REVIEW

Cost–effectiveness analysis of inhaled corticosteroids in asthma: a review of the analytical standards

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Abstract

Purpose: To determine whether published cost–effectiveness studies on inhaled corticosteroids (ICS) in asthma adhered to basic analytical standards as defined in health economic textbooks and in guidelines assessing and comparing efficacy and safety. Methods: Original cost–effectiveness studies published between 1990 and 2000 in general medical or economic journals were reviewed to assess the adherence to five fundamental methodological principles: (1) design of the study, (2) choice of perspective and corresponding costs, (3) choice of outcome measure, (4) marginal cost analysis, and (5) sensitivity analysis and discussion about external validity. For each principle, the studies were ranked as high, medium or low quality. Results: Most of the 18 studies included were ranked medium on the first two principles. The studies adhered to a higher degree to the remaining three principles. Only three studies were high ranked in all five principles. The number of principles fulfilled increased over time. Studies comparing pharmaceutical products from competing companies were typically short-term studies, designed for other purposes than health economic analyses, and, in general, did not use therapeutically equivalent dosing. Conclusions: Attention should be drawn to the study design, the weak correspondence between perspective and costs, and especially to the impact of bias in health economic results when comparing different doses of ICSs.

INTRODUCTION

Cost–effectiveness analysis is currently an accepted analytical technique to establish the relationship between costs and effectiveness of a particular intervention. In pharmaco-economics, cost–effectiveness analysis is used to assess if one drug (or combination of drugs) is more cost-effective than another under similar circumstances. Pharmacoeconomic studies are often an important component in price-regulation and reimbursement decisions, as well as in drug formulary listings and marketing. Hence, several countries have developed guidelines for performing such studies [see (1) for an overview].

Inhaled corticosteroids (ICS) were introduced in 1972 and were at first limited to the treatment of severe asthma. In the second half of the 1980s, increased understanding that asthma is an inflammatory disease and that ICS have an anti-inflammatory effect developed. More recently, studies demonstrated that ICS therapy reduces the risk of asthma-related hospitalisation and outpatient visits (2–4).

Published review articles suggest that the acquisition cost of ICS can be offset by a reduction in other healthcare costs (5,6). However, few reviews examined the methodologies used in the health economic studies on asthma, which is important in order to give decision-makers in health service assistance in interpreting results. One exception was Buxton (7), who concluded that scarcity of cost–effectiveness studies partly was due to the difficulty of defining an outcome measure that captures the multidimensional effects of respiratory interventions. The National Asthma Education and Prevention Program Working Group conducted a review of the literature on cost–effectiveness of asthma patient education programmes, pharmaceutical therapy, and a variety of alternative and adjunct interventions (8). They revealed many shortcomings and a lack of standard approach to evaluate the cost–effectiveness of medical technologies in asthma.
Although guidelines exist for cost–effectiveness studies, few attempts have been made to evaluate the analytical standards and adherence to basic cost–effectiveness principles in the area of asthma treatment. The purpose of this study was to examine whether published cost–effectiveness studies on ICS in asthma, published up to the year 2000, adhered to basic analytical standards as defined in economic textbooks and guidelines.

METHODS

Article selection
Articles published 1990–2000 were drawn from a Medline and Embase literature search using 15 keywords related to ICS treatment for asthma. To simplify the analysis of this study only full-length (no abstracts), original cost–effectiveness studies based on data from randomised clinical trials (RCTs) were considered. Cost of illness and cost minimisation studies, review articles, and studies on efficacy without any attempt to provide information on costs were excluded.

Methodological review
To identify principles appropriate for cost–effectiveness analysis and economic evaluation of healthcare practices in general, a literature review of guidelines and health economic textbooks was performed (9–14). Variables such as the clinical trial design, choice of comparator, cost and perspectives, results presentation and sensitivity, are evaluated. However, the therapeutic effect of inhaled agents is influenced by a number of factors, not only the pharmacological potency, but also the doses used, the treatment duration and the amount reaching the airways and lungs, the latter depending on the type of inhaler used. Hence, a review of guidelines on how to assess and compare the underlying ICS efficacy and safety data (8,15–17) complements the economic guidelines.

