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ORIGINAL

Cost-effectiveness simulation analysis of schizophrenia at the Instituto Mexicano del Seguro Social. Assessment of typical and atypical antipsychotics

Joaquín Mould-Quevedo,[a] Iris Contreras-Hernández,[a,*] Wáscar Verduzco,[b] Juan Manuel Mejía-Aranguré[c] and Juan Garduño-Espinosa[a]

[a]Health economy Research Unit, Mexican Instituto of National Insurance (IMSS), Mexico city, Mexico
[b]Psychiatric hospital, IMSS, Mexico city, Mexico
[c]Clinical epidemiology Research Unit, Medical Specialised Hospital, Paediatrics Hospital, Siglo XXI Mexican Medical Centre, IMSS, Mexico city, Mexico

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KEYWORDS
Schizophrenia;
Cost-effectiveness analysis;
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Abstract
Introduction: Estimation of the economic costs of schizophrenia is a fundamental tool for a better understanding of the magnitude of this health problem. The aim of this study was to estimate the costs and effectiveness of fi ve antipsychotic treatments (ziprasidone, olanzapine, risperidone, haloperidol and clozapine), which are included in the national formulary at the Instituto Mexicano del Seguro Social, through a simulation model.
Methods: Type of economic evaluation: complete economic evaluation of cost effectiveness. Study perspective: direct medical costs. Time horizon: 1 year. Effectiveness measure: number of months free of psychotic symptoms. Analysis: to estimate cost effectiveness, a Markov model was constructed and a Monte Carlo simulation was carried out.
Results: Effectiveness: the results of the Markov model showed that the antipsychotic with the highest number months free of psychotic symptoms was ziprasidone (mean 9.2 months). The median annual costs for patients using ziprasidone included in the hypothetical cohort was 194,766.6 Mexican pesos (MXP) (95% CI, 26,515.6-363,017.6 MXP), with an exchange rate of 1 € = 17.36 MXP. The highest costs in the probabilistic analysis were estimated for clozapine treatment (260,236.9 MXP).
Conclusions: Through a probabilistic analysis, ziprasidone showed the lowest costs and the highest number of months free of psychotic symptoms and was also the most cost effective antipsychotic observed in acceptability curves and net monetary benefi ts..

*Corresponding author:
E-mail: iriscontrerash@gmail.com; arangurejm@hotmail.com (I. Contreras Hernández).

PALABRAS CLAVE
Esquizofrenia;
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Análisis de simulación de coste-efectividad en el tratamiento de la esquizofrenia en el Instituto Mexicano del Seguro Social. Evaluación de antipsicóticos típicos y atípicos

Resumen
Introducción: La estimación de los costes económicos de la esquizofrenia constituye un aspecto fundamental para el mejor conocimiento de la magnitud del problema de salud. En este sentido, el presente trabajo de investigación tiene como propósito estimar a través de un estudio de simulación los costes y las efectividades de cinco tratamientos antipsicóticos (ziprasidona, olanzapina, risperidona, haloperidol y clozapina) que se encuentran dentro del cuadro básico del Instituto Mexicano del Seguro Social (IMSS).
Métodos: Tipo de evaluación económica: completa del tipo de coste-efectividad. Perspectiva de la investigación: costes médicos directos. La temporalidad del estudio fue de 1 año. Medida de efectividad: número de meses libres de síntomas psicóticos. Análisis: para el análisis de coste-efectividad se diseñó un modelo de Markov y se hizo una simulación de Monte Carlo.
Resultados: Efectividades: los resultados del modelo de Markov mostraron que la ziprasidona fue el antipsicótico con la mayor media de tiempo libre de síntomas psicóticos (9,2 meses). La mediana de costes anuales entre los pacientes simulados a través de la cohorte hipotética con ziprasidona resultó en 194.766,6 (intervalo de confianza del 95%, 26.515,6-363.017,6) pesos mexicanos (PMX) (tipo de cambio, 1 euro = 17,36 PMX). Los mayores costes en el análisis probabilístico se presentaron con el tratamiento con clozapina (260.236,9 PMX).
Conclusiones: Dentro de un análisis probabilístico, ziprasidona mostró los menores costes y el mayor número de meses libres de síntomas psicóticos, así como ser el antipsicótico más coste-efectivo según lo observado dentro de las curvas de aceptabilidad y de beneficios monetarios netos.

Introduction

The World Health Organization has made in public that between 24 and 25 million people suffer from schizophrenia.[1] Schizophrenia is a chronic psychotic disorder, with a prevalence in adults of 0.5-1.5%[2] It is estimated that, in Mexico, schizophrenia affects 0.7-2% of the population.[3] Health care cost for schizophrenia is 2-3% of the total spending for health care.[4]

Being schizophrenia a chronic disease, it requires long-term pharmacological treatment.[5] Antipsychotics are the principal medication used. Depending on their clinical introduction and pharmacological characteristics, these are classified in typical antipsychotics (first generation) and atypical antipsychotics (second generation). Typical antipsychotics include, for example, chlorpromazine, fluphenazine and haloperidol, and have a high antagonistic affinity for cerebral dopamine D2 receptors; whereas atypical antipsychotics, such as olanzapine, risperidone, clozapine, quetiapine, ziprasidone, and aripiprazole, apart from blocking D2 receptors, act as serotonergic receptors 5-HT 1A, 2A, 2C, 3, 6 and 7, and alpha 1 and alpha 2[6,7] noradrenergic receptors.

Although atypical antipsychotics have a more favourable side effect profile regarding parkinsonism, akathisia and dyskinesism, some of them include other risks such as arrhythmias, diabetes, weight gain, hyperlipidaemia and agranulocitosis.[7,8] This is why it is believed that choosing the better medication for schizophrenia should include these three aspects: it is the most effective, it has the fewer side effects, and it is less costly both, for the patient and the health institutions.[8,9]

Those antipsychotic drugs that prevent or reduce relapse and other health services involved may be instrumental in improving the patients' quality of life and reduce direct-treatment medical costs.[10,11] In Mexico, as far as this review has looked into, only one cost-effectiveness study has been published, where only three antipsychotic treatments were compared, namely, olanzapine, haloperidol and risperidone, for a period of 5 years.[12] However, in that analysis antipsychotics usually used in medical practice in Mexico were not included, such as ziprasidone and clozapine.

