

Pharmacoeconomic Evaluation of Treatments for Refractory Schizophrenia: Clozapine-Related Studies

Dennis A. Revicki, Ph.D.

Cost-effectiveness analyses determine whether a new therapy will find a place in clinical practice, based on the cost of its use and the health outcomes it produces, compared with other available therapies. Clozapine, indicated for treatment-resistant schizophrenia, has been evaluated in uncontrolled, mirror-image studies; clinical decision analysis models; and prospective, randomized clinical trials. Results from randomized trials demonstrate that clozapine controls symptoms of psychopathology and improves quality of life slightly more effectively than traditional neuroleptic medications. It has a lower incidence of extrapyramidal side effects than traditional medications, resulting in a lower drop-out rate. Beginning in the second year of treatment, clozapine may produce cost savings for the health care system, when its higher acquisition cost begins to be offset by reduced hospitalization. Mirror-image studies and clinical decision analysis models provide further support for these findings.

(*J Clin Psychiatry* 1999;60[suppl 1]:7-11)

During the past decade, major advances in medical technology and treatment have brought about the realization that there are insufficient financial resources to provide all of the medical care that is technically feasible or that patients might desire.¹ Thus, new medical interventions need to demonstrate value, in terms of improvement in clinical outcomes or quality of life (QOL) outcomes relative to expenditures. Since the introduction of clozapine, the psychiatric and mental health community has begun to examine whether the clinical benefits of clozapine therapy² are worth its high acquisition cost.

The direct medical costs and the indirect costs of schizophrenia are substantial. Rupp and Keith³ estimated the total annual cost of schizophrenia in 1990 to be \$33 billion. Using different assumptions regarding indirect costs, Wyatt et al.⁴ estimated the annual total costs as \$65.1 billion, including direct costs of \$18.6 billion and indirect costs of \$46.5 billion. Comparing these cost estimates with those for other illnesses shows that, considering its relatively low prevalence, schizophrenia imposes a disproportionately high cost on the health care system.

From the Center for Health Outcomes Research, MEDTAP International, Bethesda, Maryland, and the School of Public Health, University of North Carolina, Chapel Hill.

Presented at the National Consensus Conference on the Pharmacoeconomics of Treatment-Resistant Schizophrenia, held October 4, 1997, Dallas, Tex., and supported by an educational grant from Novartis Pharmaceuticals Corporation.

Reprint requests to: Dennis Revicki, Ph.D., Center for Health Outcomes Research, MEDTAP International, 7101 Wisconsin Avenue, Suite 600, Bethesda, MD 20814 (e-mail: revicki@MEDTAP.com).

This article reviews the pharmacoeconomic studies used to examine the medical cost and patient outcomes associated with clozapine therapy for neuroleptic-refractory patients with schizophrenia.

PHARMACOECONOMIC EVALUATION

Pharmacoeconomic research is focused on examining the clinical and patient outcomes and cost-effectiveness of new medications, such as clozapine, compared with existing alternative treatments.⁵⁻⁷ Total medical costs and health outcomes of interest to physicians, patients, and the health care systems are evaluated in these studies. Cost-effectiveness studies are conducted in randomized clinical trials and naturalistic clinical trials, retrospective or prospective medical claims analyses, or clinical decision models. This allows psychiatrists and other health care decision-makers to make decisions based on cost-effectiveness.

There are 9 different possible findings from a cost-effectiveness analysis (Figure 1).^{3,4} If total costs increase with a new medication, health care professionals may reject the new treatment if studies show that outcomes are no better (or worse) than those found with existing treatments. Conversely, health care professionals may accept a new treatment if it improves outcomes and decreases total medical costs. This is the ideal situation, since the new treatment provides more benefit to patients with less overall expenditures to the health care system. Potentially, this allows health care providers to treat more patients with the same resource expenditures. However, many new therapies result in higher overall medical costs and additional

Figure 1. Decisions Based on Cost-Effectiveness of a New Therapy*

		Health Outcome ^a		
		Improved	Same	Worse
Cost ^b	Increased	?	Reject	Reject
	Same	Accept	?	Reject
	Decreased	Accept	Accept	??

