Methods of Cost-Effectiveness Analysis in the Evaluation of New Antipsychotics: Implications for Schizophrenia Treatment

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Because health care payers are increasingly interested in learning whether new treatments offer value for money, there has been an abundance of research into the cost-effectiveness of pharmacologic therapies in the United States. In the past few years, a number of studies comparing the cost-effectiveness of the conventional neuroleptics with that of the atypical antipsychotics have been published. Cost-effectiveness analyses show the relationship between the resources used (costs) and the health benefits achieved (effects) for a health or medical intervention compared with an alternative strategy. Ideally, the analyses can help decision makers improve the health of the population by better allocating society’s limited health care resources. However, the extent to which cost-effectiveness data are actually used in decision making is unclear. The analyses are sometimes viewed with skepticism, in part because studies differ in their methodological approaches. Recently, the U.S. Panel on Cost-Effectiveness in Health and Medicine offered recommendations for standard methodological practices, which may help improve the quality of studies and the acceptability of the approach in the future. The issue is particularly important in light of new legislation governing how the Food and Drug Administration will regulate promotional claims made by drug companies regarding health economic information.

Discussions over the use of the atypical antipsychotics provide an example of the clinical and economic issues at stake when new medications that are more costly than standard treatments are released. Because health care payers have become increasingly concerned with having demonstrated evidence that treatments represent good value for money spent, manufacturers now frequently undertake or sponsor studies to examine the cost-effectiveness of their products. Thus, in addition to facing Food and Drug Administration (FDA) requirements that their products demonstrate safety and efficacy, manufacturers now often confront a de facto requirement from the marketplace that new products be cost-effective.

In the coming years, economic evaluations of the atypical antipsychotics are likely to play an increasingly influential role in clinical and resource-allocation decisions involved in the treatment of schizophrenia. Several questions will have to be addressed for each new agent that enters the marketplace: (1) Do the clinical benefits of this drug justify its cost? (2) To what degree do potential economic benefits related to decreased hospitalization and community care offset the costs of this agent? (3) Would the dollars spent on this medication produce greater effects if they were targeted for other treatment strategies?

The rise in the number of economic evaluations of health and medical interventions has been well documented. One recent review of the literature found over 3,500 such evaluations published from 1991 through 1996.

Within the last decade, at least 40 studies of the economics of treating schizophrenia have been published. These studies fall into different categories of economic evaluations of health and medical interventions (Table 1): cost-of-illness analyses, which are analyses of the total costs incurred by society attributable to a specific disease; cost-consequence analyses, in which components of incremental costs and consequences of alternative programs or interventions are estimated but make no attempt to construct a single metric or aggregate the results; cost-minimization analyses, which compare the net costs of interventions that produce the same net outcomes; cost-benefit analyses, in which the net social benefit of an intervention is computed as the incremental benefit of the intervention minus the incremental costs, with all benefits and costs measured in dollar terms; and cost-effectiveness...
analyses, which show the relationship between the resources used (costs) and the health benefits achieved (effects) for an intervention compared with an alternative strategy. Cost-utility analysis is a type of cost-effectiveness analysis in which health effects are often measured in quality-adjusted life-years gained (QALYs).

COST-EFFECTIVENESS ANALYSIS

Advantages

Though other forms of economic evaluation are used, cost-effectiveness analysis (CEA) has emerged as the dominant approach to economic evaluation in health and medicine. The appeal of CEA is that it yields a ratio—costs per unit of health effect achieved—that is relatively straightforward to interpret and that allows for comparisons across a broad spectrum of interventions. The cost-per-effect (C/E) ratio reflects the difference in the costs of interventions divided by the difference in their health effectiveness. If ratios are estimated in similar terms, they can be compared to illustrate the most efficient ways to maximize health benefits in the allocation of limited resources.

In contrast, cost-benefit analysis requires the monetary valuation of health benefits, which presents measurement difficulties and ethical dilemmas. Other approaches also have limitations. Cost-consequence analyses may offer advantages in terms of transparency but lack standards for methodological practices and do not produce results that can be easily compared across studies. The performance of cost-minimization analyses, which are used to compare the net costs of programs that achieve the same outcome, are less common because of the stringency of the requirement that competing programs yield similar effects.

