THE ECONOMICS OF THE TREATMENT OF SCHIZOPHRENIA

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ECONOMICS OF MENTAL HEALTH AND SCHIZOPHRENIA

Prior to the 1980s, economists paid scant attention to schizophrenia, or indeed to mental health in general (1). Early work in the field included efforts to consider the impact of organization and financing on system efficiency and to address the supply of personnel in caring for persons with mental illness. For example, McGuire (2) reviewed the market for psychotherapy and the insurability of mental health care, and Frank (3) examined the supply of psychiatrists. Researchers at RAND analyzed the impact of cost-sharing on demand for mental health care (4). The use of diagnosis-related groupings to pay for care under prospective payment was considered by Taube and his colleagues (5). Dickey and Goldman (6) reviewed the impact of various funding mechanisms in public mental health.

During the 1990s, work on insurance, regulation, and the organization of mental health services continued. Studies of insurance mandates for mental health care, such as Frank and colleagues' (7) simulation of mandates and related costs, provided valuable information to state legislators considering such laws. Observers of systems change considered major reorganizational efforts, such as those implemented through the Robert Wood Johnson Program on Chronic Mental Illness (8) and other types of organizational reforms (9–12). The 1990s also brought analysis of the increasing implementation of managed care with behavioral health carve-outs (13).

These examples of the contributions of mental health

Costs Of Schizophrenia

Early studies of the costs of mental illness (15–17) did not distinguish between the costs of different diagnostic categories (18). More recent studies have estimated specific costs for schizophrenia and other illnesses. Rice has estimated the cost of schizophrenia in the United States at \$32.5 billion in 1990 (19) and \$44.9 billion in 1994 (20). Goeree and colleagues (21) have calculated costs in Canada in 1996 to be approximately \$2.35 billion, whereas Knapp (22) has estimated the costs of schizophrenia in the United Kingdom to be 2.6 billion pounds. Some schizophrenia cost studies

focus only on service costs, such as Rund and Ruud's (23)

study of costs in Norway and Martin and Miller's (24) study

economists indicate the range of activities in the field of mental health economics, including the economics of schizophrenia. This chapter focuses on two aspects of the economics of schizophrenia: cost studies and cost-effectiveness studies. Studies of the cost of mental illnesses appeared before other types of work in the economics of mental health, and they have continued throughout the past two decades. Cost studies lay the foundation for cost-effectiveness and cost-benefit studies because they identify the range of resources that are consumed as a result of an illness. Costeffectiveness analyses of mental health programs began to appear in the early 1980s with the hallmark study by Weisbrod and colleagues (14) on the cost-benefit of assertive community treatment teams. Collectively, studies of costs and cost-effectiveness are perhaps the most important foci of the economics of schizophrenia. First, the sizable cost to society captures the attention of policy makers and taxpayers, and convinces them of the huge fiscal impact of schizophrenia. Second, decisions by clinicians, managers, and policy makers that are informed by research on costs and cost-effectiveness lead to better distribution of the resources

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of Georgia Medicaid recipients. In contrast, Rice's and Knapp's studies include both direct costs (treatment and other service costs) and indirect costs, such as lost income. But no study of the cost of schizophrenia can claim to capture all costs. As noted by McGuire (18), even comprehensive studies of the cost of schizophrenia often underestimate two types of costs: the costs to families and the costs of publicly owned capital.

Cost Perspective

Cost-of-illness studies like Rice's and Knapp's typically employ the perspective of society; that is, they consider economic costs. Economic, or social, costs are the costs of resources consumed because of an illness. Cost-effectiveness and cost-benefit analysis should always state the perspective from which the study is undertaken. Although a societal perspective presumably provides the balanced view of the neutral scientist, it is also helpful to examine costs from perspectives of particular stakeholders. For example, in an analysis of the impact of Assertive Community Treatment in Connecticut, Essock and colleagues (25) present costs from the perspectives of society, the state, and the Department of Mental Health. Comparison of the results from multiple perspectives may identify areas of cost-shifting that results from certain programs and policies. For example, a treatment that reduces hospital days may shift costs from state-run inpatient facilities to private nonprofit outpatient settings.

