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THE ROLE OF PHARMACEUTICALS IN MENTAL HEALTH CARE OUTCOMES

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This chapter discusses the role of pharmaceutical outcome evaluations in mental health care. The first section discusses the importance of pharmaceutical outcome evaluations. The second section describes techniques used in economic evaluations of pharmaceuticals (i.e., pharmacoeconomic methods). The final section discusses how mental health care outcomes data may be used in practice.

WHY OUTCOMES?

The idea that outcomes associated with the provision of health care are important is not new. In the 1960s Avedis Donabedian (1) presented health outcomes as changes in health status that were attributable to antecedent health care. For many years, however, evaluations of health care focused on the structure or process of care. As health care moves into the new millennium, financing of health care is evolving from individual providers being solely responsible for patient outcomes to an environment where payers, institutions, and providers are being held accountable for quality and cost of care. As financing of health care has moved to a more centralized locus of control, evaluation of outcomes has become more feasible and desirable. In a book titled *Who Shall Live*, Victor Fuchs (2) discussed three factors that can be balanced in our health care system: costs, quality, and access. Over time the pendulum swings from one to another of these dimensions. If costs containment goes too far, then quality or access may suffer. Likewise, it is possible in today's technologically driven environment to provide a level of quality that is affordable to only a small segment of our society. In an environment of limited resources and high demand for health care, a quality, cost, access trade-off is essential. The issue then becomes how do we define and measure quality so that these trade-offs can be made in pursuit of efficiency and/or equity. Many believe that quality should be defined and measured in terms of patient outcomes.

In simple terms, outcomes are the "end results." Improvement in outcomes is a primary reason for medical intervention, including use of pharmacologic therapies. There is a belief that the use of pharmaceuticals will have a positive impact on the "end results" of patient care. Historically, this belief is self-evident in the treatment of mental health disorders with the use of drugs to treat psychoses and depression—conditions for which treatment was revolutionized by pharmaceuticals (3,4). However, with newer, more costly pharmaceuticals, such as selective serotonin reuptake inhibitors (SSRIs) and atypical antipsychotic agents, many payers and health professionals have questioned the value that is received for the resources expended on these agents. Consequently, numerous studies have been directed at these issues. For example, SSRIs have been compared to tricyclic antidepressants (TCAs) for the treatment of depression (5–8). Payers are interested not only in the most efficacious antidepressant but also in which agent should be chosen as first- or second-line therapy, the appropriate course (length) of therapy, and whether initial therapy should be augmented with an additional agent (9–12). Given the wide variations in care and the possibility that alternative treatments could lead to similar outcomes, particularly under the less than ideal conditions of "usual care" practice, health care payers are concerned about which treatments regimens lead to the most efficient outcome. In a resource-constrained environment, it is both reasonable and responsible to ask this ques-

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tion: Would the resources expended for one alternative be more efficient if devoted to another alternative? One useful way to address this question is with data on patient and cost outcomes.

There is an inextricable but sometimes complex relationship between quality of care and outcomes. Outcomes data are one way of evaluating quality. It is noteworthy, however, that establishing quality "thresholds" requires a value judgment. What is acceptable quality to one person may be unacceptable to another at any given level of cost. Outcomes data cannot provide answers to questions that require fundamental value judgments. On a macro level, an analysis using measures of quality and cost will not define the percentage of gross domestic product (GDP) that a nation should spend to achieve a certain level of quality in health care, but rather will provide tools and information to assist decision makers in efficiently allocating scarce resources. On a micro level, there is no specific quality of life score on an instrument that indicates if or when a drug product should be reimbursed. There is no single clinical measure that indicates that a patient is in perfect health. All outcomes data require the interpretation and evaluation of a medical decision maker. Outcomes data provide one more, albeit in many cases relevant, piece of information on which to base decisions.

In the previous discussion, outcomes were defined in abstract terms (i.e., changes in health status, end results). While there is an inherent belief that many pharmaceuticals improve outcomes, for outcomes to be documented and improved, this terminology must be defined in more concrete terms. One conceptualization of health care outcomes is the economic, clinical, humanistic outcomes model (ECHO) (13). This conceptualization portrays health outcomes along three dimensions. Clinical outcomes are outcomes related to the effects of medical treatments or disease on medical events such as hospitalization or death (i.e., end results). Economic outcomes are usually expressed as costs (e.g., dollars) associated with an intervention, and are often considered as ratios of costs to some measure of the consequences of a disease and its treatment. Humanistic outcomes are measures of the impact of disease or treatment on patient's lives. In addition to these outcomes, there are many intermediate variables that are important when measuring the effects of a disease or treatment. These variables are referred to in the published literature by many names including process variables, surrogate outcomes, or intermediate variables. In many cases making a clear distinction between these consequences of pharmaceutical use is probably not necessary; however, when reviewing literature, it is important to consider whether a consequence is a "true" outcome or an intermediate variable. For example, a score on a depression inventory is probably closer to an intermediate variable, whereas events such as rehospitalization or suicide reflect the "end results" or outcomes one would like to prevent.

