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JOURNAL OF MANAGED CARE PHARMACY®

Pharmacoeconomics and Outcomes Research **EVALUATING THE STUDIES**

Brenda R. Motheral, R.Ph., M.B.A., Ph.D.

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Supplement

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Pharmacoeconomics and Outcomes Research:

EVALUATING THE STUDIES

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JMCP is dedicated to providing managed care pharmacists, associates, and students with the tools to excel in their daily practices by focusing on:

Policy: Providing a forum for in-depth discussion of issues of topical and long-term importance.

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Research: Publishing research that increases the quality of research standards used in managed care pharmacy practice and helps apply that research to improve the practice of managed care pharmacy.

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About Supplements

The *Journal of Managed Care Pharmacy* (JMCP) is pleased to present this supplement entitled, "Pharmacoeconomics and Outcomes Research: Evaluating the Studies." JMCP educational supplements are specialized papers that deal with topics and issues related to managed care pharmacy. The purposes of supplements are to provide educational value to the reader, to exchange information, and to present focused content.

Supplements are published as a separate issue of the *Journal* or as a second part of a regular issue. Topics appropriate for supplements are solicited by JMCP's Supplement Review Committee. The committee reviews supplement proposals, determining which will be published in an upcoming year. Once submitted, the supplements are subjected to the same rigorous peer review as the *Journal*.

This educational supplement describes how managed care pharmacists can and should use pharmacoeconomics and outcomes research in the

design and management of pharmacy benefits. The ability to critically evaluate data from a total health perspective is becoming increasingly important for managed care pharmacists. As the authors note, "In this decade, pharmacy benefit managers and managed care plans have moved from simply processing claims to overseeing disease management programs and designing complex pharmacy benefits. The plans they design influence not only how medication is prescribed, but also how medicine is practiced. Managed care pharmacists who can critically analyze pharmacoeconomics studies will play an important role within these organizations."

This material was originally presented in a workshop in May 1999, also sponsored by U.S. Pharmaceuticals, Pfizer, Inc. The University of Kentucky College of Pharmacy provides continuing education credit for this supplement (see p. 16).

Craig S. Stern
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Pharmacoeconomics and Outcomes Research: Evaluating the Studies

by Brenda R. Motheral,
Emily R. Cox, and Charles E. Daniels

After reading this article, pharmacists will be better able to:

- Define and describe pharmacoeconomics and outcomes research;
- Identify the differences among cost-effectiveness, cost-utility, cost-benefit, and cost-minimization analyses;
- Compare and contrast current approaches to pharmacoeconomics and outcomes research: randomized controlled trials, randomized naturalistic trials, retrospective studies and modeling;
- Make decisions that affect the management of pharmacy benefits using the results of well-designed pharmacoeconomics and outcomes studies; and

- Prepare for the development and assessment of pharmacoeconomics and outcomes studies within their organizations.

The University of Kentucky College of Pharmacy provided continuing pharmacy education credit for an all-day workshop, Pharmacoeconomics and Outcomes Research: Evaluating the Studies, at the Marriott at Glenpointe, May 12, 1999, in Teaneck, NJ. The workshop attracted pharmacists from managed care organizations, including health plans and pharmacy benefits management companies. Following morning presentations, attendees and faculty participated in afternoon breakout sessions, during which attendees had an opportunity to apply what they had learned by critically analyzing three published studies.

Brenda R. Motheral, R.Ph., M.B.A., Ph.D., chairperson of the workshop, is an assistant professor in the Department of Pharmacy Practice and Science, University of Arizona College of Pharmacy.

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Introduction

Double-digit increases in drug expenditures have occurred annually in the United States since 1995. From 1996 to 1997, drug costs increased 16.1%—a growth rate fueled by changes in the therapeutic mix and by increases in drug utilization and prices.¹ At least eight classes of drugs have experienced double-digit increases in the per-member-per-year cost. In 1996, some of the largest increases were attributed to migraine products (38.7%), antihistamines (38.5%), and diabetes products (37.7%) (see Table 1).¹ Interestingly, price increases accounted for a small percentage of the total increase in costs.¹ Double-digit increases in expenditures are expected to continue as biotechnology and computer-assisted research bring more drugs to market, the Food and Drug Administration's fast-track program allows drugs to enter the market faster, and direct-to-consumer advertising increases the demand for drug therapy.¹

To manage these cost increases, pharmacy benefit design and pharmacoeconomics can be used in tandem. However, the actual use of pharmacoeconomics data in pharmacy benefit design is uncommon. One of the thought leaders in pharmacoeconomics, Bryan Luce, Ph.D., chief executive officer, Medtap International, believes that "no knowledgeable observer would argue that pharmacoeconomics has come close to reaching its potential as a decision-assisting technique within managed care."²

Instead, the "silo" approach to decision making, which considers drug costs in isolation from other health care services, is not uncommon. Pharmacoeconomics attempts to evaluate the impact of drug utilization on total medical costs. For example, a pharmacoeconomics study could assess whether a drug compliance program reduces overall medical costs for a plan, even though it increases drug costs.

