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Economic evaluation of antipsychotic drugs for schizophrenia treatment within the Brazilian Healthcare System

ABSTRACT

OBJECTIVE: To assess the cost-utility of first and second-generation antipsychotics for treatment of schizophrenia.

METHODS: A five-year Markov model was constructed based on a survey of the records of patients seen in 2006 at a psychosocial care center in the municipality of Florianopolis, Southern Brazil. Costs were evaluated from the perspective of the *Sistema Único de Saúde* (SUS – Unified Healthcare System). Utility was measured in quality-adjusted life years obtained in the literature.

RESULTS: The Markov model indicated risperidone and haloperidol utilization before olanzapine as the most cost-effective alternatives.

CONCLUSIONS: Antipsychotic agents haloperidol and risperidone are more cost-effective than olanzapine. Strategies prioritizing the use of antipsychotics with better cost-effectiveness could optimize resource allocation without necessarily compromising the health of patients treated through the *Sistema Único de Saúde*.

DESCRIPTORS: Antipsychotic Agents. Schizophrenia. Health Care Costs Quality-Adjusted Life Years. Single Health System. Cost-Effectiveness Evaluation.

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INTRODUCTION

Schizophrenia is a chronic disease which has an important impact on quality of life. This disease is also associated with high costs of long-term treatment and with special demands made on health care services.[11] The introduction of second-generation antipsychotics for treating schizophrenia led to a debate regarding the costs of pharmacological treatment. In certain aspects, these new antipsychotic drugs show superior clinical response when compared to their first-generation counterparts. However, given of the high cost of these drugs, it is important to evaluate whether the clinical benefits justify the additional cost.

Currently, in Brazil, the *Sistema Único de Saúde* (SUS – Unified Health Care System) provides second-generation antipsychotics only to patients refractory to treatment with first-generation drugs and who are enrolled in the "*Programa de Medicamentos de Dispensação Excepcional*" (Program for Exceptional Dispensation Drugs). In Santa Catarina State, Southern Brazil, the cost of supplying second-generation antipsychotics for 4,258 patients between January 2000 and October 2006 amounted to US$ 709,019.46. Olanzapine was the third most requested drug in 2004 and second in terms of expenditures among

the 59 drugs provided by the Santa Catarina State drug dispensing program.[3] Though expenditures with this type of medication are high, more precise information on their effectiveness is still unavailable, and studies on the cost of treating schizophrenia through SUS are lacking.

Health care managers frequently rely on indicators such as the relationship between results obtained and resources allocated for making budget decisions.[11] Economic evaluation of the different forms of treatment available can optimize decision-making by taking into account budgetary factors, as long as they do not interfere directly with patient health. It is possible to assess whether expenditure with a given intervention are justifiable, helping to reconcile the growing health-related demands of the population with the available economic resources.[7,17]

The aim of the present study was to evaluate the cost-utility of first and second-generation antipsychotics in the treatment of schizophrenia.

METHODS

The use of analytical models for clinical decision-making is a relatively quick method for estimating the economic impact of a new treatment or medical technique. These models have the flexibility to analyze different patterns of treatment, health care perspectives, and treatment durations. These models are particularly valid in cases which long-term prospective studies are unfeasible, and simulate the clinical course of treatment-associated events, as well as treatment outcome based on the best available information.

We developed a Markov state transition model,[5] using a cost-utility evaluation approach, to compare the cost and effectiveness of antipsychotic agents haloperidol (first-generation), risperidone, and olanzapine (both second-generation) in the treatment of patients with chronic schizophrenia in need of continuous outpatient treatment. The model population included hypothetical cohorts of patients with chronic schizophrenia receiving antipsychotics under an outpatient maintenance regimen at a psychosocial care facility in Florianopolis, Santa Catarina State, in Southern Brazil.

