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An Appraisal of Pharmacoeconomic Evidence of Maintenance Therapy for COPD*

Anna O. D’Souza, BPharm, MS; Michael J. Smith, PhD, RPh; Lesley Ann Miller, PhD; and Jan Kavookjian, MBA, PhD

COPD is projected to be the third-leading cause of death by the year 2020. Pharmacotherapy for COPD is palliative at best, having no impact on slowing the progression of the disease. The introduction of newer therapies such as long-acting forms of bronchodilator and anticholinergic agents, together with the inclusion of inhaled corticosteroids (ICSs) in the recent Global Initiative for COPD therapeutic algorithm, have expanded the pharmacotherapy options for the treatment of COPD. This article provides a methodologic critique of the available pharmacoeconomic evidence on drug therapy for stable COPD in an effort to complement treatment guidelines and to identify any need for future pharmacoeconomic research. Relevant search strategies revealed a total of 28 economic evaluations of which 7 satisfied the study inclusion criteria. The Drummond 10-point checklist was used for the methodological critique of the economic evaluations. Five of seven pharmacoeconomic studies were conducted alongside a randomized controlled trial, and six of seven were cost-effectiveness analyses. Of the bronchodilators, the long-acting anticholinergic agent tiotropium is considered to be cost-effective relative to ipratropium. No conclusive information could be reached for the cost-effectiveness of long-acting β-agonists. A Markov analysis showed ICSs to be cost-effective for patients with moderate-to-severe COPD relative to standard care. However, assumptions of the model may bias this conclusion, and additional studies are warranted, especially compared to other treatments. The authors suggest that additional pharmacoeconomic studies be conducted to assess the cost-effectiveness of long-acting β-agonists and ICSs, between classes of bronchodilators, and between various combination therapies.

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Key words: COPD; COPD costs; COPD outcome measures; pharmacoeconomics

Abbreviations: CBA = cost-benefit analysis; CEA = cost-effectiveness analysis; CI = confidence interval; CMA = cost-minimization analysis; CUA = cost-utility analysis; GOLD = Global Initiative for Chronic Obstructive Lung Disease; HRQoL = health-related quality of life; ICER = incremental cost-effectiveness ratio; ICOR = incremental cost-outcome ratio; ICS = inhaled corticosteroid; QALY = quality-adjusted life-year; SGRQ = St. George Respiratory Questionnaire

Learning Objectives: 1. Assess tiotropium to be cost-effective compared to ipratropium. 2. Identify that inhaled corticosteroids are to be cost-effective for patients with moderate to severe COPD relative to standard care. 3. Realize that the introduction of new therapies, and the recently published Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD) treatment algorithm, that there is little published pharmacoeconomic data to help guide decisions about optimal care.

The term COPD is an umbrella term that refers to chronic bronchitis and emphysema. The increasing prevalence and lifetime duration of the illness in those affected translates into increased direct and indirect medical expenditures. In 2004, the National Heart, Lung, and Blood Institute estimated that COPD cost the US health-care system a total of $37.2 billion.¹ Therapy for COPD is multifaceted with numerous options available at each stage of the disease. Broadly defined therapeutic categories include smoking cessation, oxygen therapy, pharmacotherapy, and surgery (ie, lung volume reduction, lung transplantation, and bullectomy).² The goals of therapy in COPD patients are to reduce disease progres-
irreversible airflow limitation, some evidence suggests that about 23 to 42% of patients demonstrate reversibility, depending on the criteria used. However, the absence of reversibility does not imply that the patient does not experience any benefit from therapy with bronchodilators. A decrease in expiratory flow, as measured by FEV₁, is only one of the clinical consequences of COPD. Several pathologic changes, such as an increase in lung volumes (hyperinflation) and decreased inspiratory capacity, also occur. These parameters are better captured by improvements in outcome measures such as dyspnea, exercise tolerance, symptoms (exacerbations), and health status. Drugs are an integral part of maintenance therapy in COPD patients as they have been shown to significantly impact these outcome measures, if not FEV₁. The following two broad categories of drugs are specified for maintenance therapy of COPD: inhaled bronchodilators; and inhaled corticosteroids (ICSs). The latest Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines recommend pharmacotherapy based on the level of disease severity. Treatment ranges from as-needed bronchodilator therapy for mild COPD to maintenance therapy with bronchodilators and ICSs for moderate-to-severe COPD.

In the current cost-conscious environment, another goal of COPD management is to use health-care resources efficiently, given the enormous economic impact of the condition. To facilitate this goal, economic information regarding treatments should be made available for incorporation into treatment guidelines. For example, information from earlier pharmacoeconomic analyses helped to establish ipratropium as the drug of choice for the treatment of COPD, which complemented earlier treatment guidelines. A lack of economic evaluations of drugs (i.e., pharmacoeconomic analyses) used for the maintenance treatment of COPD was identified in the literature, primarily due to lack of pharmacotherapeutic options. Developments such as the introduction of newer therapies (i.e., long-acting bronchodilators) and evidence of the benefit of ICSs have expanded the pharmacotherapy options, with the subsequent conduct of a few economic evaluations. This new subset of the literature calls for a critical evaluation to understand the use of the results as well as to identify any potential for future research in this important area.

**Objective of Review**

The purpose of this article is to perform a critical review of pharmacoeconomic analyses using recommended guidelines for these studies. Also, an expert panel has provided suggestions on designing economic evaluations, which will be incorporated while critically reviewing the studies, specifically in COPD patients.

**Overview of Pharmacoeconomic Analysis**

A pharmacoeconomic analysis is a comparison between two or more pharmacotherapy options or strategies in terms of their costs and outcomes. Analyses are termed as partial when only costs are assessed, and full when both costs and outcomes are assessed. Full economic evaluations include cost-minimization analysis (CMA), cost-effectiveness analysis (CEA), cost-utility analysis (CUA), and cost-benefit analysis (CBA). These types of economic evaluations differ in the nature and extent of the outcomes for the alternative interventions assessed, while the identification and valuation of costs are similar. The following four types of outcome measures are identified in COPD: (1) physiologic measures; (2) clinical and symptom measures; (3) quality-of-life measures; and (4) life-expectancy measures (examples of outcomes measures are provided in Table 1).

Thus, examples of outcome measures for a CEA in...
the COPD literature would include improvement in health-related quality of life (HRQoL), forced expiratory volumes, or life-years gained. The outcome measure in a CUA is usually expressed as quality-adjusted life-years (QALYs), which incorporate a measure of patient preference, termed a utility measure, to adjust a life-year for its quality. The outcome in a CBA is the monetary equivalent of all health improvements. A CMA is a special case of a CEA in which the effectiveness measure (ie, outcome) is shown to be equivalent between the comparators, reducing the analysis to a comparison of costs.

