Selection of Antipsychotic Agents in a Psychiatric Hospital Based on Results of CATIE Study

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Abstract

Objective: To choose typical or atypical antipsychotic drugs for treatment of schizophrenic patients in a psychiatric hospital.
Method: A standard method was used; this method considers 4 main evaluation criteria and 4 secondary criteria. The typical antipsychotic drug, perphenazine, was compared with the atypical antipsychotic drugs (olanzapine, quetiapine, risperidone, and ziprasidone). The measures of efficacy of the most important criteria come from the clinical trial "Clinical Antipsychotic Trials for Intervention Effectiveness" (CATIE).
Results: The scores of the different antipsychotic drugs were as follows: perphenazine, 59.68; olanzapine, 52.98; risperidone, 51.53; ziprasidone, 46.42; and quetiapine, 45.41. Olanzapine was equal to perphenazine when the cost criteria was reduced by 72.97%.
Conclusions: The typical antipsychotic drug perphenazine is the drug receiving the best assessment for the treatment of schizophrenia. Olanzapine is an alternative if its cost is reduced.

Key words: Atypical antipsychotic drug. Typical antipsychotic drug. Cost-efficacy. CATIE study. Selection of antipsychotic drugs.

Selección de antipsicóticos en un hospital psiquiátrico basada en los resultados del estudio CATIE

Objetivo: Seleccionar antipsicóticos, clásico versus atípico, para su uso como tratamiento de elección en el paciente esquizofrénico de un hospital psiquiátrico.
Método: Se utiliza un método normalizado que tiene en cuenta cuatro criterios principales de valoración y cuatro secundarios. Se compara el antipsicótico clásico perfenazina con los atípicos olanzapina, quetiapina, risperidona y ziprasidona. Las medidas de efectividad de los criterios más importantes proceden del ensayo clínico "Ensayos clínicos de intervención sobre la efectividad de los antipsicóticos" (CATIE; Clinical Antipsychotic Trials for Intervention Effectiveness).
Resultados: Las puntuaciones de los distintos antipsicóticos fueron las siguientes: perfenazina, 59,68; olanzapina, 52,98; risperidona, 51,53; ziprasidona, 46,42, y quetiapina, 45,41. La olanzapina iguala a la perfenazina cuando se reduce la medida del criterio coste un 72,97%.
Conclusiones: El antipsicótico clásico perfenazina es el medicamento mejor valorado para el tratamiento de la esquizofrenia. La olanzapina es una alternativa si se reduce su coste.

Palabras clave: Antipsicótico atípico. Antipsicótico clásico. Coste-efectividad. Estudio CATIE. Selección de antipsicóticos.

INTRODUCTION

Pharmaceutical and Therapeutic Committees are responsible for choosing drugs in hospitals. It is not often that a new drug contributes an improvement to the existing therapeutic arsenal; which is why, in addition to the efficacy and safety criteria, other parameters for assessment must be taken into account. The selection of drugs following a standard process, which includes homogenous, standardised elements, allows the most efficient decisions to be taken.[1]

During the past 10 years, drug expenditure in psychiatric hospitals has grown by 567% due to the introduction of the new antipsychotic drugs into the market (AP).[2] The cost of Defined Daily Doses (DDD) of these drugs can be 59 times higher than the typical drug cost.[3] In 2006, this group of drugs accounted for 65.45% of the total expenditure on drugs in the hospital.[2] This introduction of APs has also modified their patterns of use in primary care. Consumption has doubled in 10 years. In 2004, 2 new AP, olanzapine and risperadone, were

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among the 3 drugs responsible for the highest cost for the National Health System.[4]

APs are mainly indicated for schizophrenia. The typical, conventional or first generation APs are very effective on positive symptoms (delirium and hallucinations, mainly auditory) but have a high incidence of neurological effects.[5] The introduction of the new, atypical or second generation APs, envisaged improving both efficacy and safety. However, the data on their superior effects on positive symptoms are very limited and their efficacy on negative symptoms (apathetic states, poor language abilities, and lack of motivation) is very arguable as this could be due to factors not attributable to drug efficacy.[6,7] The results of a meta-analysis show that, with the exception of clozapine (an AP authorised only for patients resistant to other AP due to its haematological effects), the atypical APs are no more effective than the typical ones.[8] In another meta-analysis, the results with regard to their superiority are neither solid nor homogenous.[9] With regard to the side effects, the advantages of the new APs are also questionable,[10,11] as although they appear to cause fewer neurological side effects, in most clinical trials they were administered at variable doses and compared with the classic AP haloperidol at fixed, relatively high doses.[4] In addition, there is a tendency to ignore the results of the atypical APs on the metabolism of carbohydrates and lipids, and weight gain.[4,12] As a consequence of these facts, the United States National Institute for Mental Health (NIMH) conducted the study "Clinical Antipsychotic Trials for Intervention Effectiveness" (CATIE) to compare the efficacy of the typical and atypical APs in similar conditions in real clinical practice.[13]