*Symbols: ?, ?? = cost-effectiveness value judgments.
^aNew treatment vs. old treatment.

benefits to patients, for example, fewer side effects and greater clinical efficacy. In this situation, the decision will depend on the magnitude of the change in costs and the increase in patient benefits. Medical costs or outcomes may be equivalent between the new therapy and the comparison therapy. In this case, judgment depends on any detected differences between the therapies.

Several research methods have been used in pharmacoeconomic research to evaluate clozapine since its approval:

- Uncontrolled, mirror-image studies prospectively or retrospectively follow a cohort of patients exposed to clozapine treatment, and comparisons are made between pretreatment and posttreatment resource use and costs.
- Clinical decision analysis models are constructed to simulate patterns of clinical management and treatment-related costs and outcomes. They have been used to compare clozapine treatments with existing antipsychotic treatment to estimate costs and outcomes over various time periods.
- Prospective, randomized clinical trials are specifically designed to look at the impact of different therapies on medical care use and costs and on clinical outcomes. Ideally, a naturalistic clinical trial is conducted where patients are treated and followed regardless of adherence to initially prescribed treatment in community-based settings.

More information on the methods of pharmacoeconomic studies and cost-effectiveness analysis can be obtained by reading the recent book by Gold and colleagues.⁸ Revicki⁵ and Hargreaves and Shumway⁷ review studies and discuss issues related to pharmacoeconomic evaluations of antipsychotic medications.

UNCONTROLLED, MIRROR-IMAGE STUDIES

A number of retrospective (and prospective) mirror-image studies have estimated the impact of clozapine on medical resource use and costs.⁹⁻¹³ These studies found decreases in hospitalizations and inpatient costs for cloza-

Table 1. Effect of Clozapine Therapy on Medical Costs in a Preapproval, Compassionate Use Study*

Comparison	After 1 Year of Treatment	After 2 Years of Treatment	Net Effect
Clozapine vs neuroleptic (dropouts excluded)	\$10,040	(\$9,011)	\$1,029
Clozapine vs neuroleptic (dropouts included)	9,664	(3,518)	6,146
Matched clozapine	2,559	(10,064)	(7,505)
Clozapine vs neuroleptic (14-day hospital stay)	(844)	(3,514)	(4,358)
Clozapine vs neuroleptic (30-day hospital stay)	2,580	(3,514)	(934)

*Data from reference 9. One hundred thirty-three patients were treated with clozapine, and 51 were treated with typical neuroleptics. Figures in parentheses represent savings to the mental health system; figures without parentheses represent additional costs to the mental health system.

pine. Revicki et al.,⁹ in an early retrospective study, collected resource use and cost data on 133 clozapine-treated patients with treatment-resistant schizophrenia and 51 comparison patients treated with typical neuroleptics. Data on use of medical resources were collected for the 1 year before and for up to 2 years after the start of clozapine treatment. Savings and losses in total costs with the 2 therapies, including medication, hospitalization, outpatient services, and after-care services, were compared between clozapine and comparison group patients after 1 and 2 years of treatment (Table 1). The study suggested that clozapine, after 2 years, would result in slightly higher costs (\$1029 to \$6146) or some savings (\$934 to \$7505) to the health care system.

Total per-patient medical costs of clozapine responders were about \$10,000 higher compared with the costs of the comparison patients during the first year of therapy. Savings in hospital costs were offset by the higher price of clozapine and increased use of aftercare and supportive services. However, by the second year the clozapine group's total costs were \$9000 lower on average compared with the comparison group. When patients who dropped out of clozapine therapy (usually after 90 to 120 days of treatment) were included in the analysis, the cost savings in the second year were attenuated. Matching clozapine-treated patients to neuroleptic-treated patients showed the largest cost savings: \$7500 per patient over 2 years. Based on this evidence, it appears likely that savings to the health care system may accrue after 2 years of clozapine treatment. In viewing these data, it is important to keep in mind that this was a compassionate use study, and patients who received clozapine had long histories of chronic hospitalization and required substantial supportive and rehabilitation services.

