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Pharmacoeconomic analysis of the treatment of schizophrenia with quetiapine, olanzapine, risperidone or haloperidol in Spain

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Summary

The study objective was to compare the costs of the treatment of schizophrenia with quetiapine (QUE), olanzapine (OLA), risperidone (RIS) or haloperidol (HAL) and those of the secondary effects (SE) associated. A cost-effectiveness analysis, using a Markov process, was used. The time horizon was 12 months. The study population comprised Spanish adult schizophrenic patients. The NHS perspective was taken (direct costs). The costs of several SE of medication were analysed. Use of resources and costs were calculated following the recommendations of the Spanish Psychiatric Society and other sources.

The monthly rates of the onset of SE with each medicine were calculated using a meta-analysis and systematic review of the literature.

A simple univariate sensitivity analysis was performed. QUE is as efficacious as OLA and RIS, but apparently leading to fewer cases of extrapyramidal syndrome and sexual dysfunction, with lower costs. QUE is better tolerated than HAL, but with higher costs.

Key words: pharmacoeconomic analysis, schizophrenia, quetiapine, olanzapine, risperidone, haloperidol, Spain

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Introduction

Schizophrenia (SCH) is a severe psychotic disorder whose prevalence varies according to the literature, but which is usually around 1%[1,2]. The natural history of the disease involves three phases: the acute phase (intense onset of symptoms), the stabilisation phase and the stable phase[1]. The characteristic symptoms of SCH can be divided into two groups: positive (hallucinations, delirious ideas) and negative or deficit (scarce emotional expression, apathy)[1]. These clinical characteristics are often associated with social adaptation problems and inability to work[1].

According to an economic study carried out in 1994 in Navarra, the annual cost of a schizophrenic patient was e7,395 during the first year after diagnosis, e5,561 during the second year (75.2%) and e4,000 during the third year (54.1%)[3]. The direct costs represented 46.7%, 34.7% and 42.9%, respectively, and informal care represented 36%, 40% and 42%, respectively, of total costs. Lastly, indirect costs, mainly those stemming from the loss of productive capacity of the patients, reached 16%, 24% and 14% during each of the first 3 years[3].

According to the Expert Committee of the Spanish Psychiatric Society, pharmacological treatment of an acute psychotic episode should be with atypical antipsychotics (such as risperidone (RIS), clozapine (CLO) or olanzapine (OLA)) or with conventional (typical) antipsychotics, which are highly potent (such as haloperidol (HAL))[4].

Quetiapine (QUE) is an atypical antipsychotic that blocks dopamine D_1 and D_2 receptors and serotonin 5-HT_2 receptors[5]. As with RIS, CLO and OLA, the antipsychotic QUE is efficacious in SCH that is resistant to typical antipsychotics (phenothiazines, butyrophenones, thioxanthenes and orthopramides) and, unlike the others, produces fewer extrapyramidal effects (parkinsonism, akathisia, acute dystonia, etc)[6]. Nevertheless, atypical antipsychotics are more expensive than conventional antipsychotics [7].

This study aims to evaluate and compare the cost-effectiveness of treating SCH with QUE, OLA, RIS and HAL, and that of the secondary effects (SE) of these drugs in Spain.

Methods

Pharmacoeconomic model

The study uses a pharmacoeconomic model, which is understood as a theoretical schema allowing simulations to be made of complex healthcare processes related to medication. This schema is prepared following a previously established protocol, using estimations from available data (published or not) on the efficacy, toxicity, and costs of the alternatives compared. To do this, we used a Markov process[8] with a structure similar to that of a previously published model comparing the healthcare results and costs of SCH therapy with RIS and OLA in the USA[9] (Figure 1). The Markov model was analysed using the software package DATA 3.5 for Healthcare from TreeAge.

Target population

This is the hypothetical group of patients on which the theoretical analysis was carried out and, therefore, the population to which the results of the study can be applied. The target

population was composed of Spanish adults suffering from SCH.

Study type: cost-effectiveness analysis

The type of pharmacoeconomic analysis to be performed depends on whether there are proven differences in efficacy or toxicity between the treatments. Consequently, we attempted to find all the comparative clinical trials carried out with these drugs by a bibliographic search of MEDLINE up to March 2004 and by consulting several systematic reviews and meta-analyses of SCH therapy published by the National Coordinating Centre for Health Technology Assessment in the UK[10], the Cochrane Library[11–14] or by using independent investigators[15–17].

QUE has been compared with placebo and with HAL in at least four[18–21] and six [22–27] randomised clinical trials, respectively. There is only one comparative clinical trial of QUE and RIS, the QUEST study[28], which lasted 4 months. In this study both treatments had similar efficacy, with the exception of symptoms of depression, which improved to a greater extent with QUE. To our knowledge, QUE and OLA have never been compared in a randomised controlled clinical trial[10]. The relative adverse event rates are therefore based only on one meta-analysis of indirect placebo-controlled comparisons, according to the approach of the National Coordinating Centre for Health Technology Assessment in the UK[10].

