Economic analyses of olanzapine in the treatment of schizophrenia and bipolar disorder

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Análisis económico de la olanzapina en el tratamiento de la esquizofrenia y el trastorno bipolar

Summary

Schizophrenia generates important costs for society –both direct, as a consequence of hospitalization and outpatient treatment, and indirect; related to loss of productivity. The atypical antipsychotics, such as olanzapine, have supposed an important advance in the treatment of schizophrenia. The greater cost of atypical antipsychotics with respect to conventional drugs has led to the conduction of pharmacoeconomic studies to determine its efficiency. This article reviews the complete pharmacoeconomic studies that compare olanzapine with haloperidol and risperidone in the treatment of schizophrenia. Cost analyses comparing olanzapine and haloperidol show that the former drug does not add increased cost to therapy, and even contributes to lessen expenses fundamentally as a result of a decrease in hospitalizations. In the economic evaluations comparing olanzapine and risperidone, the results are not conclusive, and in general, the total costs associated with both treatments were similar. In the treatment of bipolar disorder, although few studies have estimated the economic impact of olanzapine, it has been observed a reduction of hospitalization costs associated to the treatment with olanzapine.

Key words: *Olanzapine. Schizophrenia. Bipolar disorder. Costs. Pharmacoeconomics.*

Resumen

La esquizofrenia es una enfermedad que genera importantes costes para la sociedad, tanto directos, derivados principalmente de la hospitalización y el tratamiento ambulatorio, como indirectos, debidos a la pérdida de productividad de los pacientes. Los antipsicóticos atípicos como la olanzapina han supuesto un avance muy importante en el tratamiento de la esquizofrenia. Su mayor coste respecto a los antipsicóticos convencionales como el haloperidol ha impulsado la realización de estudios farmacoeconómicos encaminados a evaluar su rentabilidad. En el presente trabajo se revisan las evaluaciones farmacoeconómicas completas que comparan la olanzapina con el haloperidol y la risperidona en el tratamiento de la esquizofrenia. Los análisis de costes comparando olanzapina y haloperidol ponen de manifiesto que la olanzapina no añade costes al tratamiento de la esquizofrenia, produciendo incluso disminución en los mismos debido fundamentalmente a una menor hospitalización. En las evaluaciones económicas que comparaban olanzapina y risperidona los resultados no son concluyentes y, en general, los costes totales asociados a ambos tratamientos fueron similares. En el tratamiento del trastorno bipolar, aunque las evaluaciones económicas realizadas hasta la fecha son escasas, se observó una reducción en los costes de hospitalización asociada al tratamiento con olanzapina.

Palabras clave: *Olanzapina. Esquizofrenia. Trastorno bipolar. Costes. Farmacoeconomía.*

INTRODUCTION

Schizophrenia is a serious and incapacitating mental disease, with a tendency to chronification and with an estimated prevalence of approximately 1% of the general population[1], and with an annual incidence of one case per 10,000 persons[2]. In Spain, schizophrenia affects about 400,000 individuals, according to data from the World Psychiatry Association – though a large number of cases have not been diagnosed[3].

Schizophrenia generally develops during the second or third decade of life, with a broad range of symptoms which are usually classified as follows: positive symptoms, comprising hallucinations, delirium, disorganized thinking, and behavioral alterations; negative symptoms, including reduced motivation, apathy, a lack of interest in and relation with the surroundings; affective symptoms, in the form of depression, dysphoria, hopelessness and suicide ideation; and finally cognitive symptoms

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such as memory and learning problems and attention problems[4,5].

The mentioned symptoms in turn lead to important social and occupational deterioration, suicide being a serious danger among people suffering the disease. The percentage of suicide attempts ranges from 18 %-55 %[6], while the effective suicide rate reaches 10 %[7].

The treatment of schizophrenia is complex, and requires the introduction of biological therapies, in addition to a psychological approach to the problem and the implementation of aid programs for the social and occupational integration of the patient[8]. The classical antipsychotics are the principal drugs prescribed since the 1950s for treating the disease, haloperidol being the prototype of the group with extensive clinical experience[9]. These drugs have an important capacity to modify the positive symptomatology of schizophrenia, though they are of scant efficacy in treating the negative, affective and cognitive manifestations, and may even cause the latter to worsen. Moreover, their use is associated with the frequent appearance of extrapyramidal symptoms that affect patient adhesion to treatment – thereby worsening the prognosis of the disease. A particularly frequent and serious extrapyramidal symptom is late dyskinesia[10].

