

# Pharmacoeconomic Evaluation of Antipsychotic Therapy for Schizophrenia

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Medications comprise a minor portion of the costs of schizophrenia, but may have a major impact on the likelihood of successful outcome of care. Novel antipsychotic medications which demonstrate superior symptom control, an improved safety profile, and benefits to quality-of-life may also reduce patients' need for medical services and the associated costs of these treatments. This report first considers key experimental design elements involved in integrating pharmacoeconomic and clinical objectives in studies of new drug therapies for schizophrenia. We briefly discuss the choice of therapies for comparison, randomization and blinding, sample size and composition, data collection, selection of the time frame for economic evaluation, and the importance of an intent-to-treat perspective. Second, as an example we present the design and selected results from a new economic clinical trial of the novel antipsychotic olanzapine. This trial utilized a randomized, double-blind design to compare the use of medical services and the cost of treatment for 817 schizophrenic patients from the United States treated with olanzapine or haloperidol. In comprehensive health care cost comparisons that incorporated the expenditures for study medications, the total cost of health care for olanzapine-treated patients was reduced by an average of \$431 per month in comparison with haloperidol-treated patients during the initial 6 weeks of treatment. Among treatment responders receiving double-blind therapy for a maximum of 1 year, the total cost of care among olanzapine responders was reduced by an average of \$345 per month in comparison with haloperidol responders. The results of this economic evaluation suggest that olanzapine's superior treatment profile may lead to reductions in the overall costs of medical care for patients with schizophrenia. (*J Clin Psychiatry 1997;58[suppl 10]:50-54*)

**I**ncreasing concern about the costs of health care has resulted in the need for physicians to consider not only efficacy and safety when choosing a therapy but also the costs of various alternatives, which can be calculated from the outcomes of therapy. Understanding the cost-effectiveness of therapeutic alternatives is especially pertinent for schizophrenia, which imposes an extraordinary economic burden on the patient, the health care system, and society because of its early onset, devastating effects, and long-term course. In the United States, the disease consumed an estimated \$32.5 billion in resources in 1990, comprising 22% of all costs of mental illness, and approximately 2.5% of all health care costs.<sup>1,2</sup>

The high risk of hospitalization and prolonged length-of-stay in inpatient care associated with schizophrenia ac-

count for the majority of this remarkable cost.<sup>3</sup> The course of the disease may entail lifelong reliance upon such expensive health services, as well as a constellation of other types of supportive care. Costs of treatment are high even among patients initially responsive to conventional neuroleptic care. Weiden and Olfson<sup>4</sup> estimated the costs of rehospitalization in neuroleptic-responsive schizophrenics in the United States during 1986. Within 2 years after discharge from an index hospitalization, more than 80% of the cohort had been rehospitalized, and the aggregate cost of readmission for this group approached \$2 billion. More than half of these costs (63%) were principally attributed to the loss of medication efficacy, with the remainder accounted for by medication noncompliance.

Medications comprise a minor portion of the costs of schizophrenia, estimated at approximately 2% of the direct costs of health care and 1% of the total costs resulting from the disease,<sup>2</sup> but drug therapy can have a major impact on the likelihood of hospitalization and the overall successful outcome of care.<sup>4</sup> It can be hypothesized that novel antipsychotic medications which demonstrate superior symptom control, an improved safety profile, and benefits to patient quality-of-life will also reduce patients' need for medical services and the associated costs of these treatments. Such reductions in health care expenditures may offset increases in the cost of medications that accom-

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pany the introduction of these new pharmacotherapies, and result in net reductions in the economic burden of schizophrenia.

Several recent studies have reported evidence for health care cost savings associated with the use of newer atypical antipsychotic medications in comparison with older agents,<sup>5-9</sup> but published research to date has frequently been criticized because of limitations in experimental design. The cost-effectiveness of new antipsychotic treatments has not been comprehensively evaluated in the context of a large double-blind randomized clinical trial, although an open-label randomized effectiveness trial of clozapine has recently been reported,<sup>10</sup> and a large double-blind cost-effectiveness trial of clozapine is also forthcoming (Rosenheck R, Cramer J, Xu W, et al. Manuscript submitted). The demonstration that novel antipsychotics are more cost-effective than conventional medications in a rigorous experimental context would be an important step toward the development of pharmacotherapeutic guidelines for the treatment of schizophrenia.