On the basis of this literature, five principles thought to comprise a high standard that cost–effectiveness studies should be expected to follow were identified: (1) design of the study; (2) choice of perspective and corresponding costs; (3) choice of outcome measure; (4) description of the costing methods and marginal cost analysis; and (5) sensitivity analysis and discussion of external validity. As each principle not necessarily has the same weight, we present the results of each principle in a disaggregate form.

Design of the study
Adherence to good practice in designing trials for investigating alternative treatments of asthma was evaluated on four basic criteria. First, the study should be designed as a parallel-group RCT and not as, e.g., a crossover trial in which subjects serve as their own control. The crossover design is less accepted for asthma trials comparing ICS because therapeutic effects of variable persistence may spill over from the first treatment to the administration of the second (16). Second, to account fully for the costs and effects of an intervention, results should be reported for the entire sample of recruited patients, i.e., an intention-to-treat analysis (8). In addition, costs included should not be driven by the trial itself. Hence, the economic analysis should at least have been planned and coordinated with the RCT, i.e., it should have had an impact on the study design. Third, as asthma is a chronic disease, the follow-up period should be long enough to allow assessment of effectiveness, possible dropouts and costs (8). We required a study period of at least 6 months, the same requirement as in an evaluation by the Swedish Council on Technology Assessment in Health Care (18).

Finally, the choice of dosage influences not only clinical and health outcomes, but also has an impact on the cost–effectiveness ratio. Although a doubling of doses may have a modest effect on clinical or health outcomes, it nevertheless doubles the medication cost. As drug costs normally represent most healthcare costs in mild and moderate asthma (19,20), cost–effectiveness ratios could be heavily biased when inappropriate dose combinations are used. It is beyond the scope of this study to fully evaluate the appropriate comparison of dose combinations. However, we have used a definition of therapeutically equivalent dose between fluticasone propionate (FP) and budesonide (BUD) if the FP:BUD dose ratio was 1:2 or less when a pressurised metered dose inhaler (pMDI) was used. If the drugs were inhaled through a dry-powder inhaler (DPI), e.g., Diskhaler or Turbuhaler, the corresponding equivalent dose ratio was defined as 1:1 (15,21,22). Dosages in studies comparing another ICS with BUD or FP were accepted since we were unable to find similar dose equivalents.

If all four criteria were fulfilled we ranked the study high. Consequently, a study was ranked low/medium if neither/some of the criteria was/were met.

Choice of perspective and corresponding costs
Cost–effectiveness analysis can be undertaken from a number of different perspectives. The societal perspective is the most comprehensive and incorporates, in theory, all costs and all health effects regardless of who incurs the costs and who obtains the benefits. Other
commonly used perspectives are those of the government, healthcare institutions (e.g., hospital or clinic), third-party payer, and patient and family. The choice of perspective has important methodological ramifications, and, as the included cost items differ between perspectives, the cost–effectiveness ratios will change with the perspective chosen.

We demanded a high ranked study to make it obvious what perspective was chosen and that costs included in the analyses corresponded to the perspective. If costs did not correspond to the perspective chosen, or if the perspective was not discernible, the study was ranked medium and low, respectively.

Choice of outcome measure

It is often recommended that choice of effectiveness measure should relate to a final health outcome such as life-years saved or healthy days gained (9). The numerous outcome measures for asthma can roughly be categorised into five key outcomes (8): clinical and symptom measures (exacerbations, symptom-free days, etc.), physiological measures [surrogate endpoints, e.g., peak expiratory flow (PEF)], quality-of-life measures, patient management (behavioural change and compliance), and health services utilisation, e.g., the number of hospital visits.