Olanzapine, the drug evaluated in the present study, belongs to a more recently introduced group of substances called «atypical antipsychotics». This new drug group is characterized by a lesser affinity for type 2 dopaminergic receptor (D2) block, and a high affinity mainly for 5HT2 serotoninergic receptors and other brain receptors[11]. This receptor binding profile explains the fewer extrapyramidal effects of these drugs and their capacity to reduce negative symptoms, among others.

Olanzapine offers superior efficacy in the global management of schizophrenia versus haloperidol, with a lesser incidence of side effects[12,13]. It is effective against both negative symptoms[14] and depressive manifestations[15,16], and improves cognitive function[17,18]. Likewise, the drug affords effective maintenance of patient response over the long term[19,20], with fewer side effects and an efficacy equivalent or superior to that of haloperidol[13,21-23]. Olanzapine is therefore considered to be a safe and effective drug for the treatment of schizophrenia[24,25].

In its guide of 2002, the National Institute of Clinical Excellence (NICE) in the United Kingdom established a series of guidelines for the use of atypical antipsychotics in the treatment of schizophrenia[26]. Of the NICE indications, mention should be made of the use of atypical antipsychotics as drugs of choice in the first outbreak of the disease, as well as in those patients with serious adverse effects, relapses or an unsatisfactory response to treatment with classical antipsychotics. The group of new antipsychotics is characterized by a higher purchasing cost than the conventional antipsychotics. The NICE recommends these drugs despite their increased cost, pointing out that the latter represents only a small portion of the total cost of treatment.

The present article analyzes the economic impact of schizophrenia and bipolar disorder, focusing on those aspects that largely contribute to the total cost associated with the disease. Likewise, a description is made of the principal pharmacoeconomical studies relating to olanzapine treatment, along with the articles comparing the drug with haloperidol and risperidone. To this effect, an evaluation has been made of the principal studies determining how olanzapine treatment influences the total cost of the disease. Complete economic evaluations of olanzapine are therefore presented, excluding those studies that only make reference to the cost of the drug. The literature search strategy involved consultation of the following databases: Medline (PubMed), Medes, Embase, Biosis Previews, SciSearch, and PsycInfo by the Bibliographical Service of laboratorios Lilly, S. A. The complete economic evaluations performed with olanzapine were obtained using the following key words in the context of the literature searches: health economics, antipsychotic agents, haloperidol, olanzapine, risperidone, cost-benefit analysis, cost-effectiveness, schizophrenia, bipolar disorder, manic-depressive disorder, psychotic disorders. The search included articles published up until June 19, 2003. A total of 16 complete economic evaluations were identified comparing olanzapine with haloperidol or risperidone, and have been reflected in the present study. On the contrary, no study has been identified that analyzes the economic impact of olanzapine compared with haloperidol or risperidone in the treatment of bipolar disorder.

ECONOMIC IMPACT OF SCHIZOPHRENIA

The costs associated with a disease are often classified as direct and indirect costs. The former are in turn divided into health care and non-health care costs. Direct health care costs are those directly related to health care intervention, e.g., hospitalization costs, or drug and diagnostic test costs. Direct non-health care costs are represented by the cost of transport to hospital, home care, social services, and other interventions. In turn, the indirect costs are related to loss or reduction of productivity due to morbidity or premature death attributable to the disease or its treatment[27].

Schizophrenia has a considerable economic impact, not only for the patient but also for his family, and for society as a whole. This impact is mainly attributable to the following factors: early appearance of the disease, its high prevalence, chronic character, effect upon the working capacity of the affected individual, the incapacity to live independently, a high treatment abandonment rate, and frequent hospitalization[28,29]. The costs associated with schizophrenic patient care and treatment are very high; indeed, schizophrenia is considered to be the most expensive mental disorder to treat[30-32]. In the United States, schizophrenia accounts for 22 % of the costs associated with mental pathology, and 2.5 % of global health care expenditure[33].

An increasing number of studies have identified and quantified the economic repercussions of schizophrenia[2,29,34]. The principal direct costs are attributable to the cost of hospitalization, medical consultation, diagnostic tests and drug costs[29,31,35]. Of these, hospitalization generates the most important costs[36,37,38]. In contrast, drug cost only represents 1-6% of the total direct costs in developed countries[2].

The indirect costs of schizophrenia are mainly attributable to productivity losses for both the patient and relatives, mortality and morbidity[28]. Many authors consider that the indirect costs associated with schizophrenia may be even greater than the direct costs[35-37]. In addition, there are other costs, including those related with social welfare services and costs derived from legal problems, which are classified by different authors as either direct non-health care costs or indirect costs[2]. table 1 summarizes the principal costs associated with schizophrenia.