This report will first consider the key elements of experimental design involved in the integration of pharmacoeconomic objectives into the context of clinical studies of the efficacy and safety of novel antipsychotics. We briefly discuss issues surrounding the choice of therapies for comparison, randomization and blinding decisions, considerations of sample size and composition, outcomes data collection concerns, the selection of the appropriate time frame for economic evaluations, and the importance of an intent-to-treat perspective for analysis. Second, as an example of the integration of economic and clinical objectives in the randomized clinical trial framework, we present the design and selected results from a new economic clinical trial, to be reported fully elsewhere, of the novel antipsychotic olanzapine.<sup>11</sup> This study utilized a randomized, double-blind design to compare the medical service utilization and cost outcomes of treatment for schizophrenia with olanzapine versus haloperidol. In summary, the results of this study indicated that the total cost of health care for olanzapine-treated patients was substantially lower than costs for haloperidol-treated patients during both short-term (6 weeks) and long-term (up to 52 weeks) therapy, in comprehensive health care cost comparisons that incorporated the expenditures for study medications. Reductions in cost in the olanzapine-treated group relative to the haloperidol-treated group were observed for both inpatient and outpatient services. Considered in tandem with findings from this and other trials indicating that the use of olanzapine to treat schizophrenia results in significant efficacy and safety advantages in comparison with haloperidol,<sup>12,13</sup> the results of this economic evaluation suggest that olanzapine's superior treatment profile may lead to reductions in the costs of medical care for both patients and the health care system.

## CONDUCTING ECONOMIC EVALUATIONS IN THE CONTEXT OF RANDOMIZED CLINICAL TRIALS

The controlled clinical trial constitutes the optimal experimental design to assess the efficacy and safety of new medications or other therapeutic technologies. The extension of this framework to incorporate economic evaluations of therapies is a natural and welcome development. However, as Drummond and Davies<sup>14</sup> have noted, the integration of economic and clinical studies raises challenging methodological issues. The methodology of economic clinical trials has been reviewed,<sup>15-19</sup> and the designs and findings of specific economic assessments of antipsychotic medications have been debated.<sup>5,6,20-24</sup> We will focus on selected design elements that can optimize the investigation of economic research questions within the clinical trial framework.

### Choice of Therapies for Comparison

The selection of therapies to compare is crucial for the design of economic evaluations, and the optimal therapeutic contrast from an outcomes perspective may differ significantly from the appropriate comparison for an efficacy trial. In general, the evaluation should reflect as closely as possible the actual therapeutic choices facing health care decision makers. The constraints under which trials of new drugs operate may make it difficult or impossible to compare the new therapy directly to the existing standard for treatment. If standard therapy is successfully incorporated as the reference for comparison in the trial, the strict treatment protocols utilized in studies of new pharmacotherapy may nevertheless make it difficult to model usual practice comprehensively.<sup>14,16-18</sup> Published cost-effectiveness studies in the antipsychotic area rarely include a comparator that clearly represents current standard therapy. For example, Meltzer et al.<sup>6</sup> compared patients continuing on clozapine therapy to a second group of patients who discontinued clozapine therapy. Others have used uncontrolled mirror-image designs to establish a pre-intervention standard of care condition.<sup>7,9</sup>

### Components of the Experimental Design

The advantages of randomized designs for causal inference in economic evaluations of medical therapy have been extensively treated.<sup>16,17</sup> The question of whether economic clinical trials should be open or double-blind in design is more problematic. Simon et al.<sup>16</sup> argue for the use of open designs, to model naturalistic medication management as closely as possible. Hargreaves and Shumway<sup>18</sup> are more qualified in their comments, noting that double-blind designs have clear benefits with respect to the elimination of patient, clinician, and rater expectation effects on outcomes and measures, but also acknowledging the practical difficulties and therapeutic constraints imposed by this design element. It is difficult to maintain

blinded conditions when therapy is evaluated over extended periods of time, and usual clinical practice may be incompletely represented under this design approach.