Cost Components

Costs of Treatment and other Services

The examples provided by Rice and Knapp are instructive for those conducting cost-of-illness studies and cost-effectiveness studies in the area of schizophrenia. As they show, there are many ways in which the illness is associated with greater costs. First are the costs of treatment, including medication. Treatment may be offered by public, private, or voluntary sector settings, and many persons with schizophrenia receive care in multiple places. Besides treatment, services like case management, vocational rehabilitation, and psychosocial clubhouses generate significant costs. Medical and surgical costs also may be relevant in cost-effectiveness analyses, because utilization of these services may vary depending on the adequacy of mental health care (26,27).

Lost Productivity and Family Burden

Mental illnesses, like other disorders, cause people to lose workdays (28) and sometimes even to forfeit aspirations of having any career at all. Although lost productivity is usually addressed in comprehensive studies of the costs of schizophrenia, many studies of interventions for persons with schizophrenia have ignored productivity losses, because of the high rates of disability in this population. However, new strategies for improving the employment outcomes for persons with serious mental illness, such as Individual Placement and Support (29), have made employment a realistic goal of rehabilitation. These new successes suggest that loss of productivity should be included when calculating the cost of interventions for persons with schizophrenia. In addition to the productivity losses of the individual, cost studies should attend to the work losses of family members, and other contributions of time and in-kind services (30).

Capital Costs

Economic cost studies appropriately study the opportunity costs of all resources, that is, the value of those resources in their best alternative use. In a cost-effectiveness study of a new residential model for persons with serious mental illness, Cannon and her colleagues (31) carefully considered the value of capital costs of a public hospital, which would have been underestimated if valued through traditional methods of depreciation. Capital costs can be large enough to change the most basic findings of a cost study, as shown by Rosenheck and colleagues (32). Public administrators may not consider the value of buildings and property to be part of a cost equation because it is not always part of the operating costs, but the value of the property in alternative use may be considerable.

Other Components

Especially where an intervention is expected to have an impact on co-occurring substance use disorders, it is important to attend to criminal justice costs (33). Another neglected aspect of cost studies is the costs of administering transfer payments (such as social security). Although disability payments themselves do not represent the use of new resources, the cost of administering these payments is a cost that should be counted, especially if the intervention could change the rate of receipt of disability payments or other public benefits (34). For example, an intervention that returns people to work will not only increase their productivity (a benefit), but also decrease disability payments (decrease a cost).

The importance of including any type of cost in a costeffectiveness study is related to the potential impact of the cost type on the study findings. The larger the cost per unit, or the more frequently it is used, the more carefully it should be assessed (35). But should cost-effectiveness analyses always be conducted? As indicated by the range of costs and cost perspectives that might be included, these studies can be expensive to implement. This expense is further increased because, to detect meaningful differences in a highly variable outcome such as cost, significantly more study participants may be needed than for an effectiveness study alone. The usefulness depends in large part on the likelihood that the treatment or intervention under study will have an effect on costs—either positive or negative. Cost studies are critical in the analysis of novel antipsychotic agents because of the relatively high acquisition costs of the drugs, compared to conventional antipsychotic medications, and because of the potential of these drugs to reduce the number of days that people with schizophrenia are hospitalized (36).