The study was carried out from the perspective of SUS, and we chose to evaluate the direct medical cost associated with each alternative (combinations of haloperidol, risperidone, and olanzapine) for the base year 2006. The period analyzed for the hypothetical cohort (time horizon) was of five years, with an annual discount rate (natural devaluation of costs of inputs and benefits across the time horizon) of 3%.[7]

The model was constructed using TreeAge Pro 2006 software. For its construction, we carried out a literature review of economic evaluation studies comparing different antipsychotics using modeling techniques.[1,2,4,6,12,15,16] The sequences of events employed in these studies were used as a base for the construction of Markov cycles, adapted with the aid of psychiatrists who provided care to the patients.

The Figure illustrates the sequence of events across a three-month period associated with the initial decision to prescribe antipsychotic medication. We considered the same sequence of events for all evaluated treatments. However, the probability of an event could vary between treatments. This representation corresponded to one cycle in Markov analysis and the five-year model was divided into 20 three-month cycles.

The model begins when a patient initiates treatment at the psychosocial care facility. The first node ("decision node") represents the choice of antipsychotic agent, assuming an equal probability of initiating treatment by any of the three drugs evaluated. We assumed that severe adverse effects would lead to discontinuation of treatment and consequent change of medication. Adverse effects tolerated by patients were incorporated assuming that they would affect quality of life and increase treatment costs through the need for additional medication.

Event probabilities were estimated based on information obtained in the literature on the subject (Table 1). The sequence of medication switch for patients who start treatment with haloperidol was established following the recommendations of the *Ministério da Saúde* (Brazilian Ministry of Health), laid out in the *Protocolo Clínico e Diretrizes Terapêuticas para Esquizofrenia Refratária* [Clinical Protocol and Therapeutic Directives for Refractory Schizophrenia].[a] That for patients who begin treatment with second-generation antipsychotics was defined based on the guidelines for schizophrenia treatment of the American Psychiatric Association.[13]

Patients who began therapy with haloperidol and subsequently discontinued its use, were switched to risperidone. Those who discontinued use of risperidone and required change of medication were given clozapine. Patients who did not tolerate clozapine were moved on to olanzapine. We assumed that patients who changed to olanzapine remained on this drug until the end of follow-up.

Patients who began treatment with risperidone, in case of discontinuation, were given olanzapine. Those who did not tolerate olanzapine were given haloperidol, and in case the latter was discontinued, these patients were then given clozapine.

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[a] Ministério da Saúde. Protocolos clínicos e diretrizes terapêuticas: medicamentos excepcionais. Brasília (DF); 2002.
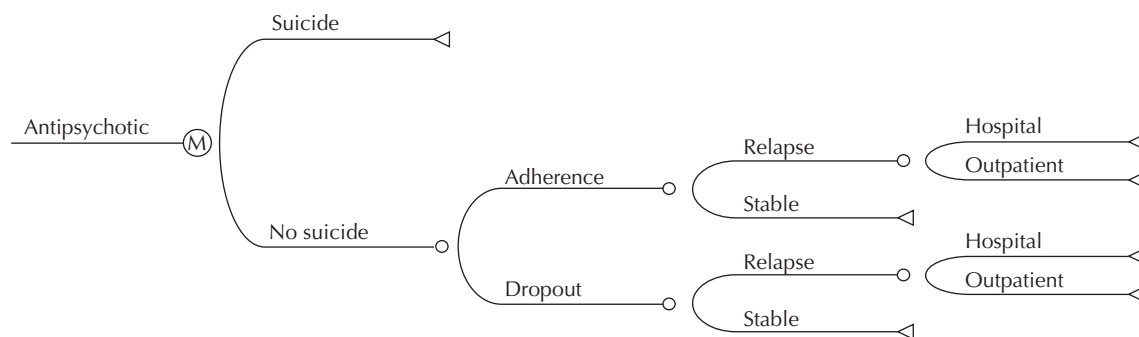
Figure. Representation of the sequence of events (decision tree) associated with treatment based on the Markov Model. Municipality of Florianópolis, Southern Brazil.