### Sample Size and Composition

Sample size requirements for economic outcomes may differ remarkably from the requirements for measures of efficacy. Large numbers of patients are needed to distinguish cost outcomes because of the substantial overall variance in these values and because random variation in high cost services such as hospitalization may disproportionately affect both average cost and the variance about the mean.<sup>14</sup> Safety and efficacy trials that incorporate economic outcomes must be powered to accommodate the latter measures.<sup>25</sup>

The inclusiveness of patient selection criteria constitutes another potential differentiating characteristic between economic evaluations and conventional clinical studies. Patient samples used in traditional psychopharmacologic studies provided limited information for health care decision makers.<sup>18</sup> The external validity of the trial's findings may be restricted if patient characteristics are tightly controlled. In the case of new drugs, this methodological issue may not be resolvable through design modifications because of constraints on patient recruitment.

### Data Collection

Two crucial aspects of the data collection strategy for economic clinical trials are a prospective measurement design and a comprehensive outcomes measurement approach. Randomized prospective data provide fundamental advantages for causal inference in studies of the economic outcomes of alternative therapies. Economic studies of antipsychotic medications have typically employed retrospective or uncontrolled mirror image designs.<sup>5-7,9,26,27</sup> There is an important need for large controlled prospective economic trials of therapeutic alternatives for the treatment of schizophrenia.

It is also important to incorporate a comprehensive measurement protocol for the economic outcomes component of controlled clinical trials of antipsychotic therapy. Many cost-effectiveness studies of antipsychotic medications have focused on limited portions of health services utilization. Studies that incorporate broader economic data collection strategies are needed to evaluate the cost-effectiveness of therapies conclusively.

### Time Frame for Evaluation

Another key decision in the design of an economic evaluation is the determination of the appropriate time frame and analytic horizon for the study. The selected time frame should reflect the period during which the costs of the intervention will be incurred, and should extend for a sufficient amount of time to ensure that the consequences of the intervention will be measured. Haddix and Shaffer<sup>28</sup>

note that a 1-year interval is often advantageous from an institutional or administrative perspective, and is sufficiently long to capture many of the relevant outcomes resulting from an intervention. An extended interval of assessment may be most appropriate for schizophrenia outcomes, given the lengthy course and perhaps lifelong therapy that can be required for the disease.<sup>29</sup> However, feasibility is a major concern in this circumstance. This is especially the case if economic evaluations are integrated with other clinical objectives in a randomized double-blind trial design.

### Intent-to-Treat Perspective

In economic evaluations, it is also important to assess the outcomes of therapy from an intent-to-treat perspective, utilizing the full measurement interval.<sup>16</sup> From this perspective, the trial asks: Which initial choice of antipsychotic medication results in the best economic, clinical, and functional outcomes? This aspect of design may be in conflict with the classical approach in controlled clinical trials, which terminates measurement when patients discontinue study medications because of treatment nonresponse, adverse events, or for other reasons. From an intent-to-treat perspective, it is essential to capture these costs of treatment failure. Otherwise, the economic benefits accruing from the superior treatment profile of a novel therapy may be underestimated, because patients in the comparison condition discontinue early and their subsequent outcomes are lost to follow-up.

This brief discussion is intended to highlight both the methodological opportunities and the challenges involved in integrating economic and clinical research questions. In recent years, there has been rapidly growing experience and many successes in the effort to merge these alternative research objectives under the umbrella of the controlled clinical trial framework. Additional research and debate are needed to clarify many issues. However, efforts in this area are highly promising, and we may expect that they will play an increasingly prominent role in the evaluation of new antipsychotic therapies and provide clinicians and other decision makers with a much broader profile of information on the outcomes of novel therapeutic strategies.