COST-EFFECTIVENESS

The success of interventions in schizophrenia, whether medications or psychosocial rehabilitation programs, is reflected in multiple domains. An antipsychotic may have an impact on cognition, on hallucinations, on affect, on disruptiveness, on sexual functioning, on extrapyramidal side effects, on weight, on employment—the list goes on and on. These are all measures of the effectiveness of the agent, some positive and some negative. Some, such as hallucinations and delusions, may be influenced much more directly by the medication than more distal outcomes such as housing or employment. Different individuals value changes in these domains differently (elimination of hearing voices that other people don't hear may be much more important to the person who is troubled by harassing voices making a steady stream of demeaning comments than to the person whose voices are good company or connect the patient to an imagined network of internationally renowned researchers). Similarly, some people are very troubled by changes in weight or sexual functioning, whereas such changes mean little to others. Hence, much as we would like a composite measure across all effectiveness domains, this reductionistic approach is fraught with untenable compromises. Just as there is variation among different patients and different providers, patients and payers ascribe different values to the same outcome (e.g., legislators who make funding allocations to public mental health systems may be more concerned about decreases in violence and patients may be more concerned with increases in quality of life). How much is a symptomfree day worth? It depends on who is asking and who is paying.

Cost-effectiveness analyses have evolved to deal with the multiple domains touched by a single treatment. Such analyses report the change in a given effectiveness measure associated with a particular cost investment in treatment. A medication may be cost-effective with respect to certain outcomes, cost-neutral for others, and costly for yet others. Lehman (37) reminds us that the current explosion of new knowledge about effective treatments and the advent of evidence-based quality standards for treating schizophrenia come at a time when cost containment is paramount in the health policy agenda. Policy makers need to know the impact of dollars invested in treatment—but not just in a

single domain like reductions in hospital care. Those who make purchasing decisions for the public systems of care under which most of the country's treatment for schizophrenia is funded need information on multiple domains of effectiveness.

An alternative to cost-effectiveness analysis is cost-utility analysis, where a comprehensive outcome indicator is calculated as a preference-weighted sum of the outcome measures. An example of a cost-utility approach is the use of quality-adjusted life years (QALYs) (38,39). As noted above, different stakeholder groups value different outcomes differently; hence, approaches such as QALYs create an effectiveness metric representative of at best only one stakeholder group, and at worst the resulting metric is representative of no one. Although elegant in presentation, as with sausages, observing their creation can reduce enthusiasm for their use. One must find or create weights to apply to the various effectiveness measures and then decide on a combination scheme—deciding, for example, what weight gain is the equivalent of what change in extrapyramidal side effects (EPSs) and what change in psychotic symptoms. Typically, one does this either by interviewing individuals representative of the population under study (e.g., treatment refractory patients with schizophrenia) or by adopting someone else's measures as close enough. Because "close enough" is a very subjective call, it is important for researchers to disclose the sources of the weighting estimates so that readers can make their own call. For example, Rosenheck and colleagues' (40) report of changes in QALYs among mostly male veterans with schizophrenia used weights derived as part of a doctoral dissertation by Kleinman (Johns Hopkins University, 1995) of mainly African-American women, only about half of whom (55%) were diagnosed with schizophrenia (the rest were diagnosed with major depression, bipolar, and other affective disorders). We were unwilling to take the leap of faith needed to generalize from groups this disparate when presenting cost-effectiveness results from our own work (41). Nevertheless, Rosenheck and colleagues are to be commended for providing the information necessary to follow back their methods to see what was used. This is not always the case.

Another type of utility analysis is the measure of symptom-free days (42). Under such analyses, interventions are compared with respect to the number of symptom-free days they produce. Following the methodology of Lave and colleagues (43), Simon and colleagues (42) credited a study participant with having one depression-free day if the study participant had 2 days with a depression score of 0.5. Many people with depression, as well as many researchers, would take issue with saying that someone was symptom free for half a year if they reported having 50% of full symptoms for each day of that year. Symptom-free days may be a poor measure within schizophrenia studies simply because, unlike with depression, symptoms and functioning are poorly cor-

related, and the likelihood of having a completely symptomfree day is rather small.

