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Cost-effectiveness analysis and budgetary impact of antipsychotics available in the Brazilian Unified Health System

Análise de custo-efetividade e impacto orçamentário dos antipsicóticos disponíveis no Sistema Único de Saúde brasileiro

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Keywords
schizophrenia, cost-benefit analysis, antipsychotic agents, technology assessment, biomedical

ABSTRACT

Objective: To carry out a cost-effectiveness and budget impact analysis of antipsychotic use in adults to treat schizophrenia from the perspective of the Unified Health System (SUS). **Methods:** A Markov model simulated the treatment of schizophrenic patients with an initial average age of 25 years and a lifetime horizon. The possibility of combining drugs resulted in 20 pharmacotherapeutic strategies. **Results:** The lowest-cost strategy, risperidone/olanzapine, obtained values of $45,092.77 with effectiveness of 15.97 QALY. The incremental cost-effectiveness ratio in dollars/QALY of olanzapine/risperidone was 2,470.24, and risperidone/ziprasidone was 352,671.90, compared to the first option. All other therapeutic combinations were dominated. The budgetary impact assessment indicated that the most cost-effective choice could generate savings of US$ 1,555.00 on average, per patient, over five years. **Conclusion:** The therapeutic proposal with the lowest cost per patient was risperidone combined with olanzapine, revealing these two drugs as a strategy with lower budgetary impact and better cost-effectiveness.

Palavras-chave:
esquizofrenia, análise de custo-benefício, agentes antipsicóticos, avaliação de tecnologia, biomédico

RESUMO

Objetivo: Realizar uma análise de custo-efetividade e impacto orçamentário do uso de antipsicóticos em adultos para o tratamento da esquizofrenia, na perspectiva do Sistema Único de Saúde (SUS). **Métodos:** Um modelo de Markov simulou o tratamento de pacientes com esquizofrenia, com idade média inicial de 25 anos e horizonte *lifetime*. Analisaram-se 20 estratégias farmacoterapêuticas. **Resultados:** A estratégia de menor custo – risperidona/olanzapina – obteve valores de US$ 45.092,77, eficácia de 15,97 QALY. A relação custo-efetividade incremental em dólares/QALY da olanzapina/risperidona foi de 2.470,24, e de 352.671,90 para risperidona/ziprasidona, em comparação com a primeira opção. Todas as outras combinações terapêuticas foram dominadas. A avaliação do impacto orçamentário indicou que a escolha mais econômica geraria economia de US$ 1.555,00 em média, por paciente, ao longo de cinco anos. **Conclusão:** A proposta terapêutica de menor custo por paciente foi a risperidona associada à olanzapina, estratégia de menor impacto orçamentário e melhor custo-efetividade.

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Introduction

Schizophrenia (S) is a severe mental disorder that, according to the World Health Organization (WHO), affects more than 21 million people worldwide (OMS, 2018). It is more frequent in men (12 million) than in women (9 million), who develop the disease when they are younger (Howes & Murray, 2014). In Brazil, its prevalence seems to be about 1% of the population, mainly young adults; 50%-60% of patients have a chronic and limiting case (Andrade *et al.*, 2002; Leitão *et al.*, 2006).

Its symptoms can be controlled, with improved quality of life, using medications. According to the Ministry of Health's Clinical Protocol and Therapeutic Guidelines (PCDT) (Brasil, 2013) for schizophrenia, all antipsychotics except clozapine can be used in patients who meet the inclusion criteria, in no order of preference (Brasil, 2013). Monotherapy is indicated according to the patient's safety profile and tolerability. In turn, therapeutic failure (Leitão *et al.*, 2006) with the first and second generations of antipsychotics after six weeks of use without improvement of at least 30% of the symptoms on the Brief Psychiatric Assessment scale (Elkis *et al.*, 2016) is not uncommon. In this case, a second attempt with another antipsychotic should be made, and associations are recommended (Brasil, 2013). More rational use of these agents not only improves therapeutic results but also reduces costs (Lubinga *et al.*, 2015; Razzouk, 2017).

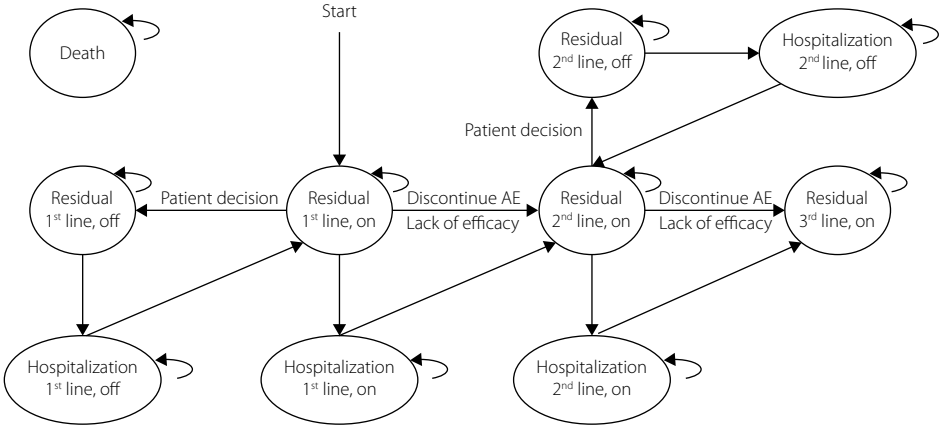
Studies on disease cost reveal a significant burden for patients and society from prolonged hospitalizations, treatment, and productivity losses related to disease and early mortality (Goeree *et al.*, 2005; Leitão *et al.*, 2006). However, studies of complete economic evaluation, such as cost-effectiveness analyses that address the widespread use of antipsychotics in the first and second treatment lines, are still scarce (Brasil, 2013; Zhou & Millier, 2018).