The study of the costs of the disease can be made from the perspective of incidence or prevalence[31,40]. The former focuses on cost from the moment in which the first diagnosis of the disease is made until death or some other defined endpoint. In a study conducted in the United Kingdom from the perspective of incidence[38], the total cost of schizophrenia per patient throughout the duration of the disease ranged from 7,900 pounds (£) to 536,000 £ per patient (values corresponding to 1990/1991), depending on the type and duration of the schizophrenic episodes. Of this total cost, the direct costs ranged from 1,700 to 316,000 £ and the indirect costs from 6,200 to 220,000 £.

When the aim is to determine the total cost of a disease in a given period of time (generally one year), and then estimate the global cost to society (referred to all patient) from the data obtained, the design of choice is a prevalence-based model. Studies of this type establish the total annual cost of the disease in the United States at values that range from $ 32,5 billion (direct costs: $ 17 billion, values for 1990) or $ 65 billion (direct costs: $ 19 billion, values for 1991)[33,39]. The differences in the estimations are due to the different methods used to attribute the indirect costs of the disease.

Few data are available on the costs of schizophrenia in Spain. Agustench et al. developed a method for estimating the costs of schizophrenia in Navarre, based on a bottom-up approach in the context of an incidence model[41]. The bottom-up design is based on the documentation of real cases, estimating the costs per individual and then extrapolating them to the total sample to determine the global cost. The results of this study indicate that the cost of the disease 1, 2 or 3 years after the diagnosis totals 7,395, 5,567 and 4,002 euros, respectively (data for 1994). The analysis of the data in particular shows the scant relative impact of medication, and the great importance of hospital resources. During the first year after diagnosis, drug costs represented 6.1 % of the direct costs, while hospital resources accounted for 51.4 % of the direct costs. Table 2 shows the main conclusions drawn by the economic impact studies commented in the present work.

A comparison of the costs of schizophrenia in Spain during a 3 year period between an area with fully developed mental health community programs (area A) and another without such programs (area B) showed the direct costs in area A to be 35 % less than in area B in the first year, 16.4 % less during the second year, and 12.2 % greater in the third year[42].

TABLE 1. Types of costs associated with schizophrenic disease

Direct costs
Medical
Hospitalization
Antispsychotics and drugs for palliating adverse effects
Medical vists
Out-hospital care (specialist consultations, emergencies)
Diagnosis and laboratory test
Non-medical
Patient transport
Home care
Social services
Indirect costs
Disease or death related productivity losses
Patient caretaker productivity losses
Other costs
Intangible costs of pain and suffering
Time spent by patient caretakers
Criminal justice services*

* Some authors classify these as non-medical direct costs or indirect costs. (Foster and Goa, 1999; Frankerburg and Hegarty, 1996).

ECONOMIC EVALUATIONS OF OLANZAPINE

One of the main problems facing the different health care systems is the limitation of financial resources. It is therefore a priority concern to optimize the use of such resources to ensure maximum profitability while maintaining or even improving quality in the provision of services.

Thus, when deciding to prescribe a given treatment, it is necessary to take into consideration not only the data obtained from therapeutic evaluations but also the results derived from pharmacoeconomical studies in order to identify therapies in which the additional benefits afforded compensate an increased cost, i.e., those treatments offering a more favorable cost-effectiveness ratio. However, the increase in therapeutic innovation seen in recent years, and the intensive use of increasingly restricted resources is often not accompanied by adequate evaluation of their effectiveness and economic repercussions.

In the beginning of the 90's, the introduction of clozapine in the United States generated controversy among clinicians, due to the increased price of this atypical

TABLE 2. Economic impact of schizophrenia

Reference	*Design*	*Country*	*Year of monetary value*	*Direct costs*	*Indirect costs*
Davies and Drummond, 1994	Incidence	UK	1990/1991	1,700-316,000 £*	6,200-220,000 £*
Rice and Miller, 1996	Prevalence	USA	1990	17 billion $	15,5 billion $
Wyatt et al., 1995	Prevalence	USA	1991	19 billion $	46 billion $
Agustench et al., 2000	Incidence	Spain	1994	3,455-1,937-1,720 €**	1,247-1,374-572 €**

*According to the type of schizophrenia and outcome. **Costs one, two or three years after the diagnosis.