From 1990 to 1997, a virtual explosion in pharmacoeconomics research occurred. The authors' search on MEDLINE under the MeSH term "cost-benefit analysis" found 688 studies published in 1990 compared with 1,942 articles in 1997—an increase of 180%. The clinical areas of greatest interest for economics evaluations during this time period were circulatory (19%), neoplasms (16%) and infectious disease (13%) (see Figure 1).³

TABLE 1

1996–1997 PMPY Cost
Increases for Selected Classes¹

Gastrointestinals	15.5%
Antihyperlipidemics	30.0%
Antidepressants	22.8%
Antidiabetics	37.7%
Antihistamines	38.5%
Estrogens	20.0%
Antivirals	29.3%
Migraine products	38.7%

Several related factors explain the dramatic increase in pharmacoeconomics research. An increasing number of alternative therapies has created more competition in the pharmaceutical industry. With the growth of managed care, decision makers strive to allocate dollars more efficiently to provide health care services. Simultaneously, rising health care costs have created a greater need to evaluate products and programs to determine if society is receiving the greatest benefit for its health care expenditures.

In this decade, pharmacy benefit managers and managed care plans have moved from simply processing claims to overseeing disease management programs and designing complex pharmacy benefits. The plans they design influence not only how medication is prescribed, but also how medicine is practiced. Managed care pharmacists who can critically analyze pharmacoeconomics studies will play an important role within these organizations.

Principles of Pharmacoeconomics Research

Pharmacoeconomics and **outcomes research** are terms that are often used interchangeably, but they have distinct meanings. **Outcomes research**, which assesses the effects of programs, policies, and medical interventions on the health status of the patient, focuses on three major types of outcomes: clinical, humanistic and economic. Examples of clinical outcomes include stroke, heart attack or epileptic seizure. Humanistic outcomes, a relatively new consideration within the medical arena, include quality of life (QOL) and patient satisfaction. Examples of economic outcomes include cost per year of life saved and cost per symptom-free day.

Pharmacoeconomics, which falls under the heading of economic outcomes, identifies, measures, and compares the costs and consequences of the use of pharmaceutical products and services. Pharmacoeconomics research is based on fundamental economic theory—measuring the efficiency of production by comparing the inputs needed to produce a unit of output. For example, in manufacturing televisions certain input costs (per-

FIGURE 1

Clinical Areas of Study³

Adapted from Pritchard.³
FIGURE 2

Economic Evaluation

The comparative analysis of alternative courses of action in terms of both their costs and consequences

sonnel, technology, overhead) are associated with each unit of output (i.e., a television). The same principle can be applied to health care (see Figure 2) in which the inputs include not only pharmaceuticals, but also physician and nursing time, laboratory work, and other hospital services. The outputs are health and economic consequences. Health consequences may include changes in life expectancy, clinical outcomes, and/or QOL. Outputs may also be measured as savings in health resources that result from changes in health consequences. For example, the use of cholesterol-lowering agents may prevent strokes, which would in turn produce savings in dollars is due to reductions in hospitalizations.

There are four major types of pharmacoeconomics analyses: cost-effectiveness, cost-utility, cost-benefit and cost-minimization. In each type of analysis, economic inputs are measured in dollars; however, the measurement of outcomes differs. More recently, a fifth type of pharmacoeconomics analysis, cost-consequence analysis (CCA), has been proposed. With CCA, multiple costs and outcomes are calculated but are not aggregated into cost-effectiveness or cost-benefit ratios. It is argued that CCA is more transparent and easily understood and that the decision maker can select the costs and outcomes considered relevant.

FIGURE 3

Cost-Effectiveness Plane

FIGURE 4

Presenting Results: CEA

$$\text{Drug A} = \frac{\$3,194}{45.6} = \$70/\text{Successful treatment}$$

$$\text{Drug B} = \frac{\$2,617}{42.9} = \$61/\text{Successful treatment}$$

$$\text{Incremental CE} = \frac{\$3,194 - \$2,617}{45.6 - 42.9} = \frac{\$214}{2.7} = \$79/\text{Additional successful case}$$

Interpretation: it costs an additional \$214 to gain one additional successful case with drug A.

Efficacy Versus Effectiveness

An important distinction exists between efficacy and effectiveness. **Efficacy analysis** asks the question, "Can this medication work?" The answer usually is established in clinical trials. **Effectiveness analysis** addresses the question, "Does this medication work in the 'real world'?" A similar distinction is sometimes made in the pharmacoeconomics literature. A study that examined economic outcomes within a clinical trial may be considered a *cost-efficacy* study. A study conducted in a more routine clinical care situation would be considered *cost-effectiveness*.

Pharmacoeconomics studies are particularly useful for therapeutic categories with several alternatives, such as cardiovascular products (see Figure 3). Assume that drug A enjoys market exclusivity. An alternative product is launched. If the new product is more effective and less costly than drug A (lower right quadrant of grid), the new drug would dominate drug A in the marketplace. However, if the new drug is more costly and less effective than drug A (upper left quadrant), drug A would dominate. In those situations where the new product is either more costly and more effective or less costly and less effective, a pharmacoeconomics evaluation would be warranted.

Cost-Effectiveness Analysis

Cost-effectiveness analysis is a form of economic evaluation intended to identify, examine and compare the relevant costs and consequences of competing drug regimens and interventions. In cost-effectiveness analysis, the consequences evaluated are clinical outcomes. Results are expressed as cost per natural unit of effectiveness, such as cost per case averted or cost per successful treatment. Because outcomes are expressed in natural units of effectiveness, and most decision makers are familiar with such measures, cost-effectiveness analysis is the most frequently used method of pharmacoeconomics analysis.