An evaluation that compares all the alternatives available in the health system has the potential to optimize the disease treatment protocol. This study sought to conduct cost-effectiveness and incremental budgetary impact analyses of the use of antipsychotics in adults for the treatment of schizophrenia, from the perspective of the Brazilian Unified Health System (SUS).

Methods

A Markov chain simulation model performs the cost-effectiveness evaluation and budget impact analysis of the pharmacological treatment of schizophrenia. The therapeutic scenarios for the treatment and the transition stages of the disease are showing in Figure 1.

The model has four states where the individual has symptoms and lives in the community using one or none of the treatment lines and death. Using TreeAge Pro® software version 2019, a Markov model simulated a hypothetical cohort of 1,000 individuals diagnosed according to the criteria used in the PCDT (Brasil, 2013). The study population consisted of men and women aged 25 years and older (Lubinga *et al.*, 2015) who had been diagnosed according to criteria based on the International Statistical Classification of Diseases and Health-Related Problems (ICD-10). The transition states simulated adherence to treatment, where the change of state occurred due to hospitalization, side effects – diabetes, weight gain, and extrapyramidal syndrome (Lubinga *et al.*, 2015) – therapeutic failure, and the patient's decision and shifts in the therapy line with a reduction in utility. Mortality encompasses deaths related to schizophrenia (Lubinga *et al.*, 2015) and the probabilities of dying from all causes (Instituto Brasileiro de Geografia e Estatística, 2010). The probabilities in the first and second lines of treatment (Citrome & Jaffe, 2003; Lubinga *et al.*,



Source: Lubinga *et al.* (2015)

Figure 1. Schematic representation of the disease stages of the simulation model.

2015) are the same for each drug. Hospitalization information (Barbosa, 2015) validated the model, except for quetiapine in the first line, which is not included in PCDT (Brasil, 2013).

The interventions and dosages purchased are those recommended by PCDT (Brasil, 2013). A specialist in the field validated the average daily doses and dosages indicated for maintaining the treatment. We used risperidone (R) 3 mg, quetiapine (Q) 400 mg, ziprasidone (Z) 80 mg, olanzapine (O) 20 mg, clozapine (C) 400 mg, chlorpromazine (CO) 600 mg, and haloperidol (H) 10 mg. The possibility of combining resulted in 20 pharmacotherapeutic treatments. These strategies result from matching four drugs (haloperidol, ziprasidone, risperidone, and olanzapine) in the first; six in the second (haloperidol, ziprasidone, risperidone, olanzapine, quetiapine, and chlorpromazine); and one, clozapine, in the third treatment line. Chlorpromazine is not in the first line of treatment due to its adverse effects (Teixeira & Rocha, 2006). We assumed a lifetime horizon for the CEA, with cycles of 1-year duration, corresponding to the natural history of schizophrenia (Goeree *et al.*, 2005), and the discount rate was 5% per year for both costs and outcomes.

Estimates referring to direct medical costs included the identification, measurement, and valuation of resources used, such as materials and drugs used, health professionals involved, and hospitality in case of hospitalization, with outpatient and hospital services for patients with schizophrenia who used antipsychotics in the SUS from January 2000 to December 2010 (Barbosa, 2015). This survey integrated the databases of the Outpatient Information System (SIA/SUS) and the Hospital Information System (SIH/SUS) using the deterministic-probabilistic relationship technique of administrative records. The patients diagnosed according to ICD-10 received one or more of the following medications: clozapine, quetiapine, olanzapine, risperidone, and ziprasidone. The resources designed for the users of the different drugs were a product of the weighting of outpatient and hospital expenses (Table 1). The monetary values of the resources for the 174,310 patients were updated according to the Broad National Consumer Price Index (IPCA) to values for January 2015 from the study by Barbosa (Barbosa, 2015). The average of the values for patients using olanzapine, quetiapine, and risperidone estimated the employment of resources; the annual mean values per patient per year for the drugs chlorpromazine and haloperidol were not included in the study. The sensitivity analysis included variations of 50% to assess the uncertainties associated with this estimate. The perspective was of the SUS, and the indirect costs were not considered.

The annual cost of each medication considered the daily dosages for maintaining treatments (Brasil, 2013), and the prices were from the Health Price Bank (BPS) (Brasil, 2019). All the resources used are valued in dollars, starting on September 11, 2019, when R$1 (1 BRL) = US$ 0.25 (Banco Central do Brasil, 2019).

The effectiveness of the treatment of the disease was measured in quality-adjusted life-years (QALYs). The main parameters used in the model are in Table 1.