antipsychotic compared with the classical drug substances. Debate thus emerged as to whether the increase in efficacy afforded compensated the increased cost of treatment[43]. Although atypical antipsychotics in general are more expensive than the classical antipsychotic agents, it should be remembered that this expense constitutes only a small part of the total cost of treating the disease[44,45]. As has already been mentioned, this drug cost has been estimated to represent 1%-6% of the direct costs of the disease in developed countries[2]. Therefore, treatment which improves the symptoms of schizophrenia and reduces patient dependency and incapacitation, i.e., which reduces both the direct and indirect costs of the disease, will have a beneficial effect on the reduction of the total cost of management - i.e., such therapy will offer a superior cost-effectiveness ratio despite its increased purchasing price. In the economic evaluation of the atypical antipsychotics, and specifically of olanzapine, an additional aspect to be taken into account is the fact that these substances reduce the extrapyramidal effects. This in turn leads to improved patient tolerance and a lesser dropout rate, as well as a reduction in the number of hospital admissions and relapses, and in the costs associated with the latter.

A study conducted in Spain presents the results of the economic evaluation of olanzapine based on a «mirror» design in patients with resistant schizophrenia to conventional antipsychotics[46]. The costs were determined analyzing resource consumption 6 months before and 6 months after the start of treatment with olanzapine. The total direct costs before treatment with olanzapine were 5,314 €, this figure being similar to the costs recorded after treatment with olanzapine (5,114 €) – the difference being non-significant. The cost of the medication during the treatment period (911 €) was compensated by a reduction in the hospitalization costs (from 4,635 to 3,608 €), due to a lesser incidence of hospital admissions.

Many studies have analyzed the economic impact of olanzapine in the treatment of schizophrenia, compared with other antipsychotics including haloperidol and risperidone. A number of reviews have also been published[2,25,34,43,47-49]. The different studies are in turn based on different methodological approaches, adapting cost analysis to the health care system of the country involved. Table 3 summarizes the 16 economic evaluations analyzed in the present study.

Comparison with haloperidol

Three studies[50-52] are based on economic analyses of data recorded in an international multicenter and double-blind trial[13] conducted in patients with schizophrenia, schizophreniform disorder or schizoaffective alterations who satisfied the DSM-III-R criterion (Diagnostic and Statistical Manual of Mental Disorders, revision III) and presented a minimum score of 18 on the Brief Psychiatric Rating Scale (BPRS). In the study, a total of 1996 patients were randomly assigned to treatment with olanzapine or haloperidol. All subjects who showed symptoms response and tolerated the medication during the acute phase (the first 6 weeks of the study) were in turn selected for a second maintenance phase (46 additional weeks). The first phase of the trial (acute phase) was completed by 66.5% of the patients administered olanzapine, and by 46.8% ($p<0.0001$) of those who received haloperidol - while in the second phase treatment was completed by 54.3% of the patients who received olanzapine, and by 44.5% of those given haloperidol ($p=0.06$). Olanzapine showed an important and superior efficacy profile in the treatment of schizophrenic psychopathology, with substantially better performance than haloperidol - statistically significant advantages being observed in olanzapine therapy with respect to changes in negative symptoms, a reduction of extrapyramidal effects and actions on prolactin levels, and in patient response rate.

Glazer and Johnstone conducted a cost analysis involving 817 patients in the United States belonging to the previous trial[50]. In the first six weeks of the acute phase of treatment, the mean cost attributable to hospitalization, ambulatory care and drugs was significantly lower among the patients administered olanzapine than in those given haloperidol ($p=0.026$). Specifically, the difference totaled 431 $ (values for 1995) per month. During the 46 weeks of the extension phase of the study, the cost analysis was limited to those patients who responded to treatment. In this phase the costs associated with olanzapine were likewise lower ($ 345 per month), though the difference failed to reach statistical significance.

The second study, based on the work of Tollefson et al., was conducted in the same sample of patients as in the previous survey, and estimated drug costs together with the hospital and outpatient medical costs[51]. The study was based on the improvements obtained on the

TABLE 3. Summary of the principal characteristics of the economic evaluations of olanzapine