Mental health care is expensive. For example, it is estimated that $44 billion is spent annually on the treatment of depression and $100 billion is spent annually on the treatment of Alzheimer's disease (14,15). The cost to treat schizophrenia has been estimated at $33 billion per year, accounting for 22% of dollars spent to treat all categories of mental illness and 2.5% of total health care expenditures (16,17). Increasing competition for scarce resources encourages decision makers to use outcomes data to evaluate the effectiveness and efficiency of treatment options for depression, Alzheimer's disease, and other mental health disorders. These issues are not new to health care providers, but the development of drug formularies as mechanisms to control costs has generated a need for outcomes studies to evaluate the benefits obtained from new pharmacologic agents. Shortly after SSRIs were released on the market, questions arose regarding whether health care outcomes were better for patients treated with SSRIs than for patients treated with traditional TCA therapy (5–7). This new class of pharmaceuticals was more costly than prior standard therapy (the TCAs), prescribed for a wide variety of patients, and had (in clinical trials) fewer side effects. Although the products were shown to be superior in some domains in clinical trials, there was a practical question regarding whether these benefits were realized in real-world practice and if so, at what net incremental cost (18). Do patients treated with SSRIs consume less acute care services, require fewer specialist visits, or have lower suicide rates? Is the total cost per acute depressive episode (successfully treated case) therefore lower with the newer products despite higher drug acquisition costs? Does treatment with SSRIs cost more, but provide better humanistic outcomes such as quality of life or quality-adjusted life years? These are the types of questions that outcomes research and pharmacoeconomic evaluations attempt to answer. This chapter does not specifically address these questions, but rather uses these questions to illustrate issues in outcomes research. It is noteworthy to recognize that not all the outcome questions of interest are likely to be addressed in a single study; rather, answers will come from an evaluation of a body of literature.

Most health care professionals are familiar with the clinical aspects of the treatment of mental health diseases. Given the substantial clinical information in the remainder of this text, this chapter focuses on evaluation of the economic and humanistic outcomes related to pharmaceutical use. Specifically, the techniques of pharmacoeconomics will be reviewed as well as the instruments for evaluating humanistic outcomes in mental health care populations.

PHARMACOECONOMICS

In the current health care environment, many decisions are driven by costs. At a minimum, health care systems are looking for systematic methods for reducing costs. Although

the fraction of the health care dollar spent on pharmaceuticals is low, it is clear that as both the pressure to reduce costs and the percentage of health care dollars spent on pharmaceuticals grow, so does interest in the costs of medications. Economists, however, are quick to point out that the acquisition cost of the pharmaceutical is not the most appropriate unit of analysis. It is possible that the acquisition cost of many pharmaceuticals may be offset by reductions in other more expensive forms of care. If the use of an expensive atypical antipsychotic leads to reductions in hospitalizations, then the "value" of the pharmaceutical from a total cost perspective is greater than the acquisition cost of the pharmaceutical. This is a key idea behind pharmacoeconomics. Pharmacoeconomics provides a set of techniques that allow consideration of the costs and consequences of alternative pharmaceutical therapies (19).

Studies are typically categorized by whether they consider costs, outcomes, or both cost and outcomes. In addition, studies can also be categorized by whether or not they consider alternatives. For example, traditional clinical trials focus on comparing the consequences of alternatives when one of the alternatives is typically a placebo. Although placebo comparison is highly relevant from the perspective of a regulatory agency striving to meet its special mandate, from the perspective of many health care decision makers a comparison with placebo is meaningful only if it is a relevant treatment alternative. Pharmacoeconomic studies best provide a comparison of relevant alternatives.

Studies that evaluate only cost for one alternative are referred to as cost descriptions. Other studies may also consider consequences. In these cases the study would describe both the costs and consequences of a single alternative leading to a cost-outcome description. If two alternatives are compared but only costs are considered, then the study is a cost evaluation. However, the primary concern of pharmacoeconomics is the comparison of both costs and consequences simultaneously for two for more relevant alternatives. There are four specific techniques that are typically used when conducting pharmacoeconomic studies (20):

- Cost-minimization analysis
- Cost-effectiveness analysis
- Cost-utility analysis
- Cost-benefit analysis

In each of these cases the numerators are the costs of inputs for a given decision. For example, if the total cost of care for the treatment of depression is considered, input costs might include cost of drug, cost of physician visits (family practitioner, internist, and specialist), behavioral therapy, hospitalization, and emergency department use. (Cost is discussed in greater detail below.) Next, the appropriate outcomes or consequence must be specified in the denominator.