The purpose of this study is to choose the AP drug, typical versus atypical, for use as the treatment of choice in schizophrenia in a psychiatric hospital, using a standard procedure that takes different AP evaluation criteria into account and efficacy measures of the CATIE study, among others.

MATERIAL AND METHODS

The method used to evaluate the APs is a multi-attribute decision analysis[14,15]; including different criteria or evaluation attributes of the AP and their weights.

The APs studied in the CATIE clinical trial are compared in the following way: perphenazine as the typical AP and olanzapine, quetiapine, risperidone, and ziprasidone as atypical APs.

CATIE Clinical Trial

The CATIE clinical trial was carried out in 1493 chronic schizophrenic patients aged between 18 and 65 years, at 56 clinical centres in the United States. The study used broad inclusion criteria and minimum exclusion criteria, and permitted patients with concomitant conditions and receiving other drugs to be included. Initially, the patients were randomly assigned to be treated with olanzapine, perphenazine, quetiapine, or risperadone (double-blind) and were followed up for up to 18 months or until the treatment was suspended for some reason (stage 1). Ziprasidone was not authorised by the Food and Drug Administration (FDA) until after the study had commenced, so it was included in the trial later on. The main efficacy criteria was withdrawal of the treatment for any reason (lack of efficacy, intolerance, or patient choice), a frequent event in the treatment of schizophrenia.[13] The patients who stopped the treatment in stage 1 were able to participate later in a double-blind, randomised study with a different AP to the initial one.[16] Finally, patients stopping the treatment with olanzapine, quetiapine, risperadone, or ziprasidone in the initial stages due to lack of efficacy were randomly assigned to be treated with clozapine in an open trial or to a blind treatment with an AP they had not taken earlier on.[17]

Adjudicating the Weights1

The comparative criteria for assessing the APs were classified into main and secondary according to the weights of their scores. The main criteria are: efficacy, safety, and cost, with a weight of 3 for the first 2 and of 2 for the latter. The secondary criteria are: experience with use, pharmacokinetics, and the pharmacological interactions with a weight of one each. Added to this study are the attributes of opinion and patient compliance with weights of 2 and 1, respectively. The scores are transformed using a scale of 0 to 1 (Table 1).

Measurement of the Criteria

The efficacy measures were defined for each criterion (Table 1). The natural measures of each AP in the study, current values (cV), are standardised to obtain a homogeneous unit. The unit values are transformed using a lineal scale of 0 to 100, values corresponding to the worst (WU) and the best plausible value (BU) found in literature for any AP (although it is not included in the study).[14,15]

The efficacy, safety, and patient compliance are defined as the percentage of patients stopping the treatment because of lack of efficacy, intolerance, or the patient's choice, respectively, in stage 1 of the CATIE[13] study. The WU and BU values are obtained from the stages after the trial.[17]

The patient's opinion and the cost as quality-adjusted life years (QALY)[18] and the monthly cost/patient in € by intention to treat in the CATIE clinical study,[3,13,18] respectively, are measured. In the measurement of both criteria by intention to treat, to the initial AP are assigned the results and the costs of both this initial AP and of those administered later on, once the treatment with the AP initially selected had been interrupted. The experience with use was quantified by the number of years on the market,[19,20] the pharmacokinetics by the number of administrations/day,[3,20,21] and the interactions by the number of clinically relevant moderate or serious pharmacological interactions (according to frequency, if documented and if it is necessary to avoid or take precautions when jointly administering the drugs).[21-23]

Table 1. Calculation of the Utility of the Alternatives[a]