Reference	*Drugs (mg/day)*	*Size of study population*	*Design*	*Study period*	*Country*	*Most efficient option*
Glazer and Johnstone, 1997	HAL (5-20) OLZ (5-20)	817 patients	General costs analysis	52 weeks	USA	OLZ > HAL
Hamilton et al., 1999	HAL (5-20) OLZ (5-20)	817 patients	General costs analysis	52 weeks	USA	OLZ > HAL
Tunis et al., 1999	HAL (5-20) OLZ (5-20)	1,155 patients	Cost-effectiveness analysis	52 weeks	USA	OLZ > HAL
Sacristán et al., 1997	HAL (5-20) OLZ (5-20)	Hypothetical patient cohort	Cost-effectiveness based on a Markov decision model	5 years	Spain	OLZ > HAL
Le Pen et al., 1999	HAL (11.5 ± 4) OLZ (12.9 ± 4.3)	275 patients	General costs analysis	52 weeks	France	OLZ > HAL
Almond and O'Donnell., 2000	HAL (15) OLZ (10) RSP (6)	Hypothetical patient cohort	Markov decision model	5 years	UK	OLZ ~ HAL ~ RSP
Jerrell, 2002	HAL (14.2 ± 8.9) OLZ (12.9 ± 4.5) RSP (4.7 ± 1.7)	108 patients	Cost-effiectiveness	12 months	USA	HAL > OLZ ~ RSP
Fuller et al., 2002	OLZ (11.5 ± 5.5) RSP (3.3 ± 1.8)	610 patients	Retrospective costs analysis	2 years	USA	RSP > OLZ
Lewis et al., 2001	OLZ (12.7 ± 5.2) RSP (5.6 ± 1.75) CLZ (378 ± 141)	91 patients	General costs analysis	10 months	UK	RSP > OLZ > CLZ
Lecomte et al., 2000	HAL (10) OLZ (15) RSP (5)	Hypothetical patient cohort	Semi-Markov simulation model	1 years	Belgium	RSP > HAL > OLZ
Byerly et al., 2003	OLZ (18) RSP (3.5)	70 patients	Before and after treatment costs analysis	18 months	USA	RSP > OLZ
Edgell et al., 2000	OLZ (10-20) RSP (4-12)	150 patients	General costs analysis	28 weeks	USA	OLZ > RSP
Karki et al., 2001	OLZ (17 ± 4) RSP (6 ± 2) CLZ (481 ± 183)	150 patients	Cost-effectiveness analysis	6 months	USA	OLZ > CLZ > RSP
Palmer et al., 1998	HAL (15) OLZ (10) RSP (6)	Hypothetical patient cohort	Cost-effectiveness based on a Markov decision model	5 years	USA	OLZ > HAL > RSP
Palmer et al., 2002	HAL (15) OLZ (10) RSP (6)	Hypothetical patient cohort	Cost-effectiveness based on a Markov decision model	5 years	Mexico	OLZ ~ RSP > HAL
Zhao, 2002	OLZ (10.5 ± 4.6) RSP (4 ± 3.4)	1,333 patients	Retrospective costs analysis	1 year	USA	OLZ > RSP

OLZ: olanzapine; HAL: haloperidol; RSP: risperidone; CLZ: clozapine; >: costs analysis favorable to: ~: minimum differences (costs practically the same).

BPRS scale and on the determination of quality of life (QLS). Treatment with olanzapine during the acute phase led to a cost reduction of $ 388 per patient (values for 1995, p = 0.033). During the maintenance phase the cost reduction totaled $ 636 (p = 0.128) in favour of olanzapine.

Tunis et al., carried out a cost-effectiveness analysis in 1,155 patients from English-speaking countries belonging to the study of Tollefson et al., effectiveness being measured according to the changes obtained in the SF-36 health questionnaire scores (Medical Outcomes Study Short Form)[52]. The total costs (per patient) during the 52 weeks of treatment were $ 9,387 less for olanzapine than with haloperidol. Olanzapine produced 5.75 units of improvement in physical health and 1.66 units of improvement in mental health versus haloperidol – yielding a cost-effectiveness increment ratio of $ 1,633 in savings for each point of improvement on the physical health scale, and $ 5,655 in savings for each point of improvement on the mental health scale for olanzapine versus haloperidol.

In Spain a clinical decision study was made based on the Markov model and designed to evaluate the cost-effectiveness of olanzapine versus haloperidol over a period of five years[53]. The study was carried out in schizophrenics patients, and included as efficacy measure the months of partial-complete remission achieved, accor-

ding to the results of the BPRS scale. The analysis, which included the direct medical costs, showed the mean cost-effectiveness of olanzapine according to the BPRS scale to be 700.03 euros for each month of partial-complete remission, compared with 809.94 euros in the case of haloperidol (values for 1995). The patients treated with olanzapine showed 6.7 months more of partial-complete remission than the group treated with haloperidol, yielding an incremental cost with olanzapine of 195.43 euros for each additional month of partial-complete remission versus haloperidol.

