

Approaching value in asthma management: The need to integrate clinical and economic research with the basic science

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In the management of asthma, clinical decision making is primarily directed toward achieving the best outcome for the patient. However, the interests of the provider, insurer, and employer must also be taken into account. Integral to this process is an understanding of the need to weigh therapeutic objectives against economic concerns. This process involves consideration of the potential for clinical benefit as opposed to adverse treatment effects, as well as direct and indirect costs. Data from clinical trials provide the foundation for evaluating these factors. Randomized clinical trials, postmarketing studies, surveillance programs, and observational claims analyses all contribute valuable information to facilitate this process. Taken together, the results of such analyses form a foundation for providing effective, safe, and cost-efficient care through the practice of evidence-based medicine. (*J Allergy Clin Immunol* 2002;109:S503-10.)

Key words: *Asthma, economics, pharmacoeconomics*

Evidence-based medicine is a movement away from reliance on professional judgment and toward a more structured assessment of clinical knowledge. This approach provides a method of weighing health effects, economic impact, and patient preferences. The validity of clinical findings in the literature, including the effectiveness, applicability, and potential adverse effects of interventions, can be critically assessed and then evaluated by use of this decision-making tool.

Rigorously constructed evidence tables, based on the relevant literature, are used to support evidence-based medicine. Predetermined criteria must be established for both the inclusion and exclusion of studies. For evidence grading, a consistent methodology that minimizes individual interpretation must be used. For example, in establishing a rank order for clinical investigations, the greatest weight may be given to randomized, controlled trials (with placebo controls or active comparators), followed by indirect comparisons in which 2 sets of randomized trial data are used; open-label, nonrandomized trials; and,

finally, expert opinion. Table I presents a hierarchy of evidence grading.¹ Statistical analysis is used to validate findings of clinical importance.

This structured analysis must address the need for determining the economic impact of a therapy, as well as both real and perceived barriers to the intervention.²

The rationale for economic analysis is to provide a valid, replicable, and scientific structure by which to weigh the relative costs and benefits of implementing health care alternatives, with scarce resources being directed toward valuable ends.³ This type of analysis requires a comparison of the relative costs and benefits of the treatment alternatives. The range of the alternatives selected and the costs and benefits that are included and measured determine the extent and validity of the analysis. The value of the analysis is determined by the analytical methods and the precision, relevance, and acknowledged limitations of the data.

Economic analyses can be derived from cost-effectiveness studies and observational cohort analysis. Cost-effectiveness studies are the most frequently reported pharmacoeconomic analyses. These studies include a methodology that measures health benefits in units (such as years of life saved or improvements in lung function) while assessing the monetary costs required to achieve these results in financial terms.⁴ This integration of cost data and health outcomes places a dollar value on results attained and permits an analysis of the financial impact of alternative treatments. These studies are based on randomized clinical trials, with all their inherent strengths and limitations. Although such studies are important, they do not represent a perfect science. The alternative, to disregard these analyses, would suggest that cost of care was not important.⁵ Alternative economic analyses are based on observational cohort studies that use medical and pharmacy claims databases. These analyses allow for the study of a broader range of patients over longer periods and permit the documentation of actual costs or charges associated with health care. Each of these methodologies also has its own strengths and limitations, and the validity of each is enhanced when both provide similar conclusions.

The hierarchy of research designs does not have a formal place for observational studies.⁶ Some interpretations of evidence-based medicine would state that nonrandomized trials should be discarded.⁷ This recommendation is based on the perception that observational studies may overestimate treatment effect. However, two recent publications have demonstrated that randomized clinical trials and observational studies produce similar results with a compa-

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TABLE I. Hierarchy of evidence

1. Evidence from one or more randomized, controlled clinical trials
- 2a. Evidence from one or more controlled clinical trials that lack randomization
- 2b. Evidence from cohort or case-controlled trials that employ careful study design and are contained in one data set
- 2c. Evidence from multiple studies that compare treated and untreated subjects
3. Descriptive, respected clinical experience including reports of expert committees

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TABLE II. Goals of therapy

Prevent chronic and troublesome symptoms
 Maintain (near) normal lung function
 Maintain normal activity level
 Prevent recurrent exacerbations and the need for emergency department visits or hospitalization
 Provide optimal pharmacotherapy with minimal adverse effects
 Meet patients' and families' expectations and satisfaction with care

able magnitude of the effect size. Benson and Hartz⁸ evaluated observational studies and randomized controlled trials in 19 diverse therapeutic areas and assessed the magnitude of treatment effects with these 2 different methodologies. These authors concluded that there was concordance between the two techniques. Concato et al⁹ compared meta-analyses of randomized clinical trials and cohort or case-controlled studies addressing 5 therapeutic questions. These investigators noted that observational studies did not overestimate the magnitude of treatment effect. The inclusion of observational data allows for the inclusion of many robust databases that are now available as an indirect benefit of developing computer technology and the need for large health insurance companies to study resource use. The results of a single study, regardless of the methodology, must be interpreted with caution. The convergence of evidence from multiple studies with different designs provides the most robust conclusions.

