# A Cost-Effectiveness Clinical Decision Analysis Model for Schizophrenia

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*Abstract*

**A model was developed to estimate the medical costs and effectiveness outcomes of three antipsychotic treatments (olanzapine, haloperidol, and risperidone) for patients with schizophrenia. A decision analytic Markov model was used to determine the cost-effectiveness of treatments and outcomes that patients treated for schizophrenia may experience over a 5-year period. Model parameter estimates were based on clinical trial data, published medical literature, and, when needed, clinician judgment. Direct medical costs were incorporated into the model, and outcomes were expressed by using three effectiveness indicators: the Brief Psychiatric Rating Scale, quality-adjusted life years, and lack of relapse. Over a 5-year period, patients on olanzapine had an additional 6.8 months in a disability-free health state based on Brief Psychiatric Rating Scale scores and more than 2 additional months in a disability-free health state based on quality-adjusted life years, and they experienced 13% fewer relapses compared with patients on haloperidol. The estimated 5-year medical cost associated with olanzapine therapy was $1,539 less than that for haloperidol therapy. Compared with risperidone therapy, olanzapine therapy cost $1,875 less over a 5-year period. Patients on olanzapine had approximately 1.6 weeks more time in a disability-free health state (based on Brief Psychiatric Rating Scale scores) and 2% fewer relapses compared with patients on risperidone. Sensitivity analyses indicated the model was sensitive to changes in drug costs and shortened hospital stay. Compared with both haloperidol and risperidone therapy, olanzapine therapy was less expensive and provided superior effectiveness outcomes even with conservative values for key parameters such as relapse and discontinuation rates.**

***(Am J Man Care 1998;4:345-355)***

*For related articles, see pages 360 and 369.*

Schizophrenia afflicts about 1% of persons during their lifetime and usually is diagnosed in young adults.[1] It affects patient functioning and well-being, and for the patient's family there is the additional burden of caring for a person with significant disabilities. Financial resources for medical care are insufficient to provide all the healthcare that patients and their families might desire or that is technically feasible.[2] Consequently, there is increased emphasis on demonstrating the cost-effectiveness of new medical technologies. The release of premium-priced antipsychotics such as clozapine, risperidone, and olanzapine has encouraged the analysis of the cost-effectiveness of psychiatric treatments.[3,4] New antipsychotic medications that prevent or reduce relapse and the associated use of inpatient services also may affect total medical costs.

Conventional neuroleptics are effective in the treatment of positive symptoms and much of the psychopathology associated with schizophrenia.[5,6] However, conventional neuroleptics have limited effects on negative symptoms; many patients experience only partial response and relapse while being treated. Furthermore, these neuroleptics are associated with significant and troublesome side effects, such as extrapyramidal symptoms (EPS), which reduce patient compliance with treatment.[6-8] In the past few years, several atypical antipsychotics have been introduced into practice. In short-term clinical trials, olanzapine was more effective than haloperidol in decreasing psychopathology and negative symptoms.[9,10] With long-term olanzapine therapy, there was continued maintenance of these clinical outcomes with no

From MEDTAP International, Inc., Bethesda, MD (C.S.P. D.A.R, and R.E.B.), and Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, IN (L.A.G. and S.H.H.).

This study was funded by Lilly Research Laboratories, Eli Lilly and Company.

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evidence of significant EPS.[11] Olanzapine reduced rates of relapse compared with haloperidol and improved quality-of-life outcomes.[12] It remains to be demonstrated whether the differences in clinical efficacy and safety between atypical antipsychotics and the conventional neuroleptics will result in decreases in the use and cost of medical services, offsetting the higher price of the atypical antipsychotics.

The cost-effectiveness of new antipsychotics can be evaluated by using clinical decision analysis modeling.[13-15] Modeling is a relatively rapid method (compared with prospective studies) to estimate the economic impact of a new medical treatment and provides the flexibility to incorporate different treatment patterns, healthcare perspectives, and duration of treatment. Modeling is particularly valuable when a long-term prospective study would be impractical or infeasible.[4]