Some Challenges

Cost-effectiveness analysis is not without problems. One of them involves the great disparity in the methods that have been used in studies. Researchers have noted that the methodology employed in CEs varies widely across analyses and that evaluations of the same interventions using different methods can sometimes lead to very different results. These discrepancies reflect a number of factors, including a lack of understanding about the conceptual model, uncertainty about how techniques should be applied, and differences in opinion about the best ways to obtain estimates of costs and health benefits.

U.S. Panel on Cost-Effectiveness in Health and Medicine Recommendations

The U.S. Panel on Cost-Effectiveness in Health and Medicine was charged with assessing the current state of science in the field and with providing recommendations for the conduct of studies in order to improve their quality and encourage their comparability; it sought to develop recommendations for methodological practices in the field. Among other recommendations, the Panel urged that cost-effectiveness analyses include a reference case or analyses that incorporate standard methodological practices and are intended to improve comparability across studies. For the measurement of costs, the Panel recommended that costs for both the intervention being studied and the comparison condition include changes in health care resources, changes in non–health-care resources, and changes in time.

For schizophrenia treatment, health care resources would include medication, short-term acute hospital care, physicians’ services, the costs of community care, long-term psychiatric hospital care, and costs associated with monitoring or treating side effects of the medication. Non–health-care services would include items such as welfare payments and costs involved in rehabilitation and training. Time costs include the unpaid provision of care by family members and the time patients spend seeking care or being treated.

For the measurement of health effects, the Panel recommended that results be presented in terms of quality-adjusted life-years gained (QALYs). Clinical trials of new drugs for schizophrenia, which frequently last from 8 to 12 weeks, have assessed health effectiveness by using clinical rating scales such as the Positive and Negative Syndrome Scale or the Brief Psychiatric Rating Scale. While these measures are appropriate for demonstrating the clinical effectiveness of treatments and are familiar to clinicians who treat schizophrenia, they are limited for informing societal decisions about which of many competing interventions produces the greatest overall gain in health for the resources expended. To address such a question, it is useful to evaluate the cost-effectiveness of diverse interventions in similar terms. Comparisons of cost-effectiveness ratios across treatments would then illustrate the most efficient ways to furnish health benefits.

Cost-effectiveness analyses in which health effects are measured in QALYs are sometimes termed cost-utility analyses. QALYs are useful as a measure of health benefit because they capture both quantity- and quality-of-life effects, because they reflect individual values for different health outcomes, and because they permit comparisons across diverse interventions. The QALY approach depicts life as a series of quality-weighted health states, in which quality weights reflect the desirability of living in each state. A higher weight reflects a more preferred state. Generally, a health state is rated on a scale in which a

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weight of 0.0 corresponds to death and a weight of 1.0 corresponds to good health or best attainable health. The quality weight for each state is multiplied by the time spent in the state; these products are summed to obtain the total number of QALYs.

The advantage of using QALYs in cost-effectiveness analyses for societal resource-allocation decisions has been recognized in recommendations of the U.S. Panel on Cost-Effectiveness in Health and Medicine, in guidelines for the economic evaluation of pharmaceuticals in both Australia and Canada, and in the large and growing number of studies in the medical literature for interventions as diverse as those for cardiovascular treatment, cancer, and acquired immunodeficiency syndrome (AIDS).

Methods for determining quality weights continue to be an active area of research and debate. Defining quality of life in schizophrenia can be complex because cognitive impairment often hinders patients’ ability to respond to questions. One possibility is to assess health-related utility from proxy respondents, who may be caregivers, family members, or physicians, through the use of generic health-state classification systems, which describe patients’ health along a series of dimensions such as mobility, pain, emotion, and cognition. An example of a health-state classification system is the Health Utilities Index, containing 8 dimensions: vision, hearing, speech, emotion, pain, ambulation, dexterity, and cognition. The idea behind using such systems is that patients can be classified, based on clinical information, into appropriate strata, each of which reflects a unique combination of dimensions and levels of severity. Once the individual is mapped into the system, previously obtained preferences of individuals in the community for various cells of the system would be used for the quality weights. Among the techniques employed to obtain the community-based preference weights are the “standard gamble” and “time trade-off” methods, which involve asking respondents to value health states by explicitly considering how much they would be willing to sacrifice—in terms of a risk of death or of time lived in good health—in order to avoid being in the state. Another option is to ask respondents to rate the strength of their preferences for particular health states on a scale.