A more recent study of 93 patients with treatment-resistant schizophrenia measured clinical and QOL outcomes, as well as medical service use and costs.¹² Medical costs were estimated for 2 years before and 2 years after clozapine treatment. Clozapine responders who continued

therapy for an extended period demonstrated significant improvements in Brief Psychiatric Rating Scale (BPRS) total scores ($p < .0001$) and in QOL scores ($p < .0001$). Clozapine responders (37 patients), compared with clozapine dropouts (10 patients), showed a significant decrease in the use of hospital services (pretreatment mean = \$44,810; posttreatment mean = \$2592) and reduction in total medical costs (pretreatment mean = \$71,779; posttreatment mean = \$25,905). Clozapine patients who dropped out were treated with atypical neuroleptics, and almost no change in hospital or total medical costs was observed. When dropouts were included in the analysis, the estimated average patient total cost was about \$77,000 per year before clozapine treatment and about \$60,000 per year during treatment.

Pretest/posttest (mirror-image) studies have been criticized for weaknesses in research design, uncertainties about diagnosis, the absence of randomly assigned and equivalent control groups, selection bias and artifacts, and incomplete follow-up and exclusion of dropouts from analyses. The failure to include the costs of treatment dropouts may introduce bias since patients discontinuing treatment because of side effects or lack of efficacy consume significant inpatient and other medical services. The noncomparative cohort studies can provide some insight into the medical costs associated with clozapine. These studies, however, have severe limitations; thus, caution is required in interpreting their findings.

CLINICAL DECISION ANALYSIS MODELS

Modeling techniques have not been widely applied to the evaluation of medical cost and outcomes of antipsychotic medications for treatment of schizophrenia. Clinical decision analysis and modeling methods attempt to simulate patterns of clinical management and the cost-effectiveness of alternative treatment regimens. The structure and parameters for models are based on medical literature, clinical trials, and physician judgment. Clinical judgment is used to provide estimates of model parameters that are not available from empirical sources. Sensitivity analysis is used to test the robustness of the model and its parameter estimates by varying the uncertain values to see whether they impact the estimates of cost-effectiveness. However, models are only as good as their underlying data and the nature of the assumptions made in model construction. Table 2 shows the results of 3 studies¹⁴⁻¹⁶ that applied decision analysis models to examine the effects of clozapine compared with typical neuroleptics in treatment-resistant schizophrenia.

Revicki and Brown¹⁴ constructed a model to estimate the long-term (5-year) effects of clozapine versus standard neuroleptic therapy for treatment-resistant schizophrenia. The model was based on data from clinical studies from the late 1980s and early 1990s. In addition, this study estimated quality-adjusted life-years (QALYs) (i.e., survival

Table 2. Summary of Clinical Decision Models Comparing Cost of Treatment With Clozapine With Cost of Treatment With Neuroleptic (in U.S. Dollars)

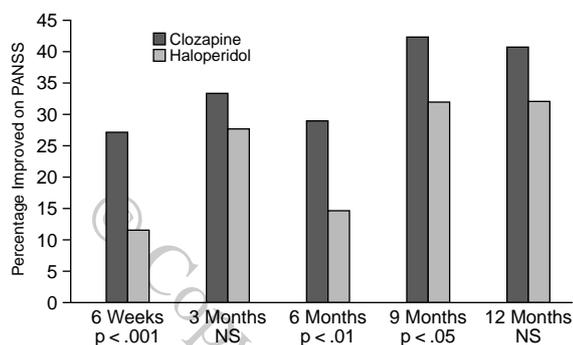
Study	Duration	Medical Cost Estimate	Cost-Effectiveness Ratio
Revicki and Brown, 1992 ¹⁴	5 years	Clozapine: \$63,820 Neuroleptic: \$68,284	Clozapine dominant
Davies and Drummond, 1993 ¹⁵	Lifetime	Not reported	Annual savings with clozapine therapy: \$146 Lifetime savings: \$2133
Oh et al, 1997 ¹⁶	1 year	Clozapine: \$48,992 Neuroleptic: \$69,988	Clozapine dominant

weighted for QOL outcomes) using patient and physician preferences for schizophrenia-related health states.¹⁷ They found that clozapine treatment resulted in slightly lower costs and better patient outcomes. Although the model used by Davies and Drummond¹⁵ estimated lifetime costs, medical cost estimates were not directly reported. They found little difference in costs between patients treated with clozapine and those treated with other agents, but an index of health outcomes based on BPRS and Clinical Global Impressions scale scores showed that clozapine had significant benefits compared with typical neuroleptic therapy.