As with randomized clinical trials, claims analysis should be carefully designed, study the appropriate population, assess relevant outcomes, and include similar statistical analysis for validation of the results. Large case-control and cohort studies can be used to determine associations of infrequent events and therapy. The Saskatchewan epidemiologic studies (discussed in detail below) are examples of population studies that have been used in decision making.¹⁰⁻¹³ A limitation of this form of analysis is that it is significantly easier to demonstrate an association than to fail to reject the null hypothesis. Failing to reject the null hypothesis may reflect the sample size or the methodology of the study. According to the hierarchy table of evidence, it appears that economic analysis can be performed both from the randomized clinical trial and the observational cohort and case-controlled studies, levels 1 and 2 evidence.

ASTHMA MANAGEMENT: UNDERSTANDING THE VALUE EQUATION

The goals of disease management are to produce the best clinical outcome with an acceptable risk/benefit ratio. For patients with asthma, the National Institutes of Health Expert Panel Report 2 on the diagnosis and management of asthma outlines 6 general goals of therapy (Table II).¹⁴ The patient's goals are foremost, but regulators, payers, employers, and providers are also important constituents in clinical decision making. Patients want a pharmaceutical that will cure disease and/or improve functioning and quality of life. Regulators want to ensure that medications are safe and effective. Payers and employers want therapeutics that are cost-effective. A consensus effort is needed to control costs by achieving better value for the money spent on health care.¹⁵

The value equation examines the therapeutic index of the medication or intervention needed to achieve the goals of care and the expenses required to achieve these objectives. The therapeutic index is defined as the ratio of benefits achieved as opposed to the adverse effects of the treatment. Expenses consist of all of the direct and indirect costs. In many analyses, no indirect costs are reported. Indirect costs are usually modeled on multiple assumptions because employment records are difficult to obtain because of concerns regarding confidentiality.

The value equation may have different variables for each of the customers, according to their specific perspectives. The patient wants a therapy that is effective, safe, and easy to use and that does not add substantially to the cost of care. For the patient, effectiveness means the achievement of the goals of asthma management: prevention of symptoms and exacerbations, maintenance of normal activity, and satisfaction with care. The patient is also concerned about costs. The primary concern is the cost of treatment, including medications and resource use. In addition, patients are apprehensive about lost wages or productivity because of illness.

The insurer wants to achieve these same goals in a cost-effective manner. In other words, the insurer wants to use the most effective treatment that will minimize costs while still attaining the results desired by the patient. Medications can be perceived as an investment in care; they should reduce symptoms and exacerbations with minimal adverse effects. In theory, an ideal drug is one that produces the best clinical outcomes and customer (the patient and employer) satisfaction with the lowest expenditure of limited medical resources.

The employer shares concerns similar to those of the insurer. The employer's costs for purchasing health insurance reflect the costs of the insurer for administering the health plan to its members. In addition, the employer and insurer share concerns regarding the potential for lost productivity of the patient. Absenteeism of a valued employee is costly. Productivity is reduced if a patient was awake the previous night because of active disease experienced by the patient or a family member.

The physician provides advice regarding the selection of therapies for the patient's health care and promotes the use of such treatments. The provider is actually marketing a treatment regimen, even though this is not traditionally viewed as a role of the physician. The provider must convince (promote to) the patient, and sometimes the health plan, of the effectiveness and appropriateness of the treatment. In addition, the physician should share the goals of the other consumers. The physician who is treating a patient with asthma may use objective measures of lung function to assess the effectiveness of therapy. The Expert Panel Report 2 has selected normalization of lung function as a primary goal of therapy.¹⁴ This is a provider measurement tool that can be used to predict improvement in other outcomes. Improvement in lung function correlates with lower rates of exacerbations¹⁶ and with enhanced patient-oriented outcomes in clinical trials.

Randomized clinical trials and observational studies

A comprehensive, standardized approach is appropriate for evaluating the literature to facilitate the practice of evidence-based medicine. An understanding of the various types of clinical trial designs is crucial to this process.

Clinical decision making is initially based on findings from randomized clinical trials that are generated primarily for the purpose of obtaining licensing for pharmaceuticals. These trials are followed by larger postmarketing trials that typically have similar study designs with standardized, objective, criteria. Such studies are used to gain effectiveness claims and to support clinical decision makers in choosing whether to prescribe a therapeutic agent. Clinical experience is the next level of data used to determine whether a physician continues to prescribe a medication. Surveillance programs monitor for potential adverse effects of new medications but do not usually focus on efficacy.¹⁷ Recently, observational studies that include information from medical and pharmacy administrative claims databases have been used to demonstrate associations between claims for medication and the use of resources, such as the emergency department or hospital, or mortality from disease.