Criterion	Scale		cV	U[b]	W	UXP
	WU	BU				
	0	100				
Efficacy (% of patients that stop the treatment because of lack of efficacy)	42.86	11.11			0.21	
Olanzapine			15	87.75		18.8
Perphenazine			25	56.25		12.1
Quetiapine			28	46.80		10.0
Risperidone			27	49.95		10.7
Ziprasidone			24	59.40		12.7
Safety (% of patients stopping treatment because of intolerance)	21.43	0			0.21	
Olanzapine			19	11.34		2.4
Perphenazine			16	25.34		5.4
Quetiapine			15	30		6.4
Risperidone			10	53.34	11.4	
Ziprasidone			15	30		6.4
Cost (monthly cost/patient in €)	301.20	2.5			0.14	
Olanzapine			192.00	36.56		5.2
Perphenazine			39.99	87.46		12.5
Quetiapine			95.32	68.93		9.8
Risperidone			52.08	83.40		11.9
Ziprasidone			86.94	71.73		10.2
Opinion of the patient (quality of life adjusted years)	0.704	0.731		0.14		
Olanzapine			0.717	48.15		6.9
Perphenazine			0.720	59.26		8.5
Quetiapine			0.718	51.85		7.4
Risperidone			0.704	0		0
Ziprasidone			0.716	44.44		6.3
Patient compliance (% of patients who abandon the treatment on their own decision)	35.71		20			0.07
Olanzapine			24	74.54		5.3
Perphenazine			30	36.35		2.6
Quetiapine			33	17.25		1.2
Risperidone			30	36.35		2.6
Ziprasidone			34	10.88		0.8
Experience with use (years on the market)	4	54			0.07	
Olanzapine			10	12		0.9
Perphenazine			47	86		6.1
Quetiapine			9	10		0.7
Risperidone			14	20		1.4
Ziprasidone			4	0		0
Pharmacokinetics (no. of administrations/day)	3	1			0.07	
Olanzapine			1	100		7.1
Perphenazine			1	100		7.1
Quetiapine			2	50		3.6
Risperidone			1	100		7.1
Ziprasidone			2	50		3.6

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Table 1. Calculation of the Utility of the Alternatives[a]

Criterion	Scale		cV	U[b]	W	UXP
	WU	BU				
	0	100				
Interactions (no. of clinically relevant moderate or serious side effects)	53	1			0.07	
Olanzapine			7	88.46		6.3
Perphenazine			14	75		5.4
Quetiapine			8	86.54		6.2
Risperidone			7	88.46		6.3
Ziprasidone			7	88.46		6.3
Total utility						
Perphenazine						59.68
Olanzapine						52.98
Risperidone						51.53
Ziprasidone						46.42
Quetiapine						45.41
Total utility (without cost criteria)						
Olanzapine						47.78
Perphenazine						47.18
Risperidone						39.63
Ziprasidone						36.22
Quetiapine						35.61
Cost / utility (e) (cV of cost criteria /total utility without cost criteria)						
Perphenazine						0.85
Risperidone						1.31
Ziprasidone						2.40
Quetiapine						2.68
Olanzapine						4.02
Incremental cost (e)/incremental utility (incremental cost per unit of utility gained)[c]						
Olanzapine-perphenazine						253.35

[a]BU indicates best utility; U, utility; W, weight WU, worst utility; cV, value of the measure of the criteria.
[b]The formula[15] for transforming cV into utility (U) is: U=100×(cV-WU)/(BU-WU).
[c]Difference between the cV of the cost criteria of the alternatives (e)/difference between the total utilities of the alternatives (without cost criteria).

Total Score for Each Drug

To establish the total utility of each AP we added the results of the utility to the weight of each criterion. A score is thus obtained for each of the AP.[14,15] The calculations are made using the SELMED computer programme[24] (Table 1).

The cost/utility of each AP (cost/difference between total score and the score corresponding to the cost criteria) and the incremental/incremental utility between alternatives (difference between costs/differences between utilities) were calculated. A sensitivity analysis was also performed with some of the measurements of the criteria.

RESULTS

Table 1 sets out the total scores obtained for each AP. The typical AP perphenazine obtained the best total utility score. The descending order of choice of the AP in terms of their utility is: perphenazine, 59.68; olanzapine, 52.98; risperidone, 51.53; ziprasidone, 46.42; and quetiapine, 45.41.

Perphenazine obtained a higher score in the cost, patient opinion, experience with use and pharmacokinetic criteria, and the worst score regarding the interaction criteria. Olanzapine has the highest utility score in efficacy, patient compliance, pharmacokinetics, and interactions parameters and the lowest in safety and cost.

