

Cost-effectiveness of different clinical interventions for reducing the burden of schizophrenia in Spain

Gutierrez-Recacha P, Chisholm D, Haro JM, Salvador-Carulla L, Ayuso-Mateos JL. Cost-effectiveness of different clinical interventions for reducing the burden of schizophrenia in Spain.

Objective: To estimate the cost-effectiveness of interventions for reducing the burden of schizophrenia in Spain.

Method: The study examined the cost-effectiveness of seven different types of clinical interventions at the level of Spanish population: i) current situation; ii) older antipsychotics alone; iii) new antipsychotics alone (risperidone); iv) older antipsychotics plus psychosocial treatment; v) new antipsychotics plus psychosocial treatment; vi) older antipsychotics plus case management and psychosocial treatment; vii) new antipsychotics plus case management and psychosocial treatment.

Results: Interventions based on the combination of haloperidol with psychosocial treatment or psychosocial treatment plus case management proved to be the most efficient strategies.

Conclusion: The relatively modest additional cost of concurrent psychosocial treatment has significant health gains, thereby making such a combined strategy for schizophrenia more cost-effective than pharmacology alone.

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Significant outcomes

- The addition of a psychosocial treatment to pharmacotherapy increases both the efficacy and the cost-effectiveness of interventions for reducing the burden of schizophrenia.
- The advantages derived from the addition of psychosocial treatments seem to be far more pronounced than those derived from simply switching from older to newer antipsychotics.
- It is necessary to rethink the controversy over the cost-effectiveness of interventions with older vs. newer antipsychotics due to the appearance of generic atypical antipsychotics.

Limitations

- Epidemiological and outcome data have been extrapolated from either regional studies or international meta-analyses.
- The use of the disability-adjusted life years as a measure of health gain may not cover the full range of consequences that may follow an intervention.
- Social and economic variations limit comparisons with other country-level studies.

Introduction

A classic World Health Organization (WHO) study on incidence in the early 1980s examined the presence of the disorder in ten different countries. Using a restrictive case definition of schizophrenia, the study estimated an approximate mean incidence of 10 per 100 000 inhabitants per year (1). The Global Burden of Disease Project (GBD) reports a world percentage prevalence of 0.4% for schizophrenia (2). In a recent 14-country study on disability associated with physical and mental conditions, positive symptoms of schizophrenia (active psychosis) were ranked the third most disabling condition, higher than paraplegia and blindness, by the general population (3). In the GBD study, schizophrenia accounted for 1.1% of total disability-adjusted life years (DALYs) and 2.8% of years lived with disability. The economic cost of schizophrenia to society is high. The estimated cost of schizophrenia to the USA in 1991 was US\$19 billion in direct expenditure and US\$46 billion in lost productivity (2). Schizophrenia is an expensive illness to treat even in developing countries (4). However, data on the burden of disease, whether expressed in epidemiological or in economic terms, is an insufficient basis for allocating resources and setting priorities for action. Effectiveness studies, such as the recent Pan-European Schizophrenia Out-patient Health Outcomes (5–7), tend to find superior effects and better tolerability outcomes in pharmacological treatment with atypical antipsychotics. The prescription of atypicals increases (8), but their use implies higher costs than those associated with older antipsychotics. Cost-effectiveness analysis of current intervention strategies, including consideration of the amount of burden that can be avoided, should be an integral part of mental health system evaluation, which can provide an accurate basis for allocation decisions. The relative cost-effectiveness of different treatments for schizophrenia has recently been studied in a number of articles focusing on different populations (9–13).

Aims of the study

In the present study, for the first time in the area of schizophrenia management, a population level analysis is applied to assess the cost-effectiveness of seven clinical interventions (current situation, older antipsychotics alone, new antipsychotics alone, older antipsychotics plus psychosocial treatment, new antipsychotics plus psychosocial

treatment, older antipsychotics plus case management and psychosocial treatment, and new antipsychotics plus case management and psychosocial treatment) at the level of the Spanish population.

