Methods of Cost-Effectiveness Analysis in the Assessment of New Drugs for Alzheimer's Disease

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New treatments for Alzheimer's disease highlight the complex clinical and financial issues at stake with new pharmacotherapies. This paper describes cost-effectiveness analysis as a method for assessing these issues. Cost-effectiveness analyses show the relationship between resources used and health benefits achieved for a medical intervention compared with an alternative strategy. In analyses of treatments of Alzheimer's disease, costs include health care resources, such as diagnostic tests, medications and efforts to monitor or treat side effects, acute hospital care, physicians' services, home health care, and nursing home care; non-health-care resources, such as support services provided by paid caregivers; and time spent by family members in unpaid provision of care and by patients in seeking care or undergoing an intervention. Effectiveness of interventions can be assessed by measuring changes in patients' cognitive functioning or by measuring years of life gained and the quality of life during those years. Cost-effectiveness studies often make use of disparate data sources, including data collected as part of randomized controlled clinical trials, and they often use mathematical models to support estimates. Because economic evaluations of new interventions for Alzheimer's disease will likely play an increasingly influential role in clinical and resource allocation in the coming years, physicians and other health system stakeholders should familiarize themselves with the techniques of cost-effectiveness analysis and become critical consumers of the literature describing these analyses. (*Psychiatric Services* 48:1440–1444, 1997)

Treatments for Alzheimer's disease, which is a progressive neurodegenerative disorder, offer a potent example of the clinical and financial issues at stake with new pharmacotherapies. Alzheimer's disease is a devastating illness, affecting patients' cognition, memory, judgment, speech, ambulation, and continence. It typically leads to impaired functioning and high rates of depression, agitation, and psychosis, and patients often eventually need total care. Alzheimer's disease has a high prevalence, affecting 4 million Americans (1). With the aging of the U.S. population, it is projected to affect more than 10 million individuals by 2040 (1,2).

The economic burden of Alzheimer's disease is enormous: estimates of the total direct and indirect costs resulting from the disorder are between $40 and $70 billion annually (3–5). One study estimated that the annual cost of caring for a patient with Alzheimer's disease averaged about $47,000 per year (in 1990 dollars) whether the patient lives at home or in a nursing home (6).

The purpose of this paper is to describe cost-effectiveness analysis as a method of assessing new drugs for Alzheimer's disease. Although methods of cost-effectiveness analysis for medical treatments have been advanced for at least two decades (7), several new issues are involved in the use of such techniques in assessing the cost-effectiveness of medication for Alzheimer's disease.

First, the pace of development and approval of new drugs to treat Alzheimer's disease has increased. Two cholinesterase inhibitors have been approved by the Food and Drug Administration (FDA)—tacrine (Cognex) in 1993 and donepezil (Aricept) in 1996—and work on medications that act through other mechanisms is under way (8).

Second, the health care system is growing ever more concerned with demonstrating that new products offer value. In practical terms, increased emphasis is placed on costs

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of treatments in addition to traditional concerns about their risks and clinical effectiveness. For new medications for Alzheimer's disease, new questions must be confronted. Do the clinical benefits of the drugs justify their costs? To what degree do potential economic benefits related to decreased medical and supportive care for patients with Alzheimer's disease offset the costs of medications? Would dollars spent on medications for Alzheimer's disease produce greater effects if they were targeted to alternative interventions?

Third, new recommendations for conducting cost-effectiveness analysis have recently been published by the U.S. Panel on Cost-Effectiveness in Health and Medicine (9). Although economic analyses of pharmacotherapies for Alzheimer's disease have been conducted (10), methods of cost-effectiveness analysis recommended by the panel have not been applied formally to evaluate these medications.

Finally, economic evaluations of new drugs for Alzheimer's disease will likely play an increasingly influential role in clinical and resource allocation decisions in the coming years. Thus clinicians should familiarize themselves with techniques used in analysis of cost-effectiveness and become critical consumers of this literature.