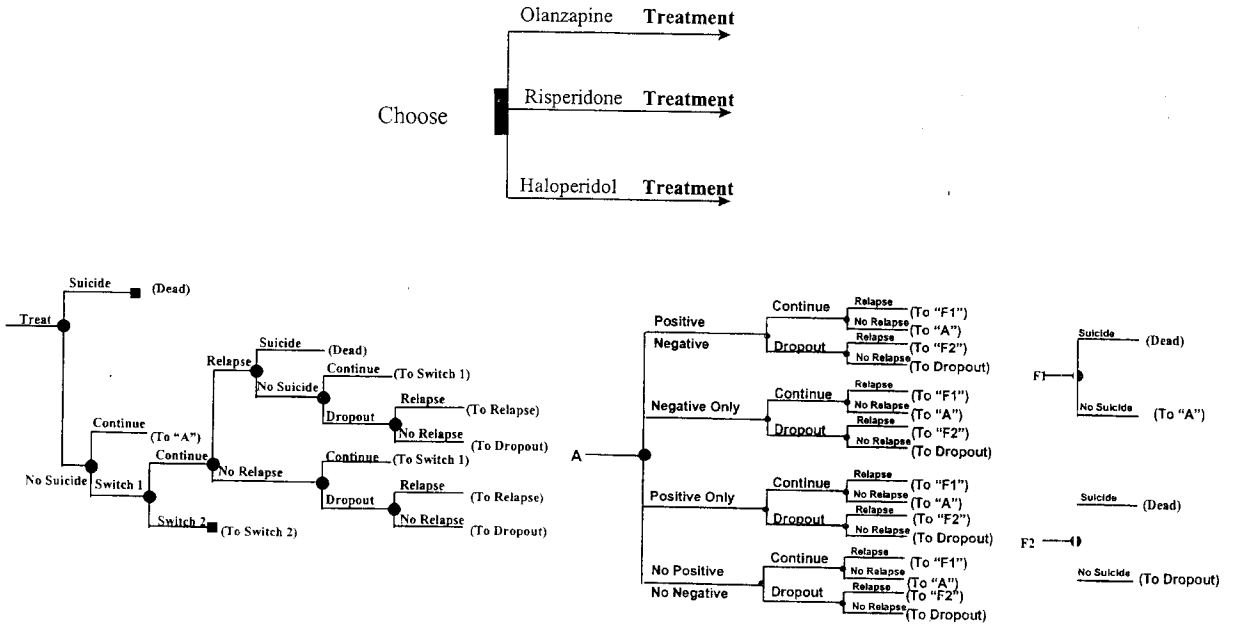
In decision analytic modeling, various mathematically based computer simulations (eg, Markov transition-state models) can be constructed and used to estimate the medical costs and effectiveness outcomes of hypothetical cohorts of patients exposed to different therapies. The structure and parameters of the model are determined by outcomes from clinical trials, medical literature, and expert clinician judgment. The intent is to simulate the clinical management pathways, clinical events associated with patient treatment, and outcomes of treatment based on the best available information. Uncertainty in the model parameters is examined by sensitivity analyses, where single and multiple parameters can be varied to test the robustness of the findings. Models can incorporate various measures of effectiveness outcomes. For some models, patient health outcomes are expressed as quality-adjusted life years (QALYs). QALYs represent patient survival (or time in the model) weighted by an indicator of patient quality of life. Normally, health-state utilities are used as these weights.[16-18]

A clinical decision analysis model was developed to estimate the 5-year direct medical costs and effectiveness outcomes of olanzapine treatment compared with haloperidol or risperidone treatment for patients who had experienced multiple episodes of schizophrenia. The model excluded patients with first-episode schizophrenia and treatment-resistant schizophrenia.

## ··· METHODS ···

To the extent possible, the parameter values for the selected model were taken from two international double-blind clinical trials comparing olanzapine with haloperidol (1996 randomized patients)[11] and olanzapine with risperidone (339 randomized patients).[19]

**Figure 1.** Schizophrenia Treatment Clinical Decision Model



These clinical trial data were the best available for the purpose of the model, although compared with other patients with schizophrenia, the patients in these trials may represent a biased sample because they had agreed to participate in a long-term follow-up study. In cases in which clinical trial results were unavailable, parameter estimates were based on published medical literature and expert advice from an 11-member international advisory panel composed of psychiatrists and health economists.

The decision analysis model was constructed by using SMLTREE™ software (version 2.2, Boston, MA) and was validated with TreeAge DATA™ software (TreeAge Software, Inc, version 3.5, Williamstown, MA). A simplified version of the decision tree is presented in Figure 1. The patient enters the model at "choose" node, where there is an equal probability of beginning treatment with one of three available drug therapies: olanzapine, risperidone, or haloperidol. The patient starts the selected drug therapy at the "treat" node, which represents the start of the Markov process for each drug in the model. The Markov process iterates in 3-month (91.25 days) cycles until the 5-year end point is reached (ie, 20 cycles). For a patient who does not commit suicide, a drug-dependent probability of continuing therapy or switching to another drug is assigned at the next chance node.