When a study finds a medication is cost-effective, it means that the medication is cost effective relative to one or more com-

peting alternative therapies. If we define effectiveness in this example as successful treatment, we can see that drug A costs \$3,194 and produces 45.6 successfully treated cases, whereas drug B costs \$2,617 and produces 42.9 successfully treated cases. The average cost-effectiveness would be \$70 per successful treatment for drug A and \$61 for drug B. A decision maker might decide to approve drug B for the formulary at a supposed savings of \$9 per patient.

However, an incremental analysis is required to provide a complete picture of relative cost-effectiveness. Such an analysis subtracts the cost of drug B from the cost of drug A, then divides by the successful cases from drug A minus the successful cases from drug B (see Figure 4). The incremental analysis demonstrates that an additional \$214 must be spent to gain one additional successfully treated case with drug A. The decision maker must then decide whether the additional cost of drug A is worth the additional gain in effectiveness.

Cost-Utility Analysis

Cost-utility analysis (CUA), an extension of cost-effectiveness analysis, is a method of adjusting for the *quality* of outcomes. Results often are expressed as cost per quality-adjusted life-year (QALY) gained. Outcomes are adjusted for quality by using "utility" values or weights. In this context, utility represents the preference expressed for a particular health state. Utility values range from 0 to 1, with 0 being death and 1 representing perfect health. Examples of health state utility values include: living with menopausal symptoms, with a utility value of 0.99; severe angina, with a utility value of 0.50; and hospital confinement, with a utility value of 0.33.

The following example examines the cost utility of three products—A, B, and C. The life-years gained with drug A is two years; with drug B, one year; and drug C, three years (see Table 2).

The utility values assigned to drugs A, B and C are 0.7, 0.8

TABLE 2 Example of Cost-Utility Analysis

Drug	A	B	C
Life-Years Gained	2	1	3
Utility Value	0.7	0.8	0.5
QALYs Gained	1.4	0.8	1.5

and 0.5, respectively. To calculate the QALYs for each drug, multiply the number of life-years gained by the utility value: drug A: $2 \times 0.7 = 1.4$ QALY; drug B: $1 \times 0.8 = 0.8$ QALY; and drug C: $3 \times 0.5 = 1.5$ QALY.

Although treatment with drug C results in three life-years gained per patient, the utility assigned is 0.5, which could be due to intolerable side effects. With drug B, one life-year is gained, but the utility, 0.8, is much higher, perhaps due to a superior side-effect profile. Based solely on life-years gained, drug C appears preferable to drug A and drug B. However, after adjusting the life-years gained for the quality of those years, drug C and drug A appear very similar.

The use of CUA is increasing. Focusing on life-years gained is appealing from a societal viewpoint because the concern is not whether, for example, cholesterol is reduced but whether life expectancy and QOL increase. CUA presents results in a common unit of analysis (cost per QALY), allowing researchers and decision makers to make comparisons across widely different therapeutic classes and health technologies. However, CUA also has limitations. Application in the managed care setting is limited because many decision makers are unfamiliar with this type of study, and the results are more applicable to a societal viewpoint.

Cost-Benefit Analysis

Unlike the other types of pharmacoeconomics evaluations, **cost-benefit analysis** measures consequences in dollars. The goal of cost-benefit analysis is often to achieve the highest return on investment of dollars. Cost-benefit analysis was defined by Prest and Turvey in 1955 as:

"A practical way of assessing the desirability of projects, where it is important to take a *long view* (looking at repercussions into the future) and a *wide view* (allowing for side-effects of many kinds on many persons, industries, regions, etc.) i.e., [cost-benefit analysis] implies the numeration and evaluation of all the relevant costs and benefits."⁴

Immunization programs are good examples to use in demonstrating cost-benefit analysis. When a child is immunized, the effect is described from the long view—the life expectancy of the

TABLE 3 Examples of the Types of Costs

Productivity/indirect costs

- Loss of worker productivity

Intangible costs

- Pain and suffering

Direct medical

- Medicine, physician visit, hospital, etc.

Direct non-medical

- Transportation, lodging, etc.

child. This type of analysis also evaluates products from the wide view—immunizing a child also protects all of the children with whom that child comes into contact.

One limitation of cost-benefit analysis lies in the difficulty of placing a dollar value on health. Even though this occurs in the judicial system in awarding punitive damages to the plaintiff for loss of life or suffering, placing a dollar value on lives saved or lost continues to be controversial in the health care system.

Cost-Minimization Analysis

The fourth method, **cost-minimization analysis**, compares the cost and consequences of two or more alternative therapies with equivalent outcomes. The applications of cost-minimization analysis might include comparing a generic with a brand name drug or comparing the administration of a drug in different settings (e.g., inpatient versus outpatient). Cost minimization has limited applicability because few scenarios exist in which truly equal effectiveness can be established.

Identifying, Measuring, and Valuing Costs

Perspective

Determining the perspective from which the analysis will be conducted is an important component of pharmacoeconomics studies. Will the analysis be conducted from the perspective of the payor (e.g., managed care or the government), the patient, society or the institution? For example, a cost-benefit analysis of a vaccination program might be conducted from two perspectives—the payor's and society's.

Evidence from the literature highlights how different conclusions can be reached depending on the perspective taken.⁵ A cost-benefit analysis of varicella vaccine administration was not found to be cost beneficial from the payor's perspective; for every dollar spent, the benefit would have been less than \$1. But from society's perspective, the program showed a net benefit. Specifically, when indirect cost savings were included in the analysis, such as savings due to lost work days avoided by parents, \$5.40 of benefit was obtained for every dollar spent.