Table 2. Calculation of Cost Criteria. Months of Treatment With Each Antipsychotic Drug in Stage 1 of CATIE[a]

Antipsychotic Drug	N	NM	N´	N´M	(NM+N´M)
Olanzapine	118	2124	210	1932	4056
Perphenazine	64	1152	192	1075.2	2227.2
Quetiapine	57	1026	269	1237.4	2263.4
Risperidone	87	1566	245	1176	2742
Ziprasidone	37	666	145	507.5	1173.5

[a]CATIE indicates clinical antipsychotic trials for intervention effectiveness; N, patients finishing stage 1[18]; NM, months of treatment with each antipsychotic drug corresponding to N (N×18 months)[13]; N´, patients interrupting the treatment in stage 1[18]; N´M, months of treatment with each antipsychotic drug corresponding to N´(N´olanzapine×9.2months; N´ perphenazine×5.6months; N´quetiapine×4.6 months; N´risperidone×4.8 months; N´ziprasidone×3.5 months).[13]

Risperidone is the best scored for safety and the worst in the opinion of the patient. Quetiapine obtained the lowest score for efficacy, as did ziprasidone for patient compliance and experience with use (Table 1).

Olanzapine total utility is slightly higher than perphenazine if the cost criteria are not taken into account, with scores of 47.78 and 47.18 respectively (Table 1). In Tables 2, 3, 4 and 5, and in Figure 1, we show the calculation of this parameter by intention to treat. Perphenazine has a monthly cost per patient of €39.99 and olanzapine of €192 (Table 5). Perphenazine has the highest score in this criterion due to its lower cost/day (Table 4); the costs of administering olanzapine and quetiapine, once the patients stopped the treatment with perphenazine in stage 1 of the CATIE study, represent 82.65% of the total assigned to this AP (Table 5). The lowest score of olanzapine is mainly due to its higher cost/day (Table 4), and the greater number of months of treatment in stage 1 (Table 2), the costs of these accounting for 90.69% of the total (Table 5).

Olanzapine has the highest cost per utility unit with a value of €4.02 and perphenazine the lowest with a value of €0.85 (Table 1).

Tabla 3. Calculation of Cost Criteria. Months of Treatment With Each Antipsychotic Drug During the 18 Months of the CATIE[a]

Treatment After Stage 1	Antipsychotic Drug Initially Assigned (Stage 1), No.				
	Olanzapine	Perphenazine	Quetiapine	Risperidone	Ziprasidone
Olanzapine	4056[b]	366	414	420	232
Perphenazine	20	2227.2[b]	13	31	0
Quetiapine	292	362	2263.4[b]	238	139
Risperidone	353	251	346	2742[b]	191
Ziprasidone	175	76	289	245	1173.5[b]
Fluphenazine	22	14	39	17	3
Aripiprazole	47	5	65	58	89
Clozapine	155	70	195	178	54
Total	5120	3371.2	3624.4	3929.0	1881.5

[a]CATIE indicates clinical antipsychotic trials for intervention effectiveness; No., total months of treatment with each AP.[18]
[b]Months of treatment with the initial antipsychotic drug in stage 1 (Table 2).

Table 4. Calculation of Cost Criteria. Daily Doses and Costs of the Antipsychotic Drugs Used in the Calculations

	Dose,[a] mg	Cost/Day,[b] €
Olanzapine	20.1	8.5
Perphenazine	20.8	0.09
Quetiapine	543.4	5.65
Risperidone	3.9	1.37
Ziprasidone	112.81	5.1
Fluphenazine	10	0.09
Aripiprazole	15	5.02
Clozapine	300	1.77

[a]The modal average doses of stage 1[13] are used. In the case of fluphenazine, the same daily cost as that of perphenaine has been used, as its oral form is not marketed in Spain and this presents similar pharmacological characteristics. The dose of aripipriazole and clozapine are the Defined Daily Doses.[3]
[b]The drugs marketed at their lowest Public Sale Price according to the Catalogue of Medications[3] have been considered.

The incremental cost per utility unit gained from switching to the perphenazine or olanzapine alternative is €253.35 (Table 1).

Olanzapine would have the same total utility as perphenazine if the measurement of the criteria was reduced to 72.97%, with a value of €51.9/month/patient, as is shown in the sensitivity analysis (Figure 2).