Disability-adjusted life years (DALYs), where one DALY equals one lost year of healthy life, can also be used to express years lost, both to premature death and to disabilities associated with living with schizophrenia (44). In contrast to QALYs and estimates of symptom-free days, DALYs are proxies for negative outcomes (45) and, as such, the calculation of cost-effectiveness centers around how many DALYs are saved by using a particular intervention. In a population where individuals may live for a long period of time with a relatively debilitating illness like schizophrenia, measures of mortality alone do not adequately capture the impact of the disability. DALYs are calculated by adding together the number of years between mortality and life expectancy (years of life lost, YLL) and the number of years lived with a disability (YLDs). Calculating YLDs requires making assumptions about the relative impact of illness onset, duration, and severity on healthy living (for example, making an assumption that a first psychotic episode at age 15 is worse than a first episode at age 25). As with QALYs, these metrics can be derived by surveying individuals with schizophrenia or their proxies, with the accompanying assumptions that how one weights hypothetical events is the same as the trade-offs one would make if one could trade fewer days of healthy life for more days of life with particular disabilities. Because such ratings are inherently untestable by rigorous methods, whether reliable or not, their validity remains suspect. Further, the calculation of DALYs "presupposes that life years of disabled people are worth less than life years of people without disabilities" (46), and may even rank some individuals' lives as worse than death (47). Schizophrenia brings with it an increased risk of suicide (48), which is consistent with DALYs ranking some lives as worse than death. However, assuming that person A and person B, in reality, would make the same choices as to what fates are worse than death presumes an ecologic validity to DALY ratings that may be unwarranted.

Cost-utility measures such as QALYs, DALYs, and measures like symptom-free days, have enormous appeal because of their ability to reduce multiple effectiveness domains to a single bullet measure. By deriving a single measure, one can compare any treatment approach to any other treatment approach. Where the measure is reduced to dollars (as in QALYs), one may even compare the values of interventions between different conditions (38), for example, if dollars expended on diabetes reap more benefits than dollars spent on schizophrenia. But the assumptions built into such bullet measures may have limited usefulness for informing decisions at the level of the individual patient, prescriber, or health care payer. These individuals weigh their particular circumstances, and may be unwilling to have others' preferences serve as proxies for their own. Instead, these stakeholders are asking more specific questions. For example, the mental health commissioner asks, "If I put an extra \$3 million in the pharmacy budget for medication X, what can I expect this to buy me in terms of the other domains under my purview, and what is the downside risk? What will it buy me in terms of reductions in hospital use, improvements in vocational functioning, reductions in violent episodes, and reductions in side effects?" Similarly, patients and families paying for medications ask, "If I increase/decrease my spending by changing to medication X, what changes am I likely to see in the voices I hear, in my employability, in my sexual functioning, and in my body movements?"

An alternative to composite measures are measures that contrast costs invested to a variety of outcome domains, some of which will be more important to some stakeholders than to others. An analogy is a proposal for a city park to be funded from multiple sources. Depending on one's perspective (e.g., whether you would use the park, how the park would impact the value of your property, your safety, your recreational options, what you are called on to invest), the park may or may not be a good idea. And, depending on who is paying for what, and which outcome domains are most important to you, you may stand to get a lot or a little out of the dollars going into the park. The challenge is to present the data on costs and effects in such a way that the various payers (the city, private foundations, neighborhood organizations, individual contributors) can each look from their own perspective, see what the expected gains and losses are in the outcome domains they care about most (less street noise, more open space, more dogs, more people drawn to the neighborhood), perform their own idiosyncratic weighting of these factors, and decide if they are in favor of the park or not.

In contrast to cost-utility analysis, cost-effectiveness analysis does not reduce the impact of an intervention into one measure. Some outcomes may be clearly preferential or "dominant choices" (e.g., lower costs and higher effectiveness). Other outcomes are not as clearly dominant, and in these cases it may be useful to show the likely range of cost compared to multiple domains of effectiveness. One method of examining these ranges is to create sampling distributions for costs and effectiveness measures to show the precision of estimates as well as their mean. For example, bootstrap techniques use every study participant's data to create an empirical sampling distribution of the test statistic and plot these estimates as a cost-effectiveness plane. Bootstrapping techniques offer one means of describing confidence intervals for incremental cost-effectiveness ratios (ICERs) (49,50). Cost data are often highly positively skewed, and ICERs provide less biased estimates of confidence intervals in highly skewed cost data (43,51,52).