TABLE 4

Adjusting Costs for Differential in Timing—Discounting⁷**Why discount?**

■ Time preference for receiving money and time preference for receiving public goods—social discount rate

Drummond recommendations

■ Present costs in their undiscounted form, so others can investigate the implications of using different discount rates.

■ Undertake a base case analysis using the rates of 3% and 5%, currently recommended by analysts from the U.S. Public Health Service Panel on Cost-Effectiveness in Health and Medicine.

■ Undertake a sensitivity analysis, making sure to include 0%, 3%, and 5%.

■ In situations where the discount rate has a substantial impact on study results, alert decision makers to the importance of selecting a discount rate.

Identifying and Measuring Costs

Another important step in conducting pharmacoeconomics evaluations is identifying and measuring costs. Customarily, pharmacoeconomics evaluations measure four basic types of costs: direct medical costs, direct nonmedical costs, indirect costs and intangible costs (see Table 3, p.7).

Direct medical costs are resources spent on medical services or products, including physician visits, emergency department visits, medication, hospitalizations, and nursing or pharmacy staff time. **Direct nonmedical costs** can include transportation for medical treatment, boarding for family during treatment, and other expenses related to the provision of medical care but incurred outside the medical sector.

Although controversial, **indirect costs** are included in many studies. Loss of productivity due to temporary illness or disability or to permanent loss of employment are examples of indirect costs. These costs are often measured as the wage rate of an individual multiplied by hours of work lost. In studies focusing on migraine and other chronic conditions, indirect costs are an important consideration, particularly from the employer's perspective. One study found that patients lost an average of 2.2 days of work per month when suffering from migraine. The costs associated with these lost days can be significant to employers.⁶

Intangible costs are those costs associated with real or perceived pain and suffering caused by the illness or resulting from

treatment. Although difficult to measure, the cost of pain and suffering is assessed in the courts daily. However, in health care, these costs are difficult to measure and quantify, and thus usually omitted from pharmacoeconomics evaluations.

Measuring Units

Measuring direct costs is essentially counting units—number of physician visits, number of days missed from work, number of doses, etc., and multiplying by the dollar value of that unit. To measure productivity losses, patient self-report data can be used, although this technique is somewhat controversial due to concerns about recall accuracy, among other things. For example, in the migraine study mentioned earlier, patient self-reports were used to measure hours of work missed and to assess how productive patients felt at work when suffering from a migraine. But were the missed days reported really due to migraine headaches? Such questions pose credibility issues for researchers when using recall data.

Valuing Costs

Once resources have been identified and measured, they must be valued or assigned a unit cost. Opportunity cost is an important concept in valuing resources and is defined as the amount an input could earn in its best alternative use. Opportunity costs are difficult to assess, so the market price of a good or service is typically used. This method assumes a competitive market exists and uses the market price as a proxy for valuing medical resources. Because the health care market falls short of a competitive market in many ways, charges or reimbursement rates often serve as proxies in valuing pharmaceuticals and other medical resources. However, this method poses certain problems.

Once costs have been valued, they then should be adjusted for differences in timing by discounting future costs to a present value. The importance of discounting relates to our time preference for receiving money. We would rather receive benefits today than a year from now. Conversely, we would prefer to incur costs later rather than in the immediate future. The same time preference for receiving money exists in industries such as health care. Drummond has established criteria for which discount rates should be used to adjust costs for differences in timing (see Table 4).⁷

The importance of discounting is highlighted by the following example (see Table 5).⁷ In health care, particularly when treating a patient with a chronic disease, up-front costs may lead to benefits that are not observed until five or 10 years in the future. With benefits of \$95,000 and costs of \$90,000, a \$5,000 net benefit is observed when no discounting is conducted. Given a positive net benefit, a decision maker would probably decide to implement such a program. However, if the future benefits are discounted—even at a low rate of 3%—the positive net benefit is no longer observed.⁸

TABLE 5**The Importance of Discounting⁷****HYPOTHETICAL EXAMPLE OF DISCOUNTED VERSUS UNDISCOUNTED COSTS AND BENEFITS***

	Year					Sum (\$) at Discount Rate	
	0	1	2	5	10	0%	3%
Benefits (\$)	0	0	0	70,000	25,000	95,000	78,985
Costs (\$)	50,000	10,000	10,000	20,000	0	90,000	86,387

*Assume that no costs or benefits are realized in any year other than those presented.

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Study Designs

Four major types of study designs are used in pharmacoeconomics evaluations: clinical trials, naturalistic (or large simple) trials, models, and retrospective analyses. No study design is inherently superior to another for conducting pharmacoeconomics research. The approaches are complementary, and each has distinct advantages and disadvantages that should be considered.

Clinical Trials

The most familiar type of study to clinicians is probably the clinical trial. It typically has strong internal validity but can be of questionable relevance in the real world. Clinical trials are characterized by random assignment of subjects to study groups, a control group (often a placebo), and blinding of subjects and investigators. Clinical trials are the gold standard for demonstrating efficacy of drug therapies.

Two major advantages exist in conducting a pharmacoeconomics study using a clinical trial approach. First, the pharmacoeconomics study often can be piggybacked onto an existing clinical trial. Second, subjects are randomized to treatments, which enhances the internal validity of clinical trials (the confidence that the observed effect is due to the treatment and not some other factor). A major disadvantage is that the results are often of questionable relevance to routine practice because such controlled conditions are rarely found in clinical practice.