DISCUSSION

The standard procedure for a multi-attribute decision analysis used in this work is a method described in the literature for selecting drugs for use in hospitals.[14] It is an alternative to the classic cost-efficacy alternative when it is essential to take multiple factors into account to choose among several alternatives. In this method, the variation of the weights of each criterion, as well as their values on the utility scale, could change the total utility of each

Table 5. Calculation of Cost Criteria. Cost per Intention to Treat[a]

Treatment After Stage 1	Antipsychotic Drug Initially Assigned (Phase 1), C				
	Olanzapine	Perphenazine	Quetiapine	Risperidone	Ziprasidone
Olanzapine	57 460	5185	5865	5950	3286.67
Perphenazine	3	334.08	1.95	4.65	0
Quetiapine	2749.67	3408.83	21 313.68	2241.17	1308.92
Risperidone	806.02	573.12	790.03	6260.90	436.12
Ziprasidone	1487.50	646	2456.50	2082.50	9974.75
Fluphenazine	3.30	2.10	5.85	2.55	0.45
Aripiprazole	393.23	41.83	543.83	485.27	744.63
Clozapine	457.25	206.50	575.25	525.10	159.30
Total	63 359.97	10 397.46	31 552.09	17 552.14	15 910.84
Cost/pax	192	39.99	95.32	52.08	86.94

[a]C indicates monthly cost of each antipsychotic drug (€)=No. of months (Table 3)×30 days×daily cost (Table 4)/18 month; cost/pax, monthly cost/patient=C/No. patients assigned to each antipsychotic drug (Figure 1).

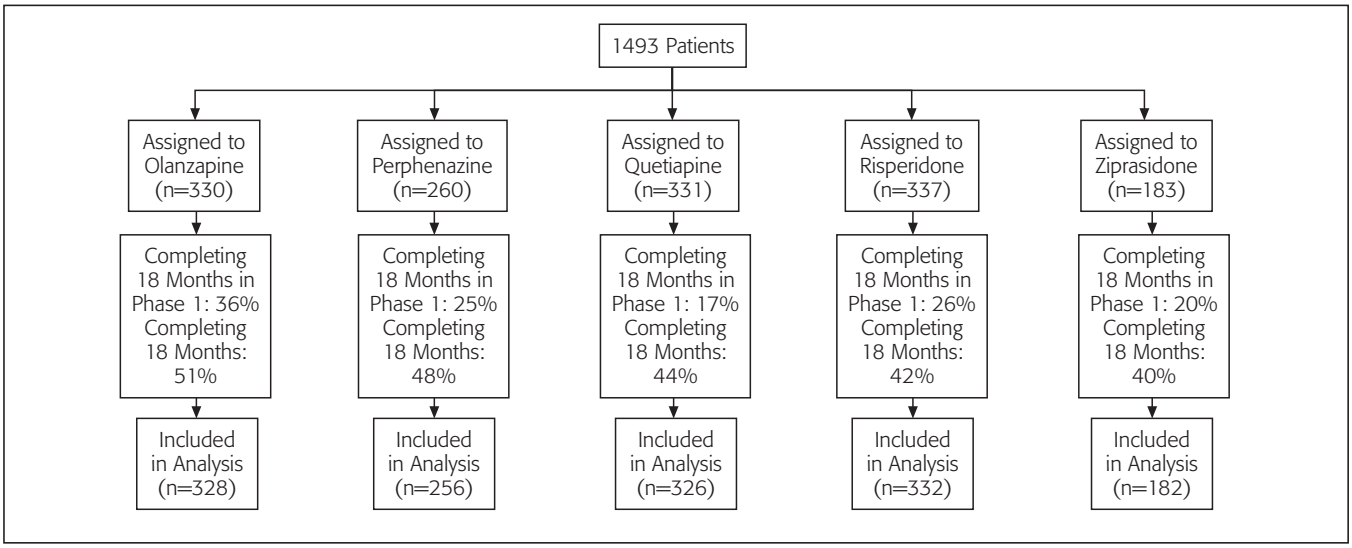

Figure. 1. *Progression of participation in the CATIE study. CATIE indicates clinical antipsychotic trials for intervention effectiveness.*

drug.[14] The weights assigned by default to the different evaluation attributes for the APs in this study have been obtained from the literature and classified according to their importance.[1] Two new criteria have been added—compliance and the opinion of the patient—as these measurements can be obtained from the CATIE study due to their importance in the treatment of schizophrenia.[13,18] Patient opinion, expressed in QALY, has been considered as a main attribute as the QALY are a measurement of the effect of the drugs used in the pharmacoeconomic analysis of cost-utility, with a score of 2 and not 3, as this is not a main criterion for evaluation in the CATIES clinical trial.