Patients who remain on the original drug in each of the three treatment pathways of the model continue (to "A" in Figure) to one of four symptom transition states. In each 3-month cycle, transition states represent four possible combinations of positive and negative symptoms (positive and negative symptoms, only positive symptoms, only negative symptoms, and no positive and no negative symptoms), with or without the occurrence of EPS. The transition probabilities associated with each combination of positive and negative symptoms affect the likelihood of staying in the same symptom state in the next 3-month cycle or changing to another symptom state. Once the patient enters a symptom transition state, there is a possibility of continuing or dropping out of treatment. Patients who continue may or may not relapse. A patient who does not relapse returns to node A. A patient who relapses proceeds to node $F_1$ or $F_2$ in the Figure.

A patient who switches therapy and continues on the Switch 1 drug may relapse. At each relapse, the possibility of suicide is encountered again. Patients who do not commit suicide may continue on the Switch 1 drug or drop out of treatment. Patients who drop out may relapse (ie, return to the relapse branch of the drug they were taking before dropping out) or continue as dropouts, cycling back to the dropout branch and remaining off therapy for that 3-month cycle. A patient in the Switch 1 pathway may also switch drug therapy again. In this case, the patient continues on clozapine, the only Switch 2 drug, for all remaining cycles in the model because it is assumed that these patients are treatment resistant. Patients who switch out of their initial treatment are not cycled through the four-symptom transition states, because transition-state data were not available for such patients. Instead, they continue in a switch state with probabilities of relapsing or dropping out, or both, for the remaining time in the model.

The sequences of switches from one drug to another for use in the model were determined by the advisory panel. A patient starting olanzapine may switch to risperidone, and a patient starting risperidone may switch to olanzapine. A patient starting therapy on haloperidol may switch to either olanzapine (50%) or risperidone (50%) at Switch 1; treatment failure on the selected drug is followed by a trial of the alternate drug at Switch 1. Because of limitations in the data available at the time of model development, it was necessary to assume that any switches occurred only in the first 6 months of treatment (ie, within two cycles).

## Data

A simplifying assumption that suicide attempts only occur during relapses was used in the model. In the initial 3-month cycle of the model, an assumption was made that there was a 2% suicide attempt rate irrespective of drug treatment.[20] For subsequent cycles, estimates for the suicide attempt rate were 1% for olanzapine, 2% for haloperidol, and 2% for risperidone. In the clinical trial comparing olanzapine with haloperidol, the suicide attempt rate for olanzapine was half that for haloperidol. In the clinical trial comparing olanzapine with risperidone, there were no suicide attempts by patients on olanzapine, and the suicide attempt rate was 1.8% for patients on risperidone. Thus, the rate used in the model for olanzapine may be an overestimate.

Rates for discontinuing therapy in 3-month cycles for the first year of the model for olanzapine, risperidone, and haloperidol are shown in Table 1. In cycles 1 and 2, discontinuation refers to switching from one drug to the next in the sequence; in cycles 3 and 4, discontinuation refers to dropping out of treatment. An assumption was made that treatment discontinuations occur only in the first 12 months of

therapy; patients who continued on therapy for at least 12 months were assumed to have a sufficient response. Footnotes in Table 1 provide details about the derivation of the discontinuation rates.

**Table 1.** Discontinuation Rates* by Therapy in Cycles 1-4

| Cycle | Month | Olanzapine† | Risperidone‡ | Haloperidol§ |
|---|---|---|---|---|
| 1 | 0-3 | 27.1 | 32.7 | 49.2 |
| 2 | 4-6 | 13.1 | 13.6 | 17.0 |
| 3 | 7-9 | 6.7 | 6.1 | 8.4 |
| 4 | 10-12 | 5.1 | 4.7 | 8.6 |

*In determining rates, we only considered discontinuation of therapy due to lack of efficacy or adverse events. In cycles 1 and 2, "discontinuation" refers to patients switching from the current drug to an alternate drug (see text for information on drug sequencing). After cycle 2, discontinuation refers to the patient dropping out of treatment.
†Rates for cycles 1 and 2 are weighted averages from the olanzapine-risperidone and olanzapine-haloperidol clinical trials. Rates for cycles 3 and 4 are from the olanzapine-haloperidol clinical trial.
‡Cycle 1 and 2 rates were derived from the olanzapine-risperidone clinical trial. In cycle 1 the rate for the risperidone group was 1.207 times the rate for the olanzapine group (1.207*27.1%=32.7%). In cycle 2 the rate for the risperidone group was 1.039 times the rate for the olanzapine group (1.039*13.1%=13.6%). The rates for risperidone were set equal to the rates for olanzapine in cycles 3 and 4 due to lack of data.
§Cycles 1-4 are from the olanzapine-haloperidol clinical trial.