## COST-EFFICACY OF OLANZAPINE

This section briefly reports the design and limited results from a large clinical trial comparing the economic outcomes of treatment for schizophrenia with olanzapine or haloperidol,<sup>11</sup> presented as an example of the integration of clinical and economic objectives in the randomized double-blind trial framework. Complete results of the study will be reported elsewhere.

### Design of the Trial

The economic portion of the study was designed to evaluate the effect of olanzapine versus haloperidol treat-

ment on cost outcomes for patients with schizophrenia from the perspective of the health care system. The data for the economic evaluation were obtained from a multicenter double-blind randomized clinical trial of 1996 patients with schizophrenia, schizophreniform disorder, or schizoaffective disorder. The sample subset selected for the evaluation of cost outcomes consisted of 817 patients who had a DSM-III-R diagnosis of schizophrenia and resided in the United States. Enrollees were males or females aged 18 years or older with a baseline Brief Psychiatric Rating Scale (BPRS) total score of 18 or larger, or no longer tolerating current neuroleptic therapy (except haloperidol). Patients were excluded if they presented with other serious, unstable illnesses, recent experience of DSM-III-R substance use disorders or organic mental disorder, or were unable to communicate sufficiently with clinical study personnel. Data were available at baseline and for at least one post-baseline assessment for all patients included in the analyses. At baseline, there were no significant differences in the demographic and clinical characteristics of the patients.

Patients were randomly assigned to receive either olanzapine (N = 551) 5 to 20 mg/day or haloperidol (N = 266) 5 to 20 mg/day for an initial period of 6 weeks of double-blind therapy. Eligible patients could continue double-blind therapy for an additional 46 weeks (for a maximum of 1 year of double-blind therapy). Continuation of double-blind therapy into this extension phase was based upon clinical judgment and the achievement of a maximum Clinical Global Impression (CGI) Severity of illness scale score of 3 or a decrease of 3 or more and a maximum score of 3 in the CGI adverse events scale. Thus, cost comparisons for long-term therapy were limited to the subsample of responders to the study medications.

Patients' use of medical services, including protocol-specific physician and other services, was collected throughout the duration of the trial. Utilization data were collected on the number of hospitalizations and inpatient length-of-stay experienced by patients, as well as the numbers of day hospital treatment sessions, visits to the emergency room, outpatient visits to psychiatrists, visits to other physicians and other mental health care providers, home visits by health professionals, and the use of study and concomitant medications. Services and medications were assigned an estimated cost in 1995 dollars, using a standardized list of prices. The cost of an average daily dose of haloperidol was estimated to be \$0.08 per day; the cost of olanzapine was estimated to be \$7.58 per day, based on the average wholesale price of the medication. Mean medical costs per month for the olanzapine-treated group and the haloperidol-treated group were compared during the acute phase of treatment (Weeks 1–6) and during the maintenance phase (Weeks 7–52) for patients demonstrating a successful treatment response only.

## Selected Results

During acute therapy, the mean cost of inpatient and outpatient medical services for the olanzapine treatment group was \$640 per month lower than the mean cost incurred by the haloperidol treatment group, exclusive of medication costs. After incorporating differences in the cost of medications, a net reduction of \$431 per month in total medical costs was observed for the olanzapine treatment group. The log-transformed result for this net difference was statistically significant ( $p = .026$ ).

As noted above, during the 46-week extension phase, the cost comparison was limited to patients who demonstrated a successful treatment response to haloperidol or olanzapine. Haloperidol-treated patients completed the acute phase at significantly lower rates than olanzapine-treated patients ( $p < .001$ ). During this maintenance phase, the mean cost of inpatient and outpatient medical services for the olanzapine responders was \$557 per month lower than the mean cost incurred by haloperidol responders. After incorporating the costs of study medications, the mean monthly cost of treatment for the olanzapine responders was \$345 lower than the cost for the haloperidol responders. There was no statistically significant treatment effect for the log-transformed difference in total medical costs for this phase of the study.