Surrogate endpoints must be explicitly related to some health benefit since it is health per se that should be maximised. In one influential article on outcomes measure in health economic analysis, it was concluded that surrogate endpoints cannot be recommended in cost–effectiveness analysis (13), which corresponds to the statement in the consensus report from the European experts on methodological issues. According to this document, "surrogate endpoints are not recommended as effectiveness measures of cost–effectiveness analyses unless (a) they have a clear meaning to decision makers, (b) they are unambiguously correlated with health status and capture all the relevant differential effects on the outcomes of the options compared" (14).

This review distinguished between physiological (surrogate) endpoints and (non-surrogate) health-related outcomes without regarding the appropriateness of the measures used. To receive a high rank, a health-related outcome measure should be reported. If only other types of outcomes were reported, the study was ranked low (this principle has no medium rank).

Description of the costing methods and marginal cost analysis

Costs should ideally reflect the value of the input in its best alternative use. Unit prices for inputs and medical procedures do not necessarily reflect the minimum cost as they could be based on average costs, and not patient-specific costs. Another way is to use charges or fees, e.g., for hospital admissions for studies in the United States, but the usual approach is to use cost-to-charge ratio to convert billing information into economic cost estimates (10). A third alternative, often used in Europe, is to use accounting costs, e.g., for a physician visit. A fourth approach is to conduct a whole cost estimation, based on information about inputs such as salary cost per time unit, cost of facilities, administration, etc.

When comparing two healthcare programmes, the incremental cost–effectiveness ratios (ICER) is the appropriate measure (9,10,14,23). When choosing between different technologies, the ICER tells us cost per unit of benefit when switching from one treatment to another, e.g., incremental cost per symptom-free day gained. Average cost, on the other hand, reflects the cost per benefit independent of other treatments.

To be ranked high, we required that a study present sufficient information for assessing the costing methods and that the ICER approach was used in case one alternative was not dominant1. If only one of these criteria was fulfilled, the study was ranked medium, and if none was fulfilled, the study was ranked low.

Sensitivity analysis and discussion of external validity

Conventional statistical methods are only applicable if the data are sampled. In cost–effectiveness studies, data are often sampled for some items of resource use, e.g., number of physician visits, days in hospitals, etc. However, costs are often generated from other sources. Sensitivity analysis is therefore the primary method for allowing for uncertainty in economic evaluations (9). By varying a single or multiple (more thorough) variables at a time, the sensitivity of the results is studied. Furthermore, data from RCTs may have a low degree of external validity due to a strict research protocol. Therefore, a discussion on the ability to generalise the results to the real-world setting is important.

Both a discussion about the external validity and sensitivity analysis (regardless of single- or multi-dimensional) were necessary to achieve a high rank. If only one or none of these was reported, the study was ranked medium or low, respectively.

Analysis

We ranked the five principles as high, medium or low based on the aforementioned criteria. For each of the five principles, the articles were then compared by type of journal publication, whether the study compared two

1“Dominant” indicates an alternative that is both less costly and produces a better outcome than the other alternative(s).
or more competing products, by the pharmaceutical company sponsoring the study, and by the year of publication (old: 1993–1996; new: 1997–2000). These comparisons were chosen to reveal methodological differences in medical and non-medical journals, in studies comparing doses of the same product or competing products, whether the stakeholders could have had an impact, and if there has been a growing awareness for health economic methods over time.

RESULTS

Article selection

The literature search generated 194 matching articles but included many articles without any cost-effectiveness analysis and reviews; therefore, only 46 articles were further considered. Of these, another 30 papers were rejected as they were descriptive cost of illness analyses, reviews or meta-analyses, or did not include a comparison of alternative treatments. Another two articles were found in the articles’ reference lists. Hence, 18 articles were included in this analysis (see reference list).