The results of this work are determined by the results of the CATIE[13] study with regard to the criteria with the greatest weight. The reasons justifying the CATIE clinical trial were the controversy existing in scientific literature with regard to the efficacy and safety superiority of the atypical APs in comparison to the typical ones,[4,6-11] and their high cost.[3] Almost one third of the total cost of treating schizophrenia can be attributed to APs in patients taking second generation APs.[25] In addition, this study was conducted in conditions similar to those in current practice. The efficacy of a typical AP was compared directly with all the new APs on the market at the moment, using interruption of treatment as the main criterion, a simple, common criterion in the treatment

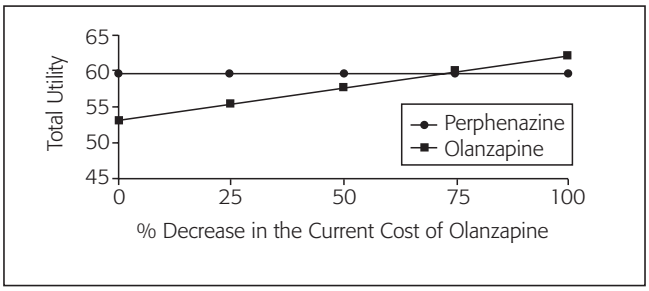

Figure 2. *Sensitivity analysis.*

of schizophrenia. The CATIE study was sponsored by the United States National Institute for Mental Health without any participation on the part of the pharmaceutical industry and, therefore, without the methodological bias attributed to the trials with AP in these cases.[4,26]

Perphenazine and olanzapine have very similar utility values if the cost criterion is not taken into consideration. Perphenazine is the drug with the highest score in this parameter and olanzapine has the lowest. This fact is due to the different monthly cost/patient of each AP (Table 5). In this study, in this criterion, only the direct costs by intention to treat attributable to the AP have been taken into consideration. The CATIE study also evaluates the costs of hospitalisation and external resources (excluding psychosocial rehabilitation services), and no significant differences were found in the proportion of patients, assigned to the different APs, receiving the different types of services, nor in their costs.[18] With regard to the cost/day of APs, perphenazine has a very low value (Table 4) as it is an old drug which has been available for 47 years (Table 1), while the other APs are still under patent, with the exception of risperidone, as generic drugs of which have now been on the market for a few years.[3] The marketing of generic drugs with olanzapine would change the results of this study, as can be seen in the sensitivity analysis (Figure 2). The higher number of months of treatment with olanzapine in stage 1 (Table 2), and as a consequence of the higher cost (Table 5), is shown in the higher score in the efficacy criteria and patient compliance (Table 1).

The doses of the APs used in the assessment of some of the parameters with the most weight in the study are those used in the CATIE study and may have influenced the results (Table 4) The daily doses of olanzapine, quetiapine, and ziprasidone were higher than their corresponding DDD, while perphenazine and risperidone were lower.[3] However, the doses used are based on the information supplied by the manufacturer of each drug and on the knowledge gained in clinical practice.[13] This fact could

be due to the fact that the doses authorised by the agencies responsible for approving the medicines in the different countries for their clinical use do not always coincide with the optimum therapeutic doses[27] and, on the other hand, the results could be influenced, as is the case of risperidone, which at doses of less than 6 mg is less likely to cause extrapyramical effects.[13] Risperidone is the best scored antipsychotic drug from the safety point of view (Table 1).

Perphenazine shows best utility score in the quality of life criterion. This parameter was quantified by the QALY by intention to treat, in the same way as the other studies on AP treatment of schizophrenia.[28] In this value the patient's state of health with regard to his symptoms and the side effects produced by the APs[18] are taken into consideration. To evaluate the symptoms, the Scale for Positive and Negative Symptoms in Schizophrenia was used (PANSS) to identify the symptoms and the patients' cognitive condition were used. Although there is some controversy regarding the psychopathological mediators of quality of life in schizophrenia, there seems to be consensus with regard to the impact on negative symptoms. The negative symptoms and the seriousness of the symptoms are responsible for the association established in different studies between the scores on the PANSS and quality of life scales.[29] In spite of its dosing lower than its DDD, and that this was chosen to reduce the possible extrapyramidal symptoms,[13] perphenazine has the best score (Table 1). In a study published with regard to schizophrenic patients whose treatment needed to be changed due to lack of response or adverse effects, the typical APs showed higher scores than the atypical on the quality of life scale chosen.[30]

One limitation of this study is that the results are applicable to chronic schizophrenic patients and not schizophrenics in their first episodes; however the first account for a high percentage of total patients. In an epidemiological psychiatric study conducted in Navarra a rate of subjects affected by recognisable schizophrenia of 0.52% of the general population aged 17 years or over.[31] In the literature published figures for first episodes of schizophrenia in a year are of 1.2-2.4 per 10 000 inhabitants of the general population (rate adjusted by age and referring to the population at risk).[31] Consequently, of the total schizophrenic population, between 2.31% and 4.62% are patients in their first episodes.