Recently, Oh and others,¹⁶ for the Canadian Coordinating Office for Health Technology Assessment, constructed a clinical decision model to estimate the total medical costs and QALYs for clozapine versus neuroleptic treatment (haloperidol or chlorpromazine) for treatment-refractory schizophrenia. They incorporated all available published data up to 1996. The 1-year estimated medical costs were U.S. \$48,992 for clozapine and U.S. \$69,988 for neuroleptic treatment, and clozapine resulted in more QALYs gained (clozapine 1-year QALY = 0.86; neuroleptic 1-year QALY = 0.82). They concluded that clozapine therapy for treatment-resistant schizophrenia patients resulted in cost savings and improved patient functioning and well-being.

In summary, findings from modeling studies suggest that clozapine therapy is associated with cost savings in the management of treatment-resistant schizophrenia patients in Canada, the United Kingdom, and the United States. Sensitivity analyses done with varying model parameters confirm the overall findings. It is necessary to keep in mind, however, that models can only estimate medical costs and outcomes associated with different treatment regimens. Modeling studies identify key gaps in the research literature, are very flexible, and are able to incorporate and test alternative scenarios to estimate cost-effectiveness. Models have several limitations, such as imprecision and possible bias and dependence on the availability and completeness of epidemiologic and clinical data. Health care decision makers are often skeptical of

Figure 2. Clinical Outcomes in a 1-Year Double-Blind Comparative Study Conducted by the Department of Veterans Affairs, Showing Percentage Improved on the Positive and Negative Syndrome Scale*



*Data from reference 18. Crossover cases are excluded from this analysis.

the results of modeling studies,^{5,7} but greater transparency of model structure, assumptions, and parameters (and their source) considerably improve understanding of the limitations of models.

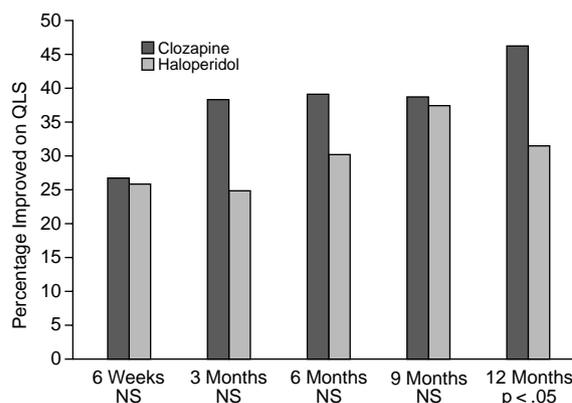
PROSPECTIVE, RANDOMIZED CLINICAL TRIALS

Randomized clinical trials that include a pharmacoeconomic component have the advantages of unbiased assignment to treatment and systematic assessment of clinical efficacy, QOL, medical resource use, and costs. Two clinical trials have been completed that compare clozapine with standard neuroleptic treatment: a 1-year double-blind comparative study of Department of Veterans Affairs (VA) patients with refractory schizophrenia,¹⁸ and a 2-year study of Connecticut state mental hospital patients with refractory schizophrenia.¹⁹

In the VA study, 205 patients were randomly assigned to treatment with clozapine (mean dose = 552 mg/day) and 218 to treatment with haloperidol (mean dose = 28 mg/day).¹⁸ Assessments included the Positive and Negative Syndrome Scale (PANSS) and the Heinrichs/Carpenter Quality of Life scale.²⁰ The criterion for clinical outcomes response was a 20% improvement in PANSS total scores. The study took the perspective of the VA health care system, with medical service use and costs measured using the VA automated system. In this study, 57% of patients taking clozapine remained on the medication for the entire 12-month period, whereas only 28% started on haloperidol treatment stayed on the original therapy. There was crossover between medications: about 33% of patients who stopped haloperidol were started on clozapine, and approximately 40% of those who stopped clozapine received neuroleptic therapy.

