Economic consequences of the adverse reactions related with antipsychotics: an economic model comparing tolerability of ziprasidone, olanzapine, risperidone, and haloperidol in Spain

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Abstract

Frequency of adverse reactions (ARs) related with antipsychotics usage is high. Along with clinical implications, economic impact might be important. The purpose of this study was to model the economic consequences of ARs related with ziprasidone, olanzapine, risperidone, and haloperidol in Spain, by means of a cost-effectiveness model developed using a Markov modeling approach. The model simulated treatment of a cohort of 1000 schizophrenics for 12 months, initiating treatment with one of four antipsychotic drugs; haloperidol, risperidone, olanzapine and ziprasidone. Conditional probabilities of developing any of four adverse events were calculated. Treatment was modified (decrease dose, switch medication) according to incidence of ARs and physician judgments, obtained from a local cross-sectional study and clinical trials previously published. The analysis was conducted in year 2002 from a third party payer perspective. Results are shown as annual cost per month with psychotic symptoms controlled and included univariate sensitivity analysis. The therapeutic strategy starting with ziprasidone showed the lower costs and the greater number of months with symptoms controlled in most scenarios evaluated versus the other options considered, although the differences were weak: 9.6, 9.3, 9.5 and 9.5 controlled months per patient in base scenario, with annual cost per patient per month with symptoms controlled of €1035, €1084, €1087 and €1090 for ziprasidone, haloperidol, risperidone and olanzapine, respectively. Results were robust to one-way sensitivity analysis. Despite the unlike drug prices of antipsychotics, a considerable economic impact due to adverse reactions was seen in our setting. These results should be taken into account by health decision makers and clinicians in the management of patients with schizophrenia.

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Keywords: Adverse reactions; Antipsychotics; Cost-effectiveness; Economic evaluation; Markov-model; Spain; Ziprasidone

1. Introduction

Schizophrenia is a severe chronic mental disease characterized by a constellation of symptoms including hallucinations, delusions, cognitive disorders, sadness, social isolation, suicidal ideation, etc., which represents a significant health problem worldwide (Andreasen, 1995). Schizophrenia affects 1–2% of the population at risk (Betemps and Ragiel, 1994; Pinals and Breier, 1997), which would represent in Spain approximately 300,000 schizophrenic patients (Mata et al., 2000). Although the prevalence rate of this disease can be considered relatively low, its treatment constitutes one of the main items in most health budgets in developed countries; in the United States, it has been estimated that the cost of schizophrenia (approximately 22.7 billion US dollars of 1993) would account for 2.5% of...
In addition to the potential impact on the course and/or symptoms of the disease of the occurrence of the above-mentioned adverse reactions, these have significant economic implications, including short-term implications resulting from treatment non-compliance and discontinuation possibly caused by the occurrence of such adverse reactions. Such short-term implications mainly include the need for switching therapy, the recurrence of psychotic symptoms and an increased risk of schizophrenia exacerbation with the resultant hospitalization.

Although the international scientific literature is full of pharmacoeconomic assessments of interventions in schizophrenia, there are not many studies in which an approach has been made to the economic cost derived from patient management and treatment as a direct result of the occurrence of adverse reactions (ARs) related to the use of these treatments. Thus, the purpose of this study was to carry out an assessment, for the Spanish sanitary system, of the economic implications for our setting of the ARs caused by current antipsychotic drugs, the results of which are reported in this paper.

2. Material and methods

2.1. Type of economic evaluation

In order to assess the economic implications of the ARs associated to treatment with antipsychotics, a cost-effectiveness analysis has been performed using a decision analysis that simulates the annual cost of antipsychotic treatment, including the cost involved by the modification of the therapeutic regime and the cost of management of ARs and their consequences, and compares the cost between different therapeutic options. This model has previously been validated in other psychotic populations (Russell and Mackell, 2002). The economic impact of the adverse reactions on the annual cost of antipsychotic therapy can thus be analyzed.