Figure 57.1 shows such an approach when considering the cost-effectiveness of clozapine compared to conventional agents among long-stay state hospital patients (41). The cluster of points displays the sampling distribution of the ICER. Most of the points fall in the lower-right quadrant, indicating that clozapine is most likely to be less costly and

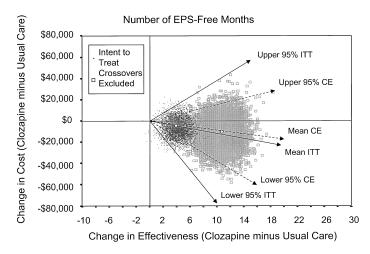


FIGURE 57.1. Ten thousand bootstrap replications plotted in the cost-effectiveness plane (intent-to-treat, N = 136 clozapine and N = 87 usual care; treatment crossovers excluded, N = 89clozapine and N = 30 usual care). The x-axis and y-axis, respectively, show the difference between clozapine and usual-care groups in estimated number of extrapyramidal side effects (EPS)-free months and total cost during a 2-year period. The quadrant to the lower right of the origin (0,0) contains those estimates where clozapine was found to be less costly and more effective than the usual care (80% of the estimates for the intent-to-treat analyses and 81% of the estimates when treatment crossovers are excluded). (From Essock SM, Frisman LK, Covell NH, et al. Cost-effectiveness of clozapine compared with conventional antipsychotic medication for patients in state hospitals. Arch Gen Psychiatry 2000;57:992, with permission. Copyright 2000 American Medical Association.)

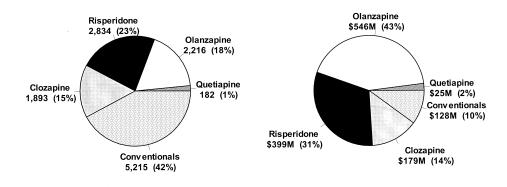
more effective than conventional antipsychotic agents from the cost perspective (total societal cost) and for the effectiveness measure in question (reduction in EPS). Such displays of information give the reader/policy maker a sense of the tightness of the point estimate and the risk of falling in a quadrant other than the one indicating cost-effectiveness. One can use these sampling distributions to create cost-acceptability curves from the viewpoint of particular payers for particular outcomes (e.g., the likelihood that the intervention will be cost effective for the payer who is willing to risk \$1, \$10, or \$100 to obtain an 80% likelihood of return in sexual functioning).

Saul Feldman (53) has held positions as the head of the National Institute of Mental Health (NIMH) Staff College and chief executive officer of one of the country's largest managed behavioral health care organizations. Thus, he has been in a position to make policy based on research, and to inform policy makers with research. He has posed the question, Is good research good if it does not inform policy

and practice? It is incumbent on mental health services researchers to report their findings in ways that speak to funders and service system managers, which means providing estimates of the most likely outcome as well as the likelihood of alternative outcomes.

COST OF THE NEWER ANTIPSYCHOTIC MEDICATIONS

In general, the acquisition cost of the newer antipsychotic medications is greater than that of conventional ones. These acquisition costs are reflected in formulary budgets. Once a relatively small component of treatment costs, formulary budgets in psychiatric settings have risen dramatically in the past decade, and the market share of the newer agents has risen as they have replaced the less costly conventional agents. Figure 57.2 shows the distribution of antipsychotic prescriptions paid for by Medicaid in 1998 (left) and the



Frequency (in thousands)

Cost (in millions)

FIGURE 57.2. Distribution of (*left circle*) and total dollars paid (*right circle*) by Medicaid for antipsychotic medication prescriptions during 1998. Newer antipsychotic medications represented slightly over half of the total prescriptions, and they were responsible for 90% of the total cost.

dollars Medicaid paid for these prescriptions (right). These data show that the newer agents account for 58% of all antipsychotic prescriptions paid for by Medicaid but for \$1.15 billion (90%) of the \$1.28 billion in Medicaid costs for antipsychotic prescriptions. These charts dramatically display the disparity in medication costs associated with the newer versus the conventional agents.