This study evaluated the economic consequences of a conventional versus a novel pharmacotherapy for schizophrenia, utilizing the randomized clinical trial framework. Extensive data on medical service utilization were collected prospectively for a large sample of patients, expectation effects on outcomes and outcome measures were controlled through the blinding mechanism, and the study was designed to evaluate both the outcomes of short-term therapy for all patients and the impact on long-term therapy for treatment responders. These and other components of the experimental design lend confidence to the interpretation of findings from the trial, which indicate that treatment for schizophrenia with olanzapine can result in substantial reductions in total health care costs in comparison with haloperidol treatment, even when the purchase price of novel pharmacotherapy is included in the calculation of cost outcomes.

This example also illustrates the compromises in design encountered when economic objectives are added to the classical framework developed to evaluate the efficacy and safety of medications. The patient inclusion criteria for the study, although broad in many respects, necessarily exclude some categories of patients, e.g., persons with comorbid substance dependence, who must be included in future comprehensive economic evaluations of the cost-effectiveness of antipsychotic therapies. The protocol-driven care and patient disposition procedures necessitated by the efficacy and safety objectives of the trial also restrict the generalizability of findings to a greater or lesser degree.<sup>16</sup> In the present instance, it is likely that the

observed cost benefits of olanzapine for long-term therapy are conservative, because these results were based only on data from responders to therapy and excluded the outcomes for patients who discontinued before completing the study. A significantly greater proportion of haloperidol-treated patients discontinued the trial during the acute phase of therapy. Thus, the cost outcomes for the extension phase of the study do not reflect differences in response and relapse rates that favor olanzapine. It is probable that the results of this trial underestimate the medical costs of haloperidol in comparison with expectations for the usual care context.

## CONCLUSION

It is likely that interest will continue to grow in the study of the economic and functional outcomes associated with novel antipsychotic therapies, and these research questions will need to be addressed at progressively earlier stages of investigational studies. The prospective randomized clinical trial framework provides a powerful inferential tool for the evaluation of economic as well as clinical hypotheses, but the adaptation of this design to meet both types of objectives presents both opportunities and challenges to researchers. It is important to ensure that complementary or potentially opposed design objectives of classical clinical trials and economic studies are carefully considered in the development and conduct of studies, and the implications of these design decisions are appreciated in the interpretation of findings. Regardless, in the future, it is probable that large prospective randomized trials such as the example study summarized here will become a standard for evaluating the cost-effectiveness of new therapies for schizophrenia.

*Drug names:* clozapine (Clozaril), haloperidol (Haldol and others), olanzapine (Zyprexa).