At present, assessment studies published on cost-effectiveness of new antipsychotics have been developed by economic-analytic models.[13] These models are part of a methodology relatively fast to assess the economic consequences of a new drug, and they are flexible enough to incorporate into the analysis different treatments, perspectives and treatment duration.[12,14] But their limitation is that they need to employ prospective studies to validate the information compiled within one modelling study, which prevents generalising them easily for other populations.[15,16]

The information in this study will be useful for the health institution itself through its operative staff, since

a description of the medical practice style will be made depending on the use of resources available to treat schizophrenia and its accounting cost within the same institution. This type of assessments is a current priority for social security institutions in developing coutries.[17]

In this respect, the objective of the present study is to assess cost and effectiveness with five antipsychotic treatments (ziprasidone, olanzapine, risperidone, haloperidol and clozapine) within the basic medication set at the IMSS (Mexican Social Security Institute) by means of a Markov model, to afterward proceed to perform a cost-effectiveness analysis in order to identify which treatment is the most cost-effectively adequate to a third level hospital within the IMSS. This investigation also aims at improving the so far scant resource provision within the institution and, if possible, promoting the quality of medical care at the IMSS.

Method

Research design. Simulation study by means of an economic-analytic model, with a complete cost-effectiveness economic evaluation. Cost-effectiveness analyses compare direct and indirect costs and savings on costs by two or more medical treatments to obtain a similar result evaluated as a natural health index, for example, number of patients prevented from suffering a certain side effect or adverse effect, such as hospitalisation.[18] Total net costs or incremental costs of an operation are estimated to be later divided by the difference of clinical results (effectiveness) obtained from the different operations. In sum, cost-effectiveness reasons are obtained by making the following calculation:

Incremental cost-effectiveness ration (ICER) = total net costs (incremental costs) / net effectiveness (incremental effectiveness) for two alternative medical treatments (A and B).[15]

Pharmacological treatments. Costs and outcomes from a treatment with ziprasidone, olanzapine, risperidone and clozapine were compared between themselves and against a typical antipsychotic (haloperidol). The doses used in this investigations were based on the clinical information provided by the IMSS physicians and the international guidelines,[19,20] as well as on the usual presentation in the Mexican market. Daily doses used were: haloperidol 10mg, risperidone 4mg, olanzapine 10mg, ziprasidone 80mg and clozapine 300mg. Table 1 shows daily costs and treatment at IMSS in 2005 depending on doses and presentations to conduct the pharmacoeconomic analysis. The currency exchange rate in 2008 was 1 Euro=17.36 Mexican pesos.

Probabilities. The results for this model were taken from the Finnish model of Sorensen[21] and Bobes et al.,[14] for probabilities of non-compliance with antipsychotic treatment resulting from an adverse effect. In that study, therapeutic non-compliance probabilities resulted as follows: ziprasidone 80mg, 70.2%; risperidone 5mg, 66.4%; olanzapine 13.2mg, 65.9%; and haloperidol 8mg, 63.5%. According to the experts' opinion at the psychiatric hospital of San Fernando, in Mexico, adherence to treatment with clozapine 300mg is 69.5%. In addition, the probability of suffering adverse events during antipsychotic treatment (including patient presenting with akathisia, clinically relevant weight gain [> 7%], sexual dysfunctions or a combinations of these) was taken from Sorensen's study,[21] which is supported by different studies[22-29] that point that haloperidol shows a 49.9% probability, 28.3% ziprasidone, 44.5% olanzapine, and 41.5% risperidone. Probabilities for ziprasidone were mostly obtained from the article by Sorensen.[21] For example, the probability that under drug treatment the patient presents only with akathisia as a side effect is 20.8% with haloperidol, 15.2% with risperidone, 7.9% with olanzapine and 7.9% with ziprasidone. However, the probability that a patient shows only clinically relevant weight gain was 11% with haloperidol, 14.9%with risperidone, 28.2%with olanzapine, and 10%with ziprasidone.

Finally, the probabilities above mentioned were complemented with results from the pharmacoeconomic study of Bobes et al.,[14] where it was shown the side-effect type and frequency with the use of antipsychotics analysed in the Outcomes Research Study in Schizophrenia (ORSS).[22] Table 2 shows probabilities used in that model.

In the case of clozapine and frequency of side effects related with this antipsychotic, the information was obtained from the experts in psychiatry with experience

Table 1 Treatment, presentation, and cost of daily treatment of drugs

Treatment	Presentation	IMSS Price (box in Mexican pesos)*	Daily cost (in Mexican pesos)*
Ziprasidone	40 mg (28 tablets)	736.7	52.6
Risperidone	2 mg (40 tablets)	598.5	29.9
Haloperidol	5 mg (20 tablets)	3.5	0.3
Olanzapine	10 mg (14 tablets)	822.9	58.8
Clozapine	100 mg (30 tablets)	800.2	80

*Currency exchange rate to Euros as of 2008 is 1 Euro = 17.36 Mexican pesos.
Source: Data base of Health Economy and Technology Evaluation Division of Mexican Social Security Institute (IMSS), 2005.

in the use of this drug at the psychiatric hospital of San Fernando, a third level hospital.

Research perspective. The cost-effectiveness analysis was done from the perspective of the public service provider (IMSS). That is, only direct medical costs were included in the analysis, i. e. hospital stay, emergency service, department and laboratory analysis, pharmacologic treatment, outpatient and consultation, and inter-consultation. Length of time: 1 year. Effectiveness is measured by the length of time (in months) without psychotic symptoms, which indicates that acute schizophrenic symptoms are under control and that the patient does not require hospitalisation. No other measures, such as QALY, were taken because, in a cost-effectiveness study, these could cause even larger limitations in measuring the outcomes in patients suffering mental diseases, as it has been documented in other studies.[30]

Use of resources. Sources to set the use of resources in the cost-effectiveness analysis were obtained mainly from the opinion of experts at the psychiatric hospital of San Fernando (third level IMSS) and this information was supported by a sample of patients' records from the same hospital, patients that had received some of the antipsychotics included in this study. Furthermore, all the experts included in the investigation (7 psychiatrists) certified to have experience with all the antipsychotics analysed, with good knowledge of the use of resources required in each case within their own hospital. The prices used in the model were obtained from the official cost per unit of the IMSS published in the Mexican Official Journal,[31] (Tuesday, 9 March 2004; First Section; p. 107-8. Available at: http://dof.gob.mx/index.php). In addition, the prices of laboratory analysis were taken from the monthly report of laboratory automated studies provided by the Siglo XXI Mexican Medical Centre[31] (November 2003). Furthermore, the prices of the antipsychotics used in the medical interventions at the IMSS were obtained from the transparency portal (*Portal de Transparencia*) at the institute Web page[32] (www.imss.gob.mx).