Material and methods

Cost-effectiveness framework

The methodology developed by the GBD project not only facilitates analysis of worldwide diseases in terms of global burden (14–16). Disability measures, such as DALYs, also make it possible to carry out a differential analysis of diverse interventions on certain diseases in terms of cost-effectiveness. The WHO is currently engaged in a project entitled Choosing Interventions that are Cost-effective. Using uniform methodology, the project has generated cost-effectiveness data in 14 epidemiological subregions of the world regarding key interventions capable of reducing leading contributors to disease burden (<http://www.who.int/choice/en/>). A standardized approach for cost-effectiveness analysis has been developed for all interventions in different settings (17). In this national-level application of the methodology, intervention costs and effects were modelled for the total Spanish population in the year 2000. Demographic information on the general population in Spain and its distribution by sex and age group in the year 2000 was taken from the census elaborated by the Spanish National Statistics Institute (Instituto Nacional de Estadística or INE; <http://www.ine.es>).

Scenario of interventions

A number of possible interventions at the level of the Spanish population were considered in this analysis. The current scenario was defined as that characterized by the treatment patterns used in Spain in the year 2000 regarding the use of antipsychotics with estimates provided by International Marketing Services Health España. In this year, 39% were receiving conventional oral antipsychotics (haloperidol), 29% risperidone, 15% olanzapine and 16% depot antipsychotics. Six types of alternative interventions were considered for the cost-effectiveness analysis: older antipsychotics alone, new antipsychotics alone, older antipsychotics plus psychosocial treatment, new antipsychotics plus psychosocial treatment, older antipsychotics plus case management and psychosocial treatment, and new antipsychotics plus case management and psychosocial treatment.

Population model for schizophrenia

Intervention effectiveness was determined via a state-transition population model, PopMod (17). Key transition rates included the incidence of schizophrenia in the population, case fatality and remission (defined as full recovery of a case). Moreover, a disability weight was specified (on a 0–1 scale, where 0 equals no disability) for time spent in different states of health (such as acute psychosis).

Using a lifetime analytic horizon, but with a treatment implementation period of just 10 years, population-level effects were derived by comparing total number of healthy years lived by the population with and without intervention. The difference between these two simulations represents the population-level health gain (DALYs averted) resulting from the intervention, compared with doing nothing. In addition to the base-case analysis, the impact of social preferences was evaluated via non-uniform age weights (which give less weight to years lived at younger and older ages), and a 3% discount rate.

Epidemiology and natural history of schizophrenia

Details on the methods used for the estimation of the epidemiology of schizophrenia in the general population of Spain have been described elsewhere (18). Briefly, the main sources for the estimation of incidence of schizophrenia in Spain were the findings of a complete prospective follow-up study by Vázquez-Barquero et al. (19) in Spain's northern region of Cantabria. The population selected included all patients suffering from a first episode of schizophrenia who, over a 2-year period, had had their first dealings with any of Cantabria's public mental health services. Annual incidence [0.80 new cases of schizophrenia per 10 000 inhabitants per year (general population) or 1.9 new cases per 10 000 inhabitants per year (if only the age range for population at risk is considered)] are consistent both with international data (1) and with figures reported in other Spanish epidemiological studies carried out in different regions (20, 21).

Based on these incidence figures, an estimate of the prevalence of schizophrenia in Spain's population was calculated using the WHO's disease modelling tool for burden estimates and projections, DisMod II (22). The resulting prevalence was 3.0 per 1000 inhabitants per year for men, and the slightly lower figure of 2.86 per 1000 inhabitants per year for women. Although there are no rigorous Spanish studies providing prevalence

estimations for the entire population, results are coherent with prevalence figures for schizophrenia included in the Spanish Psychiatric Case Registers (PCRs) for a number of different Spanish provinces (23).

With regard to remission – defined as full, terminal remission (i.e. persons who are no longer a case, and return to being a 'susceptible' member of the population) – the GBD study used two different rates across age/sex groups: one for developed countries (10%), and another for developing countries (29%), both calculated for a period of 11.5 years. The instantaneous rate per person in a developed country was estimated at 0.010 (1 per 100). This percentage seems to be consistent with other studies involving similar definitions of the term 'remission'.

Case fatality rates were calculated based on a standardized mortality ratio of 1.4. The lack of any rigorous Spanish research into the relative risk of mortality and remission in patients with schizophrenia led us to accept GBD 2000 study estimates, which were based on the most recently available meta-analysis of excess mortality in mental disorders (24).