Alzheimer's drugs and managed care

With the FDA's approval of tacrine in 1993, physicians for the first time could offer a medication to treat the cognitive deterioration caused by Alzheimer's disease. In controlled trials, the drug produced a small but statistically significant slowing in cognitive decline among patients who were able to complete 30 weeks of treatment (11,12). Most patients could not tolerate the dosages provided, due either to reversible elevations in liver enzymes or to other side effects. Because of the potential for hepatotoxicity, the drug was approved only after three rounds of deliberations and issuance of guidelines recommending a gradual dose titration and frequent monitoring of liver function. Many U.S. health maintenance organizations declined to place the drug on their formularies, denied coverage, or required physicians to obtain special authorization before prescribing the drug (13).

Preliminary reports indicate that donepezil is better tolerated than tacrine by a greater proportion of patients (14). The absence of hepatotoxic effects eliminates the need for intensive monitoring of liver enzymes. However, clinical trials suggest that the efficacy of donepezil is also modest—similar to the modest efficacy of tacrine—and current understanding of the neurophysiology of Alzheimer's disease suggests that any clinical benefit from the drug, like that of tacrine, will be transient. Thus health care payers and managed care organizations continue to be faced with a considerable dilemma: weighing the clinical need and immense expected demand for Alzheimer's disease therapies against the cost and limited effectiveness of current medications.

Although physicians and patients have always weighed clinical benefits versus risks in evaluating potential treatments, in the new health care environment—which is characterized by an integration of delivery systems and centralization of decision making in the use of health care resources—cost has become part of the equation. Medications compete for positions in drug formularies and for shares of drug budgets; newer, more expensive products face greater scrutiny from drug utilization review organizations and other oversight bodies.

Cost-effectiveness in health and medicine

The cost-effectiveness principle

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. The cost-effectiveness ratio reflects the difference in the interventions' costs divided by the difference in their health effectiveness. Cost-effectiveness analyses allow for comparisons across a broad spectrum of interventions and clinical conditions as long as the numerators and denominators from different ratios are reported in similar terms and are obtained by similar methods (15). Such analysis has been used to study a broad range of drugs, including those used in the treatment of hypertension (16), hypercholesterolemia (17), and complications from AIDS (18, 19), as well as psychiatric treatments, including psychotherapy and atypical antipsychotic drugs such as clozapine for the treatment of schizophrenia (20).

Costs

In cost-effectiveness analysis, costs are thought of as the value of the resources consumed as part of a health intervention. (In economic terms, the real cost of a resource is the value of the resource in its next best use to society.) Moreover, costs are defined in net terms: that is, they include both the costs and potential savings resulting from use of an intervention. As recommended by the Panel on Cost-Effectiveness in Health and Medicine, costs—for both the intervention under study and the comparison condition—should include several components, such as changes in health care resources, changes in non-health-care resources, and changes in the use of time.

For cost-effectiveness analyses of treatments for Alzheimer's disease, health care resources would include diagnostic tests, medications, short-term acute hospital care, physicians' services, home health care, nursing home care, long-term psychiatric hospital care, and any costs associated with monitoring or treating the drug's side effects. Non-health-care resources would include items such as support services provided by paid caregivers.

Time costs should include the unpaid provision of care by family members and the time patients spend seeking care or undergoing an intervention. Conceptually, time represents a real cost, because time spent obtaining or providing care could be productively spent in other endeavors. Treatments that reduce caregiver time and burden may have a substantial impact on nonmedical and time costs, regardless of their impact on medical costs (6).

Once appropriate components of these different domains of cost are identified, they must be assigned a value. Because it is difficult to know the actual value of the resources consumed in the production of services, analysts often use approximations. For example, the cost of medication is often approximated by the price of the drug; the cost of a physician visit or hospital admission is often valued using the appropriate Medicare fees. Caregiver time is often valued by using the average hourly wage of home health care workers, who would have to be hired if the patient's caregiver were not performing these tasks.

Health effectiveness

Clinical trials of new drugs for Alzheimer's disease have assessed health effectiveness using intermediate measures such as scores on the Mini Mental State Examination (MMSE), the Alzheimer's Disease Assessment Scale—Cognition (ADAS-Cog), or other instruments as their primary endpoints (11,12,14). Conceivably, a cost-effectiveness ratio of a new drug for Alzheimer's disease could show the cost per unit change on the MMSE or ADAS-Cog for patients who receive the drug compared with patients who receive placebo. The advantage of using a scale such as the MMSE is that it focuses on a dimension of primary interest—cognitive functioning—and is familiar to clinicians who treat patients with Alzheimer's disease.