Finally, patients who began therapy with olanzapine but discontinued treatment were given risperidone. In case risperidone was discontinued, these patients were given haloperidol, and in case haloperidol was discontinued, patients were given clozapine. We assumed that patients switched to clozapine remained with this medication until the end of treatment.

This configuration is based on studies that indicate clozapine as the only antipsychotic agent effective in treating refractory patients.[13] We assumed that patients that did not drop out of treatment during the first 12 months would remain on the initial drug until the end of treatment.

Exacerbation of psychotic symptoms requiring hospital admission or outpatient treatment in specialized facilities was regarded as a relapse. Patients adhering to treatment without relapse were considered as not needing change of medication.

Regarding the outcome measure, treatment effectiveness was determined in Quality Adjusted Life Years (QALYs).[7] This measure takes into account both the amount and quality of life gained by use of a given treatment. Quality of life was estimated based on instruments that evaluate perception of a given health status by assigning it a value ranging between two extremes: 0 (death) and 1 (perfect health). This value, known as

Table 1. Probabilities used for each cycle of the Markov model according to antipsychotic agent used, based on information from the literature.

Cycle (month)	Haloperidol	Risperidone	Olanzapine	Clozapine	No treatment
Discontinuation					
1 (0-3)[a]	0.492	0.327	0.271	-	-
2 (4-6)[a]	0.170	0.136	0.131	-	-
3 (7-9)[b]	0.084	0.061	0.067	0.04	-
4 (10-12)[b]	0.086	0.047	0.051	0.04	-
5-20 (13-60)[b]	0.000	0.000	0.000	0.04	-
Relapse					
1 (0-3)[b]	0.077	0.057	0.044	0.04	0.495
2 (4-6)[b]	0.069	0.059	0.049	0.04	0.063
3 (7-9)[b]	0.069	0.059	0.049	0.04	0.0315
4 (10-12)[b]	0.069	0.059	0.049	0.04	0.0315
5-20 (13-60)[b]	0.0329	0.0235	0.0235	0.04	0.0225
Suicide					
1-20 (0-60)[c]	0.02	0.02	0.02	0.02	0.02
Hospitalization following relapse					
1-20 (0-60)[d]	0.6	0.6	0.6	0.6	0.6

[a] Glennie,[8] Jayaran et al,[9] Knapp et al.[11]
[b] Drummond et al,[7] Glennie,[8] Jayaran et al,[9] Knapp et al.[11]
[c] Lecomte et al.[12]
[d] Drummond et al.[7]

utility, is multiplied by the time for which the individual remains in that health status.[7] Each medication was assigned a utility value, estimated in international studies using the standard gamble method to obtain utilities related to schizophrenia treatment.[8,15]

The assessment of resources consumed by patients (costs) was carried out using information obtained from the patient charts of 59 individuals seen at a psychosocial care facility in the year 2006. We considered only costs that vary with each of the alternatives, namely: antipsychotic, secondary medication (support treatment and adverse effects), specialized medical appointments, relapse-related hospitalization, and suicide.

The unit cost of each antipsychotic agent and of secondary medication were obtained from the Santa Catarina State Secretariat of Health (SES-SC), based on the unit value paid for the last purchase made. Costs attributed to psychiatric appointments and admission to psychiatric hospital were obtained from the cost charts of the *Sistema de Informações Ambulatoriais* (SIA/SUS – Outpatient Care Information System) and the *Sistema de Informações Hospitalares* (SIH/SUS – Hospital Information System). The latest version of these charts referring to the year 2006 were used.

The cost to SUS of patient death by suicide was estimated at US$ 389.30.[10]

Information from medical charts was used to calculate the amount of resources expended. The costs attributed to each treatment regimen are described in Table 2.

Resource use associated with each medication was calculated considering daily dose, potential dose adjustment, time of permanence under each dose, total duration of treatment, and use of secondary medication. The sum of the mean cost of primary medication with the mean cost of secondary medication generated the medication cost attributed to each antipsychotic.