Cost-minimization analysis assumes, not always explicitly, that the outcomes are equal. If this is a valid assumption, then the decision is based entirely on the costs of the inputs. The classic example of a cost minimization analysis is the use of generic versus branded products. If the chemical entities and formulations are identical, then there is no reason to suspect that the outcomes associated with the use of either product would be different. In this case, the decision is based solely on the costs of the inputs. The difficulty with cost-minimization analysis is establishing that outcomes are equal. Even in the case of generic pharmaceuticals there are examples where alternative formulations have been questioned. Additionally, products may be equivalent on some outcomes such as clinically significant improvement in depression, but not with regard to others such as side-effect profiles.

Cost-effectiveness assesses the consequences in natural units. These natural units may include outcomes such as years of life saved, hospitalizations avoided, or scores on a symptom scale. Jonsson et al. (21) used the Mini-Mental State Examination as a mechanism to assess time in a nonsevere disease state. This information was incorporated into a Markov state transition model to compare the cost-effectiveness of newer medications for the treatment of Alzheimer's disease to standard care. In many cases it is possible to develop several cost-effectiveness ratios for a comparison of relevant treatment alternatives. For example, in a comparison of atypical and conventional antipsychotics, cost-effectiveness ratios such as cost per hospitalization avoided, cost per symptom free day, or cost per schizophrenic exacerbation might all have meaning.

A recent cost-effectiveness study for the treatment of depression provides an excellent example of how decision makers can utilize these tools to best allocate scarce resources. Nuijten and colleagues (8) developed a Markov process to model the cost-effectiveness of long-term treatment with a new antidepressant compared to standard treatment with TCAs. The outcomes were time without depression, direct costs, and indirect costs (lost workdays). Clinical data were obtained from the published literature and costs were measured from the perspective of the German health care system. The new antidepressant was found to be associated with a 1.5 months longer time without depression than the TCA and with less cost to the health care system. In this case the new drug was less costly and more effective; thus by definition it is a more cost-effective choice.

Cost-utility analysis is a special case of cost-effectiveness analysis, in which the denominator is quality-adjusted life years (or something conceptually similar). The quality-adjusted life year may, for example, be calculated using patient utilities (from zero to one) for being in a given health state (or series of health states) and multiply them by the number of years of life expected in each health state. This analysis benefits from combining length of life with quality of life. For example, people using different antipsychotic medications may have similar life expectancy. However, if patients taking some antipsychotics have fewer side effects or greater

efficacy, they may experience an improved quality of life. As a result, the quality of the remaining years of life may not be equal for the two treatments. Cost-utility ratios factor this quality difference into the analysis. A typical ratio presented for cost-utility analysis is a cost per quality-adjusted life year (QALY).

Cost-utility analyses have the ability to compare QALYs over multiple treatment regimens. Revicki et al. (22) completed a cost-utility analysis in a managed care setting and compared outcomes of two SSRIs, a TCA, and a stepped approach that began with a TCA that was replaced with an SSRI if the TCA treatment failed. The outcomes measures were lifetime medical costs, QALYs, and cost per QALY gained. The analysis for a base case found that lifetime medical costs ranged from $15,348 to $16,669 per patient, that QALYs gained ranged from 14.32 to 14.64, and that cost per QALY gained ranged from $2,555/QALY to $6,346/QALY. The model allowed certain factors, such as compliance, to be varied.

The final pharmacoeconomic method is cost-benefit analysis. Cost-benefit analysis values the denominator in dollars and calculates a return on investment. Cost-benefit analysis allows comparison of alternatives that lead to dissimilar outcomes. Should a hospital open a gift shop or provide a vaccination program for influenza? The answer would be provided in the following terms: for every dollar invested in a gift shop, there is a return of $1.13; for every dollar invested in a vaccination program, there is a return of $1.25. Thus the vaccination program would be the more attractive investment. A disadvantage of cost-benefit analysis is that it requires all consequences to be valued in dollars. For example, suppose use of a medical alternative increases survival by 1 year. How do you put a cost on 1 year of life? In health care, valuing in dollars such consequences as life years gained and disability days avoided may be considered difficult or unacceptable by many people.

These four methods form the cornerstone of pharmacoeconomics. There are, however, many issues that affect the conduct and interpretation of pharmacoeconomic analyses. Some of the principal issues are discussed in the following sections.

Costs

Valuation of costs in pharmacoeconomic analyses can be difficult. There are two primary issues: first, which costs should be included in an analysis, and second, how should those costs be valued. The costs of inputs in a pharmacoeconomic analysis typically include direct medical costs, direct nonmedical costs, and indirect costs. Direct medical costs include costs such as physician visits, hospitalization, emergency department use, and pharmaceuticals. Examples of direct medical costs associated with the treatment of Alzheimer's disease include diagnostic tests, medications, and efforts to monitor or treat side effects, acute hospital care, physicians' services, home health care, and nursing home care (23,24). In other words, direct medical costs include any costs that are directly related to medical treatment. Direct nonmedical costs include items such as cost of transportation to the doctor's office and cost of child care while the parent is hospitalized. An example of a direct nonmedical costs for the treatment of Alzheimer's disease is in-home day care (25). Examples of indirect costs are costs that arise from lost work or lost patient or caregiver productivity. In conducting a cost analysis, the first challenge is to decide which costs are relevant for the comparison. The issue of perspective (who pays?) becomes critical. Once this hurdle has been cleared, then the issue arises of how costs will be assigned. For example, if prescription costs during hospitalization are included in a pharmacoeconomic analysis, how should the basis for costs be established? Should it be based on actual acquisition costs, charges, or cost-to-charge ratios as a percentage of the entire hospital bill? Clearly, these types of valuation decisions need to be disclosed and discussed in pharmacoeconomic studies.