**Table 2.** Relapse Rates by Therapy per Cycle

| Cycle | Month | Olanzapine (%)* | Risperidone (%)† | Haloperidol (%)* | No Therapy (%)‡ |
|---|---|---|---|---|---|
| 1 | 0-3 | 4.40 | 5.70 | 7.00 | 49.50 |
| 2 | 4-6 | 4.90 | 5.90 | 6.90 | 6.30 |
| 3 | 7-9 | 4.90 | 5.90 | 6.90 | 3.15 |
| 4 | 10-12 | 4.90 | 5.90 | 6.90 | 3.15 |
| 5-8 | 13-24 | 2.35 | 2.35 | 3.29 | 2.25 |
| 9-12 | 25-36 | 2.35 | 2.35 | 3.29 | 2.23 |
| 13-20 | 37-60 | 2.35 | 2.35 | 3.29 | 2.23 |

*Rates for cycles 1-4 were derived from the olanzapine-haloperidol clinical trial data. The rates for cycles 5-20 were derived from Gilbert et al[21] with assistance from the expert panel.
†Rates for cycles 1-4 represent the averages of the olanzapine and haloperidol rates. Olanzapine rates serve as proxies for risperidone for cycles 5-20 due to lack of data.
‡Rates for cycles 1-4 were derived from Baldessarini and Viguera[23] in reference to data in Gilbert et al.[21] The rates for cycles 5-8 (months 13-24) were averaged from published values for months 7-12 (Gilbert et al[21]) and months 25-36 (Johnson[22]). The rates for cycles 9-20 were assumed by the clinical panel to be similar to, but slightly lower than, the rates for cycles 5-8.

Relapse rates for each cycle are shown in Table 2. Rates for the first year are from the clinical trials. After reviewing relapse rates presented in published literature,[21-23] the international advisory panel agreed on the rates shown in Table 2 for years 2–5.

Patients from the clinical trials were placed into one of the four positive-negative symptom transition states based on their scores on selected Positive and Negative Symptom Scale (PANSS) items.[24] The international advisory panel provided recommendations regarding the item selection to reflect positive and negative symptoms. The PANSS items for assessing positive symptoms were delusions, conceptual disorganization, and hallucinatory behavior. These three items were combined into a positive scale. The items for assessing negative symptoms consisted of the seven items within the PANSS negative-symptom scale.[24] Patients were considered to have positive symptoms if the positive-scale score was greater than 8 and the item score on at least one of the three positive-symptom items was greater than 3. Patients were considered to have negative symptoms if the negative-scale score was greater than 20 and the item score on at least one of the seven negative-symptom items was greater than 3.

## Indicators of Treatment Effectiveness

For the cost-effectiveness analysis, the first outcome indicator of treatment effectiveness included in the model was the proportion of patients whose last available Brief Psychiatric Rating Scale (BPRS) total score was less than 18 (items were scored from 0 to 6) during the 3-month cycles. Davies and Drummond[25] used a similar approach for estimating the effectiveness of clozapine treatment in a cost-effectiveness analysis. BPRS total scores were selected because the BPRS covers a range of psychopathology, is frequently used for the evaluation of antipsychotic treatments, and provides a clinically meaningful outcome because psychiatrists are very familiar with

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this outcome measure. The proportion of patients in the clinical trials meeting the BPRS total score criteria was calculated for the positive- and negative-symptom transition states for the three treatments. The highest possible value was 5 (undiscounted), meaning that all patients met this criteria for the entire 5-year period. Because only the initial BPRS scores for each transition state were available for risperidone-treated patients, it was assumed that the risperidone treatment group would have outcomes equivalent to those of the olanzapine treatment group throughout the remaining cycles. This approach was considered to be conservative because olanzapine showed better BPRS outcomes than risperidone in the clinical trial.

QALYs were estimated as the second outcome indicator of treatment effectiveness for the model. The utilities used in the calculation of the QALYs were estimated from standard gamble utilities assigned to hypothetical schizophrenia-related health states by 12 psychiatrists in the United Kingdom,[26] as well as from unpublished data on the differences between standard gamble utilities for haloperidol health states and utilities for atypical-antipsychotic health states. Health utilities represented the strength of a person's preference for different health outcomes or states under conditions of uncertainty.[17,18] The same QALYs were used for both the olanzapine and risperidone treatment groups.

The third outcome indicator of treatment effectiveness for the model was lack of relapse. For each cycle in each treatment pathway of the model, counts of patients who did not relapse on the original or the Switch 1 drug were determined. The nonrelapse outcome represents the cumulative (ie, 5-year) proportion of patients who did not experience relapse in each 3-month cycle. Nonrelapse rates were derived directly from the probabilities and structure of the model and were not based on independent estimates. Because dropouts were incorporated into each treatment pathway of the model, they were included in the computations of the treatment-related relapse rates.