Another Markov decision model was used to determine the cost-effectiveness of therapy with haloperidol, olanzapine or risperidone in Mexican schizophrenic patients[54]. The direct medical costs were incorporated to the model, and clinical improvement based on the BPRS scale was used as efficacy indicator, together with the absence of relapses. During a five-year period, the costs totaled 196,620 pesos for haloperidol, 225,100 pesos for olanzapine and 226,700 pesos in the case of risperidone. Olanzapine was found to be slightly superior in terms of effectiveness. The cost-effectiveness increment of olanzapine versus haloperidol was 52,740 pesos per patient improved (based on the results of the BPRS) and 212,540 pesos per relapse avoided. The cost-effectiveness increment of olanzapine versus risperidone was not calculated in the study. These results are in agreement with those published by other authors[55,56], and are summarized in table 3.

Comparison with risperidone

Although the literature offers numerous economic evaluations confronting classical and atypical antipsychotics, fewer studies are to be found in which comparisons are made within the same therapeutic group. Furthermore, the results of comparisons between atypical antipsychotics are not always conclusive.

Some studies have found risperidone to be more favorable than olanzapine. Fuller et al. compared the different costs generated 1 year before the start of treatment versus 1 year after the start of therapy in 325 patients treated with risperidone and 285 patients administered olanzapine[57]. The total costs decreased $ 1,536 in the case of risperidone, and increased $ 4,217 in the case of olanzapine, after the start of treatment. This difference was particularly attributed to the drug and hospitalization costs.

Lewis et al. analyzed costs and services utilization in patients diagnosed with schizophrenia according to the DSM-IV criterion, over a ten-month period. Thirty-one patients received clozapine, while 41 were treated with olanzapine, and 19 received risperidone[58]. The patients in the olanzapine group and in the clozapine series respectively showed greater mean monthly costs of $ 566 and $ 246 compared with the patients treated with risperidone, though the differences were not statistically significant.

Lecompte and Cookson in turn conducted an economic review of olanzapine and risperidone applying what they defined as more realistic doses, used in routine clinical practice (olanzapine 15 mg/day, and risperidone 4-6 mg/day), to some of the economic evaluations published in the literature[59]. The study concluded that risperidone should be regarded as the treatment of first choice in patients with schizophrenia, based on economic and efficacy criteria. Other articles also support the above conclusions, attributing similar or lesser costs to treatment with risperidone versus olanzapine[60,61].

However, other studies show the results of the economic analyses are favorable to olanzapine versus risperidone. In the United States, a double-blind multicenter prospective study was carried out in 150 patients diagnosed with schizophrenia, schizophreniform disorder or schizoaffective alterations according to the DSM-IV, and who yielded a minimum score on the BPRS scale of 42 points[62]. The patients were randomly divided into two equal groups, each receiving olanzapine or risperidone. The group treated with olanzapine showed clinical improvement, with savings in the costs of hospital and ambulatory care. These savings compensated the differences in drug purchasing cost between olanzapine and risperidone. Specifically, the drug costs for olanzapine were $ 2,513 versus $ 1,581 in the case of risperidone ($p < 0.001$). This difference was compensated by a reduction of $ 3,774 (or 52%) in the costs associated with hospital and ambulatory patient care. The total cost per patient in this study, with a duration of 28 weeks, was $ 2,843 less in the case of olanzapine versus treatment with risperidone ($ 5,141 versus $ 7,984, i.e., 36% less; values for 1997) ($p = 0.342$).

In 2001, Karki et al. analyzed the cost-effectiveness of three atypical antipsychotics (olanzapine, risperidone and clozapine) in seriously mentally ill patients with schizophrenia and schizoaffective disorders[63]. An open prospective design was used with the purpose of evaluating not only effectiveness but also the safety of the different treatments. The patients who failed to respond to conventional antipsychotics received one of the mentioned three atypical antipsychotics – evaluations being made at the start of treatment and after 6 months of therapy, based on the BPRS. Cost-effectiveness was calculated dividing the monthly cost of medication between the changes in BPRS scores. The cost-effectiveness results in dollars per unit change in BPRS were 2.91, 4.13 and 2.41 for clozapine, risperidone and olanzapine, respectively. The difference between risperidone and olanzapine was statistically significant ($p = 0.036$). Likewise, a multidirectional sensitivity analysis was made based on variable doses and effectiveness (BPRS result). The data obtained showed that olanzapine would be even more cost-effective in the event of a 25% reduction in risperidone dose and a 25% increase in olanzapine dose. However, on increasing the efficacy of risperidone 20% and reducing that of olanzapine 20%, the former drug would be more cost-effective - the sensitivity analysis thus indicating that cost-effectiveness of the atypical antipsychotics analyzed is much more sensitive to changes in clinical efficacy than to the costs of the medication.