Analyzing the results of pharmacoeconomic studies requires the evaluator to assess the types of costs included in each study. Large variations in results can be attributable to different cost components (25). In the medical treatment of Alzheimer's disease, the acquisition cost of the medication is only a small percentage of the total cost. One major component of treating Alzheimer's disease is the indirect costs absorbed by family members. Researchers encounter difficulties in estimating the cost of such informal care. As a result, investigators may account for those costs absorbed by family members in different ways, which may contribute to varying conclusions (26).

There may also be intangible costs. These costs include things such as pain and suffering. Intangible costs are even more difficult to value in monetary terms. In diseases where intangible costs are significant, it is important to recognize whether any effort has been made to account for these costs. In many cases they are not included. Additional analysis may need to be considered to make fair decisions.

One mechanism to quantify intangible costs is a willingness-to-pay approach. O'Brien et al. (27) performed a willingness-to-pay evaluation in a group of patients with mild to moderate depression. The study was designed to compare a new antidepressant with TCAs. The drugs had similar efficacy but different adverse event profiles. Participants were asked to rank a series of adverse effects and then to quantify the maximum amount they would pay for a new drug that reduced each adverse event. On average, participants were willing to pay an additional $14 per month to reduce the risk of blurred vision from 10% to 5%. When asked their willingness to pay to avoid multiple simultaneous side effects, the range was $23 to $77 per month.

If costs, or benefits, are analyzed over time periods that exceed 1 year it is necessary to apply discounting. Discounting costs is a concept that reflects the "time value of money."

A dollar today is worth more than a dollar received in the future. Discounting reduces the value of dollars that will be realized more than a year in the future to reflect a present value. A similar concept applies to health benefits.

Perspective

One of the major factors that influences pharmacoeconomic analyses is the perspective taken when conducting the analysis. Using the earlier cost example, if a study is conducted from the perspective of a hospital, the use of actual costs may be appropriate. However, if the same study were conducted from the perspective of a managed care organization, charge data may be more relevant. The perspective of a pharmacoeconomic analysis should always be disclosed in a publication. Given that there are many possible perspectives, it is insightful to evaluate studies from a broad perspective. The societal perspective is the broadest and takes into consideration all costs and consequences relevant to society. For various reasons, this perspective is often used as a "reference case," to permit comparisons across studies that may otherwise use differing perspectives. When measuring the impact of pharmaceuticals on mental health disorders, the perspectives of both society and providers are important (14,28,29). Because of the desire to serve the needs of health system decision makers, the perspective taken in many studies is that of the payer. A substantial number of patients prescribed antipsychotic medications have their health care paid by Medicaid (30). Therefore, the perspective of Medicaid is important when evaluating the cost of schizophrenia treatment. The payer perspective, however, may not include all costs relevant to society. For example, lost productivity may not be relevant from the Medicaid perspective. It is critical that the study perspective is disclosed when a pharmacoeconomic analysis is published or evaluated. Generalizing results from a specific setting to a different setting is unwise because the relevant costs and outcomes vary between settings.

CONDUCTING PHARMACEUTICAL OUTCOMES RESEARCH

There have been several texts and journal articles describing the steps for conducting pharmaceutical outcomes research and pharmacoeconomics (19,20). This section does not reproduce these lists of steps, but rather presents some of the issues from these materials that are pertinent to the evaluation of mental health applications.

Decision Analysis

Decision analysis is a systematic approach to structuring decisions over time. Decision trees are developed with branches representing alternative decisions or probabilistic relationships. For example, a decision may involve a choice between two drugs. These drugs may either have side effects or not, and treatment may be either successful or not successful (Fig. 39.1).

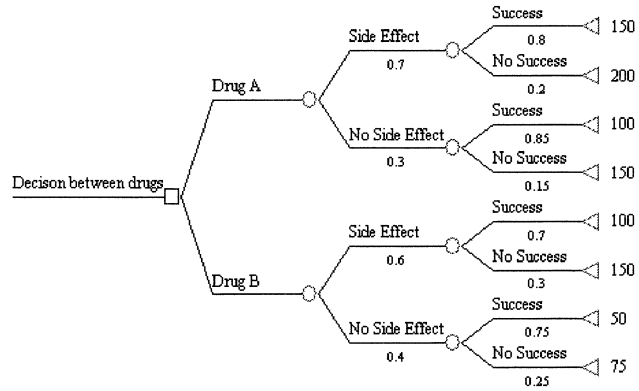

FIGURE 39.1. Example of a decision tree.