The results of a full pharmacoeconomic analysis include the costs and outcome measures of the comparators over the follow-up period of the study. This information is then represented in terms of a ratio (cost per outcome measure) called the cost-effectiveness/utility/benefit ratio for each comparator. However, this ratio does not provide any information about the cost-effectiveness of an alternative. The latter is best assessed by computing an incremental cost-outcome ratio (ICOR), which is the ratio of the difference in costs to the difference in outcome measures between two options. Thus, an ICOR will be the incremental cost-effectiveness ratio (ICER), the incremental cost-utility ratio, and the incremental cost-benefit ratio for a CEA, a CUA, and a CBA, respectively. An ICOR is interpreted as the additional cost required to produce an additional unit of outcome. Cost-effectiveness is assessed by determining the location of an ICOR on a cost-effectiveness plane (the term cost-effectiveness as used here is generic and is not referring only to CEAs) (Fig 1). The cost-effectiveness plane is a graph of the difference in costs on the y-axis and the difference in effects on the x-axis. This graph is divided into four quadrants, which represent different scenarios of the results of a pharmacoeconomic analysis. ICORs in quadrants II and IV will be negative, signifying the dominance of one alternative over another. In these instances, the alternative that dominates will be considered cost-saving. ICORs in quadrants I and III are used to assess the cost-effectiveness between two comparators, and the decision about whether a comparator is cost-effective depends on the maximum ICOR that one is willing to accept (a value $R$). Thus, the concept of cost-effectiveness does not imply that a particular comparator has to cost less but rather that its incremental cost is worth the additional benefit it provides compared to the alternative. For example, in Figure 1 two arbitrary treatments, A and B, are compared. If the ICOR is found in quadrant II when treatment A is compared to treatment B, A will dominate B and be cost-saving. On the other hand, ICORs in quadrants I and III depend on the maximum amount one is willing to accept to decide whether A or B can be considered cost-effective.

The ICOR is the focus of statistical testing in an economic evaluation, and the hypothesis tested is that the ICOR is lower than a predetermined value $R$. When data in an economic evaluation are deterministic (point estimates), a sensitivity analysis is conducted to determine the impact on the ICOR value. A sensitivity analysis entails varying different

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**Table 1—Tabular Summary of Aspects of Study and Their Description**

<table>
<thead>
<tr>
<th>Study Aspect</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study reference (type)</td>
<td>CMA/CEA/CUA/CBA</td>
</tr>
<tr>
<td>Study design (scope of costs)</td>
<td>Measurement (using prospective, quasi-experimental, retrospective, or RCT study designs), modeling (decision analysis and Markov modeling), or a combination of measurement and modeling (types of modeling include extrapolation, epidemiologic, and Markov). Perspectives include payer, society, and government, and scope of costs include direct, indirect, and intangible.</td>
</tr>
<tr>
<td>Severity of COPD in study population</td>
<td>Mild, moderate, or severe</td>
</tr>
<tr>
<td>Comparators</td>
<td>Refers to the drugs or treatment strategies that were evaluated</td>
</tr>
<tr>
<td>Outcome measures</td>
<td>Four types of outcome measures (examples) can be identified in COPD: Physiologic measures: FEV$_1$, Clinical and symptom measures: exacerbations, symptom-free days, relief of symptoms, and increase in performance status (exercise tolerance), HRQoL measures: improvement in the SGRQ score or Chronic Respiratory Questionnaire scale score, Life expectancy measures: life-years and QALYs</td>
</tr>
<tr>
<td>Outcome values</td>
<td>Outcome results from the study</td>
</tr>
<tr>
<td>Follow-up period</td>
<td>Refers to the length of time during which costs and effects were assessed</td>
</tr>
<tr>
<td>Costs</td>
<td>Total costs per patient over the corresponding study follow-up period</td>
</tr>
<tr>
<td>ICOR</td>
<td>Results of any incremental analysis as reported in the study</td>
</tr>
</tbody>
</table>

*RCT = randomized controlled trial.
parameters (e.g., unit price of a drug or minimum clinically important difference of the outcome measure) using plausible ranges that have been published in the literature or are based on expert opinion. The resultant values of the ICOR are then compared to the value of $R$. When data are stochastic (i.e., involving probability), however, several possibilities exist.16 First, the difference in costs and effects can be individually tested between comparators. Second, the resultant ICOR is statistically tested by determining a range of values in which the true value might lie. This testing is also called an uncertainty analysis as it gives an indication of the precision of the ICOR estimate. The following two methods are commonly used for uncertainty analysis: developing 95% confidence intervals (CIs) using parametric or nonparametric bootstrap methods18; and developing cost-effectiveness acceptability curves.19 The concept of 95% CIs is common to all types of statistical tests. A cost-effectiveness acceptability curve shows the probability that a given treatment is acceptable given a maximum ICER that one is willing to pay.19

**Materials and Methods**

**Search Strategy**

The search strategy included the use of the following four databases: MEDLINE PubMed; EconLit; International Pharmaceutical Abstracts; and Dissertation Abstracts. Search terms included "chronic obstructive lung/pulmonary/airway disease," "COPD"/"COLD"/"COAD," "chronic bronchitis," or "emphysema" and "cost-effectiveness," "economic evaluation," "cost analysis," "drug economics," or "pharmacotherapy." The names of drugs and drug classes were also individually used as search terms together with the COPD-specific diagnosis search terms (i.e., "ipratropium," "albuterol," "salmeterol," "formoterol," "tiotropium," "theophylline," "fluticasone," "beclomethasone," "triamcinolone," "budesonide," "inhaled corticosteroids," "short-acting β agonists," "long-acting β agonists," and "inhaled anticholinergics." Additionally, hand searches of six journals were done that included four respiratory journals and two health economics journals.
journals. Reference lists of articles obtained from the above-mentioned sources were further reviewed for additional studies. The literature searches were conducted during the period of June 2004 through December 2004.

Inclusion Criteria

Included studies were restricted to those published in the English language and spanned the period from January 1980 to December 2004. Only economic evaluations of inhaled bronchodilators and ICSs generally used for the maintenance treatment of COPD, and those treatments considered to be full (as described in the previous section) according to the Drummond classification were included. \(^1\) Studies were excluded if a separate and unique COPD population could not be identified, or if drugs of interest included antibiotics that are generally used for acute exacerbations of COPD. Studies obtained from the search strategy were examined for study inclusion using the aforementioned criteria by a single researcher (A.O.D.).