Since the long-term course and outcome of schizophrenia is as variable as its symptoms, it is possible to distinguish a number of main patterns of course for schizophrenia (each with a discrete disability weight that can be multiplied by the proportion of total cases to give an average disability weight). However, there is a lack of data on the differential effect of specific treatments on these different patterns of course. Moreover, the principal interest underlying this study is to model the effect of interventions on the 'average' case at the population level. Accordingly, a single disability weight was applied for the disorder.

Estimation of intervention effectiveness

The main effect of intervention is to reduce psychotic symptoms, which implies diminishing of associated disabilities (via changes in disability weight, compared with untreated schizophrenia). These changes can be modelled using the approach described by Andrews et al. (25), which makes it possible to convert effect sizes from treatment trials (standardized mean differences between intervention and control groups) into changes in disability weight.

Efficacy and extrapyramidal side effects of new and conventional antipsychotics compared with placebo has been estimated in a complete meta-analysis of randomized controlled trials (26). Change in the Brief Psychiatric Rating Scale

(BPRS) scores and use of anti-Parkinsonian medication were selected as outcome measures. The results of this meta-analysis are shown in terms of effect sizes, which makes them particularly suitable for the purpose of this study. Haloperidol was chosen as being representative of conventional antipsychotics, whereas four atypical neuroleptics were considered: olanzapine, quetiapine, risperidone and sertindole. In order to simplify the analysis, just one of the four new antipsychotic drugs selected by Leucht et al. was considered. Risperidone, the first second-generation antipsychotic widely used in Spain, was the choice. The effect sizes estimated by Leucht et al. were originally presented as Pearson's correlation coefficients (r). Converted to Cohen's coefficients (d), the effect sizes obtained for haloperidol and risperidone were $d = 0.465$ and $d = 0.495$ respectively. An estimate of the magnitude of the supportive effect derived from the addition of a psychosocial intervention (family therapy, social skills training and cognitive behavioural therapy) to the conventional drug treatment can also be found in a complete meta-analysis (27). The additive effect size value calculated was $d = 0.39$. Finally, two Cochrane systematic reviews by Marshall et al., one for case management (28) and another for assertive community treatment (29), were considered. Neither model shows a strong impact on clinical or social outcome. A minimum additional effect size of only $d = 0.05$ was estimated over combined pharMO/psychosocial therapy.

Estimation of intervention costs

WHO-CHOICE advocates an 'ingredients' approach to the costing of health interventions, which requires separate identification and valuation of the quantity of resource inputs needed (such as numbers of health personnel) and the price or unit cost of these resource inputs (such as the salary of a health professional) (30). Compared with doing nothing (no intervention costs or effects), two main categories of resource input and cost are incurred. Patient costs refer to all resource inputs consumed or provided at the level of the patient or provider facility (e.g. hospital in-patient days, out-patient visits, medications, laboratory tests, etc.); the unit costs of these patient-level resource inputs include the cost per in-patient day or out-patient visit, or the price of prescribed drugs and any laboratory tests carried out. Programme costs are resources used in the production of an intervention at a level above that of the patient or providing facility; these resources include central planning, policy and administration

functions, as well as resources devoted to training health providers and preventative programmes.

Programme-level resource quantities are based on existing guidelines (e.g. in relation to duration of training). A set of unit costs for each resource item in Spain has also been generated in order to calculate total costs of programme-level activities. The unit costs for the Spanish health system were developed by the PSICOST, a research group specialized in the standardized evaluation of social and health services and costs in mental health and disability (31, 32). These units have been used in the economic analysis of mental health interventions in Spain (33, 34). All these cost components are assembled and calculated within a series of cost-template sheets (CostIt) developed specifically for WHO-CHOICE (available at http://www.who.int/choice/toolkit/cost_it/en/index.html). All baseline analysis costs for the 10-year implementation period were discounted at 3%. Baseline and resulting costs were originally expressed in euros. For this text, they have been converted to US\$, using the exchange rate of 31 December 2000: 1US\$ = 1.062 euros. However, costs are also expressed in international dollars (I\$) of 2000 when they are compared with international results. An I\$ is a hypothetical currency that has the same purchasing power as the US\$ in the USA and has been proposed by the WHO-CHOICE program as a means of translating and comparing costs from one country to other using a common reference point, the US\$. Costs in local currency units are converted to I\$ using purchasing power parity (PPP) exchange rates. The PPP exchange rate used here was developed by the WHO (<http://www.who.int/choice/costs/ppp/en/index.html>).