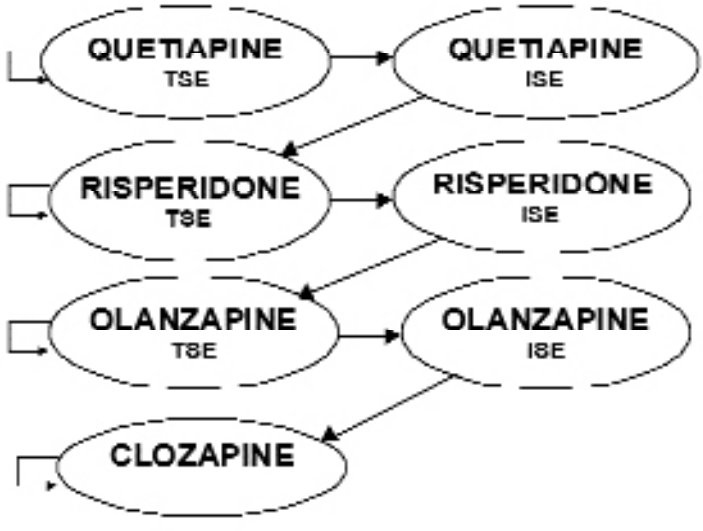
The model adopted a series of premises that are summarised in Table 1[4,6,9,15–17,29–34]. The main premise was to consider that no (clinically relevant) differences in efficacy have been proven between the treatments compared, an assumption that has been validated both by the QUEST study and by most systematic reviews and meta-analyses consulted[6,11–17], and which was the one used in the pharmacoeconomic analysis quoted above[9]. From these studies, we can deduce that there is no evidence that atypical antipsychotics are more efficacious than conventional antipsychotics in the control of SCH symptoms[15] and that the efficacy of QUE is similar to that of other atypical antipsychotics[16] and that of HAL[17]. No other possible parameters of evaluation of efficacy were considered, such as visits to the emergency room or suicides, because they were not primary variables in the clinical trials and therefore they were not collected in the systematic reviews[10–17].

Nevertheless, there is some evidence that atypical antipsychotics might produce less toxicity than conventional antipsychotics[15]. Furthermore, in the QUEST study, the probability of extrapyramidal syndrome (EPS), in particular parkinsonism, akathisia and dystonia, was lower with QUE than with RIS ($p < 0.001$)[28]. For this reason, as no differences in efficacy were proven, we decided to carry out a cost-effectiveness analysis by obviating efficacy and considering only the differences in SE and two types of costs: those stemming from the SE and the purchase costs of the antipsychotics.

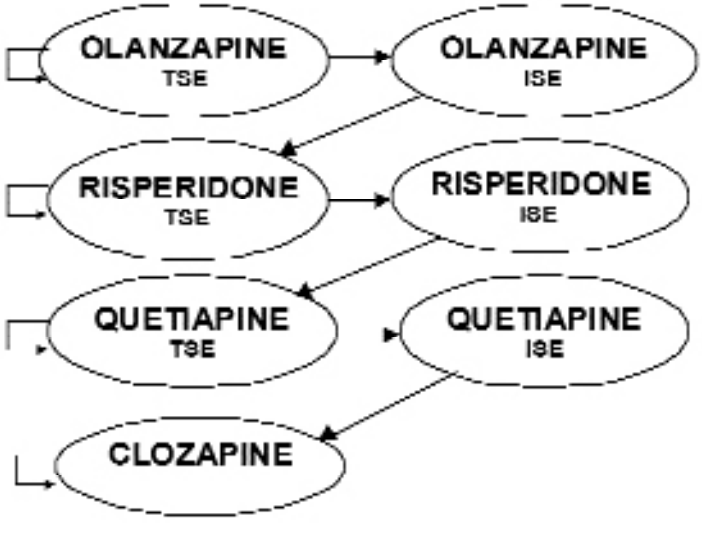
For each combination (QUE/OLA, QUE/RIS and QUE/HAL), we calculated the number of patients it would be necessary to treat (NNT) with QUE in order to avoid the onset of SE with each of the treatments, cost differences and the incremental cost-effectiveness, that is the cost of avoiding an

Figure 1. Markov's pharmacoeconomic model for schizophrenia. Initiation of therapy of the psychotic episode with (a) quetiapine, (b) olanzapine (c) risperidone and (d) haloperidol

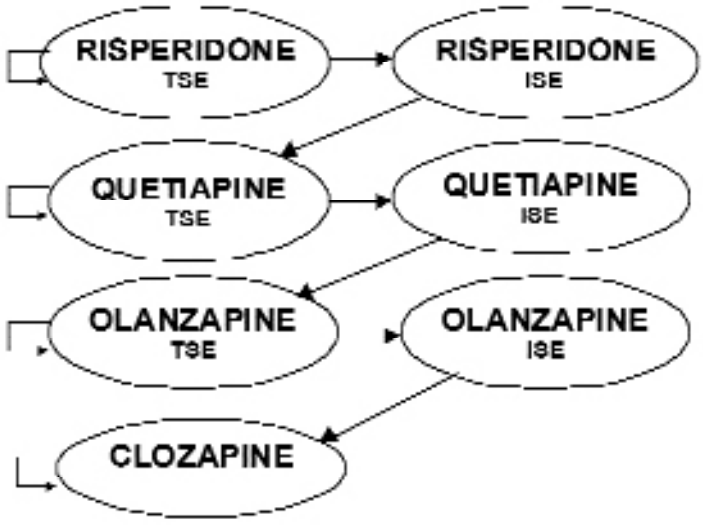
(a)