Psychiatrist appointments were quantified in mean number of appointments/month. Monthly cost of appointments was calculated by multiplying frequency of appointments by the unit cost of the appointment.

Cost of hospital admission was calculated by multiplying the mean duration of admission in days by the cost of one day's admission. Mean duration of admission was based on information obtained from patient charts. Mean duration of hospital admissions was estimated to be 22 days after a crisis or relapse, regardless of antipsychotic agent used.

We carried out one-way sensitivity analysis for all variables, using variation levels obtained from the literature or plausible in practice. For sensitivity analysis of variables associated with utility, we employed values inside the 95% confidence interval.

For sensitivity analysis of cost, the model was calculated with an increment of up to 60% in the cost of medical appointments and hospital admissions. This number was adopted based on an estimate that the cost of SUS funding for psychiatric hospitalization is equivalent to 41% of the actual cost to hospitals.[14] The cost of pharmacological treatment was calculated in order to estimate its impact on the final result of the model, assuming a variation range assigned by the researchers.

To evaluate the efficiency of medication switching, the model was recalculated using different medication switching configurations.

The study was approved by the Research Ethics Committee of the *Universidade Federal de Santa Catarina* (Process no. 270/05).

Table 2. Cost of use of health care resources. Municipality of Florianópolis, Southern Brazil.

Resource	Unit	Cost[a] (US$)	Variation in sensitivity analysis
Psychiatric appointment[b]	appointment	3.67	3.67;5.86
Hospitalization[c]	22 days	317.07	317.07;792.69
Medication			
Haloperidol	9.35 mg/day	20.50	20.50;72.81
Olanzapine	14.54 mg/day	800.49	72.81;800.49
Risperidone	3.33 mg/day	19.98	19.98;72.81
Clozapine	466.58 mg/day	740.83	72.81;740.83
Suicide	case	389.30	242.72;485.44

[a] Cost per cycle (3 months); includes antipsychotic and additional medication
[b] Santa Catarina. Secretaria de Estado da Saúde. Tabela de procedimentos do Sistema de Informações Ambulatoriais do Sistema Único de Saúde SIA–SUS. Acesso em 22 de outubro de 2006 [cited 2006 Oct 22] Available from: http://www.saude.sc.gov.br/.
[c] Santa Catarina. Secretaria de Estado da Saúde. Tabela de procedimentos do Sistema de Informações Hospitalares do Sistema Único de Saúde SIH–SUS. Acesso em 22 de outubro de 2006 [cited 2006 Oct 22] Available from: http://www.saude.sc.gov.br/

Table 3. Cost-utility results for a five-year period. Municipality of Florianópolis, Southern Brazil.

Antipsychotic	Utility (QALY)	Incremental utility (QALY)	Total cost (US$)	Incremental cost (US$)	Cost-utility ratio (US$/QALY[a])	Incremental cost-utility (US$)
Haloperidol	4.1647		3,935.15		944.89	
Risperidone	4.2156	0.0509	5,964.57	2,029.43	1,414.90	39,890.33
Olanzapine	4.2189	0.0034	10,423.12	4,458.54	2,470.57	1,329,394.88

QALY: Quality Adjusted Life Years
[a] United States Dollars per Quality Adjusted Life Year

RESULTS

Table 3 presents the results of cost and utility, the cost-utility ratio, and the incremental cost-utility of the three evaluated scenarios corresponding to the medication exchange sequences, estimated for a five-year period and using an annual discount rate of 3%.

For patients beginning treatment with haloperidol, at the end of five years, the model estimated an outcome of 4.1647 QALY with a total cost of US$ 3,935.15. For patients who began treatment with risperidone, we estimated a benefit of 4.2156 QALY at a cost of US$ 5,964.57 per patient. Estimated utility for patients beginning treatment with olanzapine was practically identical to that of patients beginning with risperidone, but with a total cost of US$ 10,423.12.