Focus of Review

This article provides important elements for future pharmacoeconomic research using examples from the current literature. Therefore, the stringent inclusion criteria employed in this review enable a detailed critique of pharmacoeconomic analyses rather than a comprehensive review of the literature. The review will specifically focus on the methods employed to produce the results in different economic evaluations, the validity of the evidence given the methods used, and the application of the results in different settings. This system of evaluating studies follows from common aspects of general recommendations made by various organizations (ie, the Commonwealth of Australia, the Ontario Ministry of Health, the Canadian Coordinating Office for Health Technology Assessment, the US Public Health Service Panel on Cost-Effectiveness in Health and Medicine, and the Task Force on Principles of Economic Analysis of Health Care Technology). In fact, some authors have evaluated guidelines from various sources and have concluded that there are common elements that relate to the methodological conduct of economic evaluations.\(^2\)\(^3\) A comprehensive outline encompassing these elements has been given by Drummond et al\(^4\) in the form of a 10-point checklist (see "Appendix") and was used for the objective critique of the included studies. Finally, a summary of the aspects of studies meeting the inclusion criteria will be provided as described in Table 1.

RESULTS

The search strategy produced an initial count of > 100 articles. A total of 28 studies resembling some type of economic evaluation were identified by reviewing the abstracts of the studies. Of these, seven satisfied the inclusion criteria, and were considered for the present critical review. This section will highlight important aspects of the methods and results of each of the seven studies using the Drummond 10-point checklist,\(^5\) with a tabulated summary provided in Table 2. Details of the outcome values and costs are also provided in Table 2.

Jubran and Colleagues\(^8\)

This CEA was performed by Jubran and colleagues\(^8\) with the specific aim of determining the impact of the toxicity profiles of oral theophylline and inhaled ipratropium on the cost-effectiveness of therapy, considering the equivalent therapeutic efficacy of the two agents. A pragmatic approach was taken for this economic evaluation using data from a retrospective chart review (from three clinical sites) to identify the study groups, effectiveness measures, and resource use. The effectiveness measure used was complication-free therapy month, which is defined as a month without an unscheduled visit to a physician and without a clinical exacerbation or a complication of therapy. In line with the perspective of the third-party payer, a comprehensive identification of direct costs included pulmonary medications, monitoring, visits, and costs related to toxic effects (which include drugs to treat toxic effects, diagnostic tests used, visits or hospitalizations, and services of consulting physicians).

Only univariate statistical testing was conducted to determine the differences in event rates and resource use. The observational cohort nature of the study required the adjustment of disease severity factors when comparing effectiveness, but this was not done. The authors seemed to justify the lack of multivariate analysis given the similarities in baseline disease severity or comorbidities between the groups in a univariate analysis. The duration of therapy was defined as the number of months between the first and the last month reported in the study period (1 year following January 1, 1987). The data were left-censored (ie, restricting the start of exposure to an arbitrary point in time), thereby not accounting for the duration of therapy before the study period. Furthermore, there were differences in therapy months during the period of observation. Standardizing outcomes with respect to the duration of therapy is acceptable provided that there is sufficient time for the event to take place. In the study, the length of therapy with ipratropium was shorter than that with theophylline (5.9 months vs 7.1 months, respectively; \(p < 0.0001\)). A strength of this study is that the authors used institution-specific unit costs to value resource use for their economic evaluation by taking advantage of the cost-accounting systems in these institutions. Since three different institutions (a Veterans Affairs clinic, a university medical center, and a health management organization) were used, the results could be generalizable to other similar settings.

Data on costs and effects were then extrapolated to 1 year using a Markov model. Incremental analyses revealed a negative ICER because therapy with ipratropium was less costly (annual cost, $932 vs $1,373, respectively) and more effective (11.30 vs 10.68 complication-free therapy months, respectively) than therapy with theophylline. One-way sen-
<table>
<thead>
<tr>
<th>Study/Year (Type)</th>
<th>Study Design (Perspective: Scope of Costs)</th>
<th>Severity of COPD</th>
<th>Comparators</th>
<th>Outcome Measures</th>
<th>Outcome Values†</th>
<th>Follow-up Period</th>
<th>Total Costs Over Study Follow-up Period</th>
<th>ICER Reported in the Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jubran et al81993</td>
<td>Retrospective + modeling (payer: direct)</td>
<td>Varying severity levels</td>
<td>(1) Oral theophylline (2) Inhaled ipratropium</td>
<td>CS: complication-free therapy month</td>
<td>(1) 10.68</td>
<td>Extrapolated to 1 yr</td>
<td>(1) $1,373 (2) $932</td>
<td>Not calculated because ipratropium was the dominant comparator</td>
</tr>
<tr>
<td>Friedman et al23/1999 (CEA)</td>
<td>RCT (payer: direct)</td>
<td>Moderate to severe</td>
<td>(1) Albuterol (2) Ipratropium (3) Albuterol + ipratropium</td>
<td>P: mean FEV₁AUC₀–₄ (in liters)</td>
<td>(1) 0.66</td>
<td>85 d</td>
<td>(1) $269 (2) $156 (3) $197</td>
<td>Not calculated because ipratropium arms were dominant comparators</td>
</tr>
<tr>
<td>Hogan et al25/2003 (CEA)</td>
<td>RCT (payer: direct)</td>
<td>Moderate to severe</td>
<td>(1) Placebo (2) Ipratropium (3) Formoterol (12 mg) (4) Formoterol (24 mg)</td>
<td>P: change in FEV₁ (in liters) CS: combined total of exacerbation-free and hospitalization-free days</td>
<td>(1) 1.290 (2) 1.427 (3) 1.513 (4) 1.484</td>
<td></td>
<td>(1) $38.93 (2) $76.34 (3) $214.91 (4) $418.92</td>
<td></td>
</tr>
<tr>
<td>Jones et al27/2003 (CEA)</td>
<td>RCT (payer: direct)</td>
<td>Mild to moderate</td>
<td>(1) Placebo (2) Salmeterol (50 μg)</td>
<td>P: proportion with &gt; 15% improvement in FEV₁ CS: proportion of symptom-free nights CS: proportion of days with a daytime symptom score &lt; 2 HRQoL: proportion of patients with an improvement of &gt; 4 U on SGRQ score</td>
<td>(1) 15% (2) 32% (1) 45.8% (2) 59.9% (1) 38% (2) 59%</td>
<td>16 wk</td>
<td>(1) £102.26 (2) £192.37</td>
<td>(2) vs (1): £4.62/d (£530‡) per patient with 15% improvement in FEV₁ (2) vs (1): £0.25/d (£39‡) per symptom-free night (2) vs (1): £0.55/d (£39‡) per patient free of exacerbation over 6 mo (2) vs (1): £0.25/d (£39‡) per patient free of moderate-to-severe exacerbation over 6 mo</td>
</tr>
<tr>
<td>Ayres et al31/2003 (CEA)</td>
<td>RCT (payer and societal: direct and indirect)</td>
<td>Moderate to severe</td>
<td>(1) Placebo (2) Fluticasone</td>
<td>P: proportion of patients with &gt; 10% improvement in FEV₁</td>
<td>(1) 19% (2) 32%</td>
<td>6 mo</td>
<td>Total costs: (1) £738.92 (2) £664.32</td>
<td>(2) vs (1): £0.25/d (£39‡) per patient with 10% improvement in FEV₁ (2) vs (1): £2.25/d (£260‡) per symptom-free night (2) vs (1): £0.55/d (£639‡) per patient free of exacerbation over 6 mo (2) vs (1): £0.25/d (£39‡) per patient free of moderate-to-severe exacerbation over 6 mo</td>
</tr>
<tr>
<td>Oostenbrink et al33/2004 (CEA)</td>
<td>RCT (societal: direct and indirect)</td>
<td>Moderate to severe</td>
<td>(1) Ipratropium (2) Tiotropium</td>
<td>CS: No. of COPD exacerbations per patient</td>
<td>(1) 1.01 (2) 0.74</td>
<td>1 yr</td>
<td>(1) £1,341 (2) £1,721</td>
<td>(2) vs (1): €667/yr per exacerbation avoided (2) vs (1): €1,067/yr per additional patient with relevant improvement in HRQoL</td>
</tr>
</tbody>
</table>