This price difference between the older and the newer antipsychotic medications, which can be a 100-fold difference (e.g., when contrasting generic oral haloperidol with nongeneric Clozaril), prompted scores of studies asking the cost impact of using the newer medications when more than simply the cost of the medication was considered. For example, if using new and expensive medication X results in fewer days hospitalized than some alternative, then, all else being equal, using X will reduce overall costs as long as the cost savings associated with fewer days in the hospital is greater than the cost difference between medication X and the alternative.

Clozapine Cost Effectiveness Studies As Case Examples

The rub, of course, is that "all else" is rarely equal in effectiveness or cost-effectiveness studies, and the early cost projections concerning the impact of using clozapine often suffered from faulty assumptions about what was equivalent. Many of these studies were pre-post comparisons that examined changes in hospital use and lacked a comparison group (54-60). For example, the study by Meltzer and colleagues (59) of patients with schizophrenia who were taking clozapine collected retrospective cost data for 2 years before and after these 47 individuals began taking clozapine and concluded that clozapine was associated with a 23% drop in treatment costs. This study generated a series of letters criticizing the study's methodology (61-63) [see also the response by Meltzer and Cola (64)]. Critics focused on the problem of the regression toward the mean that can be expected whenever study participants are enrolled during a low point in their functioning (such as may have prompted the initiation of clozapine), and on the other potential temporal and case-mix confounds associated with mirror-image studies of individuals who were selected to begin a medication through other than a random-assignment process among all eligibles.

The results of the two randomized clinical trials of clozapine's cost-effectiveness each showed much more modest benefits associated with clozapine, both in the 2-year, openlabel trial comparing clozapine to the usual care with a range of conventional antipsychotics among long-term patients in state hospitals (41,65,66), and in the 1-year masked trial comparing clozapine to haloperidol among veterans hospitalized for a year or less (67). Each trial showed clozapine to be somewhat more effective than the comparison agents, and this increase in effectiveness comes at no additional cost when costs are viewed from a societal perspective. Each trial

also showed that clozapine is more effective than the usual care in minimizing days hospitalized, enough so that the reduction in hospital days more than covers the increased cost of the medication plus increased outpatient services. But, from more narrow perspectives (e.g., the hospital formulary budget, capitated outpatient service providers), clozapine would be viewed as increasing their costs. For costeffectiveness studies to influence planning and policy making, the perspectives of these different payers need to be taken into account because it is these local incentives and disincentives that must be addressed to be sure that the fiscal incentives are lined up to promote good care. A hospital would have a great incentive to use clozapine for a heavy user of hospital services if it has a fixed budget (the case with most state hospitals), but a hospital paid a per diem would have no such incentive.

Lengthy randomized clinical trials in routine practice settings, such as the clozapine study in Connecticut state hospitals and the clozapine study in Veterans Administration (VA) hospitals, suffer from treatment crossovers. By the end of 6 months in the Connecticut study, only 11% of the usual care patients had begun a trial on clozapine, but by the end of 24 months in the study, 66% had. In the VA clozapine study, 72% of the patients assigned to masked haloperidol had ceased taking the masked medication by the end of the 1-year study period, with 49 of 157 (31%) of them switching to clozapine and the rest to conventional antipsychotics, including unmasked haloperidol (67). Because of the biases introduced by what is likely to be highly nonrandom discontinuation of the assigned treatment, the importance of intent-to-treat analyses and the unspecified biases of crossovers-excluded analyses are well documented (68). Regardless, when crossovers are common, analyses excluding crossovers offer a proxy for the best-case scenarios for each treatment condition by comparing only those who do well enough on treatment A to stay on it with only those who do well enough on treatment B to stay on it. Figure 57.1 illustrates this using data from the Connecticut clozapine study. The exclusion of treatment crossovers increases the apparent effectiveness of clozapine (the crossoversexcluded oval is shifted to the right of the intent-to-treat oval in Fig. 57.1) and decreased the estimate of the relative costliness of clozapine (the crossovers-excluded oval is shifted lower by about \$5,500) (41). Clearly, individuals who leave their assigned treatment are different in terms of costs and outcomes from those who remain in their assigned treatment condition.