Randomized clinical trials. The results of randomized clinical trials have been the basis for most pharmaceutical claims of cost-effectiveness over the past several decades. These studies are usually weeks to months in duration, require frequent recording of symptoms, and entail close monitoring of enrollees. The participants have very well-defined disease status. The patients need to have significant-enough disease to qualify for the study and to demonstrate benefit from the intervention, but not severe disease that would cause harm if they were randomly assigned to a placebo arm or failed to remain in the study. Because of concern about possible adverse effects and for the purpose of improving compliance with treatment, study subjects are more closely monitored than are individuals in a typical patient-physician relationship. Both patients and physicians are usually provided with incentives to participate in these investiga-

tions. The primary objective of the clinical trial design is to maximize internal validity, that is, the ability of the study to establish a cause-and-effect relationship between intervention and outcome.

A limitation of randomized clinical trials is that the results may not be generalizable to the population of patients as a whole. The strength of these trials in maximizing internal validity is their very weakness with regard to generalizing the information to the broader patient population. Randomized clinical trials do not include large groups of patients at either end of the disease severity spectrum, nor are they of sufficient duration to detect infrequent events. In addition, close supervision of the study participants may, in itself, modify the disease. Under such close scrutiny for short periods, patients with asthma rarely experience acute deterioration that warrants emergency department visits or hospitalization. Patients with asthma generally visit the physician less than one time per year in association with this diagnosis, as compared with multiple office visits during a randomized clinical trial. Cost-effectiveness studies therefore examine the cost of the study drug to produce the primary or secondary outcomes of clinical trials. In the case of asthma, the variables of interest might be the number of symptom-free days, the number of days free from the need for rescue medication, or the cost required to improve the FEV₁ by 10%.

Observational studies. In observational studies, administrative pharmacy and medical claims data are used to identify and monitor patients who have claims related to a specific diagnosis or prescription claims for the treatment of a specific medical condition. Outcomes are assessed by reviewing the use of resources as reflected, for instance, in pharmacy prescriptions dispensed, office visits, emergency department visits, or hospitalizations. The effect of treatment can result in an increase or decrease in these indicators. Claims for medications and services can also become the markers of disease activity and severity. As an example, the need for short-acting bronchodilators can be used as a surrogate marker of disease control.¹⁸ Specific laboratory results, such as measures of lung function, are not typically available in retrospective claims analysis.

External validity, the generalizability of study results to the overall patient population, can be maximized with observational claims analysis. The decision to begin administration of a medication is the result of the interaction between the provider and patient. This decision is based on the patient's presentation, as well as both the patient's and provider's knowledge and acceptance of the medication. A much broader spectrum of patients can be followed up. Claims analyses can be used to study larger populations for longer periods, allowing assessment of the occurrence of infrequent events (such as hospitalizations and emergency department visits). Regression analysis is used to control for comorbidities and surrogate markers of disease severity, such as the prestudy claims history. Alternatively, the population can be defined to exclude patients with certain comorbidity

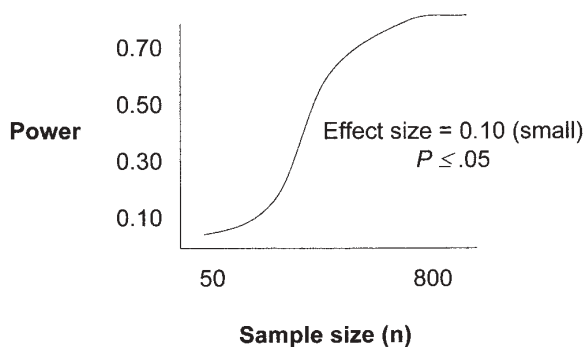


FIG 1. Small effect size and large sample size.

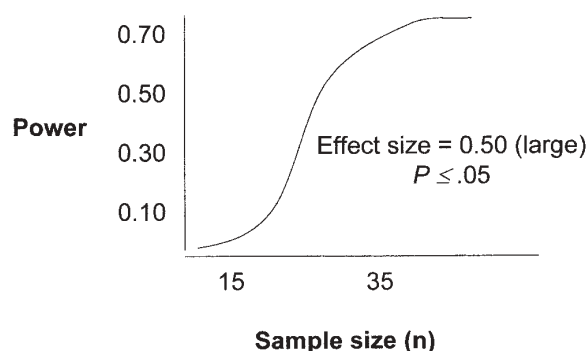


FIG 2. Large effect size and small sample size.

claims or those who receive other drug therapies that may confound the results. In assessing the effect of a therapeutic intervention, one must be certain that the change has occurred as a result of the therapy and not from natural regression or progression of disease activity. An example might be the use of antibiotics in the treatment of acute otitis media during childhood, for which the placebo response rate is 60% to 70%.¹⁹ The validity of the results of observational claims analysis is supported when they parallel and confirm the results of randomized clinical trials.

Statistical analyses. In both of these models, statistical analysis is used to validate that the observed differences noted between study groups demonstrate meaningful change. Regression analysis assesses the significance of one variable in predicting the outcome from a group of variables that are reported. As an example, one population may be younger, and therefore the adjustment will correct for this discrepancy. In randomized clinical trials, systematic baseline variations between treatment groups are corrected for by analysis of covariance, which is a form of regression most suitable for categorical independent variables (eg, a variable that identifies patients receiving drug A, drug B, or drug C). These analyses have similar intents. The baseline variations may appear to be greater in observational claims reports, but with the size of the population and acceptable statistical adjustments, the results may be more generalizable to the population in need of treatment.