For any of the nodes where a chance relationship exists (represented by circles), the probabilities associated with that event are shown (e.g., the probability of a side effect associated with drug A is 0.7). When the outcomes are valued in dollars (i.e., the cost of following a particular path), the expected values that are calculated from a decision tree analysis can provide cost estimates that are used in the numerator of a pharmacoeconomic ratio. Expected values are calculated by summing the product of the probabilities and the costs. The expected values are shown in Fig. 39.2.

In this case, assuming that the cost at the end of each branch represents the total cost of care for the selected drug, the expected costs associated with the use of drug A is \$144.25 and \$91.50 for drug B. If outcomes were assumed to be equal (i.e., cost-minimization) then the least expensive alternative would be drug B. However, outcomes are not equal. As can be seen from the decision tree, the probability of success while using drug A is greater than for drug B. If the path probabilities for the successful branches are summed for each alternative, it can be seen that the probability of successful treatment with drug A is 0.815, and the probability of successful treatment with drug B is 0.720. Therefore, the total cost of treatment while on drug A is higher, but so is the effectiveness (i.e., chance for successful treatment). The real question is one of cost-effectiveness. Is the additional cost of drug A worth the additional benefits? This would be assessed with an incremental cost effectiveness ratio:

$$\text{Incremental cost effectiveness ratio} = \frac{\text{Cost of Drug A} - \text{Cost of Drug B}}{\text{Effectiveness Drug A} - \text{Effectiveness Drug B}}$$

$$\text{Incremental cost effectiveness ratio} = \frac{144.25 - 91.50}{0.815 - 0.720}$$

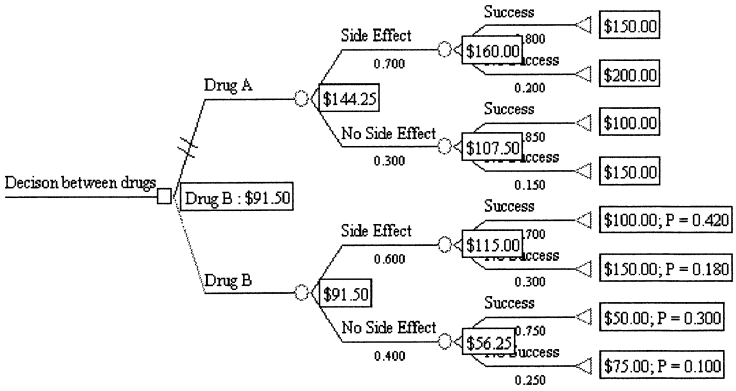

FIGURE 39.2. A solved decision tree.

Incremental cost effectiveness ratio = $555.26/each additional successful case

Is an additional successful case worth paying an additional $555.26? This is a value judgment that depends on the situation surrounding the decision. Again, outcomes research does not answer the question regarding which product should be used; it simply provides information regarding the efficiency with which these two products produce a desired outcome.

This method, while powerful, is often limited by the availability of data to drive the model and the forced simplification of models, which often results from limited driving data. It is important when reading published modeling exercises such as decision trees or Markov models to evaluate them carefully, as results are highly dependent on the specifics of the structure selected (and how closely it reflects clinical reality) and on the data selected for input. The latter problem can and should properly be addressed by sensitivity analysis, for which there are several techniques. The former problem can be tested by the careful evaluation of experts or the demonstrated ability of a model to predict measurable outcomes, a relatively uncommon exercise in pharmacoeconomics.

In general, the reader should look for some effort to discuss or examine "parameter" uncertainty, "model structure" uncertainty, and "model process" uncertainty. With regard to parameter uncertainty (the term *parameter* refers, for example, to estimates of probabilities or cost or health outcome), univariate analysis alone is often inadequate, and some attempt at multivariate evaluation is desirable. There are different formal approaches to evaluation of cost-effectiveness uncertainty using either frequentist or Bayesian approaches to generation of confidence (or "credible") regions, including simulation and the delta method. Model structure uncertainty refers to the separate uncertainty about the manner in which parameters should properly be combined (e.g., Are effects linear or nonlinear fashion? Are effects additive or multiplicative?). An approach to evaluation of this kind of uncertainty is to simply examine results for different plausible alternatives. Model process uncertainty refers to the fact that different analysts may come to different conclusions due to a spectrum of differences in approach. There are other key methodologic pitfalls in proper conduct of studies of this type (e.g., adhering to use of incremental cost-effectiveness ratios), a fact that highlights the need for readers to evaluate each study carefully.

The purpose of this discussion is not to fully explain the sometimes complex process of conducting a decision analysis, but rather to suggest the usefulness of this tool in outcomes research. It is also to encourage the reader to develop the critical skills necessary to evaluate studies of this type, much as similar skills have been developed for evaluation of ordinary controlled clinical trials. The reader is referred to *Clinical Decision Analysis* by Weinstein and Fineberg (31) for a more complete description of the process of conducting decision analyses, and to *Cost-Effectiveness in Health and Medicine*, edited by Gold (32) for in-depth discussion of many important issues in cost-effectiveness analysis.