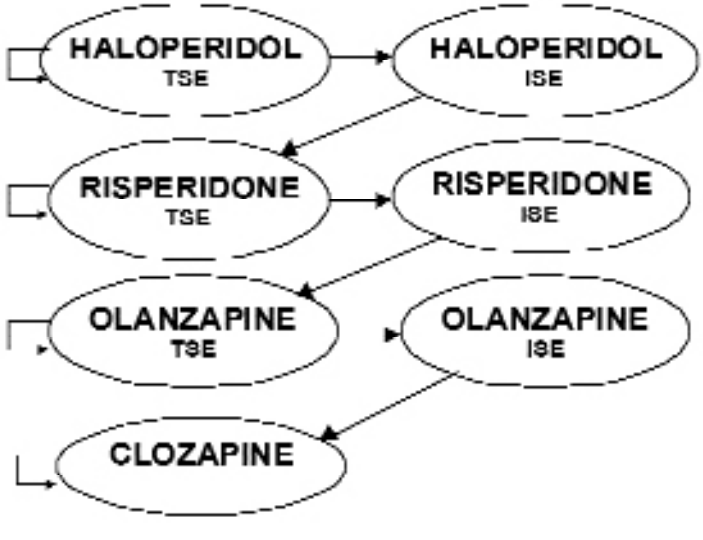
(b)



(c)



(d)



TSE, tolerable secondary effects; ISE, intolerable secondary effects.

episode of SE with QUE (as long as it is the best tolerated treatment).

States of health

SCH was modelled using a hypothetical cohort of adult patients who had experienced an acute psychotic episode treated with an antipsychotic. The patients were treated initially with QUE, OLA, RIS or HAL. If a specific patient had tolerable SE (TSE) during one cycle (and, of course, an adequate response), he or she would continue with the same treatment during the following cycle. If, on the other hand, the patient suffered from intolerable SE (ISE), treatment was changed: patients with ISE related to QUE, OLA or HAL changed to RIS, and those treated with RIS changed to QUE. 'Failures' due to the appearance of ISE with second-line treatments underwent a new change in treatment: those on RIS changed to OLA, except when this was the initial treatment, in which case they changed to QUE. ISE with the third-line antipsychotic were treated with CLO (Figure 1). These permitted transitions in the model were calculated using the recommendations of the Spanish Psychiatric Society[4] and the Clinical Practice Guidelines for attending patients with SCH from the AATRM of Catalonia[29] (Table 1).

According to the information above and as was the case with previous studies[9,35], the following states of health were considered: (i) TSE of treatment of the psychotic episode with QUE, OLA, RIS or HAL; (ii) ISE of treatment of the psychotic episode with QUE, OLA, RIS or HAL; and (iii) final absorbent state in treatment with CLO (Figure 1). The SE of the antipsychotics included in the model were as follows: (i) EPS requiring treatment (parkinsonism, akathisia and dystonia); (ii) sexual dysfunction associated with hyperprolactinaemia (SDH) (reduction in libido, anorgasmia and erection or ejaculation problems); (iii) clinically relevant weight gain (WG) (≥7% of baseline weight); and, lastly, (iv) recent type 2 diabetes mellitus (DM2). As in other studies[9,35], these ISE were considered according to their clinical relevance and impact on therapeutic effects or compliance with antipsychotic therapy[1,4,29,32–34].

Duration of cycles and time horizon

The transitions between states were made in discrete time periods known as 'cycles', which in the study had a duration of 1 month owing to the fact that the efficacy of antipsychotics is evaluated at 3–6 weeks from the start of treatment[4,29] and in the same way as in other previously published models of SCH[9,30]. Given the shortness of the cycle and the fact that none of the SE considered would lead per se to death, the state of 'death' was not taken into consideration.

As occurs in other studies[9,30], the time horizon of the simulation was 12 months owing to the fact that the maximum duration of most of the clinical trials reviewed was no more than 6 months of treatment[10,33–45]. Consequently, a simulation was made of a cohort for 12 x 1-month cycles, and it was not necessary to discount costs or benefits. Costs were counted half way through each cycle.