Markov model. To perform the cost-effectiveness analysis, a Markov model was designed to simulate treatment of a 10,000-patient hypothetical cohort suffering from chronic schizophrenia during 1 year. Possible health stages that a patient may go through over time, due to treatment and disease, were simulated with pre-determined probabilities to go from one stage onto the other, called "transition probabilities". The duration of each cycle in this model is of 1 month, totalling 12 cycles. As it is the case with Bobes et al. model, the antipsychotic treatment can be started for acute or chronic stage (for the basic analysis it was assumed that 50% of the patients start on antipsychotic treatment at acute stage and 50% at chronic stage);[14] although each stage had distinct implications, the assumption was simply made to compare one stage against the other. Figure 1, based on Bobes et al. model,[14] shows in detail Markov model used in the study to estimate cost-effectiveness reasons between different antipsychotics. Figure 1 shows a simulation of the options a patient undergoing antipsychotic in-hospital treatment may go through, started on first-line therapy (haloperidol, ziprasidone, olanzapine, clozapine or risperidone) to move onto an observation phase where adverse effects may appear (akathisia, extrapyramidal symptoms, and weight gain) leading to changing the antipsychotic therapy. In this model there are four approaches for resolving the adverse effects observed in the patients: not to perform any action, to reduce initial dosing of antipsychotic, to add a new concomitant pharmacologic treatment, or to change to other antipsychotic. Figure 2 shows possible changes that might occur in case of initial antipsychotic treatment failure, together with subsequent treatment patterns to be given to the patient in case of therapeutic non-compliance, effectiveness failure, or side effect occurrence. In the absence of adverse effects, the patient would be discharged until the symptoms were wholly under control. This model was validated using the criteria in the literature, that is, in two ways: a) Descriptive validation:[33] the model provides a simplified vision but offers an adequate perspective of reality without omitting important aspects of the disease by including all the relevant complications occurring most frequently. b) Technical verification:[34] there is internal coherence to the results; higher costs appeared when complications demanded higher use of resources and vice versa; tests of internal coherence were also performed, a process called "debugging" in the literature, resulting in extreme values along the transition probability range [0-100%], where it was observed that the model functions correctly and that it did not render incoherent results.

Sensitivity analysis. Probabilistic sensitivity analysis was performed. To this end a first-order Monte Carlo simulation was performed, simulating a hypothetical cohort of 10,000 patients both for costs and effectiveness with each one of

Table 2 Type and frequency (%) of adverse effects related to the use of antipsychotics observed at the ORSS study.[7]

Antipsychotic drug	Akathisia	Other EPS	Weight gain (≥ 7%)	Other SS associated to prolactin
Haloperidol	36.8	41.5	22.4	39.8
Risperidone	19.7	35.4	30.6	45.6
Olanzapine	11.4	24.4	45.7	36.7
Ziprasidone*	8	10.2	5.8	2.5

ORSS: Outcomes Research Study in Schizophrenia Results; EPS: Extra pyramidal symptoms.
*Data taken from the technical specifications.

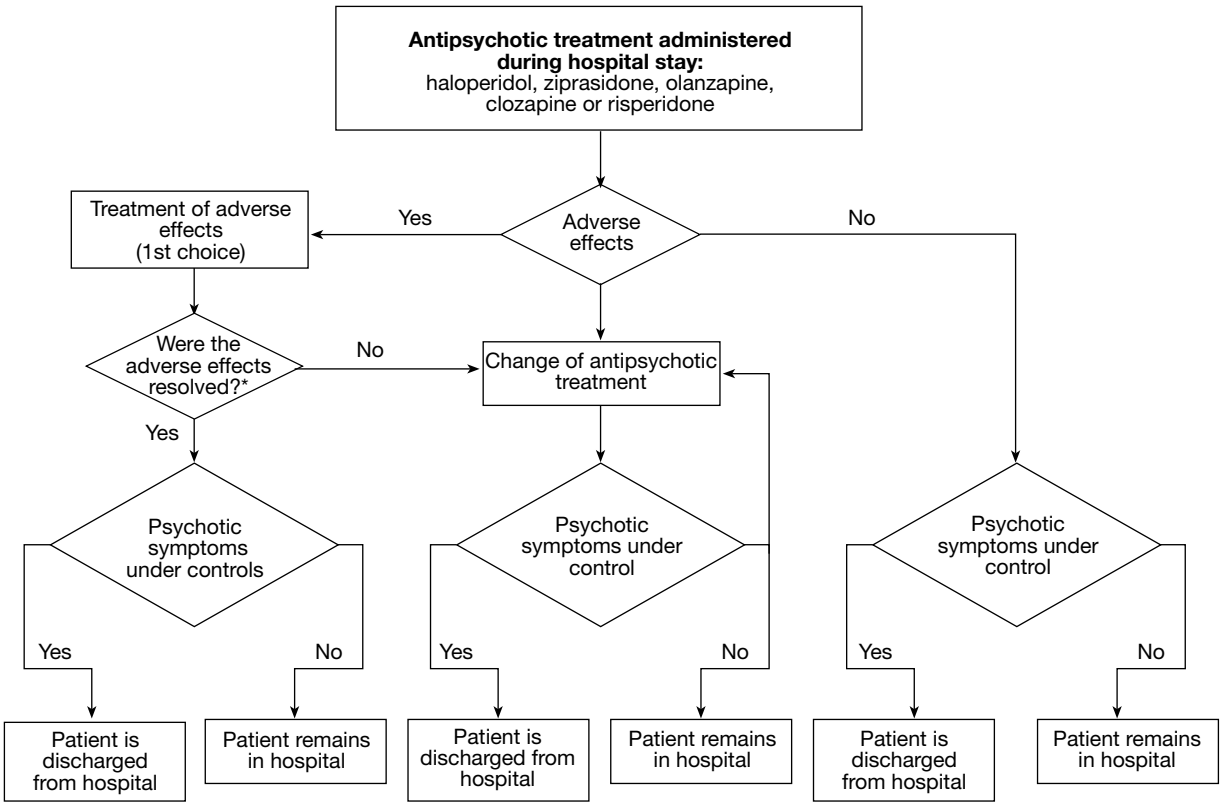

Figure 1 Possible alternatives including Markov model in antipsychotic treatment inside the hospital. Options through which a patient undergoing antipsychotic in-hospital treatment are simulated, started on first-line therapy (haloperidol, ziprasidone, olanzapine, clozapine or risperidone) to move onto an observation phase where adverse effects may appear (akathisia, extra pyramidal symptoms, and weight gain, etc.) that might lead to changing the antipsychotic therapy.
***It includes reduction of doses, change of antipsychotic treatment, use of other medication to complement treatment, and the option of not doing anything when adverse effect situation is not resolved.**

the antipsychotic treatments in the study. The acceptability curves were estimated for all the treatments. The software used for the simulation was Tree Age 2004 (©1988-2007 by TreeAge Software, Inc., Williamstown, Maryland, United States). Net monetary benefits (NMB) were calculated in the probabilistic sensitivity analysis by the following formula:

$$BNA = \mu_{EA} \times \lambda - \mu_{CA}$$

where NMB for treatment A is obtained by the difference between the effectiveness media mean found in the Monte Carlo simulation multiplied by the financial resources to pay the supplier of health public services (λ) and the cost mean for such alternative.[15]