But analyses of this kind are limited in two important respects. One is that it is difficult to interpret the scale, because the MMSE is not an interval scale; that is, the difference between a score of 28 and 29 may not have the same meaning as the difference between a score of 7 and 8. A second limitation is that the MMSE does not permit comparisons of treatments for Alzheimer's disease with interventions for other medical conditions. To inform societal decisions about which of many competing interventions produces the greatest overall gain in health for the resources expended, we need to evaluate the cost-effectiveness of diverse medical interventions in similar terms. Comparisons of cost-effectiveness ratios across treatments would then illustrate the most efficient ways to furnish health benefits: lower cost-effectiveness ratios would reflect more efficient ways to produce health.

One way to standardize cost-effectiveness ratios is to measure the health effects of different interventions in terms of their impact on life expectancy—the cost-effectiveness ratio for each alternative would reflect the costs per year of life gained. But a limitation of this approach is that life expectancy alone does not take into account the quality of the additional time that is gained; in this approach an added month of life with dementia is valued the same as an added month without dementia. Ideally, an analysis should capture such effects. The recommended approach is to measure health outcomes in terms of "quality-adjusted" life years to incorporate both the prolongation and the quality of life (7).

Time costs should include the unpaid provision of care by family members and the time patients spend seeking care or undergoing an intervention.

Cost-effectiveness analyses that use quality-adjusted life years as the measure of effectiveness have been labeled "cost-utility" analyses by some authors (21). In this paper, we follow the practice of the Panel on Cost-Effectiveness in Health and Medicine to describe such studies using the more generic term, cost-effectiveness analyses (15).

Quality-adjusted life years represent the benefit of a health intervention as time in a series of "quality-weighted" health states. The quality weights reflect the desirability of being in the state, from "perfect" health, weighted 1, to death, weighted 0. Once the quality weights are obtained for each state, they are multiplied by the time spent in the state; these products are summed to obtain the total number of quality-adjusted life years.

Methods for determining quality weights continue to be an active area of research and debate. The Panel on Cost-Effectiveness in Health and Medicine has recommended that quality weightings should reflect the perspective of a representative sample of the population (9). For example, if researchers seek to evaluate the value of new treatment protocols for breast cancer, they may elicit quality weightings from patients with breast cancer of the relevant stage and grade. Alternatively, to make comparisons among interventions for a variety of medical conditions, the panel recommends that researchers assess a broader societal perspective and elicit quality weightings from randomly selected members of the community.

One way to obtain community-based preference weights is 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. Each dimension is further subdivided by level of severity. For example, one such system, the Health Utilities Index, contains eight dimensions: vision, hearing, speech, emotion, pain, ambulation, dexterity, and cognition (22,23). The cognition dimension in turn comprises four levels of severity: able to remember most things, somewhat forgetful, very forgetful, and unable to remember anything at all.

The idea behind 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. For example, patients with Alzheimer's disease would be assigned, based on their clinical profiles, into relevant cells of the system. An observer, who could be a clinician or a family member,

would complete a questionnaire that asks about the patient's functioning on the domains of the system such as ambulation and cognition. 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. Currently, work is proceeding to test the validity of using such methods with patients with Alzheimer's disease and their caregivers (24).

Among the techniques used to obtain the community-based preference weights are the "standard gamble" and "time trade-off" methods, which involve asking respondents to value health states—for example, a state with mild chest pain and limited ambulation—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, 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.

Data sources and use of models

An area of debate among cost-effectiveness analysts in recent years concerns the use of disparate data sources and models to support estimates (25,26). One way to obtain input data on costs and health-related quality of life is to collect it as part of a randomized controlled clinical trial. Cost-effectiveness analyses using such methods are in many ways ideal, because they provide comparable data on both a group of patients who are receiving an experimental intervention and a valid control group. More commonly, however, cost-effectiveness analysts face a situation in which economic and quality-of-life data have not been collected as part of the trial, or the information that was collected is incomplete and they must rely on other sources of data.