In 1998 the results were published corresponding to a Markov model developed to estimate the medical costs and effectiveness of three antipsychotic treatments (haloperidol, olanzapine and risperidone) in patients with schizophrenia during a period of 5 years[64]. The estimations of the model parameters were based on data from clinical trials, the medical literature and, where necessary, clinical criterion. The costs analyzed were the direct costs, and effectiveness was assessed based on three indicators: the BPRS scale, years of life adjusted for quality, and the absence of relapses. The results indicated that after a period of five years, the patients treated with olanzapine had 6.8 additional months without incapacitation, compared with the group treated with haloperidol, and 1.6 weeks compared with those given risperidone. The estimated medical cost during the five year period associated to therapy with olanzapine was $ 1,539 less than with haloperidol, and $ 1,875 less than in the risperidone group. Sensitivity analysis showed the model to be sensitive to both changes in drug cost and to reductions in hospital stay. The results therefore indicated that treatment with olanzapine is both less expensive and affords greater efficacy than therapy with either haloperidol or risperidone. Other pharmacoeconomical analyses conducted with risperidone and olanzapine likewise point to olanzapine as a cost-effective option versus risperidone[65], or report only minimal differences between both[66].

ECONOMIC ANALYSES OF OLANZAPINE IN BIPOLAR DISORDER

Bipolar disorder, or manic-depressive disease, is characterized by depressive episodes (sadness, hopelessness, loss of interest, fatigue, etc.) alternating with manic episodes (delirium, ideas of grandeur, unusual irritability, increased libido, reduced need for sleep, etc.). The existence of a single maniac episode in the life of a patient is regarded as bipolar disorder. The prevalence of this pathology ranges from 0.8-1.6%[67]. Patients presenting a manic episode require medical treatment, and often also hospitalization, in order to control the symptoms and guarantee patient safety[68]. Manic episodes appearing in the course of bipolar disorder constitute a burden for society in terms of hospitalization and treatment costs, and also have an important impact on productivity[69].

Wyatt and Henter, in an economic analysis in 1991, estimated the total cost of the disease in manic-depressive adults in the United States[70]. The cost totaled $ 45 billion of which $ 7 billion corresponded to direct costs, and the remaining $ 38 billion to indirect costs in which employee productivity losses or suicide had a great weight ($ 17 billion and $ 8 billion, respectively).

Another study conducted in the United States and based on an incidence model estimated the global cost of type I bipolar disorder (or moderate or severe manic-depressive episode) throughout the lifetime of the patient as being equivalent to $ 24 billion. $ 13,3 billion corresponded to direct costs (e.g., hospitalization and outpatient costs), and $ 10,7 billion corresponded to indirect costs (e.g., unemployment, and alcohol and drug abuse)[71]. The mean cost per case ranged from $ 11,720 in the case of patients with a single manic episode to $ 624,785 in the case of chronic episodes or patients refractory to treatment.

Lithium is the most widely used treatment for bipolar disorder, and is used as a mood stabilizer. Antiseizure drugs are also used (valproic acid, carbamazepine), along with calcium channel blockers, antidepressive drugs and cholinergic agents, among others[72]. In addition to schizophrenia, olanzapine is also indicated for the treatment of moderate to severe manic-depressive episodes (i.e., type I bipolar disorder)[73]. The prevalence of such conditions is estimated to be 0.4%-1.6% in the United States[74]. In Spain, a study estimated the prevalence of the disease based on calculation of the consumption of daily lithium carbonate doses prescribed per 100,000 inhabitants during the period 1996-1998[75]. The prevalence thus obtained for type I bipolar disorder was 70 cases/1,000,000 inhabitants/day.