The results of this study are not applicable to patients presenting late dyskinesia as in the CATIE study it was avoided assigning perphenazine to patients suffering from this neurological effect.[13]

The atypical antipsychotic drug aripiprazole has not been included in the study as it was introduced into the market after the CATIE clinical trial started and, consequently, there is no data available to directly compare it with the other second generation antipsychotic drugs. After the atypical AP sertindole was launched, the General Directorate for Pharmacy and Health Products ordered its withdrawal from the market based on the risk of arrhythmia associated with its use and sudden deaths reported in patients treated with this medication.[32] In the year 2005, the European Union's Committee for Medicinal Products for Human Use (CHMP) allowed it to be marketed again, but an electrocardiogram is required before commencing treatment and regular controls must be performed during the treatment.[33] Finally, amisulphride, an old AP used since the year 1988 in France,[20] is starting to be considered "atypical" in the American literature,[34] although it has structural, pharmacological, and clinical characteristics similar to those of first generation sulpiride.[21] With regard to typical APs, the results of this study are only valid for perphenazine. Perphenazine causes fewer neurological effects than haloperidole, a typical AP commonly used as a comparative element in clinical trials with new APs. Conventional APs are a heterogeneous group of drugs with regard to their chemical structure and pharmacological properties, and mainly with regard to their incidence of side effects.[21,35]

In conclusion, typical AP perphenazine is the alternative of choice for the schizophrenic patient according to the method used. The second generation AP olanzapine also becomes an alternative when its monthly cost/patient decreases, a circumstance that is likely to occur as generic drugs of olanzapine coming onto the market. It would be interesting to conduct studies directly comparing first generation and atypical AP including not only aripiprazole but also AP with a low incidence of side effects.

References

1. Segú Tolsa JL. Elementos para la gestión del medicamento en los sistemas de salud: la visión de la microgestión. Módulo 5. Unidad Didáctica 1. Máster en Economía de la Salud y del Medicamento. Universidad Pompeu Fabra. Barcelona; 2005-2007.
2. Memoria económica. Servicio de Farmacia. Sagrat Cor, Serveis de Salut Mental. Martorell; 2006.
3. Catálogo de Medicamentos. Consejo General de Colegios Oficiales de Farmacéuticos: Madrid; 2006.
4. Gasto en medicamentos e innovación terapéutica. Butll Groc. 2004;17: 13-8.
5. Miyamoto S, Duncan GE, Marx CE, Lieberman JA. Treatment for schizophrenia: a critical review of pharmacology and mechanisms of action of antipsychotic drugs. Mol Psychiatry. 2005;10:79-104.
6. Rosenheck R, Perlick D, Binghan S, Liu-Mares W, Collins J, Warren S, et al. Effectiveness and cost of olanzapine and haloperidol in the treatment of schizophrenia: a randomized controlled trial. JAMA. 2003;290:2693-702.
7. Tollefson GD, Sanger TM. Negative symptoms: a path analytic approach to a double-blind, placebo-and haloperidol-controlled clinical trial with olanzapine. Am J Psychiatry. 1997;154:466-74.
8. Leucht S, Walhlbeck K, Haman J, Kissling W. New generation antipsychotics versus low-potency conventional antipsychotics: a systematic review and meta-analysis. Lancet. 2003;361:1581-9.
9. Davis JM, Chen N, Glick ID. A meta-analysis of the efficacy of second-generation antipsychotics. Arch Gen Psychiatry. 2003;60:553-64.
10. Halliday J, Farrington S, McDonald S, McEvan T, Sharkey V, McCreadie R. Nithsdale schizophrenia surveys 23: movement disorders, 20 year review. Br J Psychiatry. 2002;181:422-7.
11. Rochon PA, Stukel TA, Sykora K, Gill S, Garfinkel S, Anderson GM, et al. Atypical antipsychotics and parkinsonism. Arch Intern Med. 2005;165:1822-88.
12. Nasrallah HA, Newcomer JW. Atypical antipsychotics and metabolic dysregulation. Evaluation the risk/benefit equation and improving the standard of care. J Clin Psychopharmacol. 2004;24:S7-S14.
13. Lieberman JA, Stroup TS, McEvoy J, 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.