Table 1. Model parameters

Parameters	Baseline	Interval		Distribution	Reference
Utilities					
Residual state	0.424*	0.38	0.5		(Salomon *et al.*, 2012)
Impatient state	0.256*	0.18	0.35		(Salomon *et al.*, 2012) [a]
Disutilities					
Extrapyramidal effects	0.074	0.053	0.090	Beta	(Lenert *et al.*, 2004)
Weight gain	0.031	0.016	0.046	Beta	(Lenert *et al.*, 2004)
Diabetes	0.06**	0.042	0.078	Gamma	(De Oliveira *et al.*, 2015)
Probability					
Chlorpromazine					
Hospitalization	0.304	0.242	0.367	Dirichlet	(Lieberman *et al.*, 2005)
Discontinuation (AE)	0.107	0.069	0.144	Dirichlet	(Lieberman *et al.*, 2005)
Discontinuation (Ineffectiveness)	0.177	0.130	0.223	Dirichlet	(Lieberman *et al.*, 2005)
Discontinuation (Other reasons)	0.211	0.161	0.261	Dirichlet	(Lieberman *et al.*, 2005)
Haloperidol					
Hospitalization	0.219	0.162	0.275	Dirichlet	(Kahn *et al.*, 2008)
Discontinuation (AE)	0.117	0.055	0.178	Dirichlet	(Kahn *et al.*, 2008)
Discontinuation (Ineffectiveness)	0.330	0.239	0.421	Dirichlet	(Kahn *et al.*, 2008)
Discontinuation (Other reasons)	0.155	0.085	0.225	Dirichlet	(Kahn *et al.*, 2008)

Parameters	Baseline	Interval		Distribution	Reference
Olanzapine					
Hospitalization	0.077	0.048	0.105	Dirichlet	(Lieberman *et al.*, 2005)
Discontinuation (AE)	0.130	0.093	0.166	Dirichlet	(Lieberman *et al.*, 2005)
Discontinuation (Ineffectiveness)	0.099	0.067	0.132	Dirichlet	(Lieberman *et al.*, 2005)
Discontinuation (Other reasons)	0.165	0.125	0.205	Dirichlet	(Lieberman *et al.*, 2005)
Risperidone					
Hospitalization	0.102	0.061	0.144	Dirichlet	(Lieberman *et al.*, 2005)
Discontinuation (AE)	0.069	0.042	0.097	Dirichlet	(Lieberman *et al.*, 2005)
Discontinuation (Ineffectiveness)	0.192	0.149	0.234	Dirichlet	(Lieberman *et al.*, 2005)
Discontinuation (Other reasons)	0.214	0.170	0.258	Dirichlet	(Lieberman *et al.*, 2005)
Quetiapine					
Hospitalization	0.140	0.103	0.176	Dirichlet	(Lieberman *et al.*, 2005)
Discontinuation (AE)	0.102	0.069	0.135	Dirichlet	(Lieberman *et al.*, 2005)
Discontinuation (Ineffectiveness)	0.235	0.189	0.281	Dirichlet	(Lieberman *et al.*, 2005)
Discontinuation (Other reasons)	0.196	0.153	0.239	Dirichlet	(Lieberman *et al.*, 2005)
Ziprasidone					
Hospitalization	0.123	0.076	0.11	Dirichlet	(Lieberman *et al.*, 2005)
Discontinuation (AE)	0.102	0.359	0.53	Dirichlet	(Lieberman *et al.*, 2005)
Discontinuation (Ineffectiveness)	0.167	0.152	0.22	Dirichlet	(Lieberman *et al.*, 2005)
Discontinuation (Other reasons)	0.241	0.1176	0.176	Dirichlet	(Lieberman *et al.*, 2005)
Other					
Hospitalization if untreated	0.733	0.586	0.879	Beta	(Weiden & Olfson, 1995)
Recovery (AP 1st line)	0.788	0.698	0.877	Beta	(Lieberman *et al.*, 2005)
Side effects					
Extrapyramidal Symptoms (SE)					
Chlorpromazine (OR)	0.064	0.046	0.083	Beta	(Adams *et al.*, 2003)
Haloperidol (OR)	1.79	1.00	3.57	Log-normal	(Leucht *et al.*, 2013)
Olanzapine OR	0.42	0.20	0.77	Log-normal	(Leucht *et al.*, 2013)
Risperidone OR	0.78	0.42	1.61	Log-normal	(Leucht *et al.*, 2013)
Quetiapine OR	0.37	0.20	0.78	Log-normal	(Leucht *et al.*, 2013)
Ziprasidone	0.58	0.3	1.29	Log-normal	(Leucht *et al.*, 2013)
Clozapine	0.12	0.05	0.68	Beta	(Leucht *et al.*, 2013)
Weight gain *(<7%)*					
Chlorpromazine	0.095	0.076	0.115	Beta	(Dossenbach *et al.*, 2007)
Haloperidol	0.141	0.112	0.170	Beta	(Dossenbach *et al.*, 2007)
Olanzapine	0.211	0.167	0.255	Beta	(Lieberman *et al.*, 2005)
Risperidone	0.096	0.064	0.127	Beta	(Lieberman *et al.*, 2005)
Quetiapine	0.110	0.076	0.144	Beta	(Lieberman *et al.*, 2005)
Clozapine***	0.211	0.167	0.255	Beta	(Bagnal *et al.*, 2003)
Ziprasidone	0.16	0.08	0.28	Beta	(Lin *et al.*, 2016)
Diabetes					
Haloperidol	0.052	0.044	0.054	Beta	(Citrome & Jaffe, 2003)
Chlorpromazine RR	1.41	1.13	1.69	Log-normal	(Yood *et al.*, 2009)
Olanzapine RR	1.77	1.32	2.37	Log-normal	(Yood *et al.*, 2009)
Risperidone RR	1.22	0.89	1.67	Log-normal	(Yood *et al.*, 2009)
Quetiapine RR	1.21	0.89	1.66	Log-normal	(Yood *et al.*, 2009)
Ziprasidone RR	1.02	0.61	1.71	Log-normal	(Yood *et al.*, 2009)
Clozapine RR	2.28	1.24	4.2	Log-normal	(Yood *et al.*, 2009)