More specifically, clinical trials may lack an appropriate comparator. In addition, surrogate outcome markers (e.g., blood pressure) often are used to make results readily available in a timely manner. This is particularly problematic if the surrogate marker and the outcome of interest are not closely linked, which may be the case with ulcer symptoms and endoscopy-based ulcer rates.

Another limitation inherent in clinical trials is that patient compliance typically is higher than in routine care. Populations in a clinical trial are often described as "professional patients." In addition, because these patients are monitored closely, have frequent contact with providers, and receive prompting from

investigators to take their medication, patients may be more compliant with the medication regimen than they would be outside a clinical trial.

Furthermore, because patient retention is an unstated goal of clinical trials, adverse effects are managed intensively, reducing the likelihood that patients will discontinue taking medication. An example of how compliance in clinical trials can be misleading appeared in recent literature. Investigators included only clinical trial data in a meta-analysis of efficacy rates of tricyclic versus selective serotonin reuptake inhibitor (SSRI) antidepressants and found no significant difference. Since then, a number of studies have demonstrated that in more routine clinical settings, substantial differences exist between the compliance rates with tricyclics and with SSRIs, particularly in the first two months of therapy, and that this compliance can affect success rates.⁹

Naturalistic Trials

The alternative to the clinical trial is the naturalistic, or large simple, trial. Its goal is to eliminate most of the disadvantages of a clinical trial while retaining randomization and a control group. Typically, naturalistic trials are conducted in the Phase IV Postmarketing stage. Settings and providers are more representative of routine clinical practice than those in a clinical trial. Patients and providers are not blinded to the treatment received. Inclusion and exclusion criteria are less extensive. In addition, the drug being evaluated is compared with standard care rather than a placebo. The antidepressant trial discussed previously is an example of a naturalistic trial.⁹

The primary advantage of naturalistic trials is that they more accurately reflect routine clinical care. However, naturalistic trials typically can be even more expensive than clinical trials and, in many instances, are not a practical alternative. Furthermore, a naturalistic trial may not be as representative as the investigators claim. Decision makers should read the methodology carefully and decide whether the trial accurately mirrors clinical practice.

TABLE 6

Models

When to use?

- Clinical trial does not capture economic data
- Measures clinical intermediaries only
- Compares treatment with placebo
- Want to translate clinical trial data into that which better reflects routine clinical care

Models

Models are commonly used in pharmacoeconomics research and comprise an increasing portion of published studies. A model is defined as a systematic approach to decision making under conditions of uncertainty. A model is used when direct observation is not available and prospective data cannot be collected. A model does not banish uncertainty but makes the uncertainty explicit by including junctures at which a decision must be made or the likelihood of an outcome predicted. In pharmacoeconomics, investigators use two major types of models—decision-analytical and Markov. The latter are sophisticated and represent a minority of the models in the literature; decision-analytical models are used more often.

Figure 5 is an example of a decision-analytical model of ulcer pharmacotherapy. Each square box is called a **decision node**, where a choice is made about which treatment alternative to use. Two branches are shown here, but other branches could be added at this decision node, such as the dual-based or triple-based proton pump inhibitor regimens.

Once a triple therapy has been selected, the clinical course can take more than one direction. The circle on the model is

called a **chance node** or a probability node. At this juncture, a probability that the *Helicobacter pylori* bacteria will be eradicated can be assigned to one branch and a probability that it will not to the other. The assigned probabilities are based on the literature and should total 100%. The two branches at the next chance node represent the probability that the ulcer will recur and the probability that it will not. Even if the ulcer is eradicated, the probability exists that the patient will have a recurrence; this probability is much lower than if the ulcer had not been eradicated, but it exists nevertheless. Beyond those chance nodes—"ulcer" and "no ulcer recurrence"—a chance exists that an outpatient visit will occur, as well as a chance that the patient will be hospitalized.

The reader should then critically analyze a model to determine whether the model has been constructed as simply as possible, yet still represents clinical reality. The model shown here is reasonable because it captures several important elements in the course of treating a patient with an ulcer.

Table 6 details the situations in which models are useful. For example, if no pharmacoeconomics data were collected during a clinical trial but the investigators want to perform a pharmacoeconomics analysis, a model can be developed that incorporates the efficacy data from the clinical trial and cost data from other sources. If the clinical study has measured only intermediary or surrogate measures, the investigators can use a model to extrapolate those results to a lifetime.

Assume one clinical trial has compared drug X with placebo and another compared drug Y with placebo. The investigator later decides to conduct a head-to-head comparison of the two drugs. The results from the two clinical trials may be used to model the economic impact of selecting drug X versus drug Y. In addition, if the investigator has clinical trial data and wants to construct a model that more closely mirrors routine clinical care, data from medical claims databases and the literature can be used.

For example, to compare the cost of outpatient treatment of depression with tricyclics versus SSRIs, the investigator knows

FIGURE 5

Example of a Decision-Analytic Model

FIGURE 6

Types of Information in Claims Databases

from the literature that compliance is X for the SSRIs and Y for the tricyclics; the probabilities can be input into a model. The investigator might want to know other probabilities as well, such as the percentage of patients that will require a physician visit to manage side effects for each drug or the percentage who attempt suicide while taking each drug.

Like the other approaches, models have limitations. The structure and logic of a model may not reflect clinical practice. Is the comparator the most relevant alternative? For example, the model discussed previously compares an H_2 antagonist with triple therapy for ulcer treatment, but an H_2 antagonist is no longer the standard of care. Therefore, the model is of limited use.