14. Ordovás JP, Climente M, Poveda JL. Selección de medicamentos y guía farmacoterapéutica. Available from: htpp://sefh.interguias.com /libros/Tomo1_Cap1-3-1-1.pdf
15. Martínez-Bengoechea MJ, Viniegra A, Saiz de Rozas C, Arana A, Ibarra O, García MG. Criterios de selección de medicamentos para su inclusión en una guía farmacoterapéutica. Elección y ponderación. Farm Hosp. 1996;20(1):60-5.
16. Stroup TS, Lieberman JA, McEvoy J, Swartz MS, Davis SM, Rosenheck RA, et al. Efectiveness 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.
17. McEvoy J, Lieberman J, Stroup TS, Davis SM, Meltzer HY, Rosenheck RA, et al. Effectiveness of clozapine versus olanzapine, quetiapine, and risperidone in patients with chronic schizophrenia who did not respond to prior atypical antipsychotic treatment. Am J Psychiatry. 2006;163:600-10.
18. Rosenheck R, Leslie D, 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.
19. Departamentos Técnicos de los laboratorios farmacéuticos Astra Zeneca Janssen, Lilly, Merck Farma y Química y Pfizer. Barcelona; 2007.
20. Salazar M, Peralta C, Pastor J. Tratado de psicofarmacología. Bases y aplicación clínica. Madrid: Médica Panamericana; 2005.
21. The Royal Pharmaceutical Society of Great Britain. Martindale: The complete drug reference. London; 2005.
22. Mallol J, Sureda FX editors. Stockley. Interacciones farmacológicas. Barcelona; 2004.
23. Richard B editor. The Medical Letter on Drugs and Therapeutics: Compendio de interacciones adversas de medicamentos. Barcelona; 2002.
24. Martínez-Bengoechea MJ, Ibánez-Carranza JC, Arrizabalaga MJ. Computer program for pharmacy and therapeutics Commites'drug evaluations. PWS. 1996;18 5Suppl A: A25.
25. Freedman R, Carpenter WT, Davis JM, Goldman HH, Tamminga CA, Thomas M. The cost of drugs for schizophrenia. Am J Psychiatry. 2006;163:2029-31.
26. Peralta V. Ensayos clínicos, industria farmacéutica y práctica clínica. Bol Inf Ter de Navarra. 2005;13(4):29-34.
27. Davis JM, Chen N. Dose response and dose equivalence of antipsychotics. J Clin Psychopharmacol. 2004;24:192-208.
28. Polsky D, Doshi JA, Bauer MS, Glick H. Clinical trial-based cost-effectiveness analyses of antipsychotic use. Am J Psychiatry. 2006;163: 2047-56.
29. Baca E, Cervera S, Cuenca E, Giner J, Leal C, Vallejo J editores. Trastornos psicóticos. Barcelona: Grupo Ars XXI de Comunicación; 2007.
30. Jones PB, Barnes T, Davies L, Dunn G, Lloyd H, Hayhurst KP, et al. Randomized controlled trial of the effect on quality of life of second- vs first-generation antipsychotic drugs in schizophrenia. Cost utility of the latest antipsychotic drugs in schizophrenia study (CUtLASS 1). Arch Gen Psychiatry. 2006;63:1079-87.
31. Mata I, Beperet M, Madoz V y grupo Psicost. Nuevas perspectivas en la psicopatología de los trastornos esquizofrénicos. Anales del Sistema Sanitario de Navarra. 23(1). Available from: htpp://www.cfnavarra.es/ salud/anales/tex-tos/vol23/suple1/suple 3ª.htlm.
32. Anónimo. Retiradas recientes de medicamentos. Butll Groc. 1999;12: 5-8.
33. Sertindol vuelve al mercado español tras probar su seguridad cardiovascular. Available from: htpp://www.correofarmaceutico. com/rec-templating/templates/co-rreo_farmaceutico/cmp/view Document_CF.jsp
34. Leucht S, Pitschel-Walz G, Engel R, Kissling W. Amisulpride, an usual "atypical" antipsychotic: a meta-analysis of randomized controlled trials. Am J Psyciatry. 2002;159:180-90.
35. Calderón P, Gutiérrez JR, Velasco JJ. Psiquiatría. Available from: htpp://sefh.interguias.com/libros/Tomo2_Cap18.pdf