Sensitivity and uncertainty analysis

One-way sensitivity analyses were performed to determine the impact on final cost-effectiveness analysis of analytical social preferences, such as discounting and age weighting. In addition, a $\pm 10\%$ change in the disability weight effect size associated with every treatment was considered. Finally, two different costs per dose were estimated for risperidone: first, considering its price as a branded drug; secondly, considering its price as a generic, non-branded drug. Since generic versions of risperidone have just recently appeared on the Spanish mental health market, they were not available in the year 2000, the date this study is set. However, by pondering the prices of the different versions of generic risperidone currently available on the Spanish market, a minimum price

for the year 2000 was estimated: US\$0.59 per 2-mg dose, whereas the estimated cost of the same dose of branded risperidone was US\$1.66. The purpose of this sensitivity analysis is to determine whether the variation in cost per dose resulting from the appearance of generic versions of newer antipsychotics causes a significant variation in the estimated cost-effectiveness of those interventions involving atypical neuroleptics.

Additionally, uncertainty analyses were performed using the software tool McLeague, provided by WHO-CHOICE. This software represents uncertainty regarding costs and effects for decision-makers in the form of stochastic league tables. It provides additional information beyond what is offered by the traditional treatment of uncertainty in cost-effectiveness analysis, presenting the probability that each intervention is included in the optimal intervention mix for given levels of resource availability. The software program allows for covariance between costs and outcomes in the analysis. Outputs include stochastic league tables and graphs presenting the probability of inclusion of independent sets of mutually exclusive interventions in the optimal mix of interventions at different levels of resources availability.

Results

Intervention effects

Total DALYs averted annually by different schizophrenia treatments in Spain are reported in Table 1. Current interventions avert 3008 DALYs. Alternative interventions are estimated to avert between 3302 (conventional antipsychotics) and 8538 DALYs (risperidone plus case management and psychosocial treatment), when no age weight or discount are considered. With the discount, the range varies from 2808 to 7259 for the same interventions. When both age weight and discount are considered, the DALYs averted ranges from 3315 to 8571.

Differences in effectiveness of the seven interventions were remarkable. Risperidone proved to be slightly more effective than haloperidol, while the addition of supporting psychosocial treatment considerably increased the amount of health gain achieved. Case management only had a small extra impact over and above psychosocial support.

Intervention costs

Table 2 shows the estimated intervention costs per year. Total cost for each intervention is divided into three components: cost per patient, cost associated with the programme, and costs associated with specialized training. The cost calculated for the whole Spanish population in the current situation was US\$198 million (210 million euros). Total costs for alternative interventions ranged from US\$152 million (conventional antipsychotics) to US\$304 million (risperidone plus case management and psychosocial intervention). Interventions based on risperidone incur costs remarkably higher than those based on haloperidol. However, as expected, the use of a generic drug causes a pronounced drop in the cost of the interventions based on risperidone: from US\$274 to 182 million (pharmacotherapy alone), from US\$289 to 196 million (risperidone plus psychosocial intervention), and from US\$304 to 211 million (risperidone plus case management and psychosocial intervention). The addition of either psychosocial treatment or a case management programme did not remarkably increase the costs associated with each intervention.

Finally, costs obtained per treated case per year range from US\$1446 (older antipsychotics) to US\$2898 (risperidone plus psychosocial treatment and case management). The cost obtained for the current scenario was US\$2421.