Results

Effectiveness

Once all the information above was included, the results from the Markov model showed that ziprasidone and clozapine were the antipsychotics that on average showed the largest number of months free from psychotic symptoms (9.2 and 8.95 months respectively) (table 3).

Haloperidol was the one that showed the least effectiveness, mainly due to higher probability that it would present with adverse events and non-compliance to treatment during the period studied.

Costs

The hospital stay mean in days for acute psychotic treatment was less when treated with ziprasidone and haloperidol (table 4).

In addition, the average cost per patient with treatment for acute stages was lower for antipsychotic treatment with risperidone (56,695.2 Mexican pesos), and for chronic stages ziprasidone (2,946.17 Mexican pesos) for atypical antipsychotics (table 4).

Likewise, the treatment that presented the least monthly average cost was haloperidol (2,260.8 Mexican pesos).

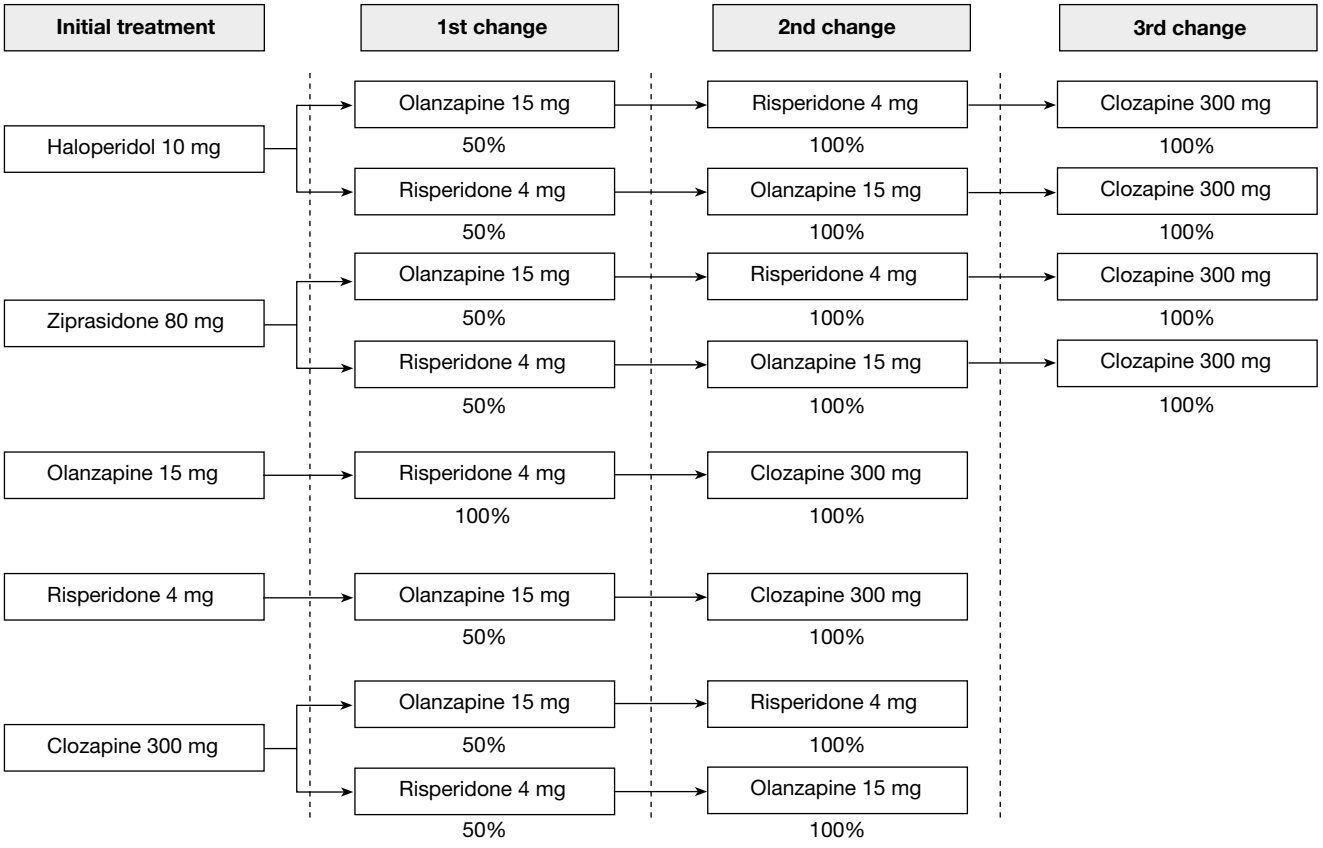

Figure 2 Changes of antipsychotic treatment if therapeutic non-compliance, loss of effectiveness or side effects would appear. Alternative treatment options are also shown to offer the patient in case initial antipsychotic treatment failed.

Table 3 Cost-effectiveness analysis between different alternatives in the study

reatment	Annual cost per patient in Mexican pesos*	Incremental cost per patient in Mexican pesos*	Annual effectiveness per patient	Incremental effectiveness per patient	Average cost-effectiveness ratio in Mexican pesos*	Incremental cost-effecti-veness ration (ICER)
Ziprasidone	183,606.3		9.199 months		19.959/ months	
Risperidone	209,604.3	25,998	8.811 months	(0.388 months)	23.788/ months	Overruled
Clozapine	263,820.7	80,213.4	8.952 months	(0.247 months)	29.471/ months	Overruled
Olanzapine	282,675.1	99,068.8	8.490 months	(0.709 months)	33.295/ months	Overruled
Haloperidol	283,650.5	100,044.3	7.530 months	(1.669 months)	37.667/ months	Overruled

*Currency exchange rate to Euros as of 2008 is 1 Euro = 17.36 Mexican pesos.