The decision analysis was performed using a Markov model (Sonnenberg and Beck, 1993; Briggs and Sculpher, 1998; Brennan and Akherst, 2000) that simulates the treatment of a cohort of 1000 patients with chronic schizophrenia for 1 year, and in which patients can change their health status according to the expected incidence of ARs, non-compliance, and expected rehospitalization rate for each type of treatment selected by ARs (Figs. 1 and 2). This model simulates the start of treatment of the schizophrenic patient with up to four different types of antipsychotics: haloperidol, olanzapine, risperidone, and ziprasidone [quetiapine has not been included because no enough data from the naturalistic source of data similar to that used for haloperidol, risperidone or olanzapine, was obtained, only information regarding less than 50 patients, see results of the EIRE study (Bobes et al., 2002, 2003a,b)], and treatment could be started on an inpatient or outpatient
basis (for the analysis of the base case scenario, it was assumed that 50% of the patients would start antipsychotic treatment on an inpatient basis, and 50% on an outpatient basis).

2.2. Measurement of the transitional probabilities of the model

The transitional probabilities of change in health status have been calculated from the probabilities of incidence of the ARs included in the model [akathisia, other extrapyramidal symptoms (EPS), weight gain ≥7%, and ARs related to prolactin increase (sexual dysfunction, amenorrhea, etc. (Table 1)) that come in turn from the epidemiological study EIRE (20–23), from the probabilities of non-compliance and rehospitalization due to non compliance obtained from the scientific literature (Van Putten, 1974; Gilbert et al., 1995; Weiden and Olfson, 1995; Hoge et al., 1990; Van Putten et al., 1981; Tollefson et al., 1997; Tran et al., 1997a; Tran et al.,

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**AR = adverse reaction**

1st option: includes dose reduction, antidote, switching antipsychotic or no action.

Fig. 1. Representation of the decision tree used in the economic model for patients starting antipsychotic treatment on an inpatient basis.

Fig. 2. Representation of the decision tree used in the economic model for patients starting antipsychotic treatment on an outpatient basis.
Table 1
Type and frequency of adverse reactions (ARs) related to the use of antipsychotics seen in the EIRE study (Outcomes Research Study in Schizophrenia) and non-compliance rate depending on the type of ARs

<table>
<thead>
<tr>
<th>Antipsychotic</th>
<th>Adverse reaction</th>
<th>Akathisia</th>
<th>Other EPS</th>
<th>Weight gain (≥7%)</th>
<th>ARs associated to prolactin increase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haloperidol</td>
<td></td>
<td>36.8%</td>
<td>41.5%</td>
<td>22.4%</td>
<td>39.8%</td>
</tr>
<tr>
<td>Risperidone</td>
<td></td>
<td>19.7%</td>
<td>35.4%</td>
<td>30.6%</td>
<td>45.6%</td>
</tr>
<tr>
<td>Olanzapine</td>
<td></td>
<td>11.4%</td>
<td>24.4%</td>
<td>45.7%</td>
<td>36.7%</td>
</tr>
<tr>
<td>Ziprasidonea</td>
<td></td>
<td>8.0%</td>
<td>10.2%</td>
<td>5.8%</td>
<td>2.5%</td>
</tr>
<tr>
<td>Expected non-compliance rate</td>
<td></td>
<td>47.0%</td>
<td>47.0%</td>
<td>41.0%</td>
<td>41.0%</td>
</tr>
</tbody>
</table>

EPS=Extrapyramidal symptoms.

* Data taken from the prescribing information approved by the US FDA.

1997b), and from the action taken by the clinician for an AR seen in the above-mentioned EIRE study, namely: reduced dosage of the current antipsychotic, addition of concomitant medication, switch in treatment to a different antipsychotic or no action (Table 2). The concomitant medication considered in this assessment included biperiden, propranolol, and/or lorazepam. Since the preferences for a change in antipsychotic were logically not available, the model assumes an equivalent probability of change for all antipsychotics except for haloperidol, in which case the model does not allow for a patient treated with atypical antipsychotics to be switched to haloperidol. For all other agents, the model assumes that, for example, if a patient is being treated with olanzapine and requires a switch in treatment, he/she can only be switched to risperidone or ziprasidone, and the probability of change in each case is 0.50. Patients with no ARs receive the same treatment until the modeled period of 12 months is completed.

The following assumptions have been made in the model:

• regardless of the efficacy shown in clinical trials, for this model the four antipsychotics evaluated have the same antipsychotic efficacy, only differing in their tolerability profile;
• impossibility of simultaneously using more than one antipsychotic;
• impossibility of switching to haloperidol if a patient starts treatment with an atypical antipsychotic;
• switching to clozapine when all possible changes have been made;
• a switch in antipsychotic treatment must always be due to ARs;
• during the hospital stay of a patient, treatment compliance is optimal;
• patients are discharged when the psychotic symptoms are controlled;
• when the patient reaches a health status free from ARs, he/she is maintained in it until modelization is completed, and treatment compliance is considered optimal.