## Medical Resource Utilization and Costs

The estimates of direct medical costs were based on the expected use of hospital, day hospital, outpatient physician and other mental health provider services, laboratory tests, and medications. Costs were inflated to 1995 dollars, where necessary, by using the appropriate Medical inflator from the Consumer Price Index.[27] Most of the data regarding medical resource utilization were provided by the expert panel and were supplemented by data from published literature. Separate estimates of medical resource utilization for 3-month cycles were made for patients who started therapy (cycle 1 in the model), who received maintenance therapy, and who had relapses. These resource utilization estimates provided the foundation for calculating the costs for each 3-month cycle in the model. The costs of suicides and suicide attempts were incorporated in the model whenever a patient experienced a relapse.

Table 3 shows medical resources used by patients in the first 3 months of therapy, 100% of whom were assumed to be hospitalized for 22 days based on national US hospital discharge data.[28] For outpatients in cycle 1, treatment included three visits to a psychiatrist and six visits to other mental health providers for group therapy sessions, treatment programs, medication, treatment of EPS, and laboratory tests for monitoring purposes. The percentage of patients

**Table 3.** Three-Month Medical Resource Utilization in Cycle 1

| Resource | Olanzapine | Haloperidol | Risperidone |
|---|---|---|---|
| Inpatient Services | | | |
| Percent requiring hospitalization | 100% | 100% | 100% |
| Hospital length of stay | 22 days | 22 days | 22 days |
| Number of psychiatrist visits in hospital | 22 | 22 | 22 |
| Outpatient Services | | | |
| Number of psychiatrist visits | 3 | 3 | 3 |
| Number of visits to non-MDs | 6 | 6 | 6 |
| Percent in residential treatment programs | 33% | 33% | 33% |
| Number of residential treatment days | 69.25 | 69.25 | 69.25 |
| Percent in partial treatment programs | 33% | 33% | 33% |
| Number of partial treatment days | 49 | 49 | 49 |
| Percent in outpatient treatment programs | 33% | 33% | 33% |
| Number of outpatient treatment days | 49 | 49 | 49 |
| Medication Dose (mg/day) | 10 | 15 | 6 |
| Number of days of medication | 91.25 | 91.25 | 91.25 |
| Percent with Extrapyramidal Symptom Treatment | 19% | 45% | 20% |
| Number of Laboratory Monitoring Tests SMAC12* | 0.25 | 0.25 | 0.25 |

*SMAC12 refers to 12-test laboratory panel.

receiving treatment for EPS was determined for olanzapine by using the higher of two percentages (19% vs 15%) obtained from clinical trial data[9,19] to maintain a conservative approach in the model. For patients on risperidone and haloperidol, rates were taken from the clinical trials (20% and 45%, respectively).[9,19]

Patients were estimated to attend treatment programs as follows: 33% in residential treatment, 33% in partial (3 h/day) treatment, and 33% in various types of outpatient (<3 h/day) treatment programs. Residential programs were attended 7 days/week and partial and outpatient programs were attended 5 days/week. No costs were included for other medically related resources because it was likely that these kinds of resources were independent of antipsychotic therapy and would contribute equally to the cost of each treatment. After the first 3-month cycle of treatment, patients received maintenance therapy, for which medical resources are indicated in Table 4. Patients who relapsed during a 3-month period had the same utilization of medical resources outlined in Table 3, with the exception that 50% of outpatient care was provided in residential programs and the remaining 50% was provided in partial treatment programs (ie, no patients participated in outpatient treatment programs during the 3-month cycle in which the relapse occurred). Table 5 includes the 3-month costs associated with various types of medical resource use.

Sensitivity analyses were performed to test the robustness of the model by changing parameter values and costs that were most uncertain: the inpatient length of stay, discount rate, suicide attempt rate, and drug dosage.

## ··· RESULTS ···

The model's base case cost-effectiveness analysis compared the estimated 5-year medical costs and BPRS-based, QALY-based, and nonrelapse-based outcomes by using a 5% discount rate (Table 6). The base case estimate of the 5-year medical cost was $92,593 with an estimated BPRS-based outcome of 3.18 for patients on olanzapine. The cost of haloperidol therapy was $94,132 with a BPRS-based outcome of 2.61, and the cost of risperidone therapy was $94,468 with a BPRS-based outcome of 3.15. Compared with haloperidol therapy, olanzapine therapy cost $1,539 less and its BPRS-based outcome was 0.57 higher. The BPRS-based outcome indicated that over 5 years, patients on olanzapine had an additional 6.8 months in a disability-free state at a lower cost. Compared with risperidone therapy, olanzapine therapy cost $1,875 less over 5 years and resulted in an additional 1.6 weeks in a disability-free health state.