In addition to size and duration limitations, frequent recording of specific outcome measures (such as FEV₁, peak expiratory flow, and reports of symptoms) is common in randomized clinical trials. These studies frequently contain rescue protocols that direct the investigators to early and appropriate interventions that further reduce the likelihood of significant exacerbations. Thus, severe exacerbations are more common in observational studies that do not have these artificial limitations.

Therapies that result in large clinical differences may require only small study populations to demonstrate statistical differences. Conversely, small and frequently clinically insignificant changes may be statistically significant if large-enough populations are studied. Large variation around the mean may produce results that

appear clinically different but lack statistical validation. The strongest findings are those that are both statistically and clinically significant. The term *effect size*, defined as the magnitude of the difference, is frequently used to explain the relationship between clinical and statistical findings. Larger effect size will have greater clinical significance; statistical confirmation of the results is easier with this increased magnitude of change. Figs 1 and 2 show the relation between effect size, number needed to treat, and statistical significance. As an example, when inhaled corticosteroids and montelukast are compared for the treatment of asthma in children,^{20,21} the number of patients who need to be treated with inhaled corticosteroids is lower because the effect size for the change in FEV₁ or peak expiratory flow is greater.

Both randomized clinical trials and observational studies accumulate data on the safety, as well as the efficacy, of a given therapy. Observational studies are frequently used to achieve safety surveillance. The medical community is comfortable with use of these studies to confirm the safety of an intervention.¹⁷

Retrospective claims analyses

As with randomized clinical trials and observational studies, retrospective claims analyses must include statistically and clinically relevant parameters. Retrospective claims analyses designed to assess the effectiveness of a specific pharmaceutical product are best performed by a neutral organization; this may be a health plan, a commercial administrative claims company, a university school of public health, or another medical institution. These studies need to include a design methodology that is analogous to that of the randomized clinical trial, be appropriately powered to answer the proposed question, and include appropriate statistical analysis.

Retrospective claims analyses are commonly used in multiple therapeutic areas. For example, such analyses have been used to demonstrate the effectiveness of medical intervention for osteoporosis with regard to reductions in the rate of fractures. Claims analysis has also been used to assess the frequency of diagnostic testing and the use of cholesterol-lowering medications.²² This type of analysis has demonstrated poor compliance with guidelines for the treatment of patients with coronary

artery disease and congestive heart failure.²² Furthermore, claims analysis has been used to determine the economic burden of migraine²³ and to assess strategies for the treatment of migraine (such as the effect of limits on the number of tablets used per month to treat this disease²⁴). Several studies have identified the economic impact of depression and the cost of care associated with the use of selective serotonin reuptake inhibitors.²⁵

Asthma, osteoporosis, coronary artery disease, migraine, and depression are all associated with high prevalence and high cost. Because of the large number of affected patients and the frequency of claims, these illnesses provide large databases for analysis. Basic scientific research in each of these areas has produced critical knowledge that has led to the development of effective therapy for these disease states. Randomized clinical trials have provided evidence to support the use of medical intervention, and retrospective claims databases are then used to assess the clinical effectiveness of, and compliance with, these treatments.

ROBUSTNESS OF FINDINGS AND INTERNAL CONSISTENCY

The robustness of a clinical conclusion is based on the strength of the analysis, that is, the magnitude of the reported differences confirmed in multiple settings and with different study designs. The validity of the results of a randomized, controlled trial may be confirmed by demonstrating consistent findings in studies in which observational claims databases are used. Discordant results between two investigational constructs suggest the possibility of errors in the findings, study designs, or analyses. In studies of asthma, improvements in FEV₁ or peak expiratory flows correlate with improvement in other patient-oriented outcomes. Better lung function is consistent with fewer symptoms, less need for rescue albuterol, and better nighttime disease control. Improvement in FEV₁ has been shown to correlate with lower exacerbation rates in asthma.¹⁶ One may hypothesize, then, that medications capable of producing greater improvement in lung function would be associated with lower rates of disease-related morbidity. This relationship may be measured in observational studies by evaluating rates of emergency department visits or hospitalization. Again, consistency should be apparent between the results of randomized clinical trials and administration claims database analysis.

The results of analyses of claims databases must be validated by internal consistency. Pivotal concerns include consideration of whether the database truly identifies the population being studied, reflects the expected prevalence of the disease according to age and sex, and reflects the expected cost. Several earlier studies in which medical and pharmacy claims databases were used demonstrated the ability to identify populations of patients with asthma.^{26,27} These studies, performed at United HealthCare, identified a population of patients who had demographics associated with the presence of asthma. The period prevalence of members with a claim

for asthma was 3.8%, which was within the expected range. The prevalence by age and sex was also consistent with that reported in other analyses. These data revealed greater prevalence of the disease in male subjects during the first years of life, no male or female predominance during the teenage years, and female predominance during adulthood. Furthermore, the costs of care were consistent with data from other calculated analyses.²⁸ The studies at United HealthCare have been conducted over several years' time and continue to demonstrate internal validity. These studies help validate the strength of the analysis from retrospective claims databases. Because these types of analysis are actual measures of cost and not estimates or extrapolations, they may serve as a referent data source for asthma care.