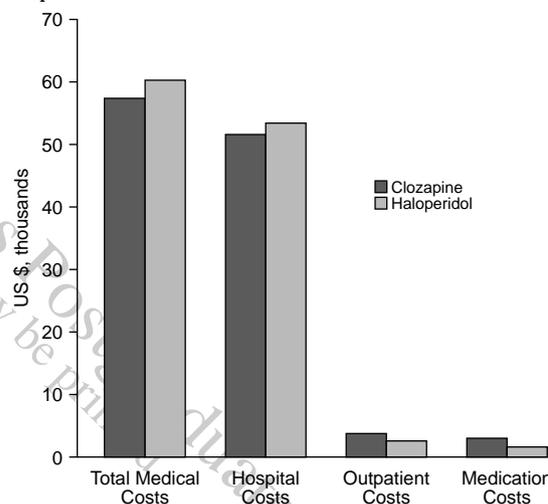
Differences on PANSS total scores favoring clozapine over haloperidol were noted at 6 weeks and throughout the study period (Figure 2). A similar pattern was noted in

Figure 3. Quality of Life Outcomes in the Study Conducted by the Department of Veterans Affairs, Showing Percentage Improved on the Heinrichs/Carpenter Quality of Life Scale*



*Data from reference 18. Crossover cases are excluded from this analysis.

Figure 4. One-Year Medical Costs in the Study Conducted by the Department of Veterans Affairs*



*Data from reference 18.

QOL outcomes (Figure 3). Differences between the groups in QOL were evident at 3 months (p < .05) and clearly favored the clozapine group at 12 months (p < .05). Although there was a difference of total medical costs favoring clozapine over haloperidol (\$57,785 vs. \$60,225), this did not reach statistical significance (Figure 4).

In the study of state mental hospital patients with refractory schizophrenia,¹⁹ 138 patients received clozapine (mean dose = 486 mg/day) and 89 received usual care. Usual care, for this study, included different standard neuroleptic therapy and other psychosocial services delivered within the state mental health care system. The study took the perspective of the state mental health care system, with assessments using the BPRS, the QOL Interview,²¹

and collection of data on health care utilization and costs. About equal numbers of clozapine-treated and usual care patients were discharged at 1 year. However, after discharge there were significant differences in 1-year readmission rates between patients on clozapine therapy and those receiving usual care (17% and 41%, respectively).

In summary, data from clinical trials indicate that clozapine is (1) more effective than standard neuroleptic therapy for symptoms of psychopathology and on measures of QOL; (2) associated with fewer extrapyramidal effects, with fewer patients discontinuing treatment compared with standard neuroleptic therapy; and (3) associated with slight cost savings, with higher medication and outpatient costs for clozapine use offset by lower hospital costs.

CONCLUSION

Pharmacoeconomic evaluations of clozapine have been completed based on different methods and perspectives. These studies expand on safety and efficacy outcomes to examine the impact of clozapine treatment on quality of life outcomes and medical costs. Prospective, randomized pharmacoeconomic investigations provide the most scientifically valid evidence of clozapine's cost-effectiveness. Evidence from the available published literature suggests that, compared with standard neuroleptic therapy, clozapine therapy is associated with similar costs after 1 year of treatment and may produce some savings after 2 years of treatment. The 1 completed and published clinical trial demonstrates slight cost savings in the clozapine-treated patients. If the preliminary findings of the study by Essock et al.¹⁹ are confirmed in the final economic analysis, it is likely that some cost savings may be seen in the clozapine-treated patients. The findings from uncontrolled cohort studies and clinical decision modeling studies provide additional support for the findings from randomized clinical trials.

It is still unclear how clinically effective the newer atypical antipsychotics (e.g., olanzapine, risperidone) will be in treating patients refractory to standard neuroleptic therapy. However, based on a review of their clinical characteristics and preliminary studies, there is some reason for optimism that these agents will be effective for the treatment of neuroleptic-refractory schizophrenia.²² Pharmacoeconomic evaluation studies that compare the clinical outcomes, quality of life outcomes, and medical costs of these medications with those of clozapine will need to be designed and completed.

Prospective, randomized studies of economic and patient outcomes are needed to evaluate the newer antipsychotics, comparing them with each other and with standard neuroleptics. Cost-effectiveness studies require long-term assessment of outcomes and costs and follow-up of treatment responders and nonresponders. The key aspect to con-

sider in evaluating the actual economic impact of newer antipsychotics will be their impact on patient outcomes and health care costs over longer time frames (e.g., 2–5 years) than have yet been studied. Pharmacoeconomic studies, combined with safety and efficacy clinical trials, provide complementary information necessary for clinical decision making and for health care system decision making.

