC than FP alone in all studies. The ICERs reported in three studies were estimated to be \$20.91, \$30.12, and \$26.04, respectively.^{38,40,41} Similarly, the result of a prospective economic analysis comparing SFC 50/250 mg twice daily versus BUD 800 mg twice daily in adults and adolescents with asthma suggested that SFC was more cost-effective than BUD alone. The cost-effectiveness ratio was found to be \$32.69 and \$48.08 in the SFC group and the BUD group, respectively.¹⁵

SFC versus ICS with leukotriene modifiers (LTM)

In three studies SFC versus ICS plus montelukast were compared, and it was found that SFC had superior clinical benefits and cost-effectiveness compared to the montelukast-containing regimen.^{42–44} The result of the ICER analyses revealed SFC to be dominant over ICS plus montelukast.^{42,43} Similarly, the results of a combined analysis of four clinical trials, two comparing SFC with montelukast and two comparing FP with montelukast as initial asthma therapy, demonstrated that first line treatment with SFC was associated with a significant lower risk of an asthma-related exacerbation and lower exacerbation-related costs. Mean daily exacerbation costs for patients who experienced an asthma-related exacerbation were \$35 for SFC, \$153 for FP, and \$184 for montelukast.⁴⁴

Leukotriene receptor antagonist (LTRA) versus ICS

In one study the differences between LTRA (zafirlukast) versus fluticasone propionate 88 µg twice daily and health care resource utilization in asthma patients were examined and the mean daily cost of asthma treatment was found to be \$2.66 per patient for patients in the FP group and \$4.17 for those in the zafirlukast group. Using symptom-free days as an effectiveness parameter yielded a mean daily cost-efficacy ratio of \$7.96 per symptom-free day for the FP group and \$21.63 for the zafirlukast group. Results of the study supported the use of FP as first-line treatment in patients with persistent asthma previously treated with SABA alone.⁴⁵

LTRA vs SFC

In two studies the relative cost-effectiveness of twice-daily treatment with SFC was determined compared to once-daily treatment with montelukast as an initial maintenance therapy

in patients with persistent asthma uncontrolled on short-acting β_2 -agonist therapy alone. In both studies it was found the use of SFC to be more cost-effective than montelukast. The ICER in both studies showed that the additional costs to achieve the benefits with SFC were minimal – \$2.89 and \$1.62, respectively.^{46,47}

Omalizumab

In two studies the cost-effectiveness of omalizumab was evaluated.^{48,49} In the first study data from the ETOPA study were gathered and it was suggested that omalizumab was a more cost-effective treatment for patients with inadequately controlled severe persistent allergic asthma; however, their analysis was based on a small open-label trial, and was limited to participants who were responsive to omalizumab.⁴⁸ The INNOVATE study was a multinational study, which estimated the cost-effectiveness of adding omalizumab to optimal standard therapy in patients with severe persistent asthma from a societal perspective. The results showed that omalizumab provided cost offsets of improved quality of life and had an attractive ICER in patients targeted as a selected subgroup of severe patients with allergic asthma who were symptomatic despite best available care and who had an increased risk of needing emergency health care during acute asthma exacerbations. Omalizumab as an add-on therapy was estimated to cost an additional \$57,600 for 0.76 additional quality adjusted life years (QALYs), resulting in an ICER of \$75,568. This is a relatively high dollar amount per QALY.⁴⁹

Cromoglycate versus ICSs

In two studies the cost-effectiveness of ICSs versus sodium cromoglycate in asthma patients was examined.^{7,50} In the first study, the cost-effectiveness of sodium cromoglycate was compared with BUD in children age 5–11 years. It was found that budesonide, when taken for maintenance treatment, after an initial period of stabilizing treatment with BUD, resulted in lower average annual cost (\$1,921 versus \$2,530) and fewer drug switches than did a strategy with sodium cromoglycate.⁷ In the second study, the cost-effectiveness of FP versus sodium cromoglycate was examined in a group of children with asthma and found that irrespective of the symptomatic or clinical measures of success that were used, there were better outcomes using FP than sodium cromoglycate. The average cost per treatment success for FP was approximately \$50 compared with \$125 for sodium cromoglycate.⁵⁰

Discussion

Evaluating the cost-effectiveness of asthma medications is important to ensure the most appropriate choice of asthma medication. It is also particularly relevant due to the increasing burden of illness and the rising costs associated with managing asthma. Assessing differences in health care costs for the treatment of asthma is challenging because of the difficulty in deriving a single representative cost for each drug.

The present systematic review (SR) was aimed at reviewing the literature on the pharmaco-economics of asthma treatment. It adds to the current literature base by providing a systematic review of studies looking at the costs and/or effectiveness of asthma medications. Of the 80 reviewed articles, 49 studies met the inclusion criteria.

Early intervention and long term treatment with anti-inflammatory therapy using an ICS was found to be a cost-effective treatment option that demonstrated a significant decrease in health care utilization and asthma-specific costs. However, higher doses of ICS were not found to be more cost-effective. Among the ICSs, FP both 100 µg/day and 200 µg/day proved to be the most cost-effective treatment. For early asthma treatment comparing ICS to a LTRA, ICS was associated with lower asthma-related costs. Similarly, the cromones were found to be a cost-effective medication when compared to placebo but not when compared to ICSs.

Although in several studies in this SR, BDP was reported as being a dominant cost-saving intervention, no published economic evaluations provided any evidence of the superiority of BDP compared to FP. Another systematic review supports the findings in this review regarding BDP as the current cheapest ICS product at doses of 200, 400, and 800 µg/day.⁵¹

In our SR adding inhaled LABA to low to moderate doses of ICS was found to be cost-effective, and adjustable maintenance dosing budesonide and formoterol in a single inhaler was found to maintain significantly lower cost than a fixed dosing strategy.^{6,8,12–14,17,20} These results indicate that when a patient is not adequately controlled on inhaled corticosteroid alone and an additional treatment step is required, switching to a combination of inhaled steroid and LABA combination in a single inhaler can improve asthma control without increasing costs, and may even provide cost savings. Although costs per successfully treated week, episode free day (EFD), and SFD for salmeterol/fluticasone were found to be considerably lower than for other ICSs, LTMs, and ICS plus LTMs,^{14,38–44} the introduction of the SMART strategy was found to be incrementally a further cost-effective management strategy based on improved patient outcomes.^{13,16}

In several studies it was demonstrated that the addition of omalizumab to standard therapy reduced the frequency of asthma exacerbations, emergency department visits, and hospitalizations.^{48,49} However, omalizumab is more expensive than any other asthma medication. The incremental costs associated with omalizumab seem considerably high compared with those of other controller medications. Therefore it needs to be targeted to the treatment of patients with poorly controlled asthma despite the use of other therapies.

Conclusion

Cost-effectiveness analyses provide important data that should be considered when selecting treatment regimens for asthma. The result of this systematic review has demonstrated that maintenance therapy with ICS is very cost-effective. In addition, in patients with asthma uncontrolled on ICS the combination of an ICS/LABA in a single inhaler represents a safe, cost-effective, and convenient treatment. The simplified strategy using budesonide and formoterol for maintenance and reliever therapy was also found to be feasible, safe, and at least as cost-effective as salmeterol/fluticasone plus salbutamol. Omalizumab, although expensive, was found in carefully selected patients to be cost-effective. An important caveat with regard to the published literature in this area is the relatively high proportion of economic evaluations which are funded by the manufacturers of specific drug treatments. Future studies should be completed independent of industry support and also should ensure that the comparator arms within studies include dosages of drugs that are equivalent.

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