ECONOMIC MODELING

Economic modeling has commonly been based on the results of large randomized clinical trials. These analyses attempt to extrapolate the results of the trials and assign dollar figures to events such as emergency department visits or hospitalizations. The cost of therapy is based on the medication assigned. Because of the low incidence of the other high-cost events (ie, the emergency department visits and hospitalizations), the medication charge becomes the largest variable in this type of analysis. Costs can then be assigned to achieve the desired improvement. These expenses are reported, for example, in terms of the cost of a 10% improvement in FEV₁ or the cost of a symptom-free day or a day free of the need for rescue medication.

Economic models must be confirmed with data from claims analyses. Administrative claims data represent the real costs or charges associated with a disease. Claims databases record the costs or charges to the health plan for the medication, visits to the physician's office, emergency department visits, and hospitalizations, factoring in copayments. These data allow for an accurate presentation of the true costs or charges associated with the care of a patient over a defined period.

STUDIES THAT INCLUDE RETROSPECTIVE CLAIMS ANALYSIS

Multiple studies that include retrospective claims analysis have appeared in peer-reviewed journals for the past decade. A group of Canadian studies in which health insurance databases were used have gained significant attention in both the medical and lay communities.¹⁰⁻¹³ These 4 reports stress the importance of reviewing large patient cohorts to learn from clinical experience. As a group of studies with careful design and statistical analysis, they serve to help establish the validity of retrospective claims analyses in the management of asthma.

In the early 1990s, the escalating epidemic of asthma-related mortality and the potential association of this event with the routine use of β -agonists generated great concern. The initial study by Spitzer et al¹⁰ attempted to

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FIG 3. Risk ratio for death from asthma as a function of the number of inhaled corticosteroid (ICS) canisters per year. (Reprinted with permission from Suissa S, Ernst P, Benayoun S, Baltzan M, Cai B. Low dose inhaled corticosteroids and the prevention of death from asthma. *N Engl J Med* 2000;343:335. Copyright © 2000 Massachusetts Medical Society. All rights reserved.)

address these issues in a population of 12,301 patients with asthma who met the criteria of having at least 10 prescriptions for one or more asthma-specific medications studied over a 10-year period. The authors concluded that the risk of death was associated with the regular use of inhaled β -agonists (especially fenoterol), whether as a direct effect of the medication or as a marker of increasing disease severity. In a follow-up publication, the authors demonstrated how the results of their first study could be alternatively interpreted if a different study design were used.¹¹ The first study used a "nested case-control" sample,¹⁰ and the second analysis evaluated the entire cohort.¹¹ The latter analysis still reported a risk associated with inhaled β -agonists, but now it was restricted to those patients using higher-than-recommended dosages of short-acting inhaled bronchodilators. These studies are important because of the descriptions of their methodology and the discussion of the variables of the study designs. As in any study, recognition of the limitations of these designs is important in interpreting the results of the analyses.

Using the same database, in a companion publication, this research group determined that the regular use of inhaled corticosteroids provided protection from asthma-related mortality.¹² Expanding on this study, the investigators more recently confirmed this conclusion in a larger analysis of 30,569 subjects in Saskatchewan over an extended period.²⁹ With a well-defined protocol and use of linear regression and statistical adjustments, the authors demonstrated that risk of death from asthma is reduced with the use of low-dose inhaled corticosteroids and that the risk is further lowered with greater compliance with this class of medication. Fig 3 shows the ratio of deaths from asthma to the number of canisters of inhaled corticosteroids dispensed during the year before the index event.

A protective effect of inhaled corticosteroids in reducing asthma mortality has also been observed in other ret-

rospective data analysis. Using national health statistics and available data on the sales of anti-inflammatory drugs, both Goldman et al³⁰ in Israel and Sly³¹ in the United States were able to demonstrate a decrease in asthma mortality in association with increasing use of these medications. The results of these studies are consistent with the findings in the Canadian analyses and support the use of administrative claims methodologies.

The two largest areas of resource use for asthma are the expenditures for pharmaceutical products and hospitalization.^{26,28} Statistics from the Centers for Disease Control and Prevention have demonstrated the persistent high rate of hospitalizations for treatment of asthma across all age groups.³² Several observational studies have been performed to assess the effect of intervention in reducing the risk of hospitalization for asthma. Two studies in which available administrative records were used demonstrated that the frequency of hospitalizations for asthma declined as the use of inhaled corticosteroids increased.^{33,34} Studying children in Göteborg, Sweden, Wennergren et al³³ reported a two-thirds reduction in hospital days and a 45% decrease in asthma-related admissions concurrent with a large increase in the use of inhaled corticosteroids for asthma. Similar findings were reported in a study of adults.³⁴ In 1997, Donahue et al¹⁸ reported findings from a confirmatory study that included retrospective claims analysis based on data from Harvard Pilgrim Health Care in Massachusetts. A total of 16,941 patients met entry criteria for the analysis. Multiple logistic regression analyses were used to establish the relative risk for hospitalization. This research identified a 0.5 relative risk of hospitalization for asthma (ie, a 50% reduction) among patients who used inhaled corticosteroids. Not unexpectedly, the authors demonstrated that the increasing use of inhaled β -agonists was associated with an increased relative risk of hospitalization. Inhaled corticosteroids had an apparent protective effect even when compliance with the use of these medications was low (Fig 4). This improvement continued with higher doses of inhaled corticosteroids, which may be used for patients with increasing disease severity. Furthermore, the use of 5 to 8 or more canisters of inhaled β -agonists was associated with a 2-fold or greater increase in the risk of hospitalization. The 50% reduction in hospitalization noted in the retrospective observation study has now been confirmed by a large, prospective clinical trial, the Childhood Asthma Management Program study.³⁵ Using different analytical techniques, the authors of all of these studies concluded that inhaled corticosteroids protect against severe exacerbations of asthma.