In retrospect, the question of whether to pay for clozapine represented a classic study in cost-effectiveness analysis, but solid pharmacoeconomic evidence was lacking when the first atypical antipsychotic became available. When the issue was viewed narrowly from the perspective of a Medicaid budget director and only the short-term costs of treatment and monitoring were considered, the drug may have looked prohibitively expensive. But when longer term costs and benefits were considered, the impact of the drug on costs looked more favorable, as a subsequent study suggested.

USEFULNESS OF PHARMACOECONOMIC DATA

The extent to which CEAs and other forms of economic information are actually used by health care decision makers remains unclear. Researchers have paid relatively little attention to this question, though a handful of surveys have examined general attitudes among selected pharmacists and managers in managed care plans. While the surveys differ in their scopes, methodologies, and sample sizes, several main conclusions emerge from the surveys about use of economic information.

Awareness and Use of CEAs Growing

Managed care decision makers are increasingly aware of, and in some cases using, cost-effectiveness information. Zellmer, for example, interviewed 157 health-systems pharmacists and found that 82% agreed with the statement, “Drug manufacturers have increased their use of comparative pharmacoeconomic claims in marketing to my managed care plan.” Sloan et al. surveyed 103 hospital pharmacists and asked whether they had seen CEAs on particular drugs. Thirty-eight percent had seen CEAs for gastrointestinal drugs, 34% for antibiotics, and 25% for thrombolytics.

Cost-Effectiveness Information a Secondary Concern

Cost-effectiveness remains a secondary consideration after clinical factors. Luce and colleagues interviewed 51 managed care plan managers and asked about the usefulness of information on clinical effectiveness, safety, cost of treatment, and cost-effectiveness. Rated on a scale from 1 (most useful) to 6 (least useful), clinical effectiveness (1.6) was thought to be most useful, followed by information on cost-effectiveness (2.6), safety (2.7), and cost of treatment (4.0). Luce et al. also found that respondents gave higher ratings to information from clinical trials as opposed to information from retrospective reviews and models. On a scale of 1 (excellent) to 4 (poor), clinical trials rated highest (1.8), followed by retrospective reviews (2.1) and models (2.6).

Mainstream Journals Promulgate CEA Use

The preferred source of cost-effectiveness information is the peer-reviewed journal article. In the Sloan et al. study, almost 70% of respondents said that they found CEA information in the peer-reviewed literature; only 20% indicated that they found it in practitioner-oriented journals, the next most frequent response. When asked,
“What would make you more likely to use economic evaluations?” 65% of respondents in a survey of 446 health professionals conducted in the United Kingdom66 replied that economic evaluations published in mainstream journals would provide an incentive for their use.

Decision Makers Lack Expertise

Many decision makers feel ill-equipped to evaluate cost-effectiveness information. One barrier to greater use of the information among managed care managers is a feeling that they do not possess adequate knowledge or training. Zellmer45 reported that almost 40% of respondents said that they were ill-equipped to analyze critically comparative pharmacoeconomic claims, for example. In the Sloan et al.60 survey, 15% listed lack of knowledge as a reason for not using cost-effectiveness analyses more often. A similar percentage noted that a better explanation of methods was needed if CEAs were to be more useful to hospitals.