Annual cost of daily maintenance dose (Brasil, 2013) (USD$)	Baseline	Interval	Distribution	Reference
Chlorpromazine 600 mg	87.60	61.32	113.88	(Brasil, 2019)
Clozapine 400 mg	748.25	523.78	972.73	(Brasil, 2019)
Haloperidol 10 mg	12.78	8.95	16.61	(Brasil, 2019)
Olanzapine 20 mg	100.38	70.27	130.49	(Brasil, 2019)
Quetiapine 400 mg	136.88	95.82	177.94	(Brasil, 2019)
Risperidone 4 mg	16.43	11.50	21.36	(Brasil, 2019)
Ziprasidone 80 mg	1,806.75	1,264.73	2,348.76	(Brasil, 2019)

Costs of Procedures per medication (Barbosa, 2015) (USD$)	Psychiatric outpatient clinic (± CI)	Psychiatric hospitalization (± CI)	Other high-cost drugs (± CI)	Other hospitalizations (± CI)	Other Outpatient Procedures (± CI)
Chlorpromazine	808.76 ± 177.10	2,168.78 ± 319.54	824.20 ± 244.57	1,166.12 ± 307.06	297.84 ± 69.44
Clozapine	1,069.46 ± 229.01	3,395.29 ± 826.45	1,150.97 ± 163.07	1,250.46 ± 632.91	353.37 ± 173.98
Haloperidol	808.76 ± 177.10	2,168.78 ± 319.54	824.20 ± 244.57	1,166.12 ± 307.06	297.84 ± 69.44
Olanzapine	804.46 ± 218.81	2,388.73 ± 294.38	867.65 ± 200.79	1,112.58 ± 206.88	308.61 ± 62.10
Quetiapine	802.65 ± 184.14	1,917.09 ± 330.80	742.99 ± 386.50	861.95 ± 146.40	651.52 ± 291.63
Risperidone	819.17 ± 128.33	2,200.52 ± 333.42	1,078.57 ± 345.95	1,307.21 ± 368.33	954.01 ± 164.78
Ziprasidone	704.58 ± 324.43	2.797.99 ± 1.462.04	222.73 ± 104.61	362.19 ± 41.60	260.54 ± 110.51

Source: The authors. AE: adverse event; OR: odds ratio; RR: relative risk. * Estimated utility as a complement to the values (Salomon *et al.*, 2012). ** Disutility calculated from utility data (De Oliveira *et al.*, 2015). *** The weight gain RR of Olanzapine compared to clozapine is equal to 1 (Bagnall *et al.*, 2003).

The incremental cost-effectiveness ratio (ICER) showed the comparative efficiencies of alternative treatment strategies. A performed deterministic and probabilistic sensitivity analysis modified the parameters according to a 95% confidence interval and when not available, 50%-150% of their base value. The acceptability threshold employed was 1 GDP per capita, or R$ 30,548.40 in 2016 (US$ 7,637.1) (Instituto Brasileiro de Geografia e Estatística, 2019). The utilities of patients with weight gain and diabetes were correlated proportionately, as well as the average medical costs.

The analysis of the budgetary impact used the method of measured demand, where the base was the alternative with the best cost-effectiveness ratio. Ten thousand simulations in a hypothetical cohort over a 5-year horizon provided the average cost and standard deviation over the period. This information estimated the savings per patient produced by changing his or her therapeutic strategy to the least expensive one in this period (5 years) and to the most cost-effective one. The construction of alternative scenarios measured the uncertainties in the research results using sensitivity analysis (deterministic and probabilistic).

Results

The data made it possible to examine and compare the costs and health outcomes that occurred throughout the patients' lives. The risperidone/olanzapine (R/O) option resulted in the lowest cost, and the non-dominated alternatives showed greater effectiveness, with a higher average cost. The olanzapine/risperidone (O/R) and risperidone/ziprasidone (R/Z) regimens achieved incremental effectiveness of 0.01 and 0.02 QALYs and an average incremental cost of $15.89 and $5,190.21, respectively to R/O. All other therapeutic combinations have been dominated.

The results for the probabilistic simulation (Monte Carlo 2nd-order) with 10,000 simulations showed an ICER of US$ 2,470.24/QALY for O/R. Table 2 shows the results of this simulation.