Probabilities of transition

Each state of health is associated with probabilities of transition to the other states and with costs. Table 2 shows the occurrence rates of SE observed during therapy of SCH with antipsychotics that are under comparison for periods of time ranging from 1.5 to 6 months. These rates were calculated using a

Table 1. Main premises and estimations considered in a pharmacoeconomic model of the treatment of schizophrenia for 1 year with an initial regimen of quetiapine (QUE), olanzapine (OLA), risperidone (RIS) and haloperidol (HAL)

Item	Estimations, premises	References
1. Difference in efficacy between QUE and OLA	Not proven	9,10,15
2. Difference in efficacy between QUE and RIS	Not proven	6,9,28
3. Difference in efficacy between QUE and HAL	Not proven	9,16,15,17
4. States of health in schizophrenia	Tolerable secondary effects (QUE, OLA, RIS, HAL) Intolerable secondary effects (QUE, OLA, RIS, HAL) Treatment with CLO	4,9,29,30
5. Co-adjuvant treatment of the antipsychotic to treat insomnia and restlessness	Lorazepam (2 mg/day, po)	4
6. Hospital visits after an acute episode	One hospital visit	4
7. Follow-up visits (primary healthcare)	One every 4 weeks	4
8. Analysis after an acute episode	One drug detection analysis and one general analysis with complete haemogram	4
9. Treatment of symptoms of EPS	Biperiden (2–12 mg/day, po)	31
10. Extraordinary visits due to an episode of EPS, SDH and WG healthcare	One in primary healthcare (EPS, SDH) to 50% (WG)	estimate One in primary
11. Change of treatment due to EPS, SDH, WG and DM2	6%, 14%, 33% and 45%, respectively	9,32–34
12. Change of antipsychotic due to intolerable secondary effects	QUE for RIS, OLA or CLO OLA for RIS or CLO RIS for QUE or OLA HAL for RIS	4
13. Extraordinary visits due to an episode of DM2	Two in primary healthcare	estimate
14. Treatment of DM2	Metformin (850–2,550 mg/day po)	31

CLO, clozapine; po, orally; EPS, extrapyramidal syndrome; SDH, sexual dysfunction associated with hyperprolactinaemia; WG, weight gain; DM2, type 2 diabetes mellitus.

meta-analysis of randomised clinical trials carried out with QUE, OLA, RIS and HAL and using a systematic review from the UK National Health Service[10,18–27,33–45].

The monthly probabilities of transition (Table 3) were calculated by the formula $p_t = 1-e^{-rt}$, with e as the base of the natural logarithm and r the rate of the event in a time t[46].

Study perspective and guidelines followed

The study was carried out from the perspective of the Spanish National Health System and, therefore, only considered direct healthcare costs.

We followed the general guidelines for the performance of pharmacoeconomic analyses in Spain[47] as well as the guidelines published by the Canadian Coordinating Office for Health Technology Assessment (CCOHTA)[48] and the principles of good modelling practice from the International Society for Pharmacoeconomics and Outcomes Research (ISPOR)[49].

Cost calculation

The costs of a condition treated with a specific drug are calculated by identifying and quantifying the healthcare resources involved and by assigning specific unit costs to the resources. In this way, the mean costs per typical patient with an acute episode of SCH who received therapy with QUE, OLA, RIS or HAL were calculated. The costs of healthcare resources used in the model are shown in euro (e) at 2003 values.

Unit costs

The unit costs of the healthcare resources considered in the analysis are shown in Table 4. The cost of antipsychotics, concomitant therapy (lorazepam) and the treatment of their SE (biperiden, metformin) are estimated using the purchase price and posologies recommended in the product monographs of the pharmaceutical formulation[5,7]. The doses for treatment of the psychotic episode were: (i) QUE: 50, 100, 200 and 300 mg, orally (po), on days 1, 2, 3 and 4, respectively, followed by 300–450 mg/day, po; (ii) OLA: 10 mg initially, followed by 5–10 mg/day, po; (iii) RIS: 2 mg and 4 mg, po, on days 1 and 2, followed by 4–6 mg/day, po; and (iv) HAL: 15–30 mg/day, po, for 2 months, followed by maintenance therapy with 1–15 mg/day, po. The costs of the medical visits, analysis for the detection of drugs of abuse and routine haemograms recommended by the guidelines of the Spanish Psychiatric Society[4] were obtained from the Soikos database of healthcare costs[50] (Table 4).

Costs of states of health

As previously mentioned, the cost of the state of health is composed of two types of costs: those stemming from the ISE (if any) and the purchase costs of the antipsychotics.

The cost of the state with TSE was calculated taking into account the fact that the Spanish Psychiatric Society recommends, after an acute psychotic episode, administering a benzodiazepine such as lorazepam to treat insomnia and restlessness, a hospital visit after discharge, outpatient visits every 4 weeks, testing to detect drugs of abuse and a general analysis with a complete haemogram[4]. If there are ISE, the costs incurred from the previous resources would have to be increased by those from the treatment of the ISE (EPS, SDH, WG and DM2). EPS was assumed to lead to one medical visit in primary healthcare (PH)[4] and is treated with biperiden (2–12 mg/day, po)[51]. Similarly, it was thought that SDH and WG would generate an extraordinary visit in PH[4], that DM2 would lead to two visits and that an oral antidiabetic (metformin, 850–2,250 mg/day, in one to three doses, po) would be prescribed[51]. The costs of states of health thus obtained for each treatment are shown in Table 5.