Potential Bias of Sponsors an Impediment

Decision makers remain skeptical of the information because of the potential bias of study sponsors. The credibility and reliability of studies are also perceived as a problem.61 Zellmer45 found that fewer than 20% of respondents agreed with the statement, “The comparative pharmacoeconomic claims made by drug manufacturers generally meet high standards for reliability.” Moreover, only 51% of respondents agreed with the statement, “My managed care plan is in a position to put pressure on manufacturers to conduct scientifically rigorous pharmacoeconomic studies.” In interviews with 43 managed care providers, Lax and Moench54 found that the foremost concern expressed was bias, followed by freedom to control the study and the validity of the study. In a study of 446 medical professionals in the United Kingdom, Drummond et al.56 reported that the greatest barrier to use of CEAs cited was that industry-funded studies were not credible, a view reported by almost 60% of respondents. In the Sloan et al. study,60 over 20% of respondents suggested that a way to make CEA more useful to hospitals was to sponsor independent research. Almost 40% of respondents in the Drummond et al. survey56 indicated that someone was needed to critically review studies for decision makers.

Timely Information Needed

Decision makers emphasize the need for more timely information. In a survey of 231 private health plan managers, Steiner et al.58,59 found that the greatest reported barriers to decision makers were (1) “no timely effectiveness data” (90%), (2) “no timely cost-effectiveness data” (70%), and (3) “no timely safety data” (60%). Among the barriers to use of cost-effectiveness analysis reported by Sloan et al.60 was the fact that studies were published too late. Almost 30% of these respondents suggested that one way to make CEAs more useful to hospitals was to make studies available sooner.

Relevant Information Needed

Decision makers want information targeted to the decisions they must make. Sloan et al.60 reported that the 2 greatest barriers to the use of cost-effectiveness analysis among hospital pharmacists were that CEAs neither reported on drugs of interest (34%) nor applied to hospitals (28%). When asked how cost-effectiveness analyses could be made more useful to hospitals, the most frequent response was to make studies generalizable to the hospital setting. Drummond et al.56 found that among the barriers reported by respondents were that savings cited in CEAs were anticipated rather than real. Other responses questioned whether the Department of Health in the United Kingdom was interested in cost containment rather than cost-effectiveness and expressed doubt that this agency could take the long-term view.

THE FDA AND USE OF PHARMACOECONOMIC DATA

The growing use of pharmacoeconomic information for promotional purposes by drug manufacturers has concerned the FDA, which has the regulatory authority to ensure that pharmaceutical advertising and labeling are neither inaccurate nor misleading.62 In the spring of 1995, the FDA Division of Drug Marketing, Advertising, and Communications released draft guidelines that would require that pharmacoeconomic claims used in promotional materials contain an appropriate level of scientific rigor and validity.63

The Food and Drug Administration Modernization Act of 1997 (also known as the Prescription Drug User Fee Reauthorization Act of 1997)64 addresses the use and dissemination of economic evaluations in communications with managed care decision makers. The new law stipulates that health care economic information provided to a formulary committee or other similar entity with respect to the selection of drugs for managed care or similar organizations be based on competent and reliable evidence. But how this standard will be interpreted remains unclear, and the FDA has yet to offer interpretive policy. A key issue in the debate is how well managed care plans can understand the information and assess it. Importantly, the legislation does not pertain to direct advertising to consumers or physicians. A Congressional report56 that accompanied the legislation specified that the rules were not intended to allow manufacturers a path for promoting off-label indications for a drug. For example, the report noted that a model of long-term consequences of relapse prevention in schizophrenia using population-based data would be permitted once the primary prevention claim was established. However, economic claims based on prolonging patient
survival would be disallowed for agents that were approved only for the symptomatic treatment of schizophrenia. This observation would suggest that intermediate outcomes linked to longer term outcomes (e.g., mortality) in models would be prohibited if the outcome had not been established in the original trial. If so, it might be difficult to use QALYs in cost-effectiveness analyses, as the Panel on Cost Effectiveness in Health and Medicine recommends for pharmaco-economic studies.

Since rules for implementing the Food and Drug Administration Modernization Act/Prescription Drug Users Fee Reauthorization Act have yet to be written by the FDA, the status of cost-effectiveness studies of the atypical antipsychotics remains ambiguous. But the underlying demand for pharmaco-economic data is likely to continue, which means the debate over the usefulness of such studies will also persist.

**Drug name: clozapine (Clozaril).**

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