2.3. Measurement of the effectiveness of treatments

The effectiveness of the antipsychotic treatments evaluated is measured as months with psychotic symptoms controlled for each of the cohorts evaluated. For this model, and since it is assumed that all antipsychotics evaluated have the same efficacy, the calculation of the months with psychotic symptoms controlled was carried out as the sum of days without hospitalization and free from adverse reactions during the 12 modeled months. For this model, it has been estimated that the patient does not have psychotic symptoms controlled for as long as he/she is on an antipsychotic therapy causing ARs and the treatment instituted by the clinician has not been effective, or the patient is admitted to hospital. The mean duration of an exacerbation of schizophrenia has been obtained from the Psychosp study, where the mean duration and costs of exacerbations of schizophrenia in Spain were analyzed, and has been established at 21.78 days (Peiró et al., 2004).

2.4. Measurement of the resources used and their associated costs

The costs used in the model are expressed in Euros of the year 2002 and have been obtained from different sources (Table 3). The costs of diagnostic and laboratory tests and medical visits have been obtained from the fees in the Nomenclator of the Official Physician’s Association of Barcelona (Nomenclator COMB, 2001), the resources used in refractory treatment, and the use of group therapy and day care unit in the literature, updated to the year 2002 based on inflation (Sacristán et al., 1997). The mean doses of antipsychotic consumption evaluated were obtained from the EIRE study, where a cross-sectional calculation was

Table 2
Action taken, with the chance of success in brackets, for an adverse reaction (AR) seen in patients taking antipsychotics in the EIRE study

<table>
<thead>
<tr>
<th>Antipsychotic</th>
<th>Adverse Reaction</th>
<th>Akathisia</th>
<th>Other EPS</th>
<th>Weight gain (≥7%)</th>
<th>ARs associated to prolactin increase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose reduction</td>
<td></td>
<td>12%</td>
<td>11%</td>
<td>10%</td>
<td>26%</td>
</tr>
<tr>
<td>(0.63)</td>
<td>(0.58)</td>
<td>(0.58)</td>
<td>(0.55)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concomitant medication</td>
<td></td>
<td>35%</td>
<td>27%</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>(0.38)</td>
<td>(0.73)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Switch in antipsychotic</td>
<td></td>
<td>5%</td>
<td>5%</td>
<td>3%</td>
<td>6%</td>
</tr>
<tr>
<td>(0.70)</td>
<td>(0.70)</td>
<td>(0.47)</td>
<td>(0.80)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No action</td>
<td></td>
<td>48%</td>
<td>57%</td>
<td>87%</td>
<td>68%</td>
</tr>
<tr>
<td>(0.00)</td>
<td>(0.00)</td>
<td>(0.00)</td>
<td>(0.00)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

EIRE=Outcomes research study in schizophrenia.
EPS=Extrapyramidal symptoms.
made of the current mean dose of different antipsychotics used in our setting (Bobes et al., 2002, 2003a,b). The purchasing costs of antipsychotic medication were obtained from the 2002 Catalogue of Medicinal Products of the General Council of Official Pharmacists’s Association of Spain (COCGCFE, 2002). Since the economic evaluation was carried out from the perspective of the National Health System (NHS), only direct medical costs as they occur are computed, and the purchasing costs of drugs are therefore calculated at their retail price plus taxes. The time horizon for the calculation has been 12 months, and no discount rate was therefore used.

2.5. Average and Incremental Cost-Effectiveness ratios (CE and ICER)

The results of the economic model are presented as average cost per month with psychotic symptoms controlled (average CE ratio) and, also, as the incremental cost per month controlled of each intervention over reference intervention which will be that with lower annual cost (ICER ratio).