Another difficulty when trying to assess relative costs is the great variability in costs across patients. For example, in the VA study just cited, health care costs in the 6 months prior to randomization were approximately \$27,000 with a standard deviation of about \$17,000 (67). For the Connecticut clozapine study, the 95% confidence interval for patients assigned to clozapine was \$96,847 to \$114,308 for year 2 versus \$103,665 to \$121,144 for those assigned to the usual care. With such variability, cost differences are

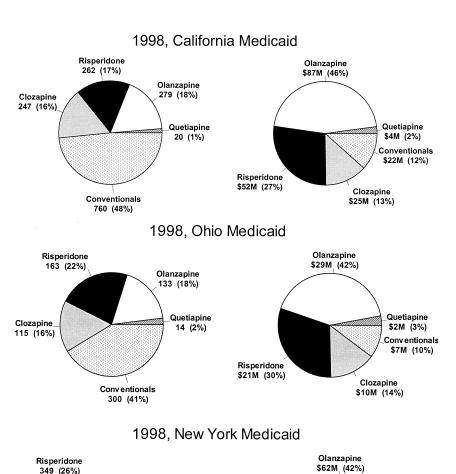
very difficult to detect, even with the relatively large sample sizes of the VA and Connecticut trials (N=423 and 227, respectively). Even for individuals who are heavy service users at study entry, mounting a trial powered to detect cost differences requires hundreds of individuals per treatment arm. If the trial were a study of outpatients who are infrequent users of expensive services like hospitals, it would require even larger samples to detect cost differences apart from medication.

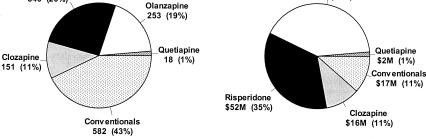
From a public health perspective, an emphasis on point estimates of costs and effectiveness is misguided when the confidence intervals are so broad. Economists would call clozapine the dominant alternative in these randomized trials (because most of the range spanned by the cost confidence intervals includes the values where clozapine costs less

than or the same as the usual care and the effectiveness measures favor clozapine or are neutral). The reduction of data to such a point estimate belies the broad distribution of possible outcomes that are likely to occur across patients. Planners and policy makers, as well as patients and their treating clinicians, need a sense of the range of possible outcomes and their relative likelihood to inform their decisions about what chances they want to take.

Costs Associated with Risperidone, Olanzapine, and Quetiapine

Figure 57.3 shows the frequency of prescribing by type of antipsychotic in three large states in different parts of the country among individuals whose medications are paid via





Frequency (in thousands)

Cost (in millions)

FIGURE 57.3. Distribution of (*left circles*) and total dollars paid (*right circles*) by Medicaid for antipsychotic medication prescriptions in California, Ohio, and New York during 1998.

Medicaid. Because Medicaid formularies allow unrestricted access to any of these medications independent of location in the country and the same financial incentives apply, one would expect to see similar rates of prescribing these medications. Indeed, the distributions do appear quite similar to each other and to the national data (Fig. 57.2). That these distributions do not reflect what we know about the relative effectiveness of these agents suggests that other factors are strong influences on medication choice and that these influences combine to create similar patterns of antipsychotic prescribing under Medicaid nationwide. In addition to factors such as effectiveness, factors as disparate as patients' past histories of medication use, order of receiving Food and Drug Administration (FDA) approval, convenience of use, acquisition costs, relative marketing budgets, and sideeffect profiles may also be at play. These figures serve as reminders that medications are started and discontinued for reasons other than effectiveness. (Data for these pie charts were extracted from the Health Care Financing Administration's (HCFA) Web site http://medicare.hcfa.gov/medicaid/ drug5.htm; potential users take note that, as of March 2000, the Web site reported Medicaid expenditures in cents rather than dollars and does not label the cost units.)