Retrospective claims analyses have also been used to demonstrate that children with asthma have more non-asthma-specific claims, probably because of respiratory comorbidities. These studies have used both medical and pharmacy claims data from a single health plan, Group Health Cooperative,³⁶ as well as a national population sample.³⁷ Again, the findings have been concordant. In addition, data from claims analysis have been used to demonstrate differences in prescribing practices

according to medical specialty²⁷ and an association between higher treatment costs for treatment of asthma and greater use of inhaled β -agonists.³⁸ These claims databases can also be used to identify patients with a specific disease to facilitate further outcome assessments. Legorreta et al³⁹ surveyed patients enrolled in Health Net to assess compliance with the National Institutes of Health guidelines for the treatment of asthma. This study not only illustrated the fact that claims data can be used to identify appropriate study groups, it also demonstrated the need for better compliance with the National Institutes of Health guidelines for asthma management.

Observational, retrospective claims analysis was used to assess the costs associated with asthma care at United Health Care.¹⁶ This analysis examined the direct costs of care for 25,000 members identified with asthma. Costs were reported in terms of actual dollars to the health plan and included provider payment, provider withhold, facility payment, pharmacist dispensing fee, drug ingredient costs, and patient copayments and/or deductible expenses. In 1993 dollars, the average per-member annual cost was \$467. The 2 largest areas of claims were for medications (38%) and inpatient expenses (32%).

Using US population data and health care survey data, Weiss et al²⁸ estimated the costs of treating patients with asthma in 1994. Using data from 14.2 million individuals with asthma, these investigators calculated direct medical expenses to be \$6107.6 million. The estimated cost of treatment per patient with asthma in 1994 was \$430. Pharmaceuticals were estimated to account for 40% of this cost; and inpatient expenses, hospital, and physician services comprised 31%. These 2 studies present confirmatory conclusions and serve to validate both methodologies. Fig 5 offers a comparative look at these 2 reports.

IMPACT OF PHARMACOECONOMICS RESEARCH

Pharmacoeconomics is a relatively new area of research but one that has attracted a great deal of attention over the past several years. Pharmacoeconomic studies have been important for improving the ability to generalize conclusions from randomized clinical trials to the broader patient population. These investigations have also been of value in shedding more light on questions that cannot be answered in short-term, randomized clinical trials, such as the effects of therapy on the risk for hospitalization and the risk of death. Such studies provide a better understanding of the costs or charges associated with asthma therapy and can confirm or negate information based on cost modeling.

A considerable amount of research that includes retrospective claims analysis of multiple disease states has now been published. These studies have frequently confirmed the results of previous randomized clinical trials and have added to the robustness of the conclusion by confirming findings in clinical practice. The US Food and Drug Administration has begun to provide guidance regarding the use of pharmacoeconomic analysis, as reflected in section 114 of the 1997 Food and Drug

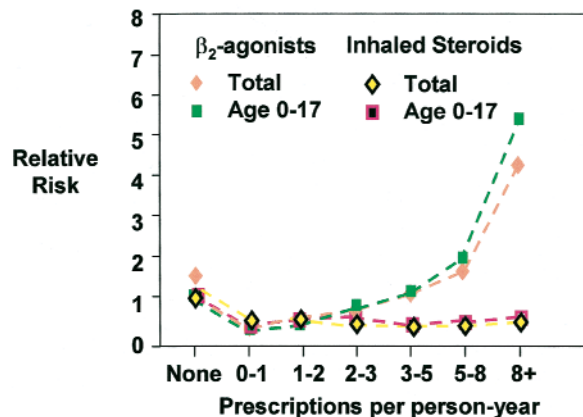


FIG 4. Inhaled corticosteroids help prevent asthma-related hospitalization. (Data from Donahue et al.¹⁸)

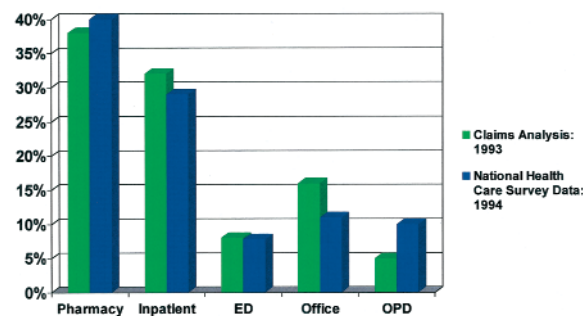


FIG 5. Annual cost of pharmacy and medical claims for asthma. ED, Emergency department; OPD, outpatient department. (Data from Stempel et al.²⁶ and Weiss et al.²⁸)