Sensitivity analysis

All the calculations considered in the previous paragraphs made up the basic case of the study (with the average values of the probabilities of transition and the costs of the states of health). To check the stability of the results and the consistency of the calculations

Table 2. Estimated probabilities of the occurrence of secondary effects after treatment of schizophrenia with quetiapine (QUE), risperidone (RIS), olanzapine (OLA) and haloperidol (HAL)[a]

Item	QUE		RIS		OLA		HAL		Duration of treatment (months)	References
	Basic case	Interval	Basic case	Interval	Basic case	Interval	Basic case	Interval		
Secondary effects[b]	0.586	0.562–0.602	0.535	0.515–0.542	0.224	0.205–0.450	0.668	0.583–0.793	6	10
EPS (requiring treatment)[b]	0.098	0.069–0.110	0.257	0.243–0.310	0.182	0.147–0.182	0.394	0.351–0.432	6	10
SDH[c]	0.182	0.000–0.272	0.432	0.300–0.600	0.353	0.167–0.470	0.460	0.460–0.720	1.5	33,36–38
Weight gain (≥ 7%)[d]	0.230	0.135–0.556	0.306	0.237–0.534	0.457	0.067–0.457	0.224	0.160–0.400	1.5	34,39–41
Type 2 diabetes mellitus[e]	0.024	0.010–0.039	0.021	0.021–0.130	0.024	0.021–0.110	0.066	0.080–0.163	6	42–45

EPS, extrapyramidal syndrome; SDH, sexual dysfunction associated with hyperprolactinaemia.

[a]It was assumed that the probabilities refer to the specified duration of treatment, taking into account the duration of most of the studies reviewed: 6 months for total adverse reactions and EPS; 1.5 months for hyperprolactinaemia and weight gain; 6 months for diabetes mellitus.

[b]We considered the average rate of appearance of the secondary effects of EPS (parkinsonism, akathisia and dystonia) and five of the most frequently observed secondary effects with antipsychotics (constipation, dizziness, dryness of the mouth, postural hypotension and insomnia) in all of the randomised clinical trials reviewed in the meta-analysis of the UK National Health Service[10]. For HAL, the average rate of the same secondary effects observed in the comparative clinical trials with QUE and RIS was considered. Interval: the minimum and maximum values obtained in the subanalyses comparing the treatments (QUE, RIS, HAL) with placebo or other typical or atypical antipsychotics were established[10].

[c]We considered the rates of appearance of the main disorders associated with hyperprolactinaemia (reduction of libido, anorgasmia, erection or ejaculation problems). In the basic case, the values used were those of the study by Bobes *et al*[33]. The extreme values were determined using those observed in a clinical trial that compared QUE and RIS[36], in the HAL studies[37], in a report that evaluated

made, a simple univariate sensitivity analysis was carried out that took the minimum and maximum values of the probabilities of transition between states (Table 3) and of the costs of these values (Table 5).

Results

NNT

The NNT with QUE to avoid an episode of EPS, SDH and WG with OLA is 12.0, 5.8 and 4.4 patients, respectively, and with RIS it is 6.3, 4.0 and 12.6 patients, respectively. To avoid an episode of EPS and SDH with HAL, 3.4 and 12.6 patients must be treated with QUE (Table 6). No differences were observed in the rate of recent DM2 with OLA or RIS, or in WG with

Table 3. Monthly probabilities of transition used in the Markov model[a]

Result	Case	QUE	RIS	QUE–RIS[b]	OLA	QUE–OLA[b]	HAL	QUE–HAL[b]
Total adverse reactions	Basic	0.0930	0.0853	0.0077	0.0366	0.0564	0.1053	–0.0123
	Minimum	0.0894	0.0822	0.0072	0.0335	0.0559	0.0926	–0.0032
	Maximum	0.0954	0.0863	0.0091	0.0722	0.0232	0.1238	–0.0284
EPS with treatment	Basic	0.0162	0.0419	–0.0257	0.0298	–0.0136	0.0635	–0.0473
	Minimum	0.0114	0.0396	–0.0282	0.0242	–0.0128	0.0568	–0.0454
	Maximum	0.0181	0.0503	–0.0322	0.0298	–0.0117	0.0694	–0.0513
SDH	Basic	0.1142	0.2502	–0.1360	0.2096	–0.0954	0.2641	–0.1499
	Minimum	0.0000	0.1812	–0.1812	0.1053	–0.1053	0.2641	–0.2641
	Maximum	0.1658	0.3296	–0.1638	0.2689	–0.1031	0.3812	–0.2154
Weight gain ≥7%	Basic	0.1421	0.1845	–0.0424	0.2626	–0.1205	0.1387	0.0034
	Minimum	0.0860	0.1461	–0.0601	0.0437	0.0423	0.1012	–0.0152
	Maximum	0.3097	0.2995	0.0102	0.2626	0.0471	0.2341	0.0756
Type 2 diabetes mellitus	Basic	0.0039	0.0035	0.0004	0.0039	0.0000	0.0109	–0.0070
	Minimum	0.0016	0.0035	–0.0019	0.0035	–0.0019	0.0132	–0.0116
	Maximum	0.0064	0.0214	–0.0150	0.0181	–0.0117	0.0268	–0.0204

QUE, quetiapine; RIS, risperidone; OLA, olanzapine; HAL, haloperidol; EPS, extrapyramidal syndrome; SDH, sexual dysfunction associated with hyperprolactinaemia.