Cost-effectiveness analysis

The model outcomes and the deterministic analysis are in table 3, where it can be observed that ziprasidone and risperidone were the antipsychotic treatments with best cost-effectiveness.

Another important point in the table is that, although haloperidol and olanzapine showed annual costs expectedly similar, olanzapine effectiveness is much higher than that of haloperidol, which makes olanzapine the dominant (or overruling) alternative for this case.

Sensitivity analysis

In this respect, the annual cost mean with patients in simulation (Markov model) with a ziprasidone-hypothesised cohort, was 194,766.6 Mexican pesos (table 5), although

Table 4 Average cost per patient in chronic and acute treatment according to type of antipsychotic

	Stay at hospital (days), mean[a]	Cost per patient undergoing treatment for acute stage (Mexican pesos[b]), mean	Monthly cost per patient undergoing treatment for chronic stage (Mexican pesos[b]), mean	Adjusted monthly cost per patient undergoing treatment for chronic stage (Mexican pesos[b]), mean
Risperidone	15.33	56,695.59	4,362.39	3,277.46
Olanzapine	17.25	69,455.64	6,108.14	4,581.11
Clozapine	18.75	77,428.75	4,140.83	3,105.62
Haloperidol	15.25	60,605.34	2,260.81	1,695.61
Ziprasidone	14.77	58,293.3	2,946.17	2,209.63

[a]Information obtained from patient clinical records carried out at Psychiatric Hospital of San Fernando in Mexico City.
[b]Currency exchange rate to Euros as of 2008 is 1 Euro =17.36 Mexican pesos.

Table 5 Annual costs and effectiveness expected according to type of antipsychotic (10,000-patient Monte Carlo simulation)

Treatment	Expected annual cost (Mexican pesos)*	Annual effectiveness expected (months free from psychotic symptoms)
Ziprasidone	194,766.6 [26,515.6-363,017.6]	9.21±1.45
Risperidone	199,532.9 [92,685.3-359,804.3]	8.82±1.48
Clozapine	260,236.9 [37,267.5-483,206.2]	8.95±1.47
Olanzapine	249,596.9 [119,847.9-509,095]	8.50±1.52
Haloperidol	255,986.2 [79,257.1-491,625.1]	7.53±1.60

*Currency exchange rate to Euros as of 2008 is 1 Euro =17.36 Mexican pesos.

the confidence intervals show that all the treatments are interconnected. Considering the free-from-psychotic-symptoms variable, ziprasidone once again showed the highest effectiveness, but with minimal differences against the other treatments (table 5).

Graphically speaking, when comparing each antipsychotic against ziprasidone (as comparing agents and over the axis), it can be observed that a larger number of points falls into the lower right quadrant, which means that ziprasidone, in each one of the cases, shows lower incremental cost with higher incremental effectiveness (fig. 3).

Equally, up to the acceptability curves (fig. 4), it appears that ziprasidone would be the best cost-effectiveness option of all the antipsychotics tested, with a probability rate closer to 60%.

Furthermore, the BM results for the treatment of schizophrenia at IMSS show that ziprasidone would be the antipsychotic treatment that would result in larger institutional savings, compared against the other treatments of the basic set. These results, however, do not show significant differences.

Discussion

This study identified ziprasidone with the best cost-effectiveness ratio to treat schizophrenia, followed by risperidone. However, these results could only be applied to third-level hospitals, as it has already been stated.[35]

In addition, there are limitations to the present study that are worth mentioning. Only 1-year prognosis was included, while the study carried out previously in Mexico assessed 5 years.[12] However, in different studies, the same 1-year time frame was employed.[14,36-38] The present model centres its efforts in the clinical benefits of each antipsychotic in such issues as tolerance and safety; also, a second effectiveness index was used, which summarised the proportion of relapse-free patients, and was similar to other articles.[36,37]

Long-term consequences and changes in quality of life, above all with relation to physical activity, work, interpersonal relation with family and other members of society were not included in the present study.[4]

Other limitation is that the suppositions included in this model may condition outcomes, so that caution must be taken when outcomes are extrapolated to other populations; other limitation is that modelling based on the opinion of experts could not be applied to all cases, but only taken as a guiding factor, due to the fact that most data were extracted from studies performed in environments differing greatly from Mexico, from the viewpoint of service provision and care patterns regarding schizophrenia. The model in figure 1 takes a hospitalisation situation for cases that do not occur in reality, where over 50% of the crisis