Sensitivity analysis

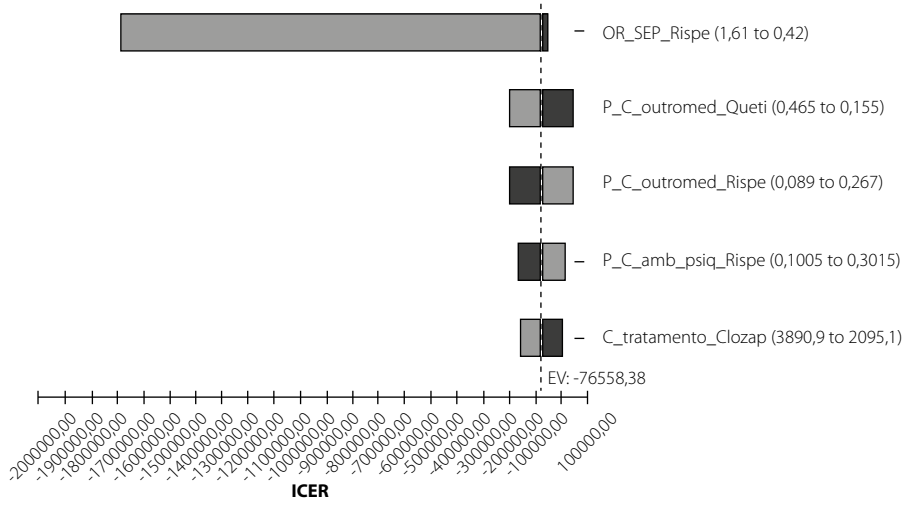
Deterministic sensitivity analysis measured the effect of variables on model responses. The incremental cost-effectiveness ratios of the different strategies, assessed against the R/O scheme, verified the impact on the dominated alternatives, or with a high ICER at a value below an acceptable threshold.

The variables capable of transforming the dominated to non-dominated alternatives were an increase in the annual proportion of outpatients treated with risperidone or a decrease in those who used quetiapine. In these cases, the alternative olanzapine/quetiapine (O/Q) is now not dominated. The tornado diagram (Figure 2) shows this variation.

Table 2. Incremental cost-effectiveness ratio

Strategy	Cost (USD)	Incremental Cost (USD)	Eff (QALY)	Incremental Eff (QALY)	Incremental C/E (USD/QALY)
Excluding dominated					
Risperidone and Olanzapine	45092.77		15.97052		
Olanzapine and Risperidone	45108.67	15.89619	15.97696	0.006435	2470.24399
Risperidone and Ziprasidone	50298.89	5190.219	15.99167	0.014717	352671.9018
All					
Risperidone and Olanzapine	45092.77	0	15.97052	0	0
Olanzapine and Risperidone	45108.67	15.89619	15.97696	0.006435	2470.24399
Olanzapine and Quetiapine	45298.8	190.1325	15.95874	-0.01821	-10439.53128
Olanzapine and Haloperidol	45577.41	468.7399	15.92521	-0.05175	-9058.520874
Haloperidol and Olanzapine	45671.3	562.6318	15.90717	-0.06978	-8062.626879
Risperidone and Quetiapine	45835.08	726.4083	15.96874	-0.00821	-88453.0348
Olanzapine and Chlorpromazine	45903.43	794.7603	15.92314	-0.05382	-14767.87103
Risperidone and Haloperidol	46115.51	1006.843	15.9354	-0.04156	-24227.54943
Haloperidol and Risperidone	46224.89	1116.224	15.92223	-0.05472	-20397.66443
Haloperidol and Quetiapine	46423.8	1315.133	15.90564	-0.07132	-18441.14246
Risperidone and Chlorpromazine	46441.01	1332.338	15.93275	-0.04421	-30139.61264
Haloperidol and Chlorpromazine	47030.86	1922.19	15.86721	-0.10974	-17515.06785
Olanzapine and Ziprasidone	49748.52	4639.85	15.98203	0.00507	915096.4141
Ziprasidone and Olanzapine	49821.44	72.91946	15.97252	-0.0095	-7673.854884
Risperidone and Ziprasidone	50298.89	550.3686	15.99167	0.009647	57053.66405
Ziprasidone and Risperidone	50372.71	73.82213	15.98872	-0.00296	-24963.74908
Ziprasidone and Quetiapine	50564.85	265.9687	15.97075	-0.02092	-12713.38249
Ziprasidone and Haloperidol	50846.01	547.1206	15.93745	-0.05422	-10090.89265
Haloperidol and Ziprasidone	50929.94	631.059	15.92601	-0.06566	-9610.529093
Ziprasidone and Chlorpromazine	51171.55	872.6618	15.93465	-0.05702	-15303.25589

Source: The authors.



Source: The authors. Caption: OR_SEP_Rispe – Odds Ratio of Risperidone Extrapyramidal Syndrome; P_C_outromed_Queti – Proportion of users of quetiapine using other drugs; P_C_outromed_Rispe – Proportion of Risperidone users using other drugs; P_C_amb_psiq_Rispe – Proportion of Risperidone users using a psychiatric clinic; C_tratamento_Clozap – Cost of Clozapine treatment.

Figure 2. Tornado Diagram (ICER) – olanzapine/quetiapine vs risperidone/olanzapine

The probabilistic sensitivity analysis performed 10,000 simulations when comparing the 20 strategies. The acceptability curve (Figure 3) suggests that at thresholds around US$ 2,500/QALY, the use of R/O and its inverse, that is, O/R, is cost-effective in 50% of the simulations. With the increase in willingness to pay, the O/R combination has a higher proportion of cost-effective iterations. The risperidone/ziprasidone alternative does not reveal a cost-effective amount higher than 1% at willingness-to-pay thresholds below $2,500/QALY.

The incremental cost-effectiveness between R/O and O/R (Figure 4) points to a more significant number of more effective results from the second drug strategy. Forty percent of them show greater effectiveness at a lower cost, with 10.37% below a willingness-to-pay threshold of US$ 3,500/QALY (0.5 GDP per capita). Still, in this quadrant, 26.28% are above this cost-effectiveness threshold. Of the total O/R simulations, 21.55% have a higher cost and lower effectiveness than R/O.