Eight studies evaluated a single ICS: two compared BUD vs. usual care without ICS, four compared different doses of BUD, one compared different doses of FP and one compared FP vs. a combination of FP and a β2-agonist. In one study, a combination of β2-agonist/anticholinergic therapy was compared with a combination of β2-agonist/ICS therapy (classified in this review as competing products). In the other nine studies, two ICS were compared. Six of these studies compared FP vs. BUD; in four of them a DPI was used as the inhaler device, and, in the other two studies, two different inhaler devices were used, e.g., pMDI vs. DPI. The remaining three studies compared FP vs. sodium cromoglycate, FP vs. triamcinolone acetonide and FP vs. flunisolide, respectively.

Ten articles were found in economic journals, and eight were published in medical journals. Six articles were sponsored by AstraZeneca (AZ) and 10 by Glaxo Wellcome (GW). The remaining two studies received grants from several sources.

For the two principles, design and costs corresponding to the perspective chosen, most studies were ranked medium (Table I). Short length of study (II studies) and design mainly for other purposes than economic evaluation (10 studies) reduced the scores. One study had a cross over design. For the remaining three principles, the studies adhered in a higher degree to the requirements.

Only three studies were highly ranked in all five principles (Table 2). One study was ranked high on four principles and medium on one principle. Studies comparing competing products were to a higher degree sponsored by GW, were published more recently and had a shorter study period than the non-competing product studies. Older studies were predominantly published in economic journals.

Design

The median length of the underlying RCTs were 3 months (mean length, 7.2 months; range, 1–30 months), and only seven studies had a study period of at least 6 months. All articles provided information on dosing, but four of the 10 studies comparing alternative ICS did not fulfill the requirements for therapeutically equivalent dosing.

Ten studies were originally designed for purposes other than economic analysis, of which seven were found in the competing-drugs studies. Only one study was designed for economic analysis. Studies published in medical journals were based more often on RCTs with a longer study period and studies not comparing competing drugs fulfilled the criteria of equivalent dosing to a higher degree (Fig. 1).

Perspective chosen and corresponding costs

Fourteen studies stated a national healthcare system, societal or third-party payer perspective. In the

| Table I. Number of studies ranked high, medium and low for each principle |
|---------------------------------|-----|-----|-----|-----|
| Design                         | 6   | 8   | 4   | 18  |
| Perspective and corresponding costs | 6   | 8   | 4   | 18  |
| Outcome measure                | 15  | –   | 3   | 18  |
| Costing methods and marginal analysis | 11  | 6   | 1   | 18  |
| Sensitivity analysis and external validity discussion | 9   | 6   | 3   | 18  |

\[1^\text{Sponsors were: the Netherlands’ Health Research Promotion Program (SGO), the Dutch Asthma Foundation, Glaxo, Astra Pharmaceuticals and Boehringer Ingelheim.}

\[2^\text{Of six studies comparing FP and BUD, only one compared the drugs on a 1:1 dose ratio (400 μg), whereas the other five had doses varying between 1:2 (except for one subgroup where the relationship was 1:1) to 1:3.2.} \]
| Study number | A1 | A2 | A3 | A4 | A5 | A6 | A7 | A8 | A9 | A10 | A11 | A12 | A13 | A14 | A15 | A16 | A17 | A18 |
|--------------|----|----|----|----|----|----|----|----|----|-----|-----|-----|-----|-----|-----|-----|-----|
| Economic Journal | 1 | 1 | 1 | 0 | 1 | 0 | 1 | 1 | 0 | 0 | 0 | 1 | 1 | 0 | 1 | 0 | 1 | 0 |
| Sponsorship | AZ | AZ | n.a. | GW | n.a. | GW | AZ | AZ | AZ | GW | GW | GW | GW | AZ | GW | GW | GW | GW | GW |
| Competing drugs | 0 | 0 | 0 | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 1 | 1 |
| Length of study (months) | 3 | 6 | 22 | 2 | 30 | 2 | 4 | 2 | 12 | 1 | 2 | 24 | 1.5 | 1.5-2 | 1.5 | 3 | 6 | 6 |
| 1. Design | | | | | | | | | | | | | | | | | | |
| Parallel-group RCT | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Length of study ≥ 6 months | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 1 |
| Equivalent dosing | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 0 | 1 | 1 | 1 | 0 | 1 | 1 |
| Economic impact on design | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 1 | 0 | 0 | 1 | 1 | 1 | 1 |
| 2. Perspective | | | | | | | | | | | | | | | | | | |
| Costs correspond | 0 | 1 | 0 | 0 | 1 | 0 | 1 | 0 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| 3. Outcome measure | | | | | | | | | | | | | | | | | | |
| High | High | High | High | High | High | High | High | High | High | High | High | High | High | High | High | High | High |
| 4. Costing presentation | | | | | | | | | | | | | | | | | | |
| ICDER or dominant | 1 | 1 | 1 | 1 | 0 | 0 | 0 | 1 | 0 | 1 | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 1 |
| 5. Validation | | | | | | | | | | | | | | | | | | |
| External validity | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 0 | 1 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |

Note: 1 = yes, 0 = no, n.a. = not applicable.

Abbreviation: ICDER = incremental cost–effectiveness ratio; AZ = AstraZeneca; GW = Glaxo Wellcome; RCT = randomised clinical trial.
remaining four studies, the perspective was unknown. Overall, only six of the studies managed to cost the resource consumption in accordance with the perspective taken, which drives the results depicted in Fig. 2. This deficiency was mainly due to a lack of information about whether adjustments for patient co-payments were made.

**Fig. 1.** Comparing the proportion of studies ranked high, medium and low under the criteria for design.

**Fig. 2.** Comparing the proportion of studies ranked high, medium and low under the criteria of perspective and costs corresponding to perspective chosen.
The competing-drugs group attained the lowest scores due to non-explicit perspective and non-corresponding costs.

Outcome measure

In the 18 articles reviewed, 16 different outcome measures (11 surrogate and five health-related outcomes) were used, of which eight were used in more than one article. The most frequently used measure was symptom-free days (II articles). Another three measures were used in three or more articles. The definition of a symptom-free day varied between articles (and study arms in one article), as did the definition of “success” among the surrogate endpoints (e.g., PEF > 90% or PEF ≥ 95% of predicted).

Three articles did not present any health-related outcomes, whereas two studies reported such measures only. Hence, the reviewed articles adhered well to the standards (Fig. 3).

Marginal costing analysis

Information on costing methods was provided in all but two studies, and five articles presented average cost analysis only. Overall, the costing method and the marginal analysis adhered well to what could be expected from a cost–effectiveness study.

Newer articles performed better than older articles due to a more detailed presentation of costing methods and of incremental cost–effectiveness ratios (Fig. 4). In four studies comparing competing products, only average cost–effectiveness ratios were presented.

Sensitivity analysis and external validity discussion

Sensitivity analysis and discussion of external validity were reported in 13 and 11 of the 18 articles, respectively. Newer articles, articles comparing competing products and GW-sponsored articles discuss the external validity of the results more frequently than older studies (Fig. 5).

DISCUSSION

Eighteen original health economic studies on inhaled ICS for treatment of asthma were evaluated according to analytical standards. Evaluation was based on conformance with five basic principles commonly found in the health economic literature and specific guidelines on how to scientifically assess and compare ICS efficacy and safety. This study does not claim to be comprehensive, as it is specifically limited to original cost–effectiveness studies based on RCT. However, with slight modifications of the criteria, the principles can be applied to evaluations of other pharmaceutical programmes.

![Outcome Measure](image-url)

**Fig. 3.** Comparing the proportion of studies ranked high, medium and low for the criteria of outcome measure chosen (medium rank not available).
In order to avoid the complex concept of quality we have used simply binary (high—low) method of analysis. We have not considered whether the criteria/principles are “very well” or “barely” fulfilled. Hence, great variation prevails within our grading. No ranking or weights has been assigned to the principles. This methodology leaves room for more through quality analysis, which is beyond the aim of this study. However, we believe this

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**Fig. 4.** Comparing the proportion of studies ranked high, medium and low under the criteria of costing methods chosen and marginal analysis performed.