Intervention cost-effectiveness

When total population-level costs and effects are merged to produce average cost-effectiveness ratios (CERs), it becomes apparent that interventions

Table 1. Total disability-adjusted life years (DALYs) averted annually by different treatments in Spain

Description of intervention	Effectiveness (DALYs averted per year)		
	Age weighted, discounted	Discounted	No age weight, undiscounted
Current situation	3020	2558	3008
Conventional antipsychotics at 90% coverage	3315	2808	3302
Risperidone (patented or generic) at 90% coverage	4033	3416	4018
Conventional antipsychotics + psychosocial treatment at 90% coverage	6531	5532	6506
Risperidone (patented or generic) + psychosocial treatment at 90% coverage	7662	6489	7632
Conventional antipsychotics + psychosocial treatment + case management at 90% coverage	8296	7027	8264
Risperidone (patented or generic) + psychosocial treatment + case management at 90% coverage	8571	7259	8538

Table 2. Intervention costs in US\$ of year 2000

Description of intervention	Costs (millions of US\$ per year)			
	Patient	Programme	Training	Total
Current situation	194	4	0	198
Conventional antipsychotics at 90% coverage	140	7	5	152
Risperidone (patented) at 90% coverage	263	7	5	274
Risperidone (generic) at 90% coverage	170	7	5	182
Conventional antipsychotics + psychosocial treatment at 90% coverage	144	7	10	161
Risperidone (patented) + psychosocial treatment at 90% coverage	272	7	10	289
Risperidone (generic) + psychosocial treatment at 90% coverage	179	7	10	196
Conventional antipsychotics + psychosocial treatment + case management at 90% coverage	182	11	15	208
Risperidone (patented) + psychosocial treatment + case management at 90% coverage	279	11	15	304
Risperidone (generic) + psychosocial treatment + case management at 90% coverage	186	11	15	211

Table 3. Cost-effectiveness of interventions in Spain in US\$

Description of intervention	Average cost per DALY averted (US\$)		
	Age weighted, discounted	Discounted	No age weight, undiscounted
Current situation	65 519	77 354	65 774
Conventional antipsychotics at 90% coverage	45 833	54 112	46 011
Risperidone (patented) at 90% coverage	68 087	80 386	68 351
Risperidone (generic) at 90% coverage	45 022	53 154	45 197
Conventional antipsychotics + psychosocial treatment at 90% coverage	24 722	29 186	24 818
Risperidone (patented) + psychosocial treatment at 90% coverage	37 713	44 525	37 859
Risperidone (generic) + psychosocial treatment at 90% coverage	25 571	30 190	25 670
Conventional antipsychotics + psychosocial treatment + case management at 90% coverage	25 069	29 598	25 166
Risperidone (patented) + psychosocial treatment + case management at 90% coverage	35 525	41 942	35 663
Risperidone (generic) + psychosocial treatment + case management at 90% coverage	24 672	29 128	24 767

based on the combination of haloperidol with psychosocial treatment or on the combination of haloperidol with psychosocial treatment plus case management, are both the most efficient strategies (each averted DALY costing US\$24 818 and US\$25 166 respectively). According to the results, the highest cost per averted DALY is found in the treatment based on patented risperidone without psychosocial intervention or case management (US\$68 351). Ratios of cost-effectiveness for the remaining interventions were approximately similar (all expressed in US\$ per DALY saved): US\$46 011 (conventional antipsychotics); US\$37 859 (risperidone plus psychosocial treatment); US\$35 663 (risperidone plus case management and psychosocial treatment). The current scenario in Spain implies a ratio of US\$65 774 per DALY averted. The use of a generic drug would reduce significantly the cost per DALY averted in interventions with risperidone, resulting in ratios similar to those found for interventions involving conventional antipsychotics. In fact, intervention with generic risperidone plus psychosocial treatment plus case management turns out to be the most cost-effective option, with a ratio of US\$24,767 per DALY averted. Results after applying age weight and discounting are given in Table 3.

Sensitivity analysis

A summary of the results obtained from the sensitivity analysis is given in Fig. 1. As it can be seen, main changes are due to the modification of social preferences and the substitution of a generic drug for the branded version of risperidone. Changes in treatment effect sizes did not cause remarkable variation in the final results.

Discussion

Limits and limitations of economic modelling

Due to the lack of rigorous Spanish studies at a national level, most epidemiological and outcome data have been extrapolated from either regional studies or international meta-analyses. However, until such time as robust evidence at a genuinely national level becomes available, these results can be seen as a valuable way of providing evidence-based guidance to evaluate the differential cost-effectiveness of schizophrenia treatments in Spain.