In a final example, we refer to a study using decision analysis to permit evaluation of a systematically developed time-ordered series of events. It incorporates previously published clinical trial data into a model to estimate long-term effects. In this study, Dardennes et al. (33) developed a decision analysis model to compare outcomes and costs of treating major depression with an SSRI, a TCA, or serotonin norepinephrine reuptake inhibitor (SNRI). The perspective of the study was that of a national health care system, and the clinical outcomes data used in the model were derived from published meta-analyses. The analysis found that the SSRI and TCA had comparable efficacy but dissimilar tolerance profiles and that the SNRI had both efficacy and tolerance advantages compared to the SSRI. Direct cost data (hospitalization, medication, physician visits, and laboratory tests) and the efficacy data from the model were entered into a decision tree. The decision tree analysis provided estimates of the expected cost of treatment per

depressive episode that could be used by the health service in its treatment approval process.

Data Sources

Data for pharmaceutical outcomes studies can come from several sources. Many pharmaceutical companies routinely include pharmaceutical outcome (other than just clinical) measurements in their development trials. In addition, post-marketing studies with direct comparisons to relevant alternatives (i.e., intended to serve the needs of pharmaceutical users rather than regulators) are becoming more common. However, conducting single studies that contain all pharmaceutical outcomes of interest for a given product are expensive, and data collection of all relevant information is difficult. Therefore, many pharmaceutical outcome studies contribute to the body of knowledge by evaluating components of the overall picture. Additionally, many pharmacoeconomic analyses are based on models. These models typically use published literature, expert opinion, or data from administrative or encounter databases to get information on probabilities and costs.

The impact of this component approach to building an understanding of pharmaceutical outcomes is that data come from many sources ranging from experimental and nonexperimental research designs to expert opinion and models based on data from multiple and frequently diverse sources. Therefore, when reviewing pharmaceutical outcomes research, it is critical to understand the potential impact of the source of information on the results.

A frequent source of outcomes data in mental health research is randomized clinical trials conducted by the pharmaceutical industry. These trials, however, are often placebo controlled and typically contain (as expected) mostly clinical information. In mental health, however, patient self-reported items (i.e., humanistic measures) are frequently included. There are also many studies that rely on chart review and quasi-experimentation to document differences in resource use for patients using various pharmaceutical agents. Examples include recent comparisons of tricyclic antidepressants and SSRIs, and atypical versus conventional antipsychotic agents. Many of these studies were retrospective and were conducted through chart reviews or administrative data using quasi-experimental techniques. Finally, economic models have been built using published data or expert opinion, where data were not available.

Historically, randomized controlled trials have been the "gold standard" (5). Studies of this type allow the efficacy and safety of a drug to be established. Unfortunately, some of the strengths of such studies can also be a source of less commonly recognized weaknesses. This is a result of the artificial treatment environment purposefully created in efficacy trials, and may be particularly an issue in mental health because of the wide gap recognized to exist between the "optimal" care provided in such trials and the realistic patterns of care experienced by most patients. The primary care provider deals with other issues that influence the effects of a medication such as side effects, dose titration, and out-of-pocket expenses. As a result, real-world effects can be difficult to extrapolate from ordinary clinical trials. This issue is discussed further below. Randomized trials failed to differentiate the SSRIs and TCAs, except for their side-effect profiles. However, SSRIs may have some advantage over TCAs in the primary care practice setting (6,28,29). In summary, data for building evidence about the value of pharmaceutical outcomes in mental health has been drawn from a number of sources using a variety of experimental and nonexperimental designs. Each of these sources of data and type of experimentation affect the degree of evidence obtained. Review of pharmaceutical outcomes research in mental health care requires careful consideration of the source and strength of the evidence presented.

HUMANISTIC MEASURES

Humanistic measures assess how disease or treatment affects patients. Humanistic measures are most important from the perspective of the patient. A primary goal for treatment of any disease should be for patients to function normally, have an acceptable quality of life, and be satisfied with their treatment. This is especially true for mental health disorders where impacts on both physical and social functioning may be significant. In many cases, patients and their friends and families might best judge the success of treatment. Until recently, humanistic measures have taken a back seat to traditional clinical measures and to some extent economic measures. This is in part due to greater variability from patient self-reported measures compared to standard clinical measures (34). The development of valid and reliable instruments is a relatively recent phenomenon. The most common conceptualization of humanistic outcomes used in the evaluation of pharmaceuticals is health-related quality of life.

Health-related quality of life encompasses factors such as functional status, physiologic status, social and emotional well-being, and life satisfaction (35). Health-related quality of life information allows health care providers and payers to make decisions based not only on clinical effectiveness, or costs but also on effects that are important to patients. Measurement of health-related quality of life may be especially important in chronic diseases for which we have no cure. There are many humanistic measures available for assessing mental health disorders. Generic and disease-specific instruments are available for a variety of disorders. Discussion of every instrument is not feasible; however, a few examples are provided.