Budgetary impact

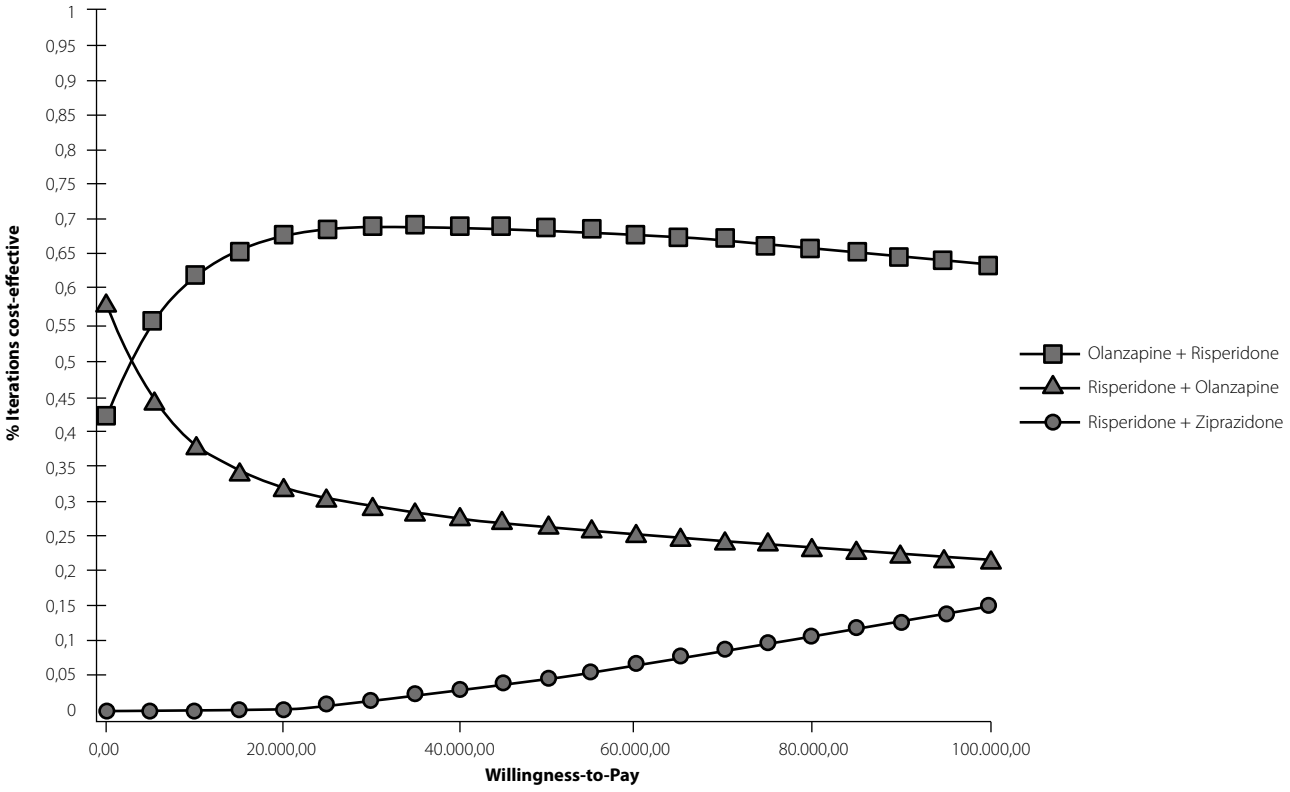
The parameters used in this analysis were the same as those used in cost-effective analyse. For a cohort of patients, for 5 years (10,000 simulations), the alternative O/R had the lowest cost of the non-dominated strategies. Savings per patient were US$ 150.74 and US$ 1,886.56, respectively, for the R/O and R/Z options. However, in the simulation over the entire lifetime horizon, the most cost-effective option is R/O. The results produced by changing a patient from his or her therapeutic scheme to O/R, as well as to R/O, were calculated as possible scenarios for all alternatives (Appendix Table 1).

Discussion

There are numerous approaches to pharmacological treatment related to schizophrenia. Except for clozapine, there is no evidence of statistically significant differences between existing therapeutic approaches (Linder *et al.*, 2009; Brasil, 2013).