Use of a population-level measure of health gain, such as the DALY, has advantages – in terms of comparability with other diseases, for instance – but does not encompass the full range of consequences

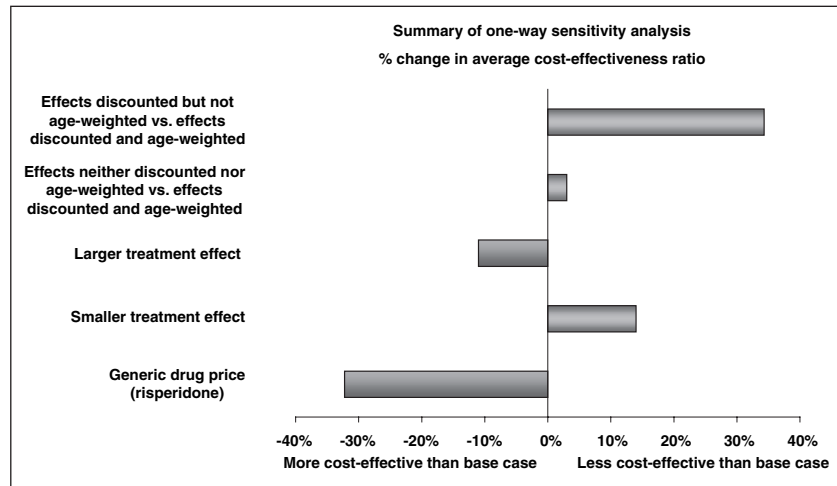


Fig. 1. Sensitivity analysis. Summary of results.

that may follow an intervention. In the context of schizophrenia, important additional benefits of treatment include reduction of family burden (including informal care-giving time) and reduced absenteeism and unemployment (productivity). Despite the pursuit of a societal perspective in WHO-CHOICE, considerable challenges in the measurement of productivity gains, as well as patient and informal carer time spent seeking or providing care, have precluded their valuation in the present analysis (17).

Health system uses of sectoral cost-effectiveness analysis

The present study sets out to examine the cost-effectiveness of interventions capable of reducing the burden of schizophrenia. The purpose of such an exercise is to locate the relative position of effective and applicable interventions for this disorder within a wider cost-effectiveness and priority-setting framework in the healthcare sector. Such information is particularly useful at a national level. A number of studies have examined the differential cost-effectiveness of a variety of schizophrenia interventions in different countries, such as Australia (11–13), Mexico (10) and Spain (36). However, the effectiveness criterion chosen by Sacristan et al. in their study on Spanish population relied on the measure of months with partial remission, since the GBD method was not available for cost-effectiveness analysis at the time the study was published. This methodology has hitherto never been applied to a schizophrenia study in the Spanish population. As for costs, the calculated mean cost for the current scenario (US\$2421) is coherent with other estimates for schizophrenia in the Spanish population obtained in different studies: US\$2300–4200 (33) and US\$2243 (34).

Comparative cost-effectiveness of interventions for schizophrenia

The treatments analysed in this cost-effectiveness study of interventions for schizophrenia enabled us to make three key comparisons: older vs. newer antipsychotics (risperidone); combined pharmacotherapy and psychosocial treatment vs. pharmacotherapy alone; and combined pharmacotherapy and case management (including psychosocial treatment) vs. pharmacotherapy alone. A higher effectiveness is expected for those interventions involving risperidone as evidence shows that risperidone is more likely to produce an improvement in the Positive and Negative Symptom Scale, to reduce relapse, and to show significantly fewer general movement disorders compared with haloperidol (37). Due to the high costs of atypical neuroleptics, interventions with haloperidol turned out to be more cost-effective in the results. However, when a generic drug is substituted for branded risperidone, costs are approximately equal, and there are no remarkable differences in cost-effectiveness between haloperidol and generic risperidone.

Concurrent psychosocial treatment along with antipsychotics is expected to improve the cost-effectiveness for schizophrenia, as a result of better compliance and because the additional costs of psychosocial treatment are largely offset by a reduced probability of admission to hospital. Finally, the addition of case management programmes seems to provide an improvement in cost-effectiveness similar to that reached by the addition of psychosocial treatment alone.