2.6. Sensitivity analysis

Since, as with any mathematical model where assumptions are made, there is some degree of uncertainty, a sensitivity analysis was performed, consisting of changing the values adopted in the base model within ranges, so that the degree of uncertainty supported by this model could be reduced. Univariate sensitivity analyses of the variables subject to a greatest uncertainty or with the greatest probability of being modified or varied have been performed, and are the followings: proportion of inpatients at the start of the model, proportion of patients in whom a switch in antipsychotic is made due to akathisia, other extrapyramidal symptoms, ARs related to prolactin increase and weight gain, mean duration of hospital stay, cost of hospitalization, proportion of treatment non-compliance due to ARs, and incidence of the ARs evaluated for all antipsychotics analyzed.

The proportion of inpatients was modified between two limit scenarios: 100% of inpatients at the start of the model and 100% of patients treated on an outpatient basis. The action taken by the clinician for an AR was modified until reaching 100% of treatment switch with a successful result for each AR alone, maintaining for the other ARs the same probability of change in treatment as seen in the EIRE study. An analysis was also made where the antipsychotic was switched in 100% of the cases in which any AR occurred. The hospital stay included in the base scenario, 21.78 days, was changed in the scenarios of 15 and 7 days’ duration, respectively. Hospitalization cost ranged from 166.43/day to 129.95/day (95% confidence interval obtained in the Psychosp study). The incidence of ARs for all antipsychotics was reduced by up to 50% and, the proportion of non-compliance due to ARs was modified to make it equal to the non-compliance rate seen in patients showing no ARs. Finally, the incidence of any of four types of ARs used in the base scenario was duplicated for ziprasidone, and also, drug titration upward for all antipsychotics considered was model individually and simultaneously.

3. Results

The model computes the total costs of each cohort of 1000 patients according to the antipsychotic used at the start of the simulation, regardless of the antipsychotic used at the end of the model. In addition to the total costs, the results are expressed as annual cost per month with the psychotic symptoms controlled (average cost–effectiveness (CE) ratio) and incremental cost-effectiveness of each option over the reference therapy (therapy with a lower total cost—incremental cost–effectiveness ratio, ICER). The results are shown for the analysis of the base scenario, where 50% of each
of the antipsychotics analyzed during 12 months of modeling is higher in both absolute and relative terms when antipsychotic treatment is started with haloperidol than when it is started with the other antipsychotics evaluated, accounting for 75.5% of the annual cost for this arm (Table 6). By contrast, when treatment was started with ziprasidone, the cost attributable to the management and treatment of ARs was the lowest of the four therapeutic options analyzed, and this item only represented 67.6% of the annual cost of treatment.

3.1. Sensitivity analysis

The sensitivity analysis carried out incorporated changes in the variables with the greatest uncertainty, such as stay duration, hospitalization cost, proportion of inpatients at the start of modelization, proportion of patients in whom antipsychotic treatment is changed when an AR is seen, 50% reduction in the incidence of ARs for all antipsychotics except for ziprasidone, and modification of the proportion of treatment non-compliance due to ARs to make it equal to that of patients with no ARs. Table 7 shows the results of the different sensitivity analyses performed, showing that the cohort starting treatment with ziprasidone, through the different scenarios, is still the dominant option (lower cost and higher number of months with psychotic symptoms controlled) in most situations, regardless of the proportion of inpatients at the start of treatment, the hospitalization cost, the switch in antipsychotic treatment in 100% of the cases of akathisia, EPS, weight gain, or ARs related to prolactin.

Table 4
List of annual costs, total and broken down by main components (hospitalization, outpatient follow-up and drug acquisition) by 1000 patients for each antipsychotic evaluated, in a modeled population of patients starting treatment, 50% as outpatients and 50% as inpatients (base scenario).

<table>
<thead>
<tr>
<th>Antipsychotic</th>
<th>Total costs (€)</th>
<th>Hospitalization costs (€)</th>
<th>Outpatient cost (€)</th>
<th>Drug costs (€)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haloperidol (10.6 mg)</td>
<td>10,057,490</td>
<td>7,632,478</td>
<td>1,297,880</td>
<td>1,127,132</td>
</tr>
<tr>
<td>Risperidone (5.3 mg)</td>
<td>10,339,961</td>
<td>7,368,961</td>
<td>1,324,561</td>
<td>1,646,439</td>
</tr>
<tr>
<td>Olanzapine (13.5 mg)</td>
<td>10,357,577</td>
<td>7,288,038</td>
<td>1,324,897</td>
<td>1,764,642</td>
</tr>
<tr>
<td>Ziprasidone (120 mg)</td>
<td>9,944,512</td>
<td>6,775,748</td>
<td>1,339,662</td>
<td>1,829,102</td>
</tr>
</tbody>
</table>

Costs expressed in Euros. In brackets, mean doses of the antipsychotics used in the model, taken from the EIRE study. For ziprasidone, the dose used in standard clinical practice has been used (after one year of post-marketing experience).