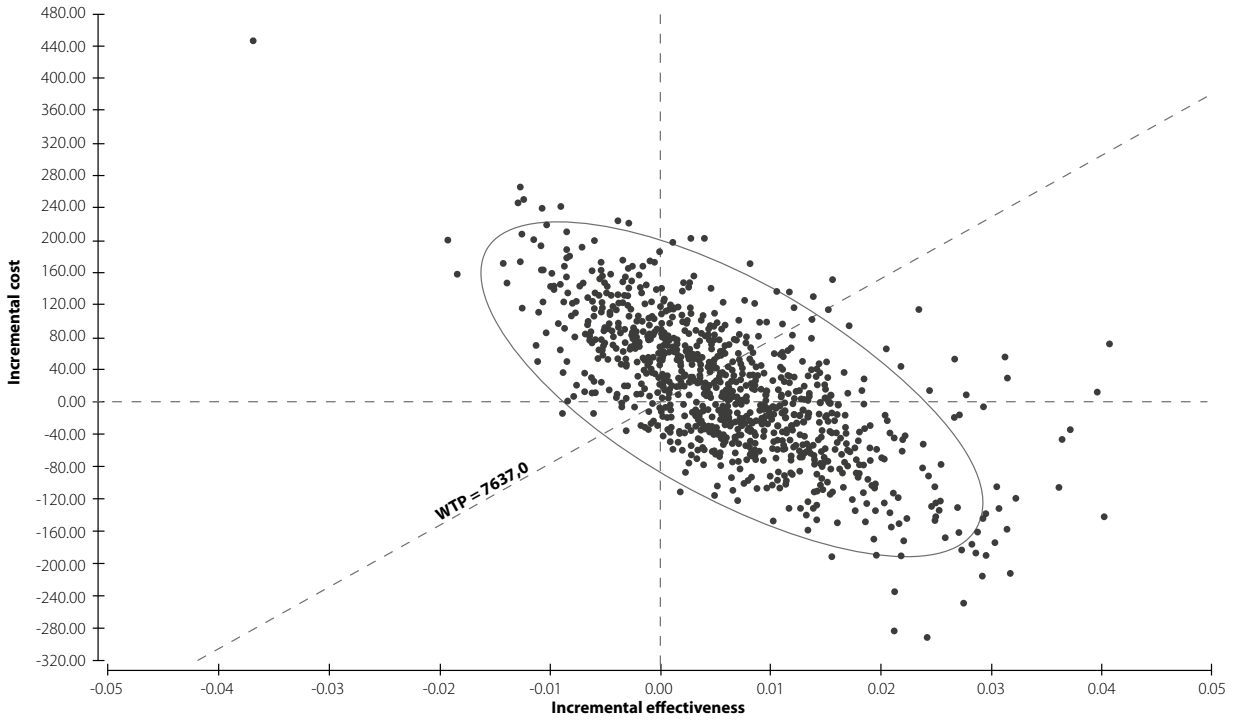
The probabilistic sensitivity analysis showed differences related mainly to the costs of the strategies, parameters with less uncertainty in the analysis. Regardless of the therapeutic line, the drugs risperidone and olanzapine were confirmed to have superior results. The option containing ziprasidone, although not dominated, given its high cost, obtained outcomes where the incremental cost-effectiveness ratio made it unfeasible with acceptable willingness-to-pay thresholds.

A systematic review on the topic found 79 cost-effectiveness assessments (Zhou & Millier, 2018) with several designs, of which 36 adopted cohort modeling through the Markov



Source: The authors

Figure 3. Acceptability Curve.



Source: The authors

Figure 4. Incremental cost-effectiveness scatter plot between O/R and R/O.

chain model chosen in this study. Studies in which comparisons were made between few medications (Zhou & Millier, 2018) (3 or 4) or with products not incorporated into SUS were not analyzed (Bagnall *et al*., 2003).

For Lin *et al.* (2016) (Lin *et al*., 2016), olanzapine was dominant over all other alternatives analyzed, while in García-Ruiz *et al.* (2012) (García-Ruiz *et al*., 2012), risperidone dominated haloperidol, and olanzapine dominated all drug strategies except for risperidone.

Lindner *et al.* (2009) (Linder *et al*., 2009) performed a cost-effectiveness analysis of antipsychotics from the perspective of SUS, evaluating haloperidol, clozapine, olanzapine, and risperidone. The answers found differ slightly from those of our study, since haloperidol was the least expensive alternative per patient, followed by risperidone and olanzapine. The incremental cost-effectiveness ratios are small and would be within acceptable thresholds (US$ 353.72 and US$ 617.64), suggesting olanzapine and risperidone are still therapeutic alternatives with good cost-effectiveness for the health system.

Lubinga *et al.* (2015) (Lubinga *et al*., 2015) used the most comprehensive spectrum of drugs, similar to those incorporated into SUS (except for ziprasidone including chlorpromazine, which is rarely studied), and built a more complete model, considering side effects, therapy changes, and hospitalized or socially living patients. In this study, the only non-dominated therapeutic alternatives were olanzapine and risperidone. The present study found a similar conclusion and suggests incorporating risperidone through a budgetary impact assessment. Our results point to this drug as one of the most worthwhile alternatives for the health system, as shown by the fact that it is in the two most cost-effective and lowest-cost alternatives.

The budgetary impact revealed that there could be savings of US$ 25.68 to US$ 4,731.56 in 5 years, depending on which therapeutic line, risperidone or olanzapine, is allocated. Average costs per patient over 5 years of treatment have measures mildly different from those for a lifetime. However, alternatives involving olanzapine and risperidone present the best solutions, although, in this short time horizon, quetiapine appears as a possibility. However, there is uncertainty regarding the choice of olanzapine/quetiapine, since in 5 years of treatment, they present values lower than the R/O, but not to the O/R. This information, added to the lifetime costs of the patient choice containing quetiapine, seems to be sufficient to consider this second option with risperidone and olanzapine. Lindner *et al.* (2009) (Linder *et al*., 2009) adopted only a 5-year time horizon, and in 2009, the prices of olanzapine and risperidone were higher than they are today. These two variables are the most likely to impact the differences found. Besides, the author did not consider adverse

effects produced by treatments such as extrapyramidal effects, weight gain, and diabetes.

The deterministic sensitivity analysis showed that the proportions of risperidone users who utilize the psychiatric clinic annually and those who use non-psychiatric drugs are the most sensitive parameters. They can transform therapeutic options into non-dominated ones. All other variables were not able to alter the model's final responses in the deterministic sensitivity analysis. The annual numbers of users of the psychiatric outpatient clinic and other medications were taken from a cohort study conducted from 2000 to 2010 with 241,079 patients diagnosed with schizophrenia from all regions of the country (Barbosa, 2015; Barbosa *et al.*, 2018). Due to the representativeness of the study sample, the average value measured is close to the real measurement and produces an uncertainty lower than the 20% entered in the model for exploratory purposes. The variation attributed to the parameters in the deterministic sensitivity analysis was higher than that of the other drugs (50%) to explore the uncertainties and does not modify the final response of the model.