Expressed in relation to gross national income, the CER found in this study falls between one and three times the gross Spanish income per capita (US\$18 842) except for the current scenario and

one alternative intervention (risperidone). Thus, most of the alternative interventions fall within a range considered by the Commission on Macroeconomics and Health (38) to be 'cost-effective' (less than three times gross national income per capita), and only one would be regarded as 'not cost-effective' (more than three times gross national income per capita).

Comparisons with other country-level studies are limited by social and economic variations and different methodological approaches. International cost-effectiveness studies evaluate effectiveness using a range of criteria – improvement in BPRS outcomes (10), variation of years lived with the disorder (35), etc. – but only those which provide estimations in terms of costs per DALY averted should be considered in order to ensure the validity of the comparison. Older neuroleptics and newer antipsychotics are compared in terms of cost-effectiveness in a recent study of the Australian population (13). According to the estimates provided by Magnus et al., replacing typical neuroleptics with risperidone implies an incremental CER of US\$48 000. According to the results found in this study, this change of treatment would increase the cost per averted DALY (considering age discount, as Magnus et al. do) by between US\$12 344 – when both psychosocial treatment and case management are applied – and US\$26 273 when only drug treatment is applied. Both estimates seem to be coherent, since some of the conclusions that the same authors reached analysing the supportive role of cost-effectiveness methodology in making mental health priority decisions (39) are close to the findings of this study; particularly, those referring to the improvement in cost-effectiveness due to the use of concurrent psychosocial treatment and the decrease in cost-effectiveness due to the widespread use of new neuroleptics as treatment of first choice.

Compared with other treatments analysed using the WHO-CHOICE methodology, schizophrenia interventions have a higher ratio of cost to health outcomes. Estimated costs for averted DALY in schizophrenia range between I\$34 662 and I\$95 463 which largely exceed the average cost for bipolar disorder interventions (for developed subregions I\$ cost per averted DALY ranges between I\$5487 and I\$21 123) (40). Disparity found in cost-effectiveness for schizophrenia compared with bipolar disorder is not accounted for by overall costs of treatment (I\$8.4–17.6 million per million of the population for bipolar disorder interventions, compared with I\$5–10.5 million per million of the population for the schizophrenia interventions considered in this study) but by discrepancies in effectiveness: the

total number of DALYs averted with the alternative schizophrenia interventions considered varied from 82 to 211 per million of the total population, whereas bipolar disorder interventions averted between 375 and 517 DALYs. These differences are even more relevant when comparing the results of the present study with those corresponding to depression interventions, as the average cost for averted DALY in primary care-based depression interventions is estimated to range from I\$1600 to I\$1700 (41). Nevertheless, comparison between cost-effectiveness results for the three disorders is clearly limited by methodological differences: whereas the estimates in this study are calculated for a particular country-level population (Spain), the figures provided for bipolar disorder and depression come from aggregate-level studies considering populations from different subregions, in which greater heterogeneity should be expected. In any case, the restricted reduction of the total burden of schizophrenia provided by the interventions considered in the present study points to a clear limitation of antipsychotic treatments and a need to further develop pharmacological and psychosocial approaches capable of delivering improved long-term functioning.

Our analysis, therefore, leads to a relevant conclusion for clinical practice: the addition of a psychosocial treatment – alone or as part of a case management programme – to pharmacotherapy – involving either older or newer antipsychotics – not only increases the efficacy of the intervention, but also its cost-effectiveness (results obtained from the uncertainty analysis confirm this conclusion: first, clouds associated with interventions including psychosocial treatment, and those associated with interventions that do not include it, fail to overlap; secondly, in the resulting stochastic league table obtained, interventions with psychosocial treatment are the first-choice alternative for resource levels over US\$141 million – graphics are not presented in this paper but are available on request from the authors). Consequently, results show the convenience of implementing psychosocial strategies to complement current pharmacological interventions, since the benefits derived from the addition of this concurrent treatment seem to be far more pronounced than those derived from simply switching from older to newer antipsychotics. In addition, this study also highlights the need to rethink the controversy over the cost-effectiveness of interventions with older vs. newer antipsychotics, due to the appearance on mental health markets of a new kind of atypical neuroleptics, sold at a generic, non-branded price.

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