Generally, some estimates are available from the published literature. For example, existing studies provide some information on the costs of caring for people with Alzheimer's disease (5,6,27). In some cases, analyses of secondary databases, such as Alzheimer's disease registries (28), may also be useful.

In addition, cost-effectiveness analyses often use mathematical models in situations where data are limited or unavailable and where a complex interplay of factors leads to considerable uncertainty about future events. For example, to assess the impact of a new drug for treatment of Alzheimer's disease on long-term costs and health outcomes, analyses would ideally be based on experimental and observational data with no assumptions. But randomized controlled trials provide data for only a short window of time, typically three to six months, and the outcomes of interest, such as nursing home admissions, commonly occur long after the trial is completed.

To inform societal decisions about which competing intervention produces the greatest gain in health for the resources expended, we need to evaluate the cost-effectiveness of diverse interventions in similar terms.

Models can help shed light on such issues by structuring the decision at hand and characterizing the information needed to fill the structure (29). Although all models are simplifications of real-world phenomena, good models allow for systematic analysis that quantifies the impact of uncertainty and tests for multiple assumptions that can be made explicit. In their recommendations, the Panel on Cost-Effectiveness endorsed the use of models as a valid mode of scientific inquiry when direct primary or secondary empirical evaluation is not possible (15).

A popular model for clinical decision making is the Markov model, which depicts the course of a disease as a progression through different stages or "states," such as mild, moderate, and severe dementia (30,31). Such models are particularly useful in studying chronic and progressive diseases, where short-term data must be used to forecast long-term outcomes (32,33). If each state is assigned a cost and quality-of-life weight, the paths of two cohorts—one with and one without the drug—can be compared in terms of their costs and quality-adjusted life expectancy. A Markov model could thus address the question of whether a new drug, through its ability to slow cognitive deterioration and thus forestall progression to a more severe stage of Alzheimer's disease and the need for more costly residential settings, would produce health care cost savings or quality-of-life improvements over the option of no treatment.

Other considerations

Because methods used in cost-effectiveness analyses can vary widely (34), it is important for readers of the literature to ask questions about how studies were conducted. Accounts of studies should be precise about the sources and characteristics of the data used. For example, in examining efficacy data derived from a randomized clinical trial, the reader should ask questions about the characteristics of the study population and thus the generalizability of the study findings; the intervention used, including drug dose, duration of treatment, and whether and why subjects dropped out; and the nature of the analyses, including whether they include all patients initially enrolled or only those who successfully completed the trial.

All of the study's assumptions should be made explicit. For example, because of the ongoing neurodegeneration characteristic of Alzheimer's disease, the impact of anticholinesterases is expected to be transient, perhaps lasting one to two years. Randomized controlled trials have lasted only six months at most,

although patients may remain on the drugs for several years. As a result, definitive information on the duration of effect is not available. Thus cost-effectiveness analyses should include sensitivity analyses to determine if conclusions change markedly when the values of key variables, such as the duration of the drug effect, are altered.

It is also important to consider the perspective or viewpoint of the analysis. An analysis assuming the perspective of a managed care plan would include only those costs borne by the plan and would likely exclude other costs, such as those associated with nursing home care. The Panel on Cost-Effectiveness in Health and Medicine recommended that cost-effectiveness analyses present results both from a societal perspective—including all costs and health effects, regardless of who receives them—and from the narrower perspective relating to the particular interests of the decision maker (15). A societal perspective was recommended because it takes the broadest viewpoint and allows for comparisons with other interventions for diverse conditions.

Finally, cost-effectiveness analysis is intended as an aid to decision making, not as a rigid standard unto itself (15).

Conclusions

Cost-effectiveness analysis can serve as an important tool for evaluating costs, risks, and clinical effectiveness in a rigorous and systematic way. As new drugs for Alzheimer's disease are developed and used, and as considerations of cost-effectiveness become more important, clinicians and other health care decision makers would be well served by becoming more discerning consumers of the information generated by cost-effectiveness analyses. ♦

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