Several studies of risperidone and olanzapine also suggest that the acquisition costs of these medications may be offset by reduction in use of more expensive health care services such as inpatient treatment. Many of these studies have methodologic shortcomings similar to those of the earlier cost studies of clozapine described above. Another concern is that industry sponsorship of many of these studies means that they do not meet the criteria for lack of an incentive for bias set forth by the New England Journal of Medicine (69), whose editors noted that the opportunities for introducing bias into economic studies are far greater than in studies of biological phenomena because of the unusually discretionary nature of model building and data selection in such analyses, and because drug costs in particular can be quite arbitrary as they are prices (not costs) set by the manufacturer. Hence, additional work is needed in this area.

In general, the studies by the medications' manufacturers show support for cost reductions favoring that manufacturer's medication [e.g., for risperidone (70) and for olanzapine (71,72)]. Although such studies form good starting points for further investigation, they need follow-up by independent investigators to assess how the agents' cost-effectiveness plays out in broader settings with representative patients, lest best-case examples be generalized to settings where they are not applicable and used to set policy there. An example of an important follow-up study is that of Conley and colleagues (73), who found that, among 84 treatment-refractory patients randomly assigned to a double-blind 8-week fixed-dose trial of either olanzapine or chlorpromazine, olanzapine appeared to have limited efficacy, showing only a 7% response. Hence, the reduction in treatment costs associated with olanzapine noted in the reviews of Palmer and colleagues (74) and Foster and Goa (75) would not be expected among treatment-refractory patients, even though these patients are heavy users of inpatient services. Under other scenarios, these patients are the very ones for whom new interventions are associated with cost savings because they have higher initial rates of utilization on which to show an impact (25,40). An independent study of risperidone compared to conventional antipsychotics among outpatients with schizophrenia using a matched comparison group found no difference in total treatment costs or effectiveness measures, although there was a trend for the risperidone-treated group to have higher costs, attributable to higher medication costs (76).

CONCLUSION AND ADDITIONAL RESOURCES

This brief review of the economics of treating schizophrenia has emphasized some of the methodologic complexities that must be acknowledged and surmounted when addressing treatment costs. The emphasis has been on illustrating the importance of bias minimization and estimation when constructing studies and reporting results, and on the importance of reporting results from the perspective of different payers and giving estimates of the variability associated with any findings reported as point estimates. It is important to tell patients, prescribers, and payers not just the best estimate of costs and effectiveness, but the likelihood that their costs and outcomes will fall within their acceptable ranges for what they are willing to pay and/or risk to gain a given outcome.

Fortunately, this evolving literature has many active champions who publish widely and lead the way in documenting the ways in which costs and fiscal (dis)incentives have impact on access to treatment, the quality of care received, and patient outcomes. Although their work cannot be summarized here, useful source books include those by Drummond and colleagues (38), Frank and Manning (77), Gold and colleagues (39), and Hargreaves and colleagues (35). The journal *Health Affairs* continues to be a particularly valuable resource for reports on mental health economics and thoughtful analyses of the economic influences on the treatment of individuals with schizophrenia.

ACKNOWLEDGMENTS

This research is the product of the collaboration of many individuals, both within and outside the Connecticut Department of Mental Health and Addiction Services (DMHAS). In particular, we would like to thank Carlos Jackson, Ph.D., of the University of Connecticut for his assistance with the data extraction and statistical analyses of the Medicaid prescription data. The research was funded

in part by U.S. Public Health Service (USPHS) grants R01 MH-48830 and R01 MH-52872 from the National Institute of Mental Health (NIMH) to Susan Essock, Ph.D., principal investigator, as well as by DMHAS. This publication does not express the views of the Department of Mental Health and Addiction Services or the State of Connecticut. The views and opinions expressed are those of the authors.

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