**Table 4.** Three-Month Medical Resource Utilization for Maintenance Therapy in Cycles 2-20

| Resource | Olanzapine | Haloperidol | Risperidone | Clozapine |
|---|---|---|---|---|
| Outpatient Services | | | | |
| Percent seeing psychiatrist or receiving group therapy | 65% | 65% | 65% | 65% |
| Number of psychiatrist visits | 1 | 1 | 1 | 1 |
| Number of group therapy sessions | 6 | 6 | 6 | 6 |
| Percent in treatment programs | 10% | 10% | 10% | 10% |
| Percent in residential treatment | 2.5% | 2.5% | 2.5% | 2.5% |
| Number of residential treatment days | 91.25 | 91.25 | 91.25 | 91.25 |
| Percent in partial treatment (>3day) | 2.5% | 2.5% | 2.5% | 2.5% |
| Number of partial treatment days | 65 | 65 | 65 | 65 |
| Percent in outpatient treatment (<3 day) | 5% | 5% | 5% | 5% |
| Number of outpatient treatment days | 65 | 65 | 65 | 65 |
| Medication Dose (mg/day) | 10 | 15 | 6 | 425 |
| Number of days of medication | 91.25 | 91.25 | 91.25 | 91.25 |
| Percent with Extrapyramidal Symptom Treatment | 19% | 45% | 20% | |
| Number of Laboratory Monitoring Tests | | | | |
| Complete blood count | 0.00 | 0.00 | 0.00 | 13.00 |
| SMAC12* | 0.25 | 0.25 | 0.25 | 0.25 |

*SMAC12 refers to 12-test laboratory panel.



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**Table 5.** Base C

| Resource |
|---|
| Suicide |
| Hospital and MD |
| Attempted Suicide |
| Hospital and MD |
| Medication |
| Olanzapine |
| Risperidone |
| Haloperidol |
| Clozapine |
| Pharmacy charge |
| Laboratory Monito |
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| Personnel |
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With QALYs as the effectiveness outcome indicator, olanzapine-treated patients had 2.3 and 0.8 additional months of disability-free health at a lower cost during the 5-year period compared with patients treated with haloperidol and risperidone, respectively. The cost of therapy with olanzapine remained lower over the 5-year period. With nonrelapse as the effectiveness outcome indicator, 31% of olanzapine-treated patients, 18% of haloperidol-treated patients, and 29% of risperidone-treated patients did not experience relapse during 3-month cycles over the 5-year period. Thus, in this model, olanzapine treatment resulted in 13% and 2% less chance of relapse at a lower cost compared with haloperidol and risperidone, respectively.

Sensitivity analyses were performed for the BPRS-based effectiveness outcomes (see Table 7). When costs and effectiveness were discounted at 0% rather

**Table 5.** Base Case Medical Resource Utilization Costs (1995 Dollars)

| Resource | Units or Unit Costs | Cost per Cycle | Source |
|---|---|---|---|
| Suicide | | | |
| Hospital and MD visits | Per case | $575 | Palmer et al, 1995[29] |
| Attempted Suicide | | | |
| Hospital and MD visits | Per case | $1,860 | Palmer et al, 1995[29] |
| Medication | | | |
| Olanzapine | 10 mg/day | $706 | Lilly Research Laboratories |
| Risperidone | 6 mg/day | $720 | *1995 Physician's GenRx*[30] |
| Haloperidol | 15 mg/day | $7.60 | *1995 Physician's GenRx*[30] |
| Clozapine | 425 mg/day | $1,322 | *1995 Physician's GenRx*[30] |
| Pharmacy charge | $5/drug | $5 | Glazer and Ershefsky, 1996[31] |
| Laboratory Monitoring Test | | | |
| Complete blood count (clozapine monitoring) | 52/year ($488) | $122 | HCFA allowable Medicare charge[32] |
| Extrapyramidal Symptom Treatment | $196 | $49 | Glazer and Ershefsky, 1996[31] |
| Personnel | | | |
| Psychiatrist visit for: | | | |
| Established outpatient (25-minute visit) | $50 | Depends on transit on state | HCFA allowable Medicare charge[32] |
| Inpatient (initial 50-minute visit) | $100 | $100 per admission | HCFA allowable Medicare charge[32] |
| Inpatient (subsequent 25-minute visit) | $47 | $470 per admission | HCFA allowable Medicare charge[32] |
| Outpatient group therapy session (non-MD visit) | $43 | Depends on transition state | Ridgewood Financial Institute, 1995[33] |
| Hospitalization | 22-day stay* | $9,460** | |
| Treatment Programs | | | |
| Residential treatment | $305 per day | $27,828 | National Association of Psychiatric Health Systems, 1995[34] |
| Partial treatment (>3 hrs.) | $218 per day | $19,903 | National Association of Psychiatric Health Systems, 1995[3] |
| Outpatient programs (<3 hrs.) | $68 per day | $6,226 | National Association of Psychiatric Health Systems, 1995[3] |