Administration Modernization Act.⁴⁰ This section states that the information must be based on “competent and reliable scientific evidence” that is related to the approved indication of the medication. Significant debate persists over the regulations pertaining to these economic data.⁴¹ Pharmacoeconomic investigations should maintain the same standards as randomized clinical trials. Observational claims studies need to address important clinical issues, have appropriate study populations, incorporate explicit inclusion and exclusion criteria, have appropriate effect size, and be powered to address the hypothesis. Although pharmaceutical companies frequently sponsor these studies, third-party involvement is necessary to ensure integrity of the data.

Pharmacoeconomic studies are important affirmations and enhancements of the evidence base that is used in therapeutic decision making. These studies are now part of the science of decision making. As in the case of any clinical report, the methodology needs to be validated and statistical analysis must be used to confirm clinically meaningful differences. The greatest strength of these reports emerges when different study designs yield confirmatory conclusions.

CONCLUSIONS

Attention to the relative interests of patients, providers, insurers, and employers can contribute to the goal of achieving value in the management of asthma. Clinical decision making should be based on these concerns, coupled with careful consideration of objective data from randomized clinical trials and observational analyses. These data should come from investigations that have been subjected to appropriate statistical analyses and that have proven robustness and internal consistency. Economic modeling can be used to extrapolate the results of trials and determine the costs associated with various therapies and outcomes. Consistent findings in these diverse forms of analysis, when confirmatory, should contribute to an improved process of care, the selection of cost-effective interventions, and the practice of evidence-based medicine.