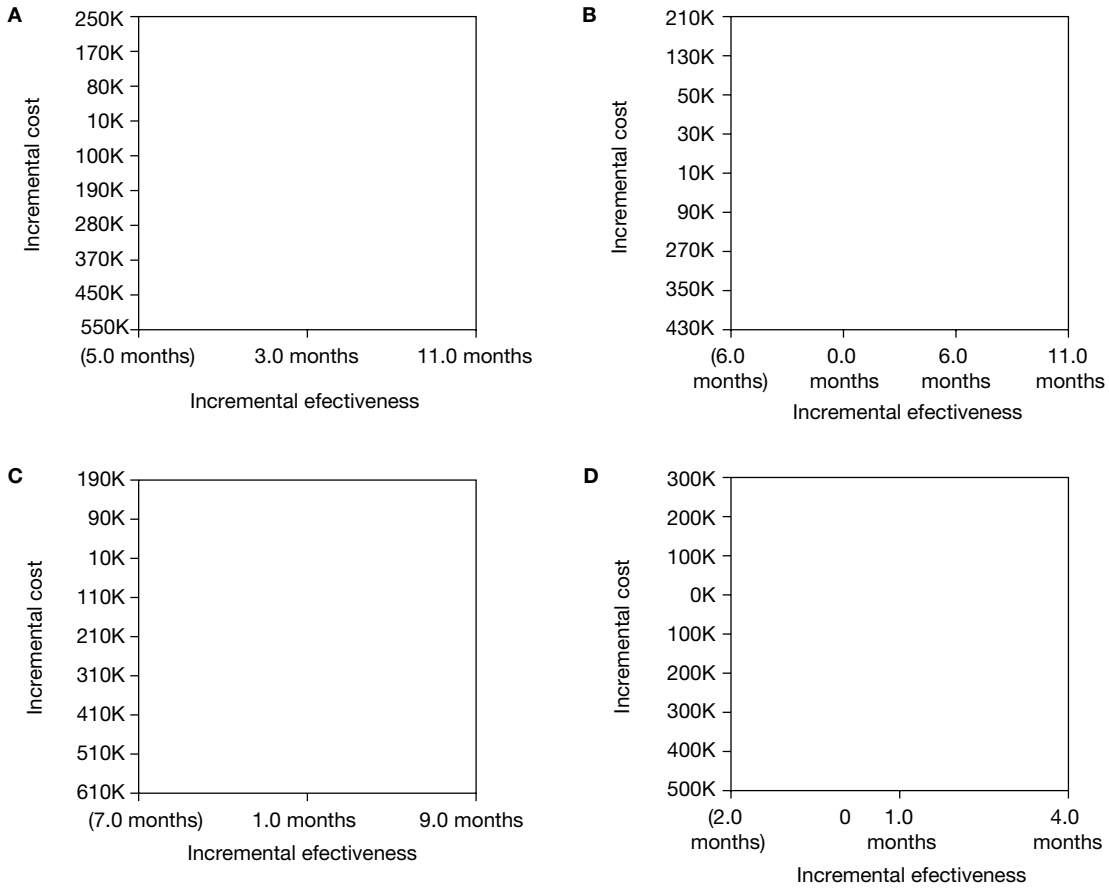

Figure 3 Incremental cost-effectiveness comparison between ziprasidone and the other antipsychotic treatments (10,000-patient Monte Carlo simulation). Free-from-symptoms effectiveness index in an acute setting. Axis Y stands for time free from these events and axis X stands for incremental cost associated to longer time without acute settings. In this case, it is a probabilistic sensitivity analysis. In this case, similarly to the point cloud, the graphic shows all the incremental cost-effectiveness potential reasons by comparing ziprasidone against the other drugs. A. Haloperidol (base) against ziprasidone. B: risperidone (base) against ziprasidone. C: clozapine (base) against ziprasidone. D: olanzapine (base) against ziprasidone.

in other places, such as Spain, for example, are resolved in an outpatient environment.[39] In this respect, this model is restrained to patients in a hospital environment and caution should be taken regarding results, since differences found are minimal.

The results found in the study are consistent with two articles published where it was pointed out that ziprasidone was the best cost-effectiveness option for antipsychotics used for the treatment of schizophrenia.[10,11] Even comparing Sorensen[21] and Bobes et al.[14] models, the outcomes are quite similar to the Mexican study (table 6).

There is no agreement in that atypical antipsychotics are better than typical antipsychotics;[40,41] in some publications no further benefits have been found with atypical antipsychotics.[41-44] Although in some studies the optimal doses were not used[45-47] or the follow-up period was not the most appropriate to assess the presence of side effects,[48] a recent meta-analysis showed that there are no significant differences between these two medication groups.[49]

Ziprasidone is one of the drugs that was not associated with higher risk of overweight[46] or diabetes mellitus and, in addition, fewer re-hospitalisations or deaths related to this medication are recorded.[40,50,51] Obesity, secondary to treatment of schizophrenia, is currently considered one of the factors that most largely contribute to increasing medical costs in this patients.[52] The dosage used in this study (80mg/day) was used in other studies[37] and it could be considered an intermediate dose of ziprasidone, and there are studies that have even used a daily dose of 40mg.[38,40,53]

Control of adverse events is one of the factors considered to be the most relevant to prevent patients from discontinuing treatment.[36,54] There is no perfect drug to treat schizophrenia;[55,56] improving existing treatments will continue to be necessary but, meanwhile, cost-effective measures should be taken.[16] An increment has been observed in economic assessments in mental health. This is partially due to the fact that it is necessary to justify extra

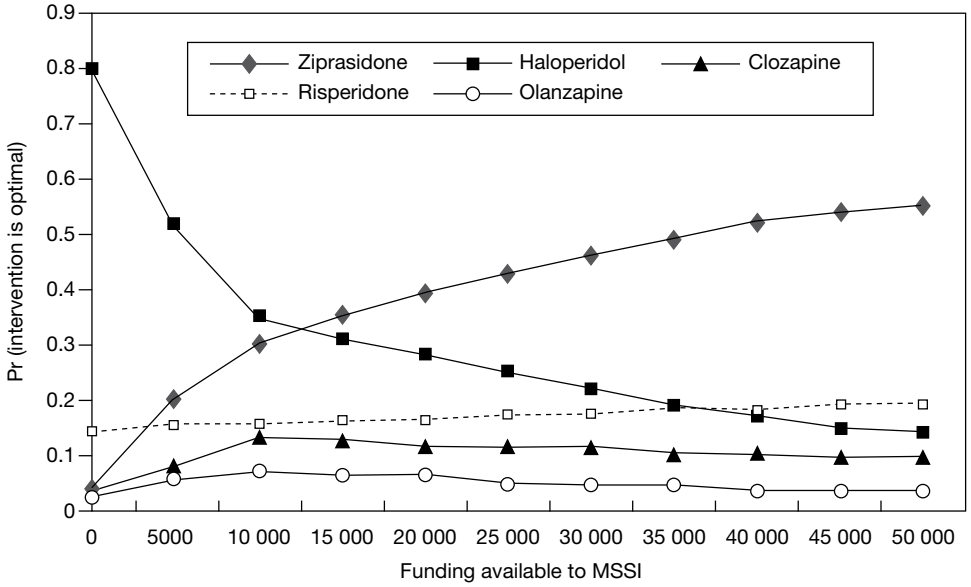

Figure 4 Acceptability curves (Monte Carlo simulation with 10,000 interactions), that identified the best cost-effective treatment. Acceptability curves show that ziprasidone appears to be the best cost-effective option of all antipsychotics, with a probability towards 60% as good disposition from IMSS to funding increases.

Table 6 Comparison of data from IMSS against those published by Sorensen[21] and Bobes et al.[22]

	Mexico		Finland[21]		Spain[22]	
	Daily dose (mg)	Months free from psychotic symptoms	Daily dose (mg)	Months free from psychotic symptoms	Daily dose (mg)	Months free from psychotic symptoms
Risperidone	4	8.81	5	8.44	5.3	9.5
Olanzapine	10	8.49	13.2	8.22	13.5	9.51
Clozapine	300	8.95		425		
Haloperidol	10	7.53	8	8.18	10.26	9.28
Ziprasidone	80	9.2	80	8.95	120	9.61

costs associated with additional benefits provided by new treatments.[9,44] It is intended for this analysis to be useful for the IMSS authorities to improve resource provision in that institution, as well as to foster an improved quality in medical attention within the IMSS. This can also be useful for all those hospitals with characteristics similar to IMSS.