Table 5
Cost-effectiveness of the antipsychotics analyzed after 12 months of treatment in a modeled population of 1000 patients starting treatment, 50% as inpatients and 50% as outpatients (base scenario).

<table>
<thead>
<tr>
<th>Antipsychotic</th>
<th>Annual cost (€)</th>
<th>Controlled months</th>
<th>Annual cost per controlled month (€)</th>
<th>Cost-effectiveness analysisa</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cost difference (€)</td>
</tr>
<tr>
<td>Haloperidol (10.6 mg)</td>
<td>10,057,490</td>
<td>9276</td>
<td>1084</td>
<td>+112,978</td>
</tr>
<tr>
<td>Risperidone (5.3 mg)</td>
<td>10,339,961</td>
<td>9503</td>
<td>1087</td>
<td>+395,449</td>
</tr>
<tr>
<td>Olanzapine (13.5 mg)</td>
<td>10,357,577</td>
<td>9505</td>
<td>1090</td>
<td>+413,065</td>
</tr>
<tr>
<td>Ziprasidone (120 mg)</td>
<td>9,944,512</td>
<td>9610</td>
<td>1035</td>
<td>Reference</td>
</tr>
</tbody>
</table>

Costs expressed in Euros and effectiveness expressed as months with controlled psychotic symptoms. In brackets, mean doses of the antipsychotics used in the model, taken from the EIRE study. For ziprasidone, the dose used in standard clinical practice has been used (after 1 year of post-marketing experience).

a Analysis of differences and incremental cost-effectiveness of each option over the reference therapy (ziprasidone), the most efficient intervention (lower cost and higher number of controlled months).
The sensitivity analysis shows that the conclusions reached in the base scenario are sensitive to a reduction in the hospital stay to 15 days or less. Furthermore, the start of the treatment with ziprasidone is sensitive to the 50% reduction in the incidence of ARs with the antipsychotics evaluated, the equalization of the non-compliance percentage to that seen in patients with no ARs, or antipsychotic switching in 100% of cases where an AR is seen, regardless of its nature. Also, ziprasidone start up is sensitive when the incidence of akathisia or EPS for this drug duplicates the value used in the base scenario, and when ziprasidone is titrated upward to 160 mg, maintaining constant the dosing for the other drugs, or all the four antipsychotics are simultaneously titrated upward to 15, 8, 20 and 160 mg for haloperidol, risperidone, olanzapine and ziprasidone, respectively.

The results of the sensitivity analysis are robust for the start with ziprasidone as compared to the cohorts where treatment is started with risperidone or olanzapine in all the scenarios analyzed, since the cost per additional month controlled over haloperidol is markedly lower to that seen for the other atypical antipsychotics (Table 7).

4. Discussion

4.1. Main findings

This study analyzes the economic impact on costs of treatment of schizophrenic patients with the antipsychotic drugs most commonly used in our setting. Quetiapine has
not been included because no enough data from the naturalistic source of data similar to that used for haloperidol, risperidone or olanzapine, was obtained in the EIRE study (Bobes et al., 2002, 2003a,b). The analysis also included ziprasidone, an atypical antipsychotic recently introduced in some Western countries that has shown an excellent tolerability profile in pre-marketing clinical development (Weiden et al., 2002; Gunasekara et al., 2002). Although in this evaluation, carried out from the perspective of the NHS, non-medical direct costs have not been considered, nor the indirect costs derived from work absenteeism, which can be eventually high (Terkelsen and Menikoff, 1995; Weiden et al., 1996), the results of this analysis show that the adverse reactions related to the use of antipsychotics are responsible for a substantial increase in the cost of treatment of schizophrenic patients, which in patients starting treatment with haloperidol may represent up to 3/4 of the annual total cost with this drug. However, for the atypical antipsychotics analyzed in this study, this cost component was substantially lower, and ziprasidone and olanzapine showed the lowest values.