REFERENCES

- Preventative Services Task Force. Guide to clinical preventative services: report of the U.S. Preventative Services Task Force. 2nd ed. Baltimore (MD): Williams & Wilkins; 1996.
- Briss PA, Zaza S, Pappaioanou M, Fielding J, Wright-De Aguerre L, Truman BI, et al. Developing an evidence-based guide to community preventative services methods. *Am J Prev Med* 2000;18:35-43.
- Mason J. The generalizability of pharmacoeconomic studies. *Pharmacoeconomics* 1997;11:503-14.
- Drummond MF, Richardson S, O'Brien BJ, Levine M, Heyland D. Users' guide to the medical literature XIII. How to use an article on economic analysis. *JAMA* 1997;277:1552-7.
- Marick C. Proponents gather to discuss practicing evidence-based medicine. *JAMA* 1997;278:531-2.
- Drummond M. Introduction: the rationale for guidelines. *Drug Info J* 1996;30:491-3.
- Sackett DL, Richardson WS, Rosenberg W, Haynes RB. Evidence-based medicine: how to practice and teach EBM. New York: Churchill Livingstone; 1997.
- Benson K, Hartz AJ. A comparison of observational studies and randomized controlled trials. *N Engl J Med* 2000;342:1887-92.
- Concato J, Shah N, Horowitz RI. Randomized, controlled trials, observational studies, and the hierarchy of research designs. *N Engl J Med* 2000;342:1878-86.
- Spitzer WO, Suissa S, Ernst P, Horwitz RI, Habbick B, Cockcroft D, et al. The use of beta-agonists and the risk of death and near death from asthma. *N Engl J Med* 1992;326:501-6.
- Suissa S, Ernst P, Boivin J-F, Horwitz RI, Habbick B, Cockcroft D, et al. A cohort analysis of excess mortality in asthma and the use of inhaled beta-agonists. *Am J Respir Crit Care Med* 1994;149:604-10.
- Ernst P, Spitzer WO, Suissa S, Cockcroft D, Habbick B, Horwitz RI, et al. Risk of fatal and near-fatal asthma in relation to inhaled corticosteroid use. *JAMA* 1992;268:3462-3.
- Suissa S, Blais L, Ernst P. Patterns of increasing beta-agonist use and the risk of fatal or near-fatal asthma. *Eur Respir J* 1994;7:162-9.
- Guidelines for the diagnosis and management of asthma. Bethesda (MD): US Department of Health and Human Services, National Institutes of Health; 1997. NIH Publication No. 97-4051A.
- Genduso LA, Kotsanos JG. Review of health economic guidelines in the form of regulations, principles, policies, and positions. *Drug Info J* 1996;30:1003-16.
- Fuhlbrigge AL, Kitch BT, Paltiel AD, Kuntz KM, Neumann PJ, Dockery DW, et al. FEV₁ is associated with the risk of asthma attacks in a pediatric population. *J Allergy Clin Immunol* 2001;107:61-7.
- Castle W, Fuller R, Hall J, Palmer J. Serevent nationwide surveillance study: comparison of salmeterol with salbutamol in asthmatic patients who require regular bronchodilator treatment. *BMJ* 1993;306:1034-7.
- Donahue J, Weiss S, Livingston J, Goetsch MA, Breininger D, Platt R. Inhaled steroids and the risk of hospitalization for asthma. *JAMA* 1997;277:887-91.
- Del Mar C, Glasziou P, Hayem M. Are antibiotics indicated as initial treatment for children with acute otitis media? A meta-analysis. *BMJ* 1997;314:1526-9.
- Peden DB, Berger WE, Noonan MJ, Thomas MR, Hendricks VL, Hamedani AG, et al. Inhaled fluticasone propionate delivered by means of two different multidose powder inhalers is effective and safe in a large pediatric population with persistent asthma. *J Allergy Clin Immunol* 1998;102:32-8.
- Knorr B, Matz J, Bernstein JA, Nguyen H, Seidenberg BC, Reiss TF, et al. Montelukast for chronic asthma in 6- to 14-year-old children. *JAMA* 1998;279:1181-6.
- Sueta C, Chowdhury M, Boccuzzi SJ, Smith SC, Alexander CM, Londhe A, et al. Analysis of the degree of undertreatment of hyperlipidemia and congestive heart failure secondary to coronary artery disease. *Am J Cardiol* 1999;83:1303-7.
- Hu XH, Markson LE, Lipton RB, Stewart WF, Berger ML. Burden of migraine in the United States: disability and economic costs. *Arch Intern Med* 1999;159:813-8.
- Goldfarb SD, Duncan BS, Dans PE, Sloan AS. HMO direct costs and health care resources use after implementation of a monthly limit on sumatriptan. *Am J Health System Pharm* 1999;56:2206-10.
- Hylan TR, Crown WH, Meneades L, Heiligenstein JH, Melfi CA, Croghan TW, et al. Tricyclic antidepressants and selective serotonin reuptake inhibitors antidepressant selection and health care costs in the naturalistic setting: a multivariate analysis. *J Affect Disord* 1998;47:71-9.
- Stempel DA, Hedblom EC, Durcanin-Robbins JF, Sturm LL. Pharmacy and medical claims database documents cost centers for 1993 annual asthma expenditures. *Arch Fam Med* 1996;5:36-40.
- Buchner DA, Carlson AM, Stempel DA. Patterns of anti-inflammatory therapy in the post guidelines era: a retrospective claims analysis of managed health care members. *Am J Managed Care* 1997;3:87-93.
- Weiss KB, Sullivan SD, Lyttle CS. Trends in the cost of illness in the United States, 1985-1994. *J Allergy Clin Immunol* 2000;106:493-9.
- Suissa S, Ernst P, Benayoun S, Baltzan M, Cai B. Low-dose inhaled corticosteroids and the prevention of death from asthma. *N Engl J Med* 2000;343:332-6.
- Goldman M, Rachmiel M, Gendler L, Katz Y. Decrease in asthma mortality rate in Israel from 1991-1995: is it related to increased use of inhaled corticosteroids? *J Allergy Clin Immunol* 2000;105:71-4.
- Sly RM. Changing asthma mortality and sales of inhaled bronchodilators and anti-asthma drugs. *Ann Allergy* 1994;73:439-43.
- Centers for Disease Control and Prevention. Forecasted state-specific estimates of self-reported asthma prevalence—United States, 1998. *MMWR Morbid Mortal Wkly Rep* 1998;47:1002-25.
- Wennergren G, Kristjánsson S, Stannegård IL. Decrease in hospitalizations for treatment of childhood asthma with increased use of anti-inflammatory treatment, despite an increase in the prevalence of asthma. *J Allergy Clin Immunol* 1996;97:742-8.
- Gerdtham UG, Hertzman P, Jonsson B, Boman G. Impact of inhaled corticosteroids on acute asthma hospitalization in Sweden 1978 to 1991. *Med Care* 1996;34:1188-98.
- Childhood Asthma Management Program Research Group. Long-term effects of budesonide or nedocromil in children with asthma. *N Engl J Med* 2000;343:1054-63.
- Lozano P, Fishman P, VonKorff M, Hecht J. Health care utilization and cost among children with asthma who were enrolled in a health maintenance organization. *Pediatrics* 1997;99:757-64.
- Lozano P, Sullivan SD, Smith DH, Weiss KB. The economic burden of asthma in US children: estimates from the national medical expenditure survey. *J Allergy Clin Immunol* 1999;104:957-63.
- Stempel DA, Durcannin-Robbins JF, Hedblom EC, Woolf R, Sturm LL, Stempel AB. Drug utilization evaluation identifies costs associated with high use of beta-agonists. *Ann Allergy Asthma Immunol* 1996;76:153-8.
- Legerre AP, Christian-Herman J, O'Connor RD, Hasan MM, Evan R, Leung K-M. Compliance with national asthma guidelines and specialty care. *Arch Intern Med* 1998;158:457-64.
- Food and Drug Administration Modernization Act of 1997, Pub. L. No. 105-115 (Nov 21, 1997).
- Neumann PJ, Claxton K, Weinstein MC. The FDA's regulation of health economic information. *Health Affairs* 2000;19:129-37.