Generic instruments are global in content and cover a number of dimensions relevant to overall health-related quality of life. One of the most widely used generic health-

related quality of life instruments is the Medical Outcomes Study Short Form 36 (MOS SF-36). The MOS SF-36 captures eight dimensions of health-related quality of life: physical functioning, role limitations due to physical functioning, bodily pain, general health, vitality, social functioning, role limitations due to emotional problems, and mental health (36).

A modified version of the Sickness Impact Profile has also been developed for use in patients with mental illnesses.

Disease-specific health-related quality of life instruments focus on dimensions that are most relevant to the particular disease and are therefore more sensitive to subtle changes in the disease or its treatment. Examples of disease specific instruments used in schizophrenia include the Quality of life Scale (37), the Social Performance Schedule (38), and the Quality of life Interview (39). Several review papers have been published on the use of quality of life instruments in mental health conditions (40–42). These articles highlight that quality of life measurement in mental health conditions, and in particular specific drug comparison, is a developing science. Many of the available studies are observational or cross-sectional. However, quality of life measurement is increasingly being built into clinical trials. There continues to be debate regarding mental health patients' ability to complete quality of life questionnaires, highlighting the importance of population-specific assessment of instrument validity and reliability. However, several articles have shown that it is possible for patients with severe mental health problems to successfully complete these forms (43,44). Lenert's group (45) has shown that even when posed the conceptually challenging task of the standard gamble, patients with mental illness have been able to perform adequately. It is important to note that although agreement is not universal, there are many researchers who believe that in principle the best source for measuring patients' quality of life or preferences is the patients themselves whenever such measurement is possible. Much has been published on this subject and in particular on the issue of whose values to use in creation of reference case analyses (to be used for comparisons across studies). But rarely is the view of the health care provider or other proxy considered superior to that of either the patient or of society in general.

Health-related quality of life has many applications in the treatment of mental health disorders. For example, Simon et al. (46) completed an analysis that evaluated clinical effectiveness, health-related quality of life, and economics of treating depression. The study took place within a staff model HMO and utilized net costs. Patients starting new antidepressant therapy were randomized to an SSRI or TCA for 24 months. The primary care providers were allowed to adjust doses and medications or discontinue medications as they deemed appropriate. The quality of life outcome was measured using the Medical Outcomes Study SF-36 Health Survey at 6, 9, 12, 18, and 24 months. The results indicated no significant difference in quality of life or severity of depression when comparing treatment groups (46). Other studies have evaluated health-related quality of life in the treatment of depression and utilized similar generic rating scales (47).

Numerous Alzheimer's disease–specific quality of life tools are available. However, there is a lack of understanding of how to quantify changes in scores. It is important to note that the cognitive impairment of Alzheimer's disease at times requires the administration of the tool to a care provider. The tools assess functions such as daily activities, memory, emotional well-being, and other aspects such as finances (48).

One other area of humanistic measurement concerns the relationship between humanistic and economic outcomes. Cost utility analysis uses patient preferences in the form of utilities to combine cost information with patient preferences. Utilities are usually measured by three techniques: rating scales, the standard gamble, or time trade-off technique (49). Utility scores differ from quality of life measurements. While some quality of life instruments can be used to capture utilities, most cannot. Utilities are a measure of overall patient well-being that lie on a scale between 0 and 1. Utilities typically measure the difference in patient's preferences between perfect health and impaired health states. At present, utilities have been measured for only a few health states. Unfortunately, utility values are difficult and expensive to measure. They require detailed patient interviews with large numbers of subjects with and without the disease. Additionally, there are many questions about patient's ability to give reliable and valid responses. While these techniques have been used in mental health care, more widespread use is dependent on the development of reliable and valid measures of utility or preference for alternative health states in mental health diseases.

USING OUTCOMES DATA IN PRACTICE

The use of outcomes data in practice is not about applying the results of a single study. Instead, using outcomes data typically requires synthesis across a body of literature. Outcomes data, and in particular economic and humanistic data, offer additional pieces of information that should be incorporated into decisions. Economic, clinical, and humanistic data are all needed to make fair evaluations of pharmaceutical products and services. In reality, however, decisions will be made even if all these data are not available.

Uses of outcomes data in practice include reimbursement decisions, internal practice decisions, external or regulatory decisions, and marketing of pharmaceutical products. Pharmacy and therapeutics committees are using outcomes data as a component of the formulary decision. Where these decisions were once made almost entirely on clinical parameters, the use of economic and humanistic data is becoming more common.

In practice, the use of terminology such as evidence-based medicine or treatment guidelines has its roots in outcomes evaluations. The evaluation of a body of literature to make decisions about best practice is the goal of evidence-based medicine. Evidence-based medicine involves explicit use of what can be identified as the best evidence in making decisions about the care of both individual patients and populations of patients (Fig. 39.1) (50). This philosophy extends into treatment guidelines that are often established by expert panels that have reviewed the available evidence in the literature regarding effectiveness of alternative treatments. While these efforts rely most heavily on clinical information, economic and humanistic data are being included in these considerations.