This study has limitations, in addition to the hypotheses assessed in the sensitivity analysis. Some of them are inherent to the modeling process, which can oversimplify the progression of the disease due to its divergence from real-world circumstances, and the use of more than one medication in the same treatment line (polypharmacy) was not considered. Different sources of international data were the basis for estimating the values of quality of life and disutility (Lubinga *et al.*, 2015; Banco Central do Brasil, 2019; Vilela *et al.*, 2005). In the sensitivity analysis, these variables showed no impact on the results. Another limitation was the possibility that any exacerbation of schizophrenia would produce hospitalization, which may not be accurate in all cases, even though it occurs in most of them (Bagnall *et al.*, 2003; NICE, 2014).

Conclusion

The analytical decision model estimated the main costs and consequences of therapeutic options for the treatment of schizophrenia in SUS. The results indicate that risperidone and olanzapine are the most cost-effective drugs for use in the first or second line of treatment. The budgetary impact assessment shows how much each therapeutic combination, when exchanged for the most cost-effective, could save per patient over 5 years. In this time horizon, the therapeutic proposal with the lowest cost per patient was olanzapine combined with risperidone; these two drugs appear to be a therapeutic strategy with less budgetary impact and a better cost-benefit ratio.

Although the combinations of other drugs used to control schizophrenia are not cost-effective, this does not necessarily mean that there is a need for disincorporation in the health system. Schizophrenia is a complex disease with no cure. Different therapeutic schemes must be available for treatment in the event of discontinuation of the use of the most cost-effective drugs.

Finally, there is a significant knowledge gap in Brazil regarding the effectiveness outcome used, the QALY, obtained from economic evaluation studies carried out in other countries. The scarcity of parameters is the main barrier to the development of simulation models more compatible with the knowledge accumulated in clinical practice in our country.

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Appendix

Table 1 Economy produced per patient by the use of O/R and R/O in relation to other therapeutic strategies

Olanzapine/risperidone			
Strategies	**Average (USD$)**	**Lower limit (USD$)**	**Upper limit (USD$)**
Olanzapine/Quetiapine	92,465	-168,31	353,2425
Risperidone/Olanzapine	150,7375	-125,9125	427,3875
Olanzapine/Haloperidol	176,415	-77,645	430,4775
Olanzapine/Chlorpromazine	243,8725	-19,605	507,3525
Haloperidol/Olanzapine	343,955	78,4025	609,5075
Risperidone/Quetiapine	422,9625	124,075	721,85
Risperidone/Haloperidol	514,8375	223,1675	806,5075
Risperidone/Chlorpromazine	586,6525	284,4775	888,8275
Haloperidol/Risperidone	593,8275	311,58	876,075
Haloperidol+ Quetiapine	731,9325	430,6825	1033,1825
Haloperidol/Chlorpromazine	982,135	686,2025	1278,0675
Olanzapine/Ziprazidone	1479,7725	1035,3025	1924,2425
Risperidone/Ziprazidone	1886,56	1412,055	2361,0675
Haloperidol/Ziprazidone	2801,7525	2218,125	3385,38
Ziprazidone/Olanzapine	3355,47	2425,195	4285,7425
Ziprazidone/Risperidone	3533,29	2602,8575	4463,7225
Ziprazidone/Quetiapine	3632,2275	2697,1775	4567,2775
Ziprazidone/Haloperidol	3726,7125	2798,2625	4655,1625
Ziprazidone/Chlorpromazine	3799,685	2867,8125	4731,56
Risperidone/olanzapine			
Strategies	**Average (USD$)**	**Lower limit (USD$)**	**Upper limit (USD$)**
Olanzapine/Risperidone	-150,7375	-397,7075	96,2325
Olanzapine/Quetiapine	-58,27	-319,0475	202,505
Olanzapine/Haloperidol	25,6775	-228,3825	279,74
Olanzapine/Chlorpromazine	93,135	-170,3425	356,615
Haloperidol/Olanzapine	193,2175	-72,335	458,77
Risperidone/Quetiapine	272,225	-26,6625	571,1125
Risperidone/Haloperidol	364,1	72,43	655,77
Risperidone/Chlorpromazine	435,915	133,74	738,09
Haloperidol/Risperidone	443,09	160,8425	725,3375
Haloperidol+ Quetiapine	581,195	279,945	882,445
Haloperidol/Chlorpromazine	831,3975	535,465	1127,33
Olanzapine/Ziprazidone	1329,035	884,565	1773,505
Risperidone/Ziprazidone	1735,8225	1261,3175	2210,33
Haloperidol/Ziprazidone	2651,015	2067,3875	3234,6425
Ziprazidone/Olanzapine	3204,7325	2274,46	4135,005
Ziprazidone/Risperidone	3382,5525	2452,12	4312,985
Ziprazidone/Quetiapine	3481,49	2546,44	4416,54
Ziprazidone/Haloperidol	3575,975	2647,525	4504,4275
Ziprazidone/Chlorpromazine	3648,9475	2717,075	4580,8225

Source: Authors