**Table 2—Economic Evaluations of Maintenance Pharmacotherapy in COPD**
sensitivity analyses using a range of costs from 0 to 10 times the baseline estimate, and a range of probabilities from 0 to 1 were performed. These ranges were justified based on the assumption that they represented all likely scenarios. Ipratropium remained the dominant strategy. Uncertainty analysis that assesses the 95% CI of the ICER was not conducted.

Friedman and Colleagues

This study by Friedman and colleagues assessed the cost-effectiveness of therapy with a combination of ipratropium and albuterol compared to therapy with each of the individual drugs using data on costs and efficacy from two clinical trials. The perspective of the analysis was not explicitly mentioned; however, the inclusion of only direct costs indicated a payer’s perspective. Costs included only those for initial and add-on drug therapy, and hospitalization costs thus excluded protocol-driven costs. The intent-to-treat principle was used to analyze only the resource-use data and not the clinical measure for which only patients with evaluable data were included (96.8%). However, the latter was not a concern due to similar withdrawal rates or reasons for withdrawal between groups.

Appropriate statistical tests (accounting for the distribution of costs and efficacy data) were conducted for differences in effects, specifically for costs. Differences in total costs were appropriately analyzed using the Kruskal-Wallis test given the nonnormal distribution of these data. Data from a clinical trial are often stochastic, which lends themselves to statistical testing and the computation of 95% CIs. A sensitivity analysis is generally required for deterministic data that do not have statistical ranges of their values. Therefore, sensitivity analysis is often not required in a pharmacoeconomic study that is conducted in a clinical trial, unless deterministic data are included. In this study, a deterministic estimate of a hospital price of $600 per day (no source was specified) was used. The substantial impact of hospitalization costs on the cost-effectiveness of the ipratropium arms necessitates a sensitivity analysis, but one was not conducted. Furthermore, additional analysis for determining the uncertainty of the ICER could have been done by using the stochastic data on efficacy and cost.

The treatment arms containing ipratropium therapy were dominant in the study with 33% fewer exacerbations and consequent decreases in resource use (ie, number of hospital days, antibiotic use, and corticosteroid use) and costs compared to the treatment arms containing albuterol therapy. In excluding protocol-driven visits, all physician visit costs were excluded and could have probably differed...
among the treatment groups. However, the conclusions of the study would not have changed since albuterol therapy resulted in a higher exacerbation frequency that would have increased costs.

Hogan and colleagues\textsuperscript{25}

This study by Hogan and colleagues\textsuperscript{25} assessed the cost-effectiveness of a new long-acting \( \beta \)-agonist, formoterol, vs that of the current standard of care, ipratropium, using efficacy data from a clinical trial\textsuperscript{26} over a 12-week time horizon. Effectiveness measures included the change in FEV\textsubscript{1} and the change in HRQoL as measured by the St. George Respiratory Questionnaire (SGRQ). A major limitation of the study precluding the use of the results in decision making is that no \textit{a priori} economic data were collected except for the use of rescue medications, which was a secondary efficacy variable in the clinical trial. Only direct costs including the cost of study drugs and rescue medications were considered in this analysis. Consideration of only these categories of resource use was done based on the assumption that other direct health-care resource uses (eg, consumption of steroids, physician visits, and other COPD-related health-care resources) was equivalent between treatments since there were no apparent differences in clinical measures. However, the comparators differed in terms of their improvement in HRQoL scores. Based on the literature cited by the authors showing that improvements in HRQoL lead to a favorable impact on health-care costs, one would think that the comparator that showed a favorable impact on HRQoL would have lower costs (formoterol therapy showed better improvement in HRQoL but had higher costs than ipratropium therapy). Thus, the assumption of the authors of similar direct health-care resource use among groups is not tenable.

No statistical testing of differences in FEV\textsubscript{1} and HRQoL were reported in the published article; however, the clinical trial reported appropriate statistical tests on an intent-to-treat population. Because stochastic data on effects were available, a sensitivity analysis was not required. However, sensitivity analyses, FEV\textsubscript{1} values (using 95% CIs of changes in FEV\textsubscript{1}), and HRQoL (using a range of −50 to +100%) were done but were not intuitively clear. Differences in costs were not tested, and CIs were not computed. Although a one-way sensitivity analysis was performed for the cost of the drug and rescue medication using a range of \( \pm 50\%\), the results of the sensitivity analysis were only reported in terms of the effect on cost-effectiveness ratios for the HRQoL effect and not on ICERs. The authors illustrated the impact of including hospitalization costs (excluded on the basis of the assumption mentioned above) on the ICERs, showing no change in study conclusions and large changes in ICER values. Citing the effect of small differences in the number of hospitalizations on ICERs, the authors further justified their exclusion of hospitalization costs. Conducting an uncertainty analysis of the ICER may have been a better approach.

Restriction of the time horizon to 12 weeks did not enable the capture of downstream costs, and their inclusion might have substantially altered the cost-effectiveness results. For example, instead of the finding that ipratropium therapy was cost-effective in terms of FEV\textsubscript{1}, the results may have shown ipratropium therapy to be cost-saving relative to placebo if downstream costs were included. The results from the study showed that when using improvement in HRQoL as the effectiveness measure, placebo dominated ipratropium (1.50 vs 1.10 SGRQ U, respectively). This does not seem intuitively clear, since ipratropium therapy has been shown to reduce the overall costs of care, which should technically improve HRQoL according to the authors’ rationale. However, the exclusion of relevant direct costs precludes finding the reason for this discrepancy. Incremental analyses showed that formoterol, 12 \( \mu \)g, cost $1,611 per additional change in FEV\textsubscript{1} and $82 per additional change in HRQoL units compared to ipratropium.