Financing

This study was financed by Pfizer México S.A. de C.V. and such financing was administered by the IMSS, through the promotion fund for research, with registration number: 2005/23/587. The IMSS was in charge of performing a six-month evaluation and a final evaluation when the project was completed. During this research project, Joaquín Mould-Quevedoa worked at the Health Economy Investigations Unit of IMSS; he currently works for Pfizer México S.A. de C.V. Juan Manuel Mejía-Aranguréc received financing support from Pfizer to write the present study. The other co-authors have no conflict of interests.

References

1. Valencia CM. Trastornos mentales y problemas de salud mental: Día mundial de la salud mental 2007. Salud Mental. 2007;30:75-80.

2. Benítez CE, Chávez LE, Ontiveros UM. Crianza y esquizofrenia. Salud Mental. 2005;28:59-72.
3. Villamil SV, Valencia CM, Diaz MLR, Medina M, Juárez F. Funcionamiento psicosocial de pacientes esquizofrénicos de acuerdo con su consumo de alcohol. Salud Mental. 2005;28: 40-8.
4. Carr VI, Lewin T, Neil AL, Halpin SA, Holmes S. Premorbid, psychosocial and clinical predictors of the costs of schizophrenia and other psychoses. Br J Psychiatry. 2004;184:517-25.
5. Davis JM. The choice of drugs for schizophrenia. N Engl J Med. 2006;354:518-20.
6. Lieberman JA, Stroup TS, Mcevoy JP, Swartz MS, Rosenheck RA, Perkins DO, et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N Engl J Med. 2005;353: 1209-23.
7. Mann JJ. The medical management of depression. N Engl J Med. 2005;353:1819-34.
8. Freedman R. The choice of antipsychotic drugs for schizophrenia. N Engl J Med. 2005;353:1286-8.
9. Hoch JS, Dewa CS. Lessons from trial-based cost-effectiveness analyses of mental health interventions. Why uncertainty about the outcome, estimate and willingness to pay matters. Pharmacoeconomics. 2007;25:807-16.
10. Arango C, Gómez-Beneyto M, Brenlla J, Gastó C, Sarrameacrespo F, Chamorro L, et al. A 6-month prospective, observational, naturalistic, uncontrolled study to evaluate the effectiveness and tolerability of oral ziprasidone in patients with schizophrenia. Eur Neuropsychopharmacol. 2007;17:456-63.
11. Bernardo M, Azanza JR, Rubio-Terrés C, Rejas J. Cost effectiveness analysis of schizophrenia relapse prevention. An economic evaluation of the ZEUS (Ziprasidone-extended-use in schizophrenia) Study in Spain. Clin Drug Invest. 2006;26:447-57.
12. Palmer CS, Brunner E, Ruiz-Flores LG, Paez-Agraz F, Revicki DA. A cost-effectiveness clinical decision analysis model for treatment of schizophrenia. Arch Med Res. 2002;33:572-80.
13. Pauker SG, Kassirer JP. Medical progress-decision analysis. N Engl J Med. 1978;316:250-8.
14. Bobes J, Cañas F, Rejas J, Mackell J. Economic consequences of the adverse reactions related with antipsychotics: an economic model comparing tolerability of ziprasidone, olanzapine, risperidone and haloperidol in Spain. Prog Neuropsychopharmacol Biol Psychiatry. 2004;28:1287-97.
15. Drummond MF, Sculpher MJ, Torrance GW, O'Brien B, Stoddart GL. Economic evaluation using decision analytic modelling. En Methods for the economic evaluation of health care programmes. New York: Oxford University Press; 2005. p. 278-322.
16. Stroup TS, Geddes JR. Randomized controlled trials for schizophrenia: study designs targeted to distinct goals. Schizophr Bull. 2008;34:266-74.
17. Muñoz-Hernández O, Garduño-Espinosa J, Pérez-Cuevas R. Higia y Panacea en la salud y la sociedad. Los sistemas de salud, un producto de la evolución social. Rev Med IMSS. 2005;43:411-7.
18. Meltzer MI. Introduction of Health Economics for physicians. Health Economics Quintet. Lancet. 2001;358:993-8.
19. Byrne P. Managing the acute psychotic episode. BMJ. 2007;334: 686-92.
20. Davis JM, Chen N. Dose response and dose equivalence of antipsychotics. J Clin Psychopharmacol. 2004;24:192-208.
21. Sorensen SV. Technical appendix for "The health and economic benefi ts of treating schizophrenia model". Technical Appendix prepared for Pfi zer. MEDTAP International. 2003;A2:1875.
22. Bobes J, Rejas J, García-García M, Rico-Villademoros F, García-Portilla MP, Fernández I, et al. Weight gain in schizophrenic patients treated with risperidone, olanzapine, quetiepine or haloperidol: results of the EIRE study. Schizophr Res. 2003;62: 77-88.
23. Gilbert PL, Harris MJ, Mcadams LA, Jeste DV. Neuroleptic withdrawal in schizophrenic patients: a review of the literature. Arch Gen Psychiatry. 1995;52:173-87.
24. Hoge SK, Appelbaum PS, Lawlor T, Beck JC, Litman R, Greer A, et al. A prospective, multicentre study of patients' refusal of antipsychotic medication. Arch Gen Psychiatry. 1990;47:949-56.
25. Tollefson GD, Beasley CM, Tran PV, Street JS, Krueger JA, Tamura RN, et al. Olanzapine versus haloperidol in the treatment of schizophrenia and schizoaffective and schizophreniform disorders: results of an international collaborative. Am J Psychiatry. 1997;154:457-65.
26. Tran PV, Dellva MA, Tollefson GD, Beasley CM, Potvin JH, Kiesler GM. Extrapyramidal symptoms and tolerability of olanzapine versus haloperidol in the acute treatment of schizophrenia. J Clin Psychiatry. 1997;58:205-11.
27. Tran PV, Hamilton SH, Kuntz AJ, Potvin JH, Andersen SW, Beasley CM. Double-blind comparison of olanzapine versus risperidone in the treatment of schizophrenia and other psychotic disorders. J Clin Psychopharmacol. 1997;17:407-18.
28. Van Putten T, May PR, Marder SR, Wittmann LA. Subjective response to antipsychotic drugs. Arch Gen Psychiatry. 1981;38: 187-90.
29. Weiden PJ, Olfson M. Cost of relapse in schizophrenia. Schizophr Bull. 1995;21:419-29.
30. Knapp M, Mangalore R. The trouble with QALYs... Epidemiol Psichiatr Soc. 2007;16:289-93.
31. Instituto Mexicano del Seguro Social. Secretaria General. Aviso: Costes unitarios de la atención médica. Diario Ofi cial de la Federación. Martes 9 de marzo de 2004 —Primera Sección pp. 106-7 [citado Mar 2004]. Disponible en: http://dof.gob.mx/index.php
32. Instituto Mexicano del Seguro Social [citado Mar 2006]. Disponible en: www.imss.gob.mx
33. Mccabe C, Dixon S. Testing the validity of cost effectiveness models. Pharmacoeconomics. 2000;17:501-13.
34. Sendi PP, Craig BA, Pfl uger D, Gafni A, Bucher HC. Systematic validation of disease models for pharmacoeconomic evaluations. Swiss HIV Cohort Study. J Eval Clin Pract. 1999;5:283-95.
35. Swartz MS, Stroup TS, McEvoy JP, Davis SM, Rosenheck RA, Keefe RS, et al. What CATIE found: results from the schizophrenia trial. Psychiatr Serv. 2008;59:500-6.
36. Obradovic M, Mrhar A, Kos M. Cost-effectiveness of antipsychotics for outpatients with chronic schophrenia. Int J Clin Pract. 2007;61:1979-88.
37. Geitona M, Kousoulakou H, Ollandezos M, Athanasakis K, Papanicolaou S, Kyriopoulos I. Costs and effects of paliperidone extended release compared with alternative oral antipsychotic agents in patients with schizophrenia in Greece: A cost effectiveness study. Annals of General Psychiatry [revista electrónica]. 2008;7:16 [citado 1 Mar 2009]. Disponible en: http://www.annals-general-psychiatry.com/content/7/1/16
38. Edwards NC, Pesa J, Meletiche DM, Engelhart L, Thompson AK, Sherr J, et al. One-year clinical and economic consequences of oral atypical antipsychotics in the treatment of schizophrenia. Curr Med Res Opin. 2008;24:3341-55.
39. Gutierrez-Recacha P, Chisholm D, Haro JM, Salvador-Carulla L, Ayuso-Mateos JL. Cost-effectiveness of different clinical interventions for reducing the burden of schizophrenia in Spain. Acta Psychiatr Scand Suppl. 2006;(432):29-38.
40. Rosenheck RA, Leslie DL, Sindelar J, Miller EA, Lin H, Stroup TS, et al. Cost-effectiveness of second-generation antipsychotics and perphenazine in a randomized trial of treatment for chronic schizophrenia. Am J Psychiatry. 2006;163:2080-9.
41. Jones PB, Barnes TR, Davies L, Dunn G, Lloyd H, Hayhurst KP, et al. Randomized controlled trial of the effect on Quality of Life of second- vs fi rst-generation antipsychotic drugs in schizophrenia: Cost Utility of the Latest Antipsychotic Drugs in