[a]Calculation of the probabilities of transition according to the formula: $p_t = 1–e^{–rt}$, where e is the base of the natural logarithm and r is the rate of the event in a time t.

[b]Negative differences indicate that, with QUE, there would be fewer adverse effects than with RIS, OLA or HAL, in contrast to the positive differences.

HAL.

Cost analysis

The approximate annual cost per patient treated initially with QUE, OLA, RIS or HAL was calculated at e1,300, e1,911, e1,493 and e286, respectively (Tables 7–9). Consequently, in the basic case, treatment with QUE would imply fewer expenses than with OLA and RIS, with savings of e611 and e193 per year per patient, respectively. Compared with HAL, the best tolerance of QUE would have an additional cost per patient of e1,014 per year (Table 9).

Cost-effectiveness analysis

Compared with OLA and RIS, QUE was the dominant treatment (better tolerated and with lower costs) as far as avoiding EPS, SDH and WG was concerned (Tables 7 and 8).

The approximate annual cost of avoiding an episode of EPS, SDH and DM2 was e3,425, e3,647, and e24,140, respectively, with QUE versus HAL (Table 9).

Sensitivity analysis

Table 4. Unit costs assigned to resources in the pharmacoeconomic model

Resource	Unit cost (e)[a] (minimum–maximum)	Reference
Quetiapine		
Seroquel® (25 mg x 6 tabs)	4.99	7
Seroquel® (100 mg x 60 tabs)	95.86	7
Seroquel® (200 mg x 60 tabs)	138.54	7
Seroquel® (300 mg x 60 tabs)	193.29	7
Risperidone		
Risperdal® (1 mg x 20 tabs)	17.55	7
Risperdal® (1 mg x 60 tabs)	50.77	7
Risperdal® (3 mg x 20 tabs)	50.65	7
Risperdal® (3 mg x 60 tabs)	140.37	7
Risperdal® (6 mg x 30 tabs)	140.37	7
Risperdal® (6 mg x 60 tabs)	234.01	7
Risperdal® (oral solution 1 mg/ml, 30 ml)	25.91	7
Risperdal® (oral solution 1 mg/ml, 100 ml)	84.71	7
Haloperidol		
Haloperidol Esteve® (50 mg x 50 tabs)	1.24	7
Haloperidol Prodes® (drops, 2 mg/ml, 15 ml)	1.52	7
Haloperidol Esteve® (drops, 2 mg/ml, 15 ml)	1.52	7
Haloperidol Prodes® (drops, 2 mg/ml, 30 ml)	2.76	7
Haloperidol Esteve® (drops, 2 mg/ml, 30 ml)	2.70	7
Haloperidol Esteve® (10 mg x 30 tabs)	3.40	7
Haloperidol Prodes® (10 mg x 30 tabs)	3.49	7
Olanzapine		
Zyprexa® (5 mg x 28 tabs)	74.90	7
Zyprexa® (10 mg x 28 tabs)	140.24	7
Clozapine		
Leponex® (25 mg x 40 tabs)	8.38	7
Leponex® (100 mg x 40 tabs)	25.75	7
Lorazepam		
Lorazepam Medical® (1 mg x 30 tabs)	1.72	7
Lorazepam Medical® (5 mg x 20 tabs)	1.83	7
Biperiden		
Akineton® (2 mg x 20 tabs)	1.79	7
Akineton® (4 mg x 50 tabs)	3.80	7
Akineton® (5 mg x 28 tabs)	74.9	7
Metformin		
Dianben® (850 mg x 50 tabs)	2.78	7
Other healthcare resources		
External psychiatric visit[b]	48.19 (29.35–85.00)	50
Outpatient medical visit[b]	7.91 (5.38–13.90)	50
Detection of drugs of abuse[b]	14.77 (11.76–17.18)	50
Complete haemogram with differential[b]	12.18 (9.35–15.29)	50

[a]Medication costs are Retail sale price + 4% VAT.

[b]Soikos database of healthcare costs, 2004[50].

Compared with OLA, QUE was the dominant treatment when the maximum values of EPS, SDH and DM2 were considered. With the minimum values, OLA was the dominant treatment in WG, and the cost of avoiding an episode of SDH with QUE was e1,079. In the same scenario, the cost of avoiding an episode of EPS or SDH with QUE was e2,309 and e1,079, respectively (Table 7).