Jones and colleagues\textsuperscript{27}

The cost-effectiveness of a new long-acting \( \beta \)-agonist, salmeterol, was assessed by Jones et al\textsuperscript{27} over a 16-week period using efficacy data from a placebo-controlled clinical trial\textsuperscript{28,29}. Four outcome measures were used, as are summarized in Table 2. The inclusion of several outcomes allows decision making using several considerations. It should be noted, however, that only the payer’s perspective was considered. An intent-to-treat analysis was conducted, which is recommended to account for the withdrawal of patients from the study. It has been suggested that if the rate of study dropout is related to disease severity, then the methods of imputing missing data such as multiple imputation may be appropriate.\textsuperscript{30} In this study, dropout rates among treatment groups were similar, but the reasons for withdrawal from the study were not mentioned.\textsuperscript{28} Consequently, the appropriateness of the method of imputing missing resource use (using the daily rate of mean resource use in this study) could not be evaluated. Appropriate statistical testing (accounting for the distribution of costs and efficacy data) was done for the efficacy measures but not for costs. However, 95% CIs for differences in costs and differences in effects were
calculated, enabling the calculation of a region of confidence where the ICER may lie.

Stochastic data did not necessitate a sensitivity analysis, but a brief mention of one was made with no mention of the variables evaluated, the ranges of the variables used, or a detailed presentation of the results of the sensitivity analysis. The interpretation of results in the “Discussion” section of the article was limited by references to studies that were not comparable to the current study (ie, a CEA of salmeterol in asthma). The generalizability is restricted because of the inclusion of protocol costs and the consequent overestimation of costs. An important aspect that is omitted is the comparison to the current standard of care, ipratropium therapy, thus providing an inadequate picture of the cost-effectiveness of salmeterol therapy.

Ayres and Colleagues³¹

Ayres and colleagues³¹ used data from a randomized, controlled trial³² to assess the cost-effectiveness of an ICS, fluticasone, from the perspective of the UK National Health Service, and the societal perspective over a 6-month time horizon. The study was one of the first pharmacoeconomic studies in COPD to assess indirect costs (ie, time lost from work and usual daily activities) in addition to direct costs, which is consistent with their perspective. It was not clear whether protocol-driven costs were excluded. Appropriate statistical tests were conducted on an intent-to-treat population for determining significant differences in effectiveness measures. The 95% CIs were computed for differences in costs. Further analysis concentrated on determining the precision of estimates of the ICER (usually recommended¹⁷) using the following two approaches: developing 95% CIs using a nonparametric bootstrap approach; and developing cost-effectiveness acceptability curves. Study results showed that the upper and lower confidence limits of the 95% CIs for the ICER consistently fell in quadrants I and II of the cost-effectiveness plane (Fig 1), indicating fluticasone therapy to be cost-effective or cost-saving, respectively. The additional cost to be paid per unit of additional outcome measure, when fluticasone was cost-effective was £0.25 per day for each additional patient with > 10% improvement in FEV₁, and £0.25 per day for each additional patient who was free of moderate/severe exacerbation.

The presence of stochastic data did not necessitate the conducting of a sensitivity analysis. However, a sensitivity analysis was performed by changing the criteria that defined the outcome, using a range from ≥ 5 to ≥ 15% for the change in FEV₁. Use of the lower bound is not sufficiently justified since the authors have already mentioned that the value of 10% is considered to be a minimum clinically important difference. The results were stable to sensitivity analysis. Fluticasone was generally considered to be cost-saving when considered from a societal perspective (in which indirect costs were included), while it was cost-effective from a payer’s perspective.

Oostenbrink and Colleagues³³

This study by Oostenbrink and colleagues³³ represents the only economic evaluation conducted alongside a clinical trial,³⁴ with a time horizon of a year. This study assessed the cost-effectiveness of a new long-acting anticholinergic agent, tiotropium, compared to the standard therapy, ipratropium, from a societal perspective. Direct costs included total resource use (not specifically restricted to respiratory-related resources), and indirect costs included the number of days that patients were unable to perform a majority of their usual daily activities. However, indirect costs were excluded while computing the cost-effectiveness ratio on the basis that < 10% of the study population (patients with moderate-to-severe COPD) had paid employment. Differences in effects and costs were tested for significance by computing the 95% CIs (the CIs of differences in effects and costs that include 0 indicate no statistical significance). In addition to testing for these differences, the uncertainty surrounding the ICER was determined by computing 95% CIs for the ICER and by constructing cost-effectiveness acceptability curves. Tiotropium therapy was shown to be more effective on all four outcome measures; however, the differences in costs revealed a higher, but insignificant, cost for tiotropium (difference in costs = €180 [95% CI, −265 to 627]). Therefore, the ICER that was computed was positive (more cost: more effectiveness). The 95% confidence region of these ICERs lay in quadrants I and II of the cost-effectiveness plane (Fig 1) with approximately 75% of this region lying in quadrant I (higher costs and better effects).

The researchers made every effort to make the results generalizable. They used the standard of care (ipratropium) as an appropriate comparator and excluded protocol-driven costs. In excluding protocol-driven costs, all costs for regularly scheduled clinic visits were excluded. However, some costs should have been included based on the average number of visits expected by a patient with COPD. An intent-to-treat analysis was conducted, specifically accounting for the costs of patients who withdraw from a clinical trial. These patients usually have
more severe disease and thereby are likely to incur greater costs, leading to an imprecise estimate of the cost-effectiveness.

Given the uncertainty in the resource use and cost estimates, the sensitivity analyses appropriately focused on varying this component of the cost-effectiveness ratio. For effectiveness data, the criteria used to demonstrate improvement in the SGRQ was varied using 6 U and 8 U in a sensitivity analysis. A type of sensitivity analysis called analysis of applicability was also performed. This analysis uses region-specific prices (in this case, the Netherlands and Belgium) and region-specific resource use to make the results more generalizable. The results of varying SGRQ criteria and the analysis of applicability did not change the study conclusions. Of particular note, the lowest price of ipratropium that was used in the base-case analysis (metered-dose inhaler) was shown to be sensitive. Another estimate of the price (based on the average prices of the metered-dose inhaler and the dry powder inhaler, weighted by the actual use of these devices) that was used in the sensitivity analysis reduced the ICER to €178 per exacerbation avoided and €289 per relevant improvement in the SGRQ. The transparency of the methods and estimates used and the presentation of the results of this study represent good practices in conducting economic evaluations.