Models sometimes are viewed as "black boxes." When a pharmaceutical company representative brings a laptop computer model comparing one of their products with a competitor's product, information about the derivation of probabilities and other estimates may not be clear. Fortunately, an increasing number of companies are making their models more transparent. In some cases, the user simply can push a button to find the source of the probability estimates and/or enter a different set of probabilities and view the changes that result in the model.

An additional limitation of models is the reliability of the probability estimates. For example, one model assumed that

95% of patients with ulcer symptoms will undergo endoscopy, which is not a reasonable assumption. Estimates of cost also need to be viewed critically.

Retrospective Analyses

The vast majority of retrospective analyses are based on information from claims databases (see Figure 6). Claims databases have several advantages. They reflect routine clinical care, are comprehensive and provide large sample sizes. The investigator can avoid some ethical concerns because randomization is not an issue in a retrospective analysis. Certain biases can be avoided—for example, patients and physicians probably will not change their behavior based on the expectation that an investigator will conduct a claims database study. In a retrospective analysis, the follow-up periods are longer than those found in most clinical trials. Typically, an investigator using a claims database can follow a sample population for one to two years. After that, the sample characteristics may change because people leave the plan. Finally, compared with clinical trials, studies of claims databases are relatively inexpensive, and the research can be done in a timely fashion.

Despite these advantages, retrospective analyses have some major limitations (see Table 7, p. 12). The biggest disadvantage is the problem of internal validity. If a study finds that drug A is associated with higher overall medical costs than drug B, one

TABLE 7

Claims Databases

Limitations

- Questionable internal validity
 - Channeling bias
- Diagnostic information
 - Undercoding, overcoding, coding changes
 - Patient identification, costs
- Missing information
 - Reimbursed services only, claim lag
- Multiple indications
- Data structure
 - Eligibility, capitation, family linkage
 - Lack of clinical and humanistic outcomes
- Representativeness
 - Plan design, demographic profile, practice patterns of MDs

TABLE 8Critical Assessment of
Economic Evaluations

- Well-defined question
- Description of competing alternatives
- Effectiveness established
- Relevant costs and consequences identified
- Costs and consequences measured accurately
- Costs and consequences valued credibly
- Costs and consequences adjusted for differential timing
- Sensitivity analysis performed
- Presentation and discussion of study results include all issues of concern to users

to use claims data to determine the cost-effectiveness of prescribing inhaled steroids to all patients with moderate-to-severe asthma. The pharmacist retrieves utilization and cost data for all asthma patients who consistently used inhaled steroids and all who took beta-agonists over one year. The data show that costs are significantly higher for patients taking inhaled steroids. Should the pharmacist conclude that steroids are not cost-effective? No, asthma patients who use inhaled steroids usually have more severe asthma than patients taking only beta-agonists. Unless the pharmacist can control for the severity of asthma, which probably cannot be done using a claims database, a retrospective analysis of this type will be inappropriate and potentially misleading.

The term for this methodologic problem is channeling bias—patients receive certain products for specific reasons. If the researcher cannot identify and control for this bias, inferring cause-and-effect relationships is inappropriate. Yet this is a common error in the pharmacoeconomics literature. Databases can easily be used to demonstrate correlations, but causation cannot be assumed.

Problems with diagnostic information and missing information are also disadvantages of using claims databases. For example, a diagnosis of depression may be undercoded for many reasons, such as the patient's or physician's fear that health insurance will be denied in the future. In addition, using a claims database to evaluate the impact of a drug with multiple indications is particularly difficult. For example, because beta-blockers are prescribed for patients with cardiovascular disease, migraine and other conditions, a diagnosis cannot be inferred solely from the fact that a patient has taken this type of medication.

Eligibility information also is critical. Only patients who were eligible to receive health insurance benefits during the entire study period should be included. Otherwise, it will be impossible to determine if a patient was not hospitalized because he or she did not go to the hospital or because the patient was ineligible for hospital coverage at that time.

Clinical outcomes may be limited when using claims databases, and humanistic outcomes are nonexistent in the databases. Although databases are typically more representative of practice than are clinical trials, plan design, demographic profile and practice patterns still may influence whether a claims database study is generalizable to other settings.

Evaluating Pharmacoeconomics Studies**Using a Checklist**

When analyzing a study, a checklist of important elements that each pharmacoeconomics study should include is a useful tool (see Table 8). The first item on the list is the study objective. Skim the abstract to determine whether the objective is clear and whether the research question is relevant. Does this study apply to an area of interest or an upcoming question? Is the approach used to research the question appropriate?

The author of a published study should state explicitly the alternative therapies being compared, even if the alternative is

cannot necessarily conclude that the use of drug A is causing the high costs, because the patients were not randomized to treatment arms.

Consider the following example: A pharmacist may be asked

FIGURE 7

Data Collection Schema

placebo or no treatment. Perspective is also a critical element because it affects how costs and consequences are measured. (Please see "Perspective," p. 7.) Few studies are conducted from the societal perspective. Rather, most current studies are conducted from the perspective of the payor.

In every pharmacoeconomics study, accurate measurement of costs is paramount. Costs and consequences should be identified clearly, measured accurately, and valued credibly, and they should be relevant to the study objective. Are the consequences truly outcomes measures, or are they surrogates? Surrogate markers include blood pressure and blood lipids for heart disease and CD4+ levels in patients testing positive for human immunodeficiency virus. Although these markers do not necessarily predict clinical outcomes, some investigators assume they do. The federal government currently is considering how surrogate markers can be used appropriately in the early stages of drug development and whether guidelines for selecting the proper surrogate markers for specific diseases are necessary.