## REFERENCES

- Rice DP, Miller LS. The economic burden of schizophrenia. In: Proceedings of the 6th Biennial Research Conference on Economics in Mental Health; September 1992; Bethesda, Md. Pages 21–22
- Rice DP, Miller LS. The economic burden of schizophrenia: conceptual and methodological issues, and cost estimates. In: Moscarelli M, Rupp A, Sartorius N, eds, Handbook of Mental Health Economics and Health Policy, vol 1. New York, NY: John Wiley & Sons; 1996:321–334
- Terkelsen KG, Menikoff A. Measuring the costs of schizophrenia: implications for the post-institutional era in the US. *Pharmacoeconomics* 1995; 8(3):199–222
- Weiden, PJ, Olfson M. Cost of relapse in schizophrenia. *Schizophr Bull* 1995;21(3):419–429
- Revicki DA, Luce BR, Weschler JM, et al. Cost effectiveness of clozapine for treatment resistant schizophrenic patients. *Hosp Community Psychiatry* 1990;41(8):850–854
- Meltzer HY, Cola P, Way L, et al. Cost-effectiveness of clozapine in neuroleptic-resistant schizophrenia. *Am J Psychiatry* 1993;150:1630–1638
- Addington DE, Jones B, Bloom D, et al. Reduction of hospital days in chronic schizophrenic patients treated with risperidone: a retrospective study. *Clin Ther* 1993;15:917–926
- Guest JF, Hart WM, Cookson RF, et al. Pharmacoeconomic evaluation of long-term treatment with risperidone for patients with chronic schizophrenia. *British Journal of Medical Economics* 1996;10:59–67
- Albright PS, Livingstone S, Keegan DL, et al. Reduction of healthcare resource utilisation and costs following the use of risperidone for patients with schizophrenia previously treated with standard antipsychotic therapy: a retrospective analysis using the Saskatchewan Health linkable databases. *Clinical Drug Investigations* 1996;11(5):289–299
- Essock SM, Hargreaves WA, Covell NH, et al. Clozapine's effectiveness for patients in state hospitals: results from a randomized trial. *Psychopharmacol Bull* 1996;32(4):683–697
- Hamilton SH, Revicki DA, Genduso L, et al. Cost-efficacy of olanzapine compared with haloperidol treatment for schizophrenia: results from a randomized clinical trial. Poster presented at the annual meeting of the American Association for Geriatric Psychiatry; March 1997; Orlando, Fla
- Beasley CM, Tollefson G, Tran PV, et al, and the Olanzapine HGAD Study Group. Olanzapine versus placebo and haloperidol: acute phase results of the North American double-blind olanzapine trial. *Neuropsychopharmacology* 1996;14:111–123
- Tollefson GD, Beasley CM, Tran PV, et al. Olanzapine versus haloperidol in the treatment of schizophrenia and schizoaffective and schizophreniform disorders: results of an international collaborative trial. *Am J Psychiatry* 1997;154:457–465
- Drummond MF, Davies L. Economic analysis alongside clinical trials. *Int J Technol Assess Health Care* 1991;7(4):561–573
- Drummond MF, Stoddart GL. Economic analysis and clinical trials. *Control Clin Trials* 1984;5:115–128
- Simon GE, Wagner E, VonKorff M. Cost-effectiveness comparisons using "real world" randomized trials: the case of new antidepressant drugs. *J Clin Epidemiol* 1995;48:363–374
- Revicki DA, Luce BR. Pharmacoeconomics research applied to psychopharmacology development and evaluation. *Psychopharmacol Bull* 1995; 31(1):57–65
- Hargreaves WA, Shumway M. Pharmacoeconomics of antipsychotic drug therapy. *J Clin Psychiatry* 1996;57[ suppl 9]:66–76
- Rajagopalan R, Kallal JE, Fowler JF Jr, et al. Practical issues in conducting pharmacoeconomic studies. *Clin Ther* 1996;18(6):1298–1306
- Frank RG. Clozapine's cost-benefits [letter]. *Hosp Community Psychiatry* 1991;42:92
- Goldman HH. Clozapine's cost-benefits [letter]. *Hosp Community Psychiatry* 1991;42:92–93
- Essock SM. Clozapine's cost-effectiveness [letter]. *Am J Psychiatry* 1995;152:152
- Rosenheck R, Charney DS, Frisman LK. Clozapine's cost effectiveness [letter]. *Am J Psychiatry* 1995;152:152–153
- Schiller M, Hargreaves WA. Clozapine's cost effectiveness [letter]. *Am J Psychiatry* 1995;152:151–152
- Bouckaert A, Crott R. The difference in mean costs as a pharmacoeconomic variable: power considerations. *Control Clin Trials* 1997;18:58–64
- Frankenburg FR, Zanarini MC, Cole JO, et al. Hospitalization rates among clozapine-treated patients: a prospective cost-benefit analysis. *Ann Clin Psychiatry* 1992;4:247–250
- Reid WH, Mason M, Toprac M. Savings in hospital bed-days related to treatment with clozapine. *Hosp Community Psychiatry* 1994;45:261–264
- Haddix AC, Shaffer PA. Cost-effectiveness analysis. In: Haddix AC, Teutsch SM, Shaffer PA, et al. *Prevention Effectiveness: A Guide to Decision Analysis and Economic Evaluation*. New York, NY: Oxford University Press; 1996:103–129
- Kane JM. Drug treatments. In: Moscarelli M, Rupp A, Sartorius N, eds, *Handbook of Mental Health Economics and Health Policy*, vol 1. New York, NY: John Wiley & Sons; 1996:125–132