Compared with RIS, QUE was the dominant treatment when minimum values were considered. In the same comparison and in the scenario of maximum values, the cost per episode of EPS, SDH and DM2 avoided with QUE was e165, e101 and e363, respectively. Nevertheless, when maximum values were considered with WG, RIS was the dominant treatment (Table 8).

Compared with HAL, the approximate cost per episode of EPS, SDH and DM2 avoided with QUE was e3,687–4,113, e2,261–2,956 and e10,679–14,855, respectively. When minimum and maximum values were considered with WG, the cost per episode avoided with QUE was e41,594 and HAL was dominant, respectively (Table 9).

Discussion

In accordance with the results of a systematic review, it is assumed that there is similarity of efficacy for QUE, OLA and RIS in the treatment of SCH, although with the first of these drugs there are fewer EPS, fewer SDH and less WG than with OLA and RIS, with lower costs. The three treatments are better tolerated than HAL, but they are more expensive.

In the evaluation of these results, we must take into account a series of limitations and strengths of the study. First, this is a theoretical model (by definition, a simplified simulation of reality) based on the results of non-pragmatic

Table 5. Costs of states of health in the Markov model (including the different purchase costs of antipsychotics) after 1 month of therapy (at 2003 euro (€) values)

State	Case	QUE	RIS	QUE–RIS[a]	HAL	QUE–HAL[a]	OLA	QUE–OLA[a]	CLO[b]
Tolerable secondary effects	Basic	118.01	136.02	–18.01	23.36	94.65	173.95	–55.94	—
	Minimum	109.10	114.23	–5.13	12.49	96.60	92.67	16.43	—
	Maximum	171.61	168.45	3.16	45.97	125.64	182.83	–11.22	—
Intolerable secondary effects	Basic	119.77	139.37	–19.60	27.07	92.70	177.13	–57.36	—
	Minimum	109.43	115.93	–6.50	14.76	94.67	93.57	15.86	—
	Maximum	176.61	176.72	–0.11	55.03	121.58	189.50	–12.89	—
Treatment with CLO	Basic	—	—	—	—	—	—	—	36.99
	Minimum	—	—	—	—	—	—	—	30.69
	Maximum	—	—	—	—	—	—	—	45.87

QUE, quetiapine; RIS, risperidone; HAL, haloperidol; OLA, olanzapine; CLO, clozapine.

[a]Negative values indicate a lower cost of state of health with QUE compared with RIS, HAL or OLA, in contrast to positive values.

[b]The state 'treatment with clozapine' is terminal and only includes the purchase price of the antipsychotic, not the cost arising from secondary effects.

clinical trials, therefore its results must be considered as calculations for a typical patient, which may be useful as a tool for making clinical decisions[8]. Second, it must be remembered that the short duration (1.5–6 months) of clinical trials with the necessary data for the model made it necessary to perform a simulation of the results half way through. Nevertheless, thanks to the Markov process, it was possible to calculate the outcome of the illness over 1 year of treatment in a more 'realistic' way than with a deterministic model[9,30].

As previously mentioned, QUE and OLA have never been compared in a randomised controlled clinical trial[10]. The relative adverse event rates are therefore based only on meta-analysis of indirect placebo-controlled comparisons, according to the approach of the National Coordinating Centre for Health Technology Assessment in the UK[10]. This assumption was a limitation of the model, because the comparability of patient populations for each treatment type is not completely demonstrated.

To try to minimise the limitations of the model, we adopted conservative suppositions (and averages) and carried out a sensitivity analysis taking into account several scenarios, which confirmed in general terms the results of the basic case.

It must be pointed out, for example, that it was supposed that there are no differences in efficacy between QUE

Table 6. Calculation of the number of patients needed to treat (NNT) with quetiapine (QUE) to avoid an episode of toxicity with olanzapine (OLA), risperidone (RIS) or haloperidol (HAL)

Treatment	No. of episodes	Total no. of patients	RRR with QUE[a]	NNT[b]
Extrapyramidal syndrome				
Quetiapine	83	842	—	—
Olanzapine	371	2,039	45.8%	12.0
Risperidone	585	2,274	61.7%	6.3
Haloperidol	326	826	75.0%	3.4
Sexual dysfunction associated with hyperprolactinaemia				
Quetiapine	6	33	—	—
Olanzapine	59	167	48.5%	5.8
Risperidone	76	176	57.9%	4.0
Haloperidol	45	98	60.4%	3.6
Clinically relevant weight gain				
Quetiapine	10	44	—	—
Olanzapine	291	636	50.3%	4.4
Risperidone	195	636	25.9%	12.6
Haloperidol	143	636	[c]	—

[a]Reduction of relative risk (RRR) with QUE compared with OLA, RIS or HAL.

[b]In the case of extrapyramidal syndrome (EPS), it is necessary to treat 6.3 patients with QUE instead of RIS in order to avoid an episode of EPS that would have occurred if these patients had been treated with RIS. To avoid an episode of EPS with HAL, it would be enough to treat with QUE only 3.4 patients scheduled to receive HAL.