As shown in the author's own checklist, time frame is another important consideration (see Table 9). Is the time frame practical? Can the research question be answered in the time allotted? For many investigations the time frame will be years, because only then can the investigators determine whether truly sustainable differences exist between the alternative treatments. However, if the study takes longer than two years, the investigators risk having patients leave the study (or the plan). These practical considerations partially account for the use of surrogate markers. Patients with a chronic disease often find it difficult to participate in a long-term study. The expense involved in following patients for extended periods of time can also be prohibitive.

The study population influences the generalizability of the results. The population in a study may vary so greatly from the population in clinical practice that the study becomes irrelevant.

The investigators should clearly define the disease state in question. In a retrospective study in which diagnoses are not always reliable, a precise definition of the criteria for inclusion

is especially important. The study location is important, as well. For example, if the study was conducted in a Veterans Affairs facility, the reader should determine if the population characteristics are different or the patients were managed differently from the reader's expected target population.

"Unresolved questions" is the final item on the checklist. What are the limitations of the study? Where does this study leave off, and what is the next set of research questions?

Analyzing A Pharmacoeconomics Study: A Case Example

A study by Testa and colleagues in the *Journal of the American Medical Association* can be used to demonstrate the process of critically analyzing a pharmacoeconomics study.¹⁰ The objective of the study was to examine the effects of short-term improved glycemic control on health care utilization and costs and QOL for patients with type 2 diabetes mellitus. This randomized, double-blind, placebo-controlled study involved 569 patients from 62 locations. A list of the outcomes measured is provided in Table 10. The outcomes measures for glycemic control were hemoglobin A_{1c} levels, fasting glucose and fasting insulin levels. Patients kept diaries to record days missed from work, days spent in bed and days at work with reduced productivity (restricted days).

After a three-week washout period, the patients were randomized to either a group on a standard diet with glipizide or a group on a standard diet with placebo for the next 12 weeks. Figure 7 illustrates the weeks at which clinical and laboratory tests were conducted and the weeks at which QOL was assessed.

The investigators presented the changes in QOL as a function of changes in hemoglobin A_{1c} levels. This analysis revealed a correlation between short-term changes in hemoglobin A_{1c} levels and changes in QOL. In the active drug group, mean changes from baseline in QOL were positive for the composite score and all domains—mental health, cognitive function, general perceived health and symptom distress. For the placebo

TABLE 9

Study Evaluation Checklist

Project objective

- Objectives clearly stated
- Question relevance
- Appropriate approach/method

Perspective

- Patient
- Physician
- Hospital
- Third-party payor
- Health care system
- Societal

Time frame

- How long will costs and benefits be measured?
- What are important milestones on the timeline?

Population

- Disease state
- Age/gender/etc.
- Location
- Setting

Outcomes measures

- What outcomes measures and endpoints have been selected?
- Are they true outcomes measures?
- Are surrogate measures used?

Costs

- What is included?
- How is it collected?
- Is it reliable?
- Is it accurate?

Unresolved questions

- Equivocal results
- General applicability
- Complementary studies

The checklist provides a framework for critically analyzing this study. The first element on the list is the study objective. Assessing the impact of glycemic control on QOL, health care utilization and costs is a relevant objective. This study was designed and conducted from the societal perspective; the data collected enabled the investigators to evaluate not only the effects of improved glycemic control on patients but also the effects on employers and society. This perspective, more than any of the others, permits the investigators to collect the widest range of data on costs. Because the objective addressed short-term control, the time frame for the study was reasonable. However, the ethics of denying treatment for 12 weeks to patients with type 2 diabetes mellitus might be viewed as questionable.

The study population does not appear to have any systematic bias. Therefore, results appear to be generalizable to other patients with similar pretreatment pathology. The outcomes measures were directly related to the study objective. However, the methods for measuring symptom distress and other QOL domains were not discussed in this paper but in a previous work. QOL as an outcomes measure remains controversial; often the data are considered "soft" in comparison to more traditional measures. Unfortunately, many investigators administer selected segments of QOL scales or, if they use an entire scale, will report data only for those segments in which results support the desired conclusion. In this study, the QOL domains assessed made sense in light of the study objective. In addition, the results in each domain (except mental health) corroborate each other, which is a positive finding.

The authors present economic data from a societal perspective using standard valuation methods for production losses. Health care use is reported for hospitalization, home nurse visits, general household assistance and ambulatory care visits. It is unclear why the authors reported an economic impact for the ambulatory visits only.

Upon first glance, because the study compared glipizide with a placebo, the relevance of the results to decision makers in managed care settings is questionable as health plans would not discourage patients with type 2 diabetes from using appropriate drug therapy to treat their diabetes. However, the study is important in that it documents, for the first time, that in addition to long-term benefits, there are short-term economic and QOL benefits of improved glycemic control.

A potential relevant implication for managed care plans is that diabetes disease management programs that aim to improve glycemic control through enhanced medication compliance may produce short-term economic savings (depending on the cost of the program) and QOL improvements, making them more likely to be adopted by employer groups and other payors. Obviously, moving from no drug therapy to drug therapy may not have the same effect as a program aimed at enhancing compliance, and this hypothesis would have to be empirically tested.

In addition, a critical question remains: Would we observe differences in economic and QOL outcomes if head-to-head comparisons were made of the various antidiabetic drugs?