Sin and Colleagues have used a decision model to answer the question of which population of patients with COPD, based on disease severity levels, would most benefit from treatment with ICSs. A Markov decision model was chosen to represent the chronic and episodic nature of COPD. A Markov model is a dynamic representation of a disease process or treatment pattern in terms of clinically and economically relevant health states to which costs and efficacy can be attributed. The purpose of the model is then to mathematically predict events such as the number of life-years gained or the total costs for a particular intervention. A Markov model was constructed using a time horizon of 3 years and health states corresponding to the disease severity stages of COPD: stage 1; stage 2; and stage 3. These stages are defined by FEV1 levels according to the definitions of the American Thoracic Society. The following four ICS strategies were compared for patients with COPD: treat no patients with ICSs; treat all patients with ICSs; treat only patients with stage 2 or 3 COPD (ie, moderate-to-severe COPD) with ICSs; or treat only patients with stage 3 COPD (ie, severe COPD) with ICSs. QALYs was the outcome measure making this the first pharmacoeconomic study in COPD to assess a final end point instead of an intermediate end point. Utility values were estimated from data from the literature and were not empirically assessed. Since a societal perspective was taken, direct and indirect costs were assessed, with the latter applicable only to those patients <65 years of age.

Transitions among health states and, consequently, movement in the model were achieved by a reduction in the rate of lung function decline. Data from the Lung Health Study were used as inputs for the progression of patients to other health states for the strategy of no ICS treatment. However, data for the progression of patients to other health states for the strategies with ICS treatment were obtained from the data of two randomized controlled trials. In this case, the major assumption was that ICS therapy impacted lung function decline in the first 6 to 12 months of therapy, but after a year of therapy the decline mirrored that of patients who had not received ICS treatment. This particular assumption may be considered particularly tentative, since there is uncertainty regarding the impact of ICS therapy on reducing lung function decline. The GOLD guidelines have concluded that ICS therapy does not impact lung function decline, based on the results of randomized controlled trials. However, one meta-analysis has found an impact based on the results of these same trials, further contributing to the uncertainty. Consequently, the impact of this assumption can result in attributing additional years of life gained due to ICS therapy, thereby overestimating the ICERs.

Data on the effectiveness of ICS therapy in terms of mortality and rate of exacerbations were obtained from a systematic review of clinical trials. Costs data were taken from Canadian sources. Considering the deterministic input of data, a Monte Carlo simulation technique was used to provide variance in the final model outputs (ie, costs and QALYs), which is considered appropriate. The only result of the sensitivity analysis conducted was of the impact of nonresponders to strategy 3 (ICS treatment for stage 2 or 3 disease). This impact was found to be stable, and the other conditions or assumptions varied were also mentioned to be stable. It is important to mention that the authors considered ICS therapy to have an impact on mortality even though results from the systematic review indicated a point estimate of 0.84 with a CI overlapping 1. Their sensitivity analysis considered the situation in which no direct mortality benefits of ICS therapy were considered, with increases in the ICERs but no change in the study conclusions.

Incremental analysis showed ICS therapy to be the most cost-effective for patients with stage 3 COPD ($11,000 per QALY gained), and second most
cost-effective for patients with stage 2 or 3 COPD ($17,000 per QALY gained). When no mortality benefits were considered, the ICERs increased to $30,200 and $34,100, respectively. The study provided important evidence that complemented recent guidelines indicating that ICS therapy be reserved only for patients with moderate-to-severe disease.

**Identification of COPD Population**

Due to the nature of the disease and the symptoms, there is a great possibility for misdiagnosis in COPD patients. Therefore, any study considering a COPD population should ensure that the potential for misdiagnosis is reduced. In the current review, except for one observational study, all the studies used data from a clinical trial that assessed the efficacy of a drug. Considering the importance of high internal validity in a clinical trial, extreme care has been taken to exclude patients with asthma or allergic respiratory disorders in this assessment. Even the observational study had access to clinical charts to confirm the diagnosis of COPD. Almost all studies used smoking history (≥ 10 pack-years), age (> 40 years), and pulmonary function test results (FEV1) to avoid misdiagnosis.

In addition to the diagnosis, the severity levels assessed in these studies were mostly moderate-to-severe, with only one study including patients with mild disease. This is not particularly a concern since it has been shown that patients with moderate-to-severe disease incur almost two to three times higher costs than those with mild disease. Also, it should be noted that the results of studies of pharmacoeconomic analysis in COPD patients are generalizable only to the population of patients with moderate-to-severe disease.

**Credible Comparators**

Expert panels in pharmacoeconomics recommend that appropriate comparators be included to assess the cost-effectiveness of a drug therapy. These comparators should generally include the standard of care that is effective and efficient. Ipratropium therapy historically has been considered to be the standard of care for the maintenance treatment of COPD. Of the seven studies included in the review, four studies included ipratropium as a comparator, providing an accurate picture of the cost-effectiveness of the drug evaluated. In the other three studies, the comparator was described as the use of standard drugs and not any specific drug. Thus, although the drug was shown to be cost-effective relative to use of other drugs, no particular comparator could be identified in those studies.

**Outcome Measures**

Guidelines for economic evaluations recommend that the choice of the outcome measure, particularly in a CEA, should relate to a final health outcome such as survival or number of life-years gained. Intermediate outputs are appropriate only to the extent that a valid link has been established between these and a final health output, or are evidenced to have some value (eg, prognostic value). Current pharmacotherapy for the maintenance treatment of COPD has not been shown to impact survival, and hence final health outcomes such as the number of life-years gained are not evidenced in pharmacoeconomic evaluations for COPD. However, intermediate outcomes such as symptom relief and the number of exacerbations have prognostic value and are important to patients, thus justifying their inclusion as outcome measures for COPD. As can be seen in Table 2, almost all studies used a combination of physiologic, clinical and symptom measures, and HRQoL measures. The study by Sin and colleagues used a quality-adjusted life-expectancy measure.

FEV1 has been the only physiologic measure used in economic evaluations, with a propensity to represent the result in terms of the number or proportion of people experiencing a certain degree of improvement, rather than some level of FEV1. This is considered appropriate since there is no universal normal level of FEV1. The degree of improvement has varied in studies, but it ranges from at least 10% to at least 15%, and is probably based on tests of reversibility. Future research should standardize this degree of improvement if it will be used as an outcome in a pharmacoeconomic analysis. Although FEV1 is an important clinical measure, its use as an outcome measure in economic evaluations of COPD patients is debatable due to its inability to capture all of the relevant improvements of the therapy.