Schizophrenia Study (CUtLASS 1). Arch Gen Psychiatry. 2006;63:1079-87.
42. Mccue RE, Waheed R, Urcuyo L, Orendain G, Joseph MD, Charles R, et al. Comparative effectiveness of second-generation antipsychotics and haloperidol in acute schizophrenia. Br J Psychiatry. 2006;189:433-40.
43. Polsky D, Doshi JA, Bauer MS, Glick HA. Clinical trial-based cost-effectiveness analyses of antipsychotic use. Am J Psychiatry. 2006;163:2047-56.
44. Rosenheck RA, Leslie DL, Doshi JA. Second-generation antipsychotics: cost-effectiveness, policy options, and political decision making. Psychiatr Serv. 2008;59:515-20.
45. Tandon R, Nasrallah HA. Subjecting meta-analyses to closer scrutiny: Little support for differential effi cacy among secondgeneration antipsychotics at equivalent doses. Arch Gen Psychiatry. 2006;63:935-7.
46. Leucht S, Komossa K, Rummel-Kluge C, Corves C, Hunger H, Schmid F, et al. Meta-analysis of head-to-head comparisons of second-generation antipsychotics in the treatment of schizophrenia. Am J Psychiatry 2009;166:152-63.
47. Davis JM, Leucht S, Glick ID. CATIE fi ndings revisited. Psychiatr Serv. 2009;60:125-6.
48. Freedman R, Carpenter WT Jr, Davis JM, Goldman HH, Tamminga CA, Thomas M. The costs of drugs for schizophrenia. Am J Psychiatry. 2006;163:2029-31.
49. Leucht S, Corves C, Arbter D, Engel RR, Li C, Davis JM. Secondgeneration versus fi rst-generation antipsychotic drugs for schizophrenia: a meta-analysis. Lancet. 2009;373:31-41.
50. Tiihonen J, Walhbeck K, Lönnqvist J, Klaukka T, Ioannidis JP, Volavka J, et al. Effectiveness of antipsychotic treatments in a nationwide cohort of patients in community care alter fi rst hospitalisation due to schizophrenia and schizoaffective disorder: observational follow-up study. BMJ. 2006; 333:224.
51. Wang PS, Schneeweiss S, Avorn J, Fischer MA, Mogun H, Solomon DH, et al. Risk of death in elderly users of conventional vs. atypical antipsychotic medications. N Engl J Med. 2005;353: 2335-41.
52. Chwastiak LA, Rosenheck RA, McEvoy JP, Stroup TS, Swartz MS, Davis SM, et al. The impact of obesity on health care costs among persons with schizophrenia. Gen Hosp Psychiatry. 2009;31:1-7.
53. Stroup TS, Lieberman JA, McEvoy JP, Swartz MS, Davis SM, Rosenheck RA, et al. Effectiveness of olanzapine, quetiapine, risperidone, and ziprasidone in patients with chronic schizophrenia following discontinuation of a previous atypical antipsychotic. Am J Psychiatry. 2006;163:611-22.
54. Heinze G, Cortés JF. Treatment preferente and attiutde toward pharmacotherapy and psychotherapy in Latin America. ULAD task force. Salud Mental. 2005;28:10-7.
55. Agid Y, Buzsáki G, Diamond DM, Frackowiak R, Giedd J, Girault JA, et al. How can drug discovery for psychiatric disorders be improved? Nat Rev Drug Discov. 2007;6:189-201.
56. Gründer G, Hippius H, Carlsson A. The 'atypical' of antipsychotics: a concept re-examined and re-defi ned. Nat Rev Drug Discov. 2009;8:197-202.