Outcomes data is beginning to be considered in the accreditation of health care organizations. Although the measures currently used are more process than outcomes oriented, the evolution toward outcomes can be seen. The National Committee for Quality Assurance (NCQA) conducts accreditation of managed care organizations and has a specific program for behavioral health accreditation. NCQA also sponsors the Health Plan Employer Data and Information Set (HEDIS) report, which is a set of standardized performance measures designed to assist consumers with decisions about purchasing health care coverage. HEDIS 2000 includes several measures relative to mental health care. These measures are organized into several categories. Under the effectiveness of care category, two measures are included: follow-up after hospitalization for mental illness, and antidepressant medication management. In the use of services category, mental health care related measures include mental health utilization, inpatient discharges and average length of stay, and mental health utilization–percentage of subjects receiving services. These measures are evolving to require managed care organizations to consider the outcomes of care they provide. As HEDIS measures continue to evolve, they are expected to raise the quality of health care.

Some of the more sophisticated users of outcomes data may be pharmaceutical companies. Most major pharmaceutical manufacturers are investing resources in departments that focus on the collection and analysis of outcomes data for their products. Although these data are frequently used in the marketing of pharmaceutical products, they are also providing information about the developing science of outcomes measurement.

Efficacy and Effectiveness

The evolution of the use of data for decision making is interesting. Health care organizations have evolved from requiring evidence of efficacy to effectiveness to efficiency. *Efficacy* is defined as how well an intervention can ideally work. This is characterized by the types of ordinary clinical trials that are commonly performed for regulatory purposes. This type of trial generally creates what is believed to be ideal conditions of treatment and limits treatment to optimal patients, conditions that can be difficult or impossible to duplicate in regular practice. Blind, prospective randomization of an adequate number of patients to a study in which outcomes are assessed by raters blind to treatment is intended to minimize observer bias and confounding, and maximize internal validity. Accordingly, clinical trials are excellent for providing confidence that there is a causal relationship between drug use and the measured endpoint. Once confidence in this relationship is established, however, questions of use in the real world arise, which beg the question of effectiveness. Efficacy results, generally using highly select, often healthier, patient populations (not least because informed consent is required) under different practice conditions (tertiary vs. primary care, frequency of follow-up, compliance issues, insurance issues, dosing/titration regimens, etc.), may simply not predict patient outcomes in usual practice. This leads to the question of *effectiveness*, defined as the extent to which health improvements are achieved in real practice settings. Does a pharmaceutical product work under real-world conditions? Is it really influencing outcomes that are important to patients, payers, and clinicians? An experimental research approach to the question of effectiveness is a type of trial referred to variously as "pragmatic trials" or "effectiveness trials." Such trials employ random treatment assignment to address confounding, but sacrifice a degree of internal validity in an effort to increase generalizability to the real world. This necessitates, for example, inclusion of as many patients as possible (minimizing exclusions), using ordinary practice settings, avoiding protocol-mandated interference in patient care, and permitting the effects of cost and payment mechanisms. The application of this useful type of trial in mental health has been described, but rarely implemented (51). Alternatively, nonexperimental research designs (e.g., cohort studies, retrospective database analyses, etc.) can often shed light on real-world outcomes when a clinical trial is impractical for reasons such as sample size, informed consent, duration of follow-up, etc. Usually, such studies must take special care to address issues of bias and confounding. When real-world data from either effectiveness trials or nonexperimental research are not available, as is often the case, the evidence basis for mental health decision makers is limited to either attempting to generalize from efficacy data or relying on some form of expert opinion.

The increasing expenditures associated with mental health disease states require decision makers to evaluate the full impact of treatment alternatives. The evaluation should include the appropriate variables to fully evaluate patient outcomes (including quality of life); an adequate evaluation of all relevant costs, which permits capture of potential offsets of simple drug acquisition costs; and consideration of issues of efficacy vs. effectiveness. The tools of pharmacoeco-

nomics and outcomes research provide decision makers with a mechanism for attempting to quantify and balance these factors to assist in the allocation of scarce mental health resources.

CONCLUSION

Measurement of economic, clinical, and humanistic outcomes is an important tool for establishing the value of competing mental health care programs and treatments. Ultimately, measures of quality of care in relation to commensurate costs should aid decisions about which programs to implement and which treatments to reimburse. Although no single study is likely to provide an answer, careful evaluation of the economic, clinical, and humanistic outcomes literature may assist decision makers in making more informed decisions. Many of the economic and clinical studies conducted to date use descriptive designs or apply modeling techniques based on the best source of available data. As the science behind outcomes measurement evolves, the level of sophistication of the information provided will improve. Information on treatment outcomes can contribute significantly to decisions that affect the quality of care received by mental health patients.

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