Exacerbations in COPD patients are considered to be extremely important from a clinical, economic, and psychological standpoint. Four studies have incorporated this measure in terms of exacerbation frequency (ie, the proportion of patients...
experiencing exacerbations), the number of exacerbation-free days, the proportion of patients who are free of exacerbations, or the number of exacerbations. Exacerbations are defined based on the duration of COPD-related symptoms or health-care resource use (Table 3). These are considered appropriate given that there is presently no consensus on the definition of an exacerbation.40–42

Scope of Costs

All studies except one23 mentioned the perspective of the study. Costs included in the studies corresponded to the perspective taken. Three studies31,33,35 used the societal perspective, which considers indirect costs. While indirect costs are important to include from a societal perspective, one has to remember that the majority of the pharmacoeconomic analyses in COPD are only relevant for patients with moderate-to-severe disease. This subset of patients is considered functionally disabled, with the result that most are early retirees. Thus, the indirect costs in terms of reduced paid production (ie, production inside the labor market) can reasonably be excluded. However, indirect costs in terms of reduced unpaid production43 (ie, production outside the labor market), that is, the reduction in performing usual activities at home and caregiver costs, all of which are due to the individual’s disease, and that due to mortality may still be relevant to consider. However, there are methodologic challenges to valuing these costs. The issue of the discounting of costs was not applicable since all but one study in this review had a time horizon of ≤1 year. A 5% rate was used in the study by Sin and colleagues35 only for costs, and not for QALYs.

The exclusion of costs that are due to the clinical trial protocol (ie, protocol-driven costs) and do not characterize real-life clinical practice is recommended to increase the generalizability of the study.44 The inclusion of such costs will lead to an imprecise estimate of the incremental cost of an intervention and consequently of the ICOR. Of the five economic evaluations conducted alongside clinical trials, only one27 did not exclude protocol-driven costs. However, for the four studies, the method of excluding these costs was not explicitly mentioned. Mostly, protocol-driven costs were identified in terms of the additional visits and tests due to the trial protocol. The costs that are incurred due to increased monitoring (eg, further treatment after lung function testing that would otherwise not occur in real practice) are harder to identify44 and were not addressed in the studies.

Statistical Analysis of Outcomes and Costs

Particularly relevant for economic evaluations that are done alongside clinical trials, the recommended analytic principle of intent-to-treat was used for all such studies. This approach is important specifically when analyzing resource use, since the cost of patients who withdraw from a clinical trial is higher compared to those who do not withdraw, either because of adverse events or worsening of their disease condition.17 If this resource use is not accounted for, it creates a bias in the cost-effectiveness ratio. The bias is further exacerbated when there is a differential rate of dropout between groups. In accordance with the approach, studies are required to mention the method of imputing missing values for these dropouts.30 Only two27,33 of five studies mentioned the method of imputing costs for dropouts.

It has been recommended that a statistical testing of differences in costs and outcomes be done before computing cost/outcome ratios and ICORs. While testing for differences in effects typically involves standard issues of statistical analysis, there are other issues that need to be considered when analyzing cost data. It is recommended that the statistical testing of differences in cost should be conducted primarily on total costs rather than individual cost components and should account for the skewed

Table 3—Definition of Exacerbations in Included Pharmacoeconomic Studies

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<th>Study</th>
<th>Definition of Exacerbation</th>
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<tr>
<td>Friedman et al23</td>
<td>Pulmonary exacerbation: a worsening of COPD-related symptoms (ie, cough, wheezing, dyspnea, and sputum production) for ≥3 consecutive d</td>
</tr>
<tr>
<td>Ayres et al31</td>
<td>A worsening of COPD symptoms requiring a change to normal treatment, including antibiotics, short courses of oral corticosteroids, and other bronchodilators; exacerbations were categorized as mild (managed by patient), moderate (requiring treatment by a physician), and severe (resulting in a hospital admission)</td>
</tr>
<tr>
<td>Oostenbrink et al33</td>
<td>A complex of respiratory symptoms (ie, new onset or worsening of more than one symptom such as cough, sputum, dyspnea, or wheeze) lasting for &gt;3 d</td>
</tr>
<tr>
<td>Sin et al35</td>
<td>Mild: worsening of symptoms requiring outpatient physician services and institution of therapy with systemic corticosteroids or antimicrobial agents (ie, exacerbation therapy). Moderate: clinical episodes requiring emergency department use or urgent physician office visits (and institution of exacerbation therapy). Severe: symptoms requiring in-patient care (and institution of exacerbation therapy)</td>
</tr>
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nature of the cost data, and that CIs of the differences in cost be presented. Of the seven studies reviewed,\textsuperscript{8,23,25,27,31,33,35} four studies\textsuperscript{23,27,31,33} tested differences in total costs. Of these four studies, one\textsuperscript{23} used the Kruskal-Wallis test appropriately. The other three studies\textsuperscript{27,31,33} computed the 95% CIs of the differences in costs. This approach is preferred since the statistical significance of the difference and the magnitude of the difference can be determined.\textsuperscript{18} The other studies did not test the difference in total costs\textsuperscript{25} or tested differences only on individual resource use.\textsuperscript{8}

While not a primary concern for the studies conducted in a clinical trial setting, the only observational study\textsuperscript{17} included in this review did not control for other factors while assessing differences in resource use between the treatment groups. Statistical control can be achieved using advanced multivariate analysis (econometric techniques). The study by Sin and colleagues\textsuperscript{35} used a Monte Carlo simulation approach to obtain output in terms of a simulated distribution of costs and effects that lends itself to the statistical testing of differences.\textsuperscript{17}

**Incremental Analysis and Testing of Uncertainty in ICOR**

All studies included in this review conducted an incremental analysis, which is important for determining cost-effectiveness. Increasingly important in economic evaluations is the testing of the uncertainty in the ICOR. Only two studies, Ayres and colleagues\textsuperscript{31} and Oostenbrink and colleagues,\textsuperscript{33} assessed the uncertainty in estimates. It should be noted that the differences in costs between treatment groups in these two studies were insignificant, implying no difference. However, the uncertainty analysis using the cost-effectiveness plane helped to determine the 95% confidence region in which the ICER may lie.