HCFA = Health Care Financing Administration.
*22-day stay from Weiden and Olfson.[18] Cost of this 22-day stay derived from Maryland Hospital discharge data from 1994 (unpublished, available from MEDTAP).
**Cost of 22-day stay based on Maryland hospital discharge data from 1994.

than 5%, the total estimated medical costs increased for all treatments and remained cost-saving for olanzapine therapy compared with haloperidol and risperidone. When costs and effectiveness were discounted at 10% rather than 5%, medical costs and outcomes decreased; olanzapine therapy still had lower costs and better effectiveness than haloperidol and risperidone therapies. When hospital length of stay was reduced from 22 to 11 days (based on Maryland hospital discharge data for 1994), treatment with olanzapine resulted in medical costs that were $1,744 higher than those for haloperidol therapy and medical costs that were $432 higher than those for risperidone therapy (effectiveness outcomes remained unchanged). When the suicide attempt rate was set to either 0% or 2% per cycle across all drug therapies, olanzapine therapy still remained cost-saving compared with haloperidol and risperidone therapies.

In an additional sensitivity analysis, the doses for olanzapine and risperidone were increased from the clinical experts' recommendations of 10 mg/day and 6 mg/day, respectively, to 15 mg/day and 7 mg/day, respectively, to more closely reflect the dosages used in the clinical trials.[9,19] Based on BPRS scores, treat-

**Table 6.** Base Case Cost-Effectiveness Analyses

| Outcome Measure | Olanzapine | | Haloperidol | | Risperidone | | Cost-Effectiveness Results* | |
|---|---|---|---|---|---|---|---|---|
| | Cost ($) | Outcome | Cost ($) | Outcome | Cost ($) | Outcome | Olz vs Hal | Olz vs Ris |
| BPRS | 92,593 | 3.18 | 94,132 | 2.61 | 94,468 | 3.15 | Cost-saving | Cost-saving |
| QALYs | 92,593 | 3.15 | 94,132 | 2.96 | 94,468 | 3.12 | Cost-saving | Cost-saving |
| Percent nonrelapse | 92,593 | 31.2% | 94,132 | 18.2% | 94,468 | 29.3% | Cost-saving | Cost-saving |

BPRS = Brief Psychiatric Rating Scale; QALYs = quality-adjusted life years; Olz = olanzapine; Hal = haloperidol; Ris = risperidone.
*Incremental cost-effectiveness results are from the perspective of olanzapine, and all costs and outcomes are discounted to present value by using a 5% rate.

**Table 7.** Sensitivity Analyses*

| Parameter | Olanzapine | | Haloperidol | | Risperidone | | Cost-Effectiveness Results† | |
|---|---|---|---|---|---|---|---|---|
| | Cost ($) | Outcome | Cost ($) | Outcome | Cost ($) | Outcome | Olz vs Hal | Olz vs Ris |
| 0% discount rate | 100,429 | 3.56 | 102,078 | 2.92 | 102,459 | 3.52 | Cost-saving | Cost-saving |
| 10% discount rate | 86,142 | 2.87 | 87,584 | 2.35 | 87,888 | 2.84 | Cost-Saving | Cost-saving |
| 11-day hospital stay | 89,822 | 3.18 | 88,078 | 2.61 | 89,390 | 3.15 | $3,060 | $14,400 |
| 0% suicide attempt rate for all drugs | 92,731 | 3.19 | 94,273 | 2.62 | 94,605 | 3.15 | Cost-saving | Cost-saving |
| 2% suicide attempt rate for all drugs | 92,602 | 3.18 | 94,136 | 2.61 | 94,471 | 3.15 | Cost-saving | Cost-saving |
| 15 mg/day Olz, 7 mg/day Ris | 95,847 | 3.18 | 95,366 | 2.61 | 96,991 | 3.15 | $844 | Cost-saving |
| 15 mg/day Olz, 6 mg/day Ris | 95,808 | 3.18 | 94,966 | 2.61 | 95,576 | 3.15 | $1,477 | $7,733 |

Olz = olanzapine; Hal = haloperidol; Ris = risperidone.
*All sensitivity analyses were conducted with the Brief Psychiatric Rating Scale as the outcome measure.
†Incremental cost-effectiveness results are from the perspective of olanzapine, and all costs and outcomes are discounted to present value by using a 5% rate unless otherwise specified.

ment with olanzapine at 15 mg/day resulted in better efficacy than treatment with haloperidol at 15 mg/day at an incremental cost of $844 per disability-free year gained. Treatment with olanzapine 15 mg/day remained cost-saving compared with risperidone 7 mg/day . With olanzapine 15 mg/day versus the base case doses of 6 mg/day for risperidone and 15 mg/day for haloperidol, the incremental cost of olanzapine was $1,477 per disability-free year gained compared with haloperidol and $7,733 per disability-free year gained compared with risperidone.