TABLE 10Improved Glycemic Control¹⁰**Outcomes Measures**

■ Glycemic control	■ Work capacity
■ Symptoms	■ Health care use
■ QOL scales	■ Economic benefits

group, mean changes were negative for all domains except mental health. In this study, no details were provided about the scales used to assess QOL; a previous study was referenced. Selected measures of symptom distress revealed that patients in the active drug group had significantly less symptom distress than those in the placebo group. With respect to productivity losses, the data show that absenteeism, bed day, and restricted days were significantly fewer in the active group than in the placebo group.

Overall, this study adequately addresses most of the elements in the checklist. The study design was reasonable, given the objective. Measuring changes in QOL can be problematic because no standardized scale exists. Given that constraint, the investigators selected reasonable domains on which to focus this study.

■ Conclusions

Although a relatively new discipline, pharmacoeconomics offers pharmacists an important tool for assessing alternative therapies. The journals are publishing pharmacoeconomics studies in increasing numbers; not all are well-designed or useful. Therefore, pharmacists must be able to critically analyze these studies to determine which are the most relevant and to feel comfortable using pharmacoeconomics data as the basis for decisions about the wide range of questions that arise in the managed care environment.

REFERENCES

1. Teitelbaum F, Parker A, Martinez R. Express Scripts/Value Rx 1997. Drug Trend Report 1998; 45: 535-44.
2. Luce BR. Pharmacoeconomics and managed care: methodologic and policy issues. *Med Decis Making* 1998; 18(suppl): S4-S11.
3. Pritchard C. Trends in economic evaluation. Office of Health Economics. 1998 Apr. No. 36.
4. Prest AR, Turvey R. Cost-benefit analysis. A survey. *Economic J* 1955; 65: 155. Cited by: Brown CV, Jackson PM. *Public sector economics*. 4th ed. Oxford, UK: Blackwell Publishers, 1990.
5. Lieu TA, Cochi SL, Black SB, et al. Cost-effectiveness of a routine varicella vaccination program for US children. *JAMA* 1994; 271: 375-81.
6. Osterhaus JT, Gutterman DL, Placheika JR. Healthcare resource and lost labour costs of migraine headache in the US. *Pharmacoeconomics* 1992; 2: 67-76.
7. Drummond MF, O'Brien B, Stoddart GL, Torrance GW. *Methods for the economic evaluation of health care programmes*. 2nd ed. New York, NY: Oxford University Press, 1998.
8. Warner KE, Luce BR. *Cost-benefit and cost-effectiveness analysis in health care: principles, practice, and potential*. Ann Arbor, MI: Health Administration Press, 1982.
9. Simon GE, VonKorff M, Heiligenstein JH, et al. Initial antidepressant choice in primary care. Effectiveness and cost of fluoxetine vs. tricyclic antidepressants. *JAMA* 1996; 275: 1897-1902.
10. Testa MA, Simonson DC. Health economic benefits and quality of life during improved glycemic control in patients with type 2 diabetes mellitus. A randomized, controlled, double-blind trial. *JAMA* 1998; 280: 1490-96.

Posttest for Pharmacoeconomics and Outcomes Research: Evaluating the Studies

Please circle the correct answer.

1. The dramatic increase in pharmacoeconomics research can be attributed to:
 - a. increasing number of alternative therapies, creating more competition
 - b. managed care
 - c. rising health care costs
 - d. all of the above
2. _____ assesses the effects of programs, policies, and medical interventions on the health status of the patient.
 - a. pharmacoeconomics
 - b. cost utility
 - c. cost benefit
 - d. outcomes research
3. Quality of life (QOL) and patient satisfaction are examples of:
 - a. clinical outcomes
 - b. humanistic outcomes
 - c. economic outcomes
 - d. medical outcomes
4. In a pharmacoeconomics analysis, inputs are measured:
 - a. as changes in a life expectancy
 - b. as changes in a clinical variable
 - c. as changes in QOL
 - d. in dollars
5. _____ is a form of economic evaluation that compares the cost and consequences of two or more alternative therapies that have equivalent outcomes.
 - a. cost-minimization analysis
 - b. cost-utility analysis
 - c. cost-benefit analysis
 - d. cost-effectiveness analysis
6. In a pharmacoeconomics evaluation, costs related to the treatment or condition being evaluated, including physician visits, emergency department visits, doses of medication, hospitalization costs, and nursing or pharmacy staff time, are referred to as:
 - a. indirect
 - b. direct nonmedical
 - c. direct medical
 - d. intangible
7. Commonly used approaches in cost-effectiveness research are:
 - a. models
 - b. clinical trials
 - c. retrospective analyses
 - d. naturalistic trials
 - e. all of the above
8. The primary advantage of naturalistic trials is:
 - a. decreased internal validity
 - b. shorter follow-up periods
 - c. lower costs
 - d. more reflective of routine clinical care
9. In pharmacoeconomics, the two major types of models used are:
 - a. decision-analytical and naturalistic
 - b. decision-analytical and retrospective
 - c. decision-analytical and Markov
 - d. Markov and clinical
10. The biggest disadvantage of retrospective analyses using claims databases is:
 - a. the small number of patients
 - b. their weak internal validity
 - c. their lack of generalization
 - d. their cost

Answer the 10 questions above by circling the letter beside the one best answer. Then tear off or photocopy the CE test and the Request for Pharmacy Continuing Education Credit form and mail, using the self-addressed envelope enclosed with the supplement. For credit, forms must reach the University of Kentucky College of Pharmacy by January 31, 2001.

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