[c]No reduction of clinically relevant weight gain was observed with QUE vs. HAL.

and RIS, although in a comparative clinical trial QUE improved symptoms of depression to a greater extent than RIS[28].

The main strengths of the model are: (i) the use of resources was calculated using the recommendations of the Spanish Psychiatric Society and other Spanish clinical action guidelines[1,4,29,31]; (ii) the probabilities of transition were calculated using an independent systematic review from the UK National Health Service[10]; and (iii) all the costs of healthcare resources were obtained from a database of Spanish costs[50].

The results of this pharmacoeconomic analysis should be confirmed in a pragmatic and randomised clinical trial in which the efficacy, tolerance and use of healthcare resources are compared between alternative therapies.

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Table 7. Results of the pharmacoeconomic analysis of schizophrenia therapy for 1 year with quetiapine (QUE) and olanzapine (OLA) (costs in euro (€) at 2003 values)

Cost analysis			
Case	*QUE*	*OLA*	*Difference*[a]
Basic	1,300.05	1,910.65	–610.60
Minimum	1,200.20	1,020.06	180.14
Maximum	1,887.38	2,008.57	–121.19

Incremental cost-effective analysis		
Secondary effect	*Case*	*Cost per episode avoided*[b]
Extrapyramidal syndrome	Basic	QUE dominates OLA
	Minimum	2,309.48
	Maximum	QUE dominates OLA
Sexual dysfunction associated with hyperprolactinaemia	Basic	QUE dominates OLA
	Minimum	1,078.68
	Maximum	QUE dominates OLA
Clinically relevant weight gain	Basic	QUE dominates OLA
	Minimum	OLA dominates QUE
	Maximum	1,224.14
Type 2 diabetes mellitus	Basic	No differences in toxicity[c]
	Minimum	No differences in toxicity[c]
	Maximum	QUE dominates OLA

[a]Negative values indicate a lower cost with QUE than with OLA, in contrast to positive values.

[b]Cost of avoiding an episode of the secondary effect with QUE (best tolerated treatment). One treatment dominates another when it is better tolerated with lower costs.

[c]There were no relevant differences in the rates of appearance of diabetes with QUE and OLA.

Table 8. Results of the pharmacoeconomic analysis of schizophrenia therapy for 1 year with quetiapine (QUE) and risperidone (RIS) (costs in euro (€) at 2003 values)

Cost analysis

Case	*QUE*	*RIS*	*Difference*[a]
Basic	1,300.05	1,492.94	–192.89
Minimum	1,200.20	1,255.87	–55.67
Maximum	1,887.38	1,854.39	32.99

Incremental cost-effectiveness analysis

Secondary effect	*Case*	*Cost per episode avoided*[b]
Extrapyramidal syndrome	Basic	QUE dominates RIS
	Minimum	QUE dominates RIS
	Maximum	165.00
Sexual dysfunction associated with hyperprolactinaemia	Basic	QUE dominates RIS
	Minimum	QUE dominates RIS
	Maximum	100.61
Clinically relevant weight gain	Basic	QUE dominates RIS
	Minimum	QUE dominates RIS
	Maximum	RIS dominates QUE
Type 2 diabetes mellitus	Basic	No differences in toxicity[c]
	Minimum	No differences in toxicity[c]
	Maximum	362.64

[a]Negative values indicate a lower cost with QUE than with RIS, in contrast to positive values.

[b]Cost of avoiding an episode of the secondary effect with QUE (best tolerated treatment). One treatment dominates another when it is better tolerated with lower costs.

[c]There were no relevant differences in the rates of appearance of diabetes with QUE and RIS.

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Table 9. Results of the pharmacoeconomic analysis of schizophrenia therapy for 1 year with quetiapine (QUE) and haloperidol (HAL) (costs in euro (€) at 2003 values)

Cost analysis

Case	*QUE*	*HAL*	*Difference*[a]
Basic	1,300.05	286.18	1,013.87
Minimum	1,200.20	160.34	1,039.86
Maximum	1,887.38	563.15	1,324.23

Incremental cost-effectiveness analysis

Secondary effect	*Case*	*Cost per episode avoided*[b]
Extrapyramidal syndrome	Basic	3,425.23
	Minimum	3,687.44
	Maximum	4,112.51
Sexual dysfunction associated with hyperprolactinaemia	Basic	3,647.01
	Minimum	2,260.56
	Maximum	2,955.87
Clinically relevant weight gain	Basic	No differences in toxicity[c]
	Minimum	41,594.40
	Maximum	HAL dominates QUE
Type 2 diabetes mellitus	Basic	24,139.76
	Minimum	10,679.27
	Maximum	14,855.14

[a] Positive values indicate a lower cost with QUE than with HAL.

[b] Cost of avoiding an episode of the secondary effect with QUE (best tolerated treatment). One treatment dominates another when it is better tolerated with lower costs.

[c] There were no relevant differences in the rates of clinically relevant weight gain with QUE and HAL.

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