Compared to the choice of beginning treatment with haloperidol, starting with risperidone represented an incremental cost of US$ 39,890.33. The incremental cost represents the monetary value necessary to achieve an increase of one additional QALY unit.

The strategy of beginning treatment with olanzapine had significantly higher cost, and was virtually identical in terms of utility, when compared to beginning treatment with risperidone. According to this result, the choice to begin treatment with olanzapine may be considered as highly unfavorable (dominated) from the economical standpoint considering the QALY outcome when compared to starting with risperidone.

According to the probabilities and assumptions adopted when constructing the model, each patient that begins treatment with one of these drugs may switch to another antipsychotic as primary medication, thus becoming subject to the costs and outcome attributed to this other drug. Among patients beginning treatment with haloperidol, by the end of five years, 37% would be on risperidone, 34% still on haloperidol, 8% on olanzapine, and another 17% on clozapine. The total cost of this scenario was inferior to that of the other scenarios evaluated, especially because most patients by the end of the period were on either risperidone or haloperidol, which are associated with lower treatment cost. The fact that only a small percentage of patients had changed to olanzapine after five years led to the lower cost associated with this scenario when compared to the other two scenarios proposed in the original model.

In the scenario in which patients began treatment with risperidone, there was a greater proportion of patients changed to olanzapine (30%) than among those who began with haloperidol. This outcome would lead to a significant increase in total cost of treatment.

Sensitivity analysis showed the model was sensitive to the choice of medication used for exchange in case of discontinuity. When patients that began treatment with risperidone changed to haloperidol in case of discontinuity instead of to olanzapine, this scenario becomes dominant among the evaluated alternatives. The remaining variables tested did not alter the order of the results.

DISCUSSION

The use of olanzapine was the major factor leading to higher treatment cost. Cost associated with this drug was higher than that associated with the other antipsychotics evaluated, and the higher the probability of the patient receiving olanzapine, the higher the total cost.

Higher treatment cost associated with olanzapine was due to the higher purchasing cost of this drug when compared to the other antipsychotics. According to the prices paid by SES-SC, while the unit cost of one 5 mg haloperidol pill was US$ 0.01, and the unit cost of one 3 mg risperidone pill was US$ 0.1, the unit cost of a 10 mg olanzapine pill was US$ 6.07. According to a survey carried out by the *Banco de Preços em Saúde* (Health Care Price Database), the unit value of a 10 mg olanzapine pill ranged from US$ 6.07 to US$ 10.02.[a]

This difference in purchasing price between different drugs may explain the differences between the present model and the results of economic evaluations conducted in other countries. A comparative analysis of drug prices in the Brazilian market versus those in other markets, such as in the United States, shows differences in the prices of medication. Differences in

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[a] Ministério da Saúde. Banco de preços em saúde [internet]. [cited 2006 Nov 30]. Available from: http://bpreco.saude.gov.br/bprefd/owa/consulta.inicio]

unit prices between antipsychotics are more marked in Brazil. For example, for the same period, prices for the same doses of the same drugs in the United States were US$ 0.27 (haloperidol), US$ 7.58 (risperidone), and US$ 11.22 (olanzapine).[a]

The difference in price between medications influences the cost of treatment and limits the applicability in Brazil of economic evaluations of antipsychotics conducted in other countries.

Generally speaking, economic evaluations of antipsychotics carried out in other countries suggest that treatment with olanzapine and risperidone generate equivalent total costs, and both costs are lower than that of haloperidol.[1,2,4,12,15,16] Such studies show that, in spite of their higher purchasing cost, second-generation antipsychotics are more cost-effective than first-generation drugs, especially given the lower probability of hospitalization.