**Conclusions**

An increasing number of pharmacoeconomic studies have been conducted in the past few years (ie, since 2002) in COPD patients due to the introduction of newer pharmacotherapies for this progressive condition. The studies are not directly comparable as different comparators are included in each study, which does not provide for a comprehensive assessment of any particular therapy as being cost-effective across settings and different patient populations. Specifically, information on the cost-effectiveness of long-acting β-agonists seems to be lacking. The long-acting anticholinergic agent tiotropium has been shown to be cost-effective relative to ipratropium in only one study.\textsuperscript{33} Although no explicit comparison has been done with a combination of albuterol and ipratropium, one can assume from the study by Friedman et al\textsuperscript{23} that this combination therapy and ipratropium therapy alone have similar costs and effects. Evidence of the cost-effectiveness of therapy with ICSs shows it to be cost-effective for patients with moderate-to-severe COPD, reflecting GOLD guidelines.\textsuperscript{44} However, the results need to be assessed in light of important assumptions of the decision model, such as the impact of therapy with ICSs on disease progression and mortality. Clearly, additional studies are needed regarding the cost-effectiveness of ICS therapy. The study by Sin and colleagues\textsuperscript{35} answered an important research question, as to which severity category of the COPD population would ICS therapy be beneficial. It is of current interest to determine how ICSs compare to other bronchodilators used for COPD in terms of cost-effectiveness.

The recent update to the GOLD guidelines (2003 update)\textsuperscript{45} modified the original 2001 guidelines\textsuperscript{8} for pharmacotherapy in COPD patients after a review of data from clinical trials\textsuperscript{46} published after 2001 was conducted. Specifically, the 2001 guidelines recommended regular treatment with long-acting bronchodilators for moderate-to-severe COPD only on the basis that it was more convenient than short-acting bronchodilators.\textsuperscript{2} The 2003 update now recommends regular treatment with long-acting bronchodilators on the basis that it is more effective and more convenient compared to short-acting bronchodilators. However, the guidelines mention that it is also more expensive. Determining whether additional benefits are worth the additional cost is one of the primary goals of pharmacoeconomic research.

Limitations of the current review stem from the exclusion criteria of the study. Specifically, there are outcome studies\textsuperscript{47–51} on the use of ICSs in the general population in which the outcomes measured were death, hospitalization, and in only two studies,\textsuperscript{50,51} exacerbation not requiring a hospitalization. These studies were observational in nature and provide important information regarding the impact of ICS therapy in the real world. Future reviews may want to consider these studies in their overall assessment.

The present review reflects the increasing interest in providing evidence to enhance the management of COPD. Although this review has provided important information summarizing the results of pharmacoeconomic studies in different patient populations and settings, it has not been able to identify any information to complement the more recent GOLD guidelines\textsuperscript{45} with pharmacoeconomic evidence. The primary reason can be related to the paucity of comparative pharmacoeconomic analyses between...
relevant treatment strategies. All of the therapies have been assessed relative to “placebo” (ie, usual care) or ipratropium. Future pharmacoeconomic research should be conducted comparing therapy with long-acting β-agonists to that with ipratropium or the standard combination of ipratropium and albuterol, and also between therapy with different classes of long-acting bronchodilators. Combination therapy is increasingly being considered in the population of patients with moderate-to-severe COPD, and future pharmacoeconomic analyses should incorporate new combinations of therapy along with the standard combination of ipratropium and albuterol. In addition, the place of therapy with the new anticholinergic agent tiotropium alone and in combination with other drugs needs to be evaluated in terms of economic and clinically relevant outcomes. At the time of this review, this information was not available. It is hoped that future pharmacoeconomic information will provide a comprehensive picture of the role of pharmacotherapy in COPD patients that will serve as a useful support to the GOLD guidelines.

APPENDIX: Drummond’s 10-Point Checklist for Critical Assessment of Pharmacoeconomic Studies

1. Was a well-defined question posed in answerable form?
   Did the study examine both costs and effects of the service or program?
   Did the study involve comparison of alternatives?
   Was a viewpoint for the analysis stated, and was the study placed in any particular decision-making context?

2. Was a comprehensive description of the competing alternatives given?
   Were any important alternatives omitted?
   Was (should) a do-nothing alternative (be) considered?

3. Was the effectiveness of the program or service established?
   Was this done through a randomized controlled trial? If so, did the trial protocol reflect what would happen in regular practice?
   Was effectiveness established through an overview of clinical studies?
   Were observational data or assumptions used to establish effectiveness? If so, what are the potential biases in results?

4. Were all the important and relevant costs and consequences for each alternative identified?
   Was the range wide enough for the research question at hand?
   Did it cover all relevant viewpoints?
   Were capital costs, as well as operating costs, included?

5. Were costs and consequences measured accurately in appropriate physical units (eg, hours of nursing time, number of physician visits, lost work days, or gained life-years)?
   Were any of the identified items omitted from measurement?
   If so, does this mean that they carried no weight in the subsequent analysis?
   Were there any special circumstances (eg, joint use of resources) that made measurement difficult? Were these circumstances handled appropriately?

6. Were costs and consequences valued credibly?
   Were the sources of all values clearly identified? (Possible sources include market values, patient or client preferences and views, policy-makers’ views and health professionals’ judgments.)
   Were market values employed for changes involving resources gained or depleted?
   Where market values were absent (eg, volunteer labor), or market values did not reflect actual values (eg, clinic space donated at a reduced rate), were adjustments made to approximate market values?
   Was the valuation of consequences appropriate for the question posed (ie, has the appropriate type or types of analysis—cost-effectiveness, cost-benefit, or cost-utility—been selected)?

7. Were costs and consequences adjusted for differential timing?
   Were costs and consequences which occur in the future “discounted” to their present values?
   Was any justification given for the discount rate used?

8. Was an incremental analysis of costs and consequences of alternatives performed?
   Were the additional (incremental) costs generated by one alternative over another compared to the additional effects, benefits, or utilities generated?

9. Was allowance made for uncertainty in the estimates of costs and consequences?
   If data on costs or consequences were stochastic, were appropriate statistical analyses performed?
   If a sensitivity analysis was employed, was justification provided for the ranges of values (for key study parameters)?
   Were study results sensitive to changes in the values (within the assumed range for sensitivity analysis, or within the CIs around the ratio of costs to consequences)?

10. Did the presentation and discussion of study results include all issues of concern to users?
    Were the conclusions of the analysis based on some overall index or ratio of costs to consequences (eg, cost-effectiveness ratio)? If so, was the index interpreted intelligently or in a mechanistic fashion?
    Were the results compared with those of others who have investigated the same question? If so, were allowances made for potential differences in study methodology?
    Did the study results discuss the generalizability of the results to other settings and patient/client groups?
    Did the study allude to, or take account of, other important factors in the choice or decision under consideration (eg, distribution of costs and consequences, or relevant ethical issues)?
    Did the study discuss issues of implementation, such as the feasibility of adopting the “preferred” program given existing financial or other constraints, and whether any freed resources could be redeployed to other worthwhile programs?

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An Appraisal of Pharmacoeconomic Evidence of Maintenance Therapy for COPD
Anna O. D’Souza, Michael J. Smith, Lesley Ann Miller and Jan Kavookjian

Chest 2006;129;1693-1708
DOI 10.1378/chest.129.6.1693

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