Institutionalization, due to exacerbation of the psychotic symptoms resulting from therapeutic non-compliance caused by inadequate or reduced tolerability to the drugs evaluated in this study, is the most important component of the cost attributable to ARs, and again the most important economic item for patients starting treatment with haloperidol, and the lowest for ziprasidone, mainly due to the lower incidence of ARs seen with this novel antipsychotic. These findings are consistent with those reported by other authors (Meltzer, 1999; Weiden and Olfson, 1995; Davies and Drummond, 1994), who also agree in pointing out hospitalization costs as the most significant components of the cost of the schizophrenic patient. It is easily concluded that a significant reduction in the hospitalization due to exacerbation of psychotic symptoms should necessarily result in cost savings in the treatment of schizophrenia for the NHS.

This pharmacoeconomic modeling study showed that starting the antipsychotic treatment with ziprasidone proved to be the therapeutic option with the most favorable cost-effectiveness ratio, since it shows a dominance relationship (lower costs and greater effects) to the antipsychotics analyzed in this study due to its better tolerability profile, as confirmed with the sensitivity analysis. Based on the results of the base scenario, an attempt was made in the sensitivity analysis to improve, within a plausible range of variability, the tolerability values with all antipsychotics assessed, except for ziprasidone for whose AR rate used in the sensitivity analysis was duplicated, so that it could be ascertained with which of the primary variables modified could this antipsychotic be sensitive from an economic viewpoint. As shown in Table 7, ziprasidone was the atypical drug with the best cost-effectiveness ratio, and consistently showed a lower incremental cost over haloperidol per additional month with psychotic symptoms controlled than olanzapine or risperidone; or was the dominant option over risperidone, olanzapine, and haloperidol. Although the sensitivity analysis showed that the conclusions of the economic evaluation were sensitive to the modification of the incidence of ARs with antipsychotic treatment, this does not appear to be feasible, since this information comes from a real-life study, the EIRE study (Bobes et al., 2002, 2003a,b), which by design underestimated the actual frequency of ARs. This makes it highly unlikely to see a lower incidence of ARs for those drugs.

On the other hand, though incorporated in the sensitivity analysis, it does not appear reasonable to expect that the proportion of patients with non-compliance in subjects with ARs could be made equal to that seen in patients who do not experience ARs under conditions of routine medical practice or real life. Similarly, the sensitivity analysis showed that the results obtained in the base scenario were sensitive to a reduction in the duration of hospitalization for relapse to less than 15 days. However, and although stay duration can depend on multiple factors (different healthcare protocols according to geographical area, presence of restlessness in the patient, age, etc.), it is true that the studies published to date that have evaluated this result report that the mean stay is longer than 15 days and range around 22 days, as reported in the recently performed Psychosp study (Peiró et al., 2004) or in other previously published studies (Sacristán et al., 1997; Weiden and Olfson, 1995). Therefore, we think that the possibility of a short stay, less than 15 days, in a patient with schizophrenic exacerbation is actually low. Also, according to the sensitivity analysis, another possibility for modifying the conclusions of the base scenario would be that the psychiatrist takes the decision to switch the antipsychotic in all cases where any of the ARs evaluated in this study is detected. Again, the results seen in the already mentioned EIRE study and in other studies (Weiden et al., 1996; Meltzer, 1999) suggest that this possibility is more theoretical that real, and that in routine medical practice for the treatment of schizophrenia, the control of the positive and negative psychotic symptoms is naturally given precedence to the control of adverse reactions such as weight gain, sexual dysfunction, etc.

Finally, the duplication of ARs incidence for ziprasidone did not modify substantially the results of the base scenario. Ziprasidone was cost-effective versus haloperidol when the incidences of akathisia and EPS were increased the 100%, and was the dominant option versus olanzapine and risperidone. Again, ziprasidone continued being the dominant option over all options when the incidence of weight-gain and prolactin-related-ARs was duplicated. These last considerations apply when antipsychotics dosing is titrated upward. Ziprasidone is sensitive to upward titration to 160 mg alone, or when simultaneously all drugs are titrated to the maximum dose considered in this evaluation (see Table 7), but it is still dominant versus olanzapine and risperidone, and cost-effective versus haloperidol.
4.2. Limitations of the study