**Fig. 5.** Comparing the proportion of studies ranked high, medium and low for the criteria of sensitivity analysis and discussion about external validity.
analysis brings forward some potential problems and ca-
veats to bear in mind in spite of the limited number of
studies—effectiveness articles.

In four of the principles for cost—effectiveness analy-
thesis, principles 2–5, the ranking of the studies increased
over time. This could reflect the greater awareness of
the common principles for conducting health economic
analyses among authors and/or reviewers.

The most frequently occurring shortcoming was the
lack of correspondence between costs and perspective.
For example, some studies stated a third-party payer
perspective but included patient co-payments in the cost
for pharmaceuticals. Other examples showed that even if
a national healthcare perspective was chosen, the analy-
thesis did not include costs other than pharmaceuticals. In
some studies, there was not even an attempt to estimate
costs for health care other than medicines. Including
non-relevant (or excluding relevant) costs drives the
cost—effectiveness ratio and can bias the results.

Design was another reason for a low ranking of sev-
eral studies. With a median study period of 3 months, it
was uncertain whether the full clinical effect was at-
tained and if relatively rare events such as hospitalisa-
tions were fully captured. An interesting observation
was the correlation between low-scored studies relying
on relatively short-term RCTs and low-scored studies on
competing therapies. These short-term studies were not
designed for economic purposes, and in neither of these
studies did the costs correspond to the stated perspective.

Another serious design problem, and until recently a
less noticed issue (17), was the variation in dose ratios
between FP and BUD (varied between 1:1 and 1:3.2). In
the following hypothetical example, we discuss the issue
of comparing appropriate doses when evaluating alterna-
tive ICS.

Assume that drugs A and B are priced the same per
weight and that they have different dose—response
curves in that drug A reaches a plateau earlier than drug
B (Fig. 6). The two compounds are evaluated at a dose rela-
tionship of 1:1, e.g., at dose x. Drug A would not be sig-
ificantly more effective than drug B, and the costs for
the two alternative medicines would be the same. As a
second case, assume that drug A would be administered
at dose x, whereas drug B will be administered at dose
y=2x, i.e., a double dose. A comparison of the two drugs
at a dose relationship of 1:2 would result in a similar ben-
et for both treatment groups. However, as the drugs
are priced exactly the same, the costs for the patient
group receiving drug B will be twice as high as the costs
for the patient group receiving drug A.

A cost—effectiveness analysis using a 1:2 dose relation-
ship would then result in a disadvantage for drug B as a
significant difference in drug costs is compared with a
non-significant difference in benefits. On the other hand,
a cost—effectiveness analysis using a 1:1 dose relationship

would result in a more favourable outcome for drug B as
the non-significant difference in benefits is attained at
identical drug costs. The implication is that the choice of
doses based on studies evaluating efficacy and safety
could result in biases in cost—effectiveness studies.

The increased reporting of health outcomes should
not be a goal per se. It is important that these measures
(both surrogate and health-related) are standardised to
enhance comparability between studies (8,23). If symp-
tom- and episode-free days are used, it is imperative that
the same definition applies in all study-arms and that the
scale is uniform. In addition, the lack of outcome unifor-
mity infringes on the credibility through the impression
that authors choose the most favourable outcome mea-
sure of the study, that is, only measures where significant
differences are detected.

CONCLUSION

Despite the fact that cost—effectiveness studies of ICS
for the treatment of asthma still suffer from shortcom-
ings in the outcomes measures used, adherence to analy-
tical standards has increased over time. However, our
review revealed shortcomings in methods for costing,
design of the study in general and methods for comparing
doses in particular. The choice of doses may cause bias in
the cost—effectiveness results and is therefore a threat
to the validity when evaluating competing therapies.

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REFERENCES


REFERENCES FOR THE 18 REVIEWED ARTICLES