On the other hand, hospital fees and the price of psychiatric appointments also differed markedly between international studies and the present model. The cost of maintaining a patient in a psychiatric hospital in the United States for a 22-day period was US$ 9,469.00, and the cost of each psychiatric appointment was US$ 50.00.[16] On the other hand, according to the present model, the cost of maintaining a patient in a psychiatric hospital in Florianopolis for a 22-day period was US$ 317.07, and the cost per psychiatric appointment was US$ 3.67. These values refer to the prices paid by SUS for each of these procedures, and may be underestimated, as pointed out by some authors.[14] The possibility that such low prices could influence the results of our model was tested by sensitivity analysis. In this analysis, the final results of our model remained unaltered with respect to the order of preference of different treatment alternatives in terms of cost-utility.

The present results attest to the importance of the individual cost of antipsychotic drugs in the total cost of treatment from the SUS perspective in Santa Catarina. According to our sensitivity analysis, as the cost of outpatient treatment with olanzapine decreases, so does the advantage in terms of cost-utility ratio of the choice of beginning treatment with haloperidol when compared to the two other scenarios evaluated. Thus, in order for the alternative of initiating treatment with haloperidol to be dominated by beginning treatment with risperidone, cost of treatment with olanzapine would have to be around US$ 330.09 for every three months. Likewise, for beginning treatment with risperidone to be dominated by beginning with olanzapine, the cost of outpatient treatment with olanzapine would have to fall to US$ 26.70 for every three months.

Utility evaluation drug showed that second-generation antipsychotics performed better when compared to haloperidol. This may be explained by the greater probability of adverse side-effects, relapses, and patient hospitalization associated with haloperidol, all of which affect quality of life. The utility attributed to stable patients under treatment with risperidone and olanzapine was similar. A systematic review carried out by Jayaram et al[9] concluded that evidence on quality of life gains associated with treatment with risperidone and olanzapine is insufficient, and that studies comparing these two drugs for this outcome do not show significant differences. Therefore, further studies evaluating quality of life gains associated with each antipsychotic are required.

Modeling techniques are simulations of clinical practice and health care results, and are thus subject to bias given the number of simplifications and assumptions required for building a model. Sensitivity analysis helps us understand the importance of variation in the model's different parameters. However, limitations should be understood and taken into consideration in a decision-making process.[5,7,17]

The probabilities used for constructing the model are derived from studies with shorter follow-ups than our economic evaluation, requiring a greater number of assumptions. We could not find sufficient data in the literature to confirm the consistency of these assumptions for our evaluation period. The probability of the outcomes in the model may differ in Brazilian settings due to differences in clinical practice among countries.

The utilities employed in the model are derived from a study carried out in Canada.[8] Problems identifying patients able to respond to a quality of life questionnaire, often inherent to the clinical condition of altered critical judgment, limited the administration of a questionnaire to patients in the psychosocial care center.

The failure to include indirect treatment costs limits the applicability of our results to a wider perspective. From the viewpoint of society, it would have been beneficial to add to the analysis of treatment alternatives costs incurred by patient, family, and community. Future economic evaluation models will be useful for reaching more precise definitions as to the efficiency of allocation of public funds for pharmacological treatment of schizophrenia, which should include data obtained in clinical trials carried out among SUS patients, with longer follow-up periods, and including other antipsychotic drugs, both first- and second-generation.

In conclusion, the economic evaluation the cost and effectiveness of schizophrenia treatment is inherently linked to the context in which it is carried out. Such

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[a] RxUSA, Prescription Drugs and Medications from a Register Pharmacy and Discount Drugstore. [cited 2006 Nov 30] Available from: www.rxusa.com

evaluations describe the consequences of a disease and its treatments to health care services and social relations, which vary from country to country, and often between the country's regions. Therefore, generalization of the results of economic evaluation studies performed in different countries seems impractical. Nevertheless, the present data are generalizable to Brazil. The establishment and fulfillment of strategies involving more cost-effective treatment flow-charts, in which patients begin treatment with risperidone and haloperidol before olanzapine may optimize resource spending without affecting patient health. From the opportunity cost perspective, greater investments can be made on improving mental health care services.

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