As with most economic evaluations, this study has some limitations. First, a simulation was performed based on a mathematical model requiring assumptions, as no actual head-to-head data for all antipsychotics reported in this model were available at the time of the assessment. The rigorosity of the model used, as well as the validity of this type of approach for pharmacoeconomic analyses, have been widely supported in the literature (Sonnenberg and Beck, 1993; Briggs and Sculpher, 1998; Brennan and Akehurst, 2000), and the fact that this same model has already been used in other psychotic populations (Russell and Mackell, 2002) allows us for ensuring that this economic evaluation technology is not only valid, but can also provide relevant results for both clinical and economic health decision-makers. Another limitation that should be discussed lies in the sources from which the frequencies of ARs were obtained, a pragmatic study (EIRE study) for all antipsychotics evaluated, and the data from clinical trials for ziprasidone. In this regard, it should be noted that we agree with the recent recommendations to have available real-life data when economic evaluations with antipsychotics are performed (World Psychiatry Association Task Force on The Usefulness and Use of Second-Generation Antipsychotic Medications, 2002; López-Ibor et al., 2002), and the availability of data on the frequency of adverse reactions from a real-life study, such as EIRE, goes in this direction. On the other hand, since EIRE was a cross-sectional study in which a timepoint analysis was made of patients undergoing antipsychotic treatment, this suggests to us that this study could be underestimating the actual frequency of ARs, as patients who could have discontinued treatment when it was started were not recorded, while for ziprasidone the actual incidence would have been recorded by prospectively using the frequency of ARs in both short and long duration clinical trials. Despite this limitation, the sensitivity analysis carried out by modifying the frequency of ARs for all antipsychotics confers robustness to the analysis of the base scenario, since the conclusions on the more favorable cost-effectiveness ratio of ziprasidone over olanzapine or risperidone are not modified. The results of the analysis when the probability of therapeutic non-compliance was reduced or the aptitude of the clinician switching the antipsychotic in 100% of cases of occurrence of ARs point in this same direction.

Other limitations to be noted are that the economic analysis was carried out from the perspective of the NHS and, therefore, other costs such as those of work absenteeism, which have been reported to be very high (Terkelsen and Menikoff, 1995; Weiden et al., 1996), or the cost of suicidal attempts, as included in other studies performed in our setting (Sacristán et al., 1997), have not been assessed. In this regard, it should be noted that the primary objective of this economic evaluation was to ascertain the economic impact for our NHS of the ARs associated with the antipsychotics most commonly used and, consequently, an evaluation of the impact on work productivity was beyond the perspective the payer has of the health benefits in our setting.

Finally, it must be noted that this model assumed that the four antipsychotics evaluated had the same therapeutic efficacy in schizophrenia, which may not be true in standard medical practice due to the difference in frequency of ARs seen for these agents and the high rate of non-compliance attributable to them. The reason to assume similar efficacy rates for involved drugs in present evaluation was the fact that the model focused and evaluated only AR impact on costs, with the idea to make aware on AR consequences for patients on antipsychotic therapies rather than on efficacy. Another limitation is that this economic assessment used, to calculate the cost of medication, a mean dose of 120 mg for ziprasidone, while the assumption of efficacy and the incidence of adverse reactions with this antipsychotic corresponds to the experience in pre-marketing clinical trials where mean doses from 98 to 115 mg were used. The post-marketing experience in countries where this medicinal product has been marketed for some time suggests that the 120 mg dose is the most common one with this drug, and that no relevant tolerability differences have been seen from clinical trials (Weiden et al., 2002; Gunasekara et al., 2002). It can therefore be expected that the assumptions included in this model occur in our setting. In this regard, it would be advisable to have longitudinal studies (retrospective or prospective) based on standard medical practice that could provide some light on the efficacy and tolerability of these drugs under “real world” conditions of use.

5. Conclusions

Despite the identified limitations, the use of pharmacoeconomic decision models such as this is of utmost interest, particularly considering that this model has allowed for a simultaneously comparison to be made of the economic impact of the adverse reactions associated with four initial strategies of schizophrenic treatment with antipsychotics, and that the approach to the cost of adverse reactions used in this study is innovative, as most economic evaluations with antipsychotics have been focused on a conventional cost-effectiveness analysis. The main component of the expenditure correspond to hospitalization costs related with symptoms relapse due to therapy non-compliance, even drug prices of antipsychotics were completely unlike. These results should be taken into account by health decision makers and clinicians in the management of patients with schizophrenia, as results of
this evaluation showed weak differences in yearly costs between alternatives evaluated.

References