Drug names: chlorpromazine (Thorazine and others), clozapine (Clozaril), haloperidol (Haldol and others), olanzapine (Zyprexa), risperidone (Risperdal).

REFERENCES

- Eisenberg J. Clinical economics: a guide to economic analysis of clinical practice. *JAMA* 1989;262:2879–2886
- Buchanan R. Clozapine: efficacy and safety. *Schizophr Bull* 1995;21:579–592
- Rupp A, Keith SJ. The costs of schizophrenia: assessing the burden. *Psychiatr Clin North Am* 1993;16:413–423
- Wyatt RJ, Henter I, Leary MC, et al. An economic evaluation of schizophrenia. *Soc Psychiatry Psychiatr Epidemiol* 1995;31:196–205
- Revicki DA. Methods of pharmacoeconomic evaluation of psychopharmacologic therapies for patients with schizophrenia. *J Psychiatry Neurosci* 1997;22:256–266
- Revicki DA, Luce BR. Methods of pharmacoeconomic evaluation of new medical treatments in psychiatry. *Psychopharmacol Bull* 1995;31:57–65
- Hargreaves WA, Shumway M. Pharmacoeconomics of antipsychotic drug therapy. *J Clin Psychiatry* 1996;57(suppl 9):66–76
- Gold MR, Siegel JE, Russell LB, et al. *Cost-Effectiveness in Health and Medicine*. New York, NY: Oxford University Press; 1996
- Revicki DA, Luce BR, Weschler J, et al. Cost-effectiveness of clozapine for treatment-resistant schizophrenic patients. *Hosp Community Psychiatry* 1990;41:850–854
- Honigfeld G, Patin J. A two-year clinical and economic follow-up of patients on clozapine. *Hosp Community Psychiatry* 1990;41:882–885
- 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
- Meltzer HY, Cola P, Way L, et al. Cost-effectiveness of clozapine in neuroleptic-resistant schizophrenia. *Am J Psychiatry* 1993;150:1630–1638
- Reid WH, Mason M, Toprac M. Savings in hospital bed-days related to treatment with clozapine. *Hosp Community Psychiatry* 1994;45:261–264
- Revicki DA, Brown RE. Clozapine treatment and economic outcomes: an analysis of lifetime medical costs and health outcomes in treatment-resistant schizophrenia. Presented at "Clozaril: A National Dialogue." Virginia Department of Mental Health, Mental Retardation, and Substance Abuse Services; July 1992; Rosslyn, Va
- Davies LM, Drummond MF. Assessment of costs and benefits of drug therapy for treatment-resistant schizophrenia in the United Kingdom. *Br J Psychiatry* 1993;162:38–42
- Oh P, Einarson TR, Iskedjian M, et al. Pharmacoeconomic Evaluation of Risperidone and Clozapine in Chronic and Treatment-Resistant Schizophrenia. Ottawa, Canada: Canadian Coordinating Office for Health Technology Assessment; 1997
- Revicki DA, Shakespeare A, Kind P. Preferences for schizophrenia-related health states: a comparison of patients, caregivers and psychiatrists. *Int Clin Psychopharmacol* 1996;11:101–108
- Rosenheck R, Cramer J, Xu W, et al. A comparison of clozapine and haloperidol in hospitalized patients with refractory schizophrenia. *N Engl J Med* 1997;337:809–815
- Essock SM, Hargreaves WA, Covell NH, et al. Clozapine's effectiveness for patients in state hospitals: results from a randomized trial. *Psychopharmacol Bull* 1996;32:683–697
- Heinrichs DW, Hanlon TE, Carpenter WT Jr. The Quality of Life Scale: an instrument for rating the schizophrenic deficit syndrome. *Schizophr Bull* 1984;10:388–398
- Lehman AF. A quality of life interview for the chronically mentally ill. *Eval Program Plann* 1988;11:51–62
- Daniel DG, Whitcomb SR. Treatment of the refractory schizophrenic patient. *J Clin Psychiatry* 1998;59(suppl 1):13–19