## ··· DISCUSSION ···

This decision analytic model was developed as a more timely alternative to a 5-year prospective study to estimate the cost-effectiveness of olanzapine therapy compared with haloperidol and risperidone therapy. The model estimated the medical resource consumption and effectiveness outcomes associated with these treatments for the average patient with schizophrenia, excluding first-episode and treatment-resistant patients. Conservative parameter estimates were used for olanzapine, limiting potential bias in its favor. A number of sensitivity analyses were performed to test the least certain parameter values and estimated costs; these analyses indicated that although the model was robust to most changes, it was rather sensitive to changes in drug dosages and to a decrease in the length of hospital stay.

The cost-effectiveness analysis was based on a decision model that estimated the costs and outcomes of three different antipsychotic treatments. Modeling provides acceptable estimates of medical costs and outcomes. However, decision models are only as good as their underlying assumptions and the quality of the data used to estimate model parameters.[3,4]

Clinical decision models are simulations of clinical practice and outcomes, and as such, they may be subject to bias given the number and nature of simplifying assumptions needed to construct them. We based much of the model on data from clinical trials and published literature. Sensitivity analyses that test model assumptions help researchers understand the importance of various model assumptions. We performed a number of sensitivity analyses, concentrating on those parameters with the greatest uncertainty.

Several limitations must be kept in mind regarding this model and its parameter values. First, in many cases it was necessary to assume that parameters for risperidone were similar to those of olanzapine because equivalent detailed data were unavailable from the published literature[35] or the clinical trial comparing olanzapine and risperidone. Thus, the model may tend to underestimate the cost-effectiveness of olanzapine compared with risperidone.

Second, there are differences (eg, in relapse rates) between the olanzapine clinical trial data and the published literature with respect to the level of detail and the ways variables were measured. Relapse rates of 12.2% for risperidone and 2.9% for olanzapine were observed in the clinical trial for the first 3 months of treatment.[19] Nevertheless, a conservative approach was maintained: the relapse rates for risperidone therapy were assumed to be the average of the olanzapine and haloperidol rates for cycles 1–4 and were set identical to the olanzapine rates for cycles 5–20 (Table 2).

Finally, there are important and significant differences between haloperidol therapy and olanzapine or risperidone therapy in measures of health utility.[26] The extent to which the outcomes included in this model adequately capture these effects is uncertain. To evaluate these assumptions, future prospective studies are needed for direct measurement of utilities in patients with schizophrenia treated with haloperidol, olanzapine, or risperidone. In addition, we assumed that the BPRS-based outcomes and utilities associated with risperidone are equivalent to those associated with olanzapine. The criterion for a successful BPRS-based outcome was set at less than 18, which is a fairly restrictive indicator of clinical outcome. This level was selected to represent mild psychopathology and clear remission. We believe the use of less restrictive criteria, such as a BPRS total score of greater than 24, would improve outcomes for the three therapies and slightly attenuate the differences in clinical effectiveness between haloperidol treatment and olanzapine or risperidone treatment. However, we do not believe the direction of findings in the model would change substantially.

These analyses demonstrate the importance of considering all aspects of patients' management and well-being rather than simply drug prices alone to determine which drugs should be available for use. The inclusion of both efficacy and utility in this economic model takes into account the improved mental and physical status of patients with decreases in episodes of schizophrenia. Thus, the model suggests that not only is 5-year treatment less costly with olanzapine, it provides a better quality of life for patients with schizophrenia.

## Acknowledgments

We acknowledge members of the international advisory panel for assistance with this model: William Glazer, Yale University; Ron Goeree, McMaster University; J. Graf von der Schulenburg, Universitaet Hannover; Nicholas Keks, The Alfred Hospital; Martin Knapp, Center for the Economics of Mental Health; Viviane Kovess, CHS La Verriere; Herbert Meltzer, Case Western Reserve University; J. Peuskens, Universitair Psychiatrisch Centrum St. Jozef; Giorgio Racagni, Center of Neuropharmacology, Luis Salvador-Carulla; and Ken Wright, University of York.

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