There are few studies that have estimated the economic impact of olanzapine in the treatment of bipolar disorder. In the literature review performed, there has not been identified any study that analyzes the economic impact of olanzapine compared with haloperidol or risperidone in the treatment of bipolar disorder. A recent study in which the economic impact of olanzapine was evaluated in patients diagnosed with type I bipolar disorder with mania or mixed episodes[69]. The design comprised an acute phase of three weeks followed by 49 weeks of open extension therapy in which the use of lithium and fluoxetine was allowed when considered necessary. In the study, 70 patients were randomized to treatment with olanzapine, and 69 to placebo, and improvements in the clinical symptoms were determined by the Young Mania Rating Scale (YMRS). During the acute phase, the group treated with olanzapine showed statistically significant improvement based on the YMRS compared with the placebo group. In the open extension phase, the olanzapine cohort presented a statistically significant improvement of 11.8 units on the YMRS from the end of the acute phase. Compared with the 12 months prior to treatment, olanzapine therapy implied savings of almost $ 900 a month during the 49 weeks of the open extension phase. These savings were mainly attributable to the reduction in hospital costs in the second period of the study. Specifically, the total cost per month in the case of olanzapine during the 49 weeks of treatment was $ 649, compared with 1,533 $ during the 12 months prior to treatment ($p < 0.01$). The hospitalization and ambulatory costs per month during the 49 weeks of the open extension phase of the study were respectively $ 248 and $ 73, versus $ 1,179 and $ 354 during the 12 months prior to the study ($p < 0.01$). The study concludes that, from an economic point of view, olanzapine

may be considered a cost-effective for use in this type of patients.

Olanzapine has also been subject to recent comparison with sodium divalproate, with the purpose of analyzing the costs associated with its use in the management of acute mania associated with bipolar disorder in a double-blind randomized clinical trial that had a duration of 12 weeks[76]. Although the ambulatory costs in the divalproate group were lower than in the olanzapine series ($ 541 and $ 1,080, respectively; p = 0.004); no significant differences were observed in the total medical costs between the two groups (divalproate: $ 13,703; olanzapine: $ 15,180; p = 0.88).

CONCLUSIONS

Schizophrenia implies an important cost to society, mainly as a result of the early patient age at onset of the disease, its chronic nature, the family dependence caused, and the frequent hospitalizations required. In this context, hospital costs represent the principal direct costs associated with schizophrenia; a reduction of the latter is therefore essential in order to curb the global expense generated by this disease. In the reduction of hospitalization costs a fundamental consideration is the prescription of effective pharmacological treatment. The drug administered must as far as possible reduce serious side effects that limit its use, since such effects lead to patient non-compliance and thus contribute to the appearance of relapses and the need for hospitalization - with the increases in global cost this implies. It is also important to stress the relevance of indirect costs in schizophrenia. In effect, the typically early patient age at onset of the disease leads to decades of severe incapacitation with two main repercussions: difficulty in finding and/or keeping an employment, and a lack of independence caused by the disease – thereby obliging the patient to live with relatives, with the associated economic losses this implies.

Olanzapine reduces the adverse symptoms associated with schizophrenia. This reduction in turn contributes to reduce the costs generated by the disease and improve patient quality of life. The increased cost of the drug substance is compensated by the reduction in extrapyramidal effects, which in turn favors tolerance and patient adhesion to therapy, decreasing the number of relapses and hospitalizations. The reduction in adverse effects and the superior therapeutic efficacy compared with haloperidol in the treatment of the negative and depressive symptoms make olanzapine the drug of choice both in the treatment of the acute phase of schizophrenia and in maintaining patient response to treatment.

The need to perform economic evaluations of marketed medications is not totally extended among health care professionals. In the particular case of selecting an atypical antipsychotic, the limited pharmacoeconomical analyses available in many cases often makes the high price limit their use compared with the conventional drugs, in spite of greater therapeutical advantages. The present study has evaluated whether the increased acquisition cost of olanzapine is compensated by a reduction in other costs, as a result of the improvements in disease treatment afforded. In this context, an analysis has been made of the principal pharmacoeconomical studies published to date and involving olanzapine in comparison with two substances widely used in the routine clinical management of schizophrenia: haloperidol and risperidone.

The studies analyzed lead to the conclusion that olanzapine affords a reduction in the total cost of treatment of schizophrenia versus haloperidol. The high purchasing cost of the former drug is mainly compensated by a reduction in hospitalization costs - thus reflecting the cost-effectiveness advantages of olanzapine for the management of schizophrenia in comparison with haloperidol.

In the economic evaluations comparing olanzapine and risperidone, the results are not conclusive. A possible explanation for the observed discrepancy is that the results of pharmacoeconomical analyses depend - among other factors - on the variables considered, the study scenario contemplated, and the prescription regimen involved (e.g., the dose used), and these parameters vary considerably from one study to another.

Olanzapine is also indicated for the treatment of bipolar disorder. Although the pharmacoeconomical studies of olanzapine in relation to this disease are limited, recent analyses emphasize the hospitalization cost reductions afforded by treatment with olanzapine.

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