Fundación BBVA

Reducing the Burden of Mental Illness in Spain

Population-Level Impact and Cost-Effectiveness of Treatments in Depression and Schizophrenia

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Summary
Resumen

The present study aims to estimate the cost-effectiveness of interventions for reducing the burden of depression and schizophrenia in Spain and evaluate their population level impact. The study examines the cost-effectiveness of different types of clinical interventions at the level of the Spanish population. For depression, the interventions considered are the following: 1) tricyclic antidepressants (imipramine); 2) SSRIs (fluoxetine); 3) psychotherapy; 4) tricyclic antidepressants plus psychotherapy; 5) SSRIs plus psychotherapy; 6) proactive collaboration management with tricyclic antidepressants; and 7) proactive collaboration management with SSRIs. In our analysis, interventions based on tricyclic antidepressants turned out to be the most cost-efficient option. For schizophrenia, the interventions considered are the following: 1) current situation; 2) older antipsychotics alone; 3) new antipsychotics alone (risperidone); 4) older antipsychotics plus psychosocial treatment; 5) new antipsychotics plus psychosocial treatment; 6) older antipsychotics plus case management and psychosocial treatment; and 7) new antipsychotics plus case management and psychosocial treatment. Interventions based on the combination of old antipsychotics with psychosocial treatment or psychosocial treatment plus case management proved to be the most efficient strategies according to our analysis.

El presente estudio pretende estimar el coste-efectividad de las intervenciones para reducir la carga asociada a la depresión y la esquizofrenia en España y evaluar su impacto a nivel poblacional. El estudio examina el coste-efectividad de diferentes tipos de intervenciones en la población española. Para depresión, las intervenciones consideradas son las siguientes: 1) antidepresivos tricíclicos (imipramina); 2) ISRSs (fluoxetina); 3) psicoterapia; 4) tricíclicos más psicoterapia; 5) ISRSs más psicoterapia; 6) manejo colaborativo proactivo con tricíclicos; 7) manejo colaborativo proactivo con ISRSs. En nuestro análisis, la intervención basada en antidepresivos tricíclicos resulta la opción más coste-efectiva. Para esquizofrenia, las intervenciones consideradas son las siguientes: 1) situación actual; 2) antipsicóticos típicos por separado; 3) antipsicóticos atípicos por separado (risperidona); 4) antipsicóticos típicos más tratamiento psicosocial; 5) antipsicóticos atípicos más tratamiento psicosocial; 6) antipsicóticos típicos más programa de continuidad de cuidados más tratamiento psicosocial; 7) antipsicóticos atípicos más programa de continuidad de cuidados más tratamiento psicosocial. Las intervenciones basadas en una combinación de antipsicóticos típicos y tratamiento psicosocial o tratamiento psicosocial y programa de continuidad de cuidados resultan las estrategias más eficientes según nuestro análisis.

Introduction

The Global Burden of Disease (GBD) study conducted by the World Health Organization (Murray and Lopez 1996) brought neuropsychiatric diseases to the forefront of the public health field. Part of the originality of the study's approach lay in the decision to set as a health measure for populations a combination of data regarding mortality caused by the different pathologies, and data on disabilities suffered by affected people. *Disability-Adjusted Life Years,* or DALYs, were used as a summarised measure of the populations' health. DALYs make it possible to jointly assess mortal and non-mortal consequences of each of the pathologies under study. When this measure was used to estimate the burden of disease, the proportion linked to world mental illnesses was found to be 10.5% of the 1990 total. The latest estimates by our research group, in collaboration with the WHO, corresponding to the year 2000, indicate that depressive disorders account for 4.5% of the global burden of disease in the world (65 million DALYs in all); this places the burden on par with ischemic heart disease, diarrhoea-related diseases, or the combined impact of asthma and Chronic Obstructive Pulmonary Disease (COPD). According to the classification based on life *Years Lost due to Disability* (YLD), four mental disorders appear among the top 10: unipolar depressive disorders, schizophrenia, alcohol abuse disorder and bipolar disorder (World Health Organization 2001a; Ustun et al. 2004a). WHO projections to 2020 indicate that the relative importance of mental disorders will account for 15% of the total, due primarily to longer life expectancy of the population and to a reduction in the burden attributable to infectious diseases.

What can be done to reduce the burden of mental disorders, and at what cost? First of all, in order to reduce burden it is necessary to have information about mental health intervention strategies that are effective, that can be generalised and adopted by the healthcare system where they are going to be implemented. There are many available tests regarding the effectiveness and the costs of a wide range of drug and psychosocial interventions for treating and managing these disorders. When it comes to deciding which of these are the most appropriate for addressing health problems from a population perspective, one of the criteria to be taken into account is the advantage of the choice in terms of cost-effectiveness. Cost-effectiveness analysis is an economic assessment technique where the effects of two or more healthcare technologies are compared in terms of natural units of effectiveness, while costs are assessed in monetary units. The following pages of this introduction provide a more detailed description of the cost-effectiveness method and its application in the healthcare field. The methods used in burden of disease studies allow us to have a single unit of effectiveness—like the DALYs mentioned above—for comparing different interventions with regard to the same pathology. However, methods based on individual preferences have also been used in the economic assessment of healthcare technologies. There are various generic healthcare-related *Quality of Life* (QoL) measures with Spanish versions that have been correctly validated (Badia 1995), but only one of them—EuroQol (Gaminde and Cabasés 1996)—offers measurement units, called *Quality-Adjusted Life Years* (QALYs), that also take into account years of life and are useful for cost-effectiveness analy-

sis. Another recent instrument, the SF-36, is one of the generic scales with the greatest potential for use in assessing clinical results. This instrument also has a validated Spanish version (Alonso, Prieto and Anto 1995) and has been used in the field of mental disorders among the general population (Ayuso-Mateos et al. 1999). Although it was designed to assess a health profile, it has managed to offer a synthetic index based on individual preferences of a sample of health conditions using the Visual Analogue Scale (VAS) and the standard set, after first reducing the health profile to six dimensions (Brazier et al. 1998).

In order to perform systematic comparisons, the World Health Organization set up the WHO-CHOICE (*CHOosing Interventions that are Cost-Effective*) project, proposing a cost-effectiveness analysis model for interventions in the healthcare field. The main characteristics of this project are also described in the following pages of this introduction.

Given the high prevalence of mental disorders and the wide diversity of intervention strategies involved, one of the criteria to be taken into account in the decision-making process within a healthcare system should be based, among other aspects, on the cost of the different options and their cost-effectiveness. Until now, most complete economic assessments in mental health have focused on specific treatment modes for psychosis and mood disorders, in particular on the cost-effectiveness analysis of different drug treatments (Knapp et al. 2002; Hotopf, Lewis and Normand 1996). Only recently have psychotherapeutic interventions (Patel et al. 2003) and healthcare organizational models in primary care (Simon, Katon and VonKorff 2001) been included in these analyses. Our research group has included these interventions in the studies it has carried out as part of the WHO-CHOICE programme focusing on depression disorders and schizophrenia.

COST-EFFECTIVENESS ANALYSIS AND HEALTH

Cost-effectiveness analysis involves a technique for selecting an option from amongst a group of competitive strategies in a setting of restricted resources. This tool was originally applied in the military, but obviously its usefulness can easily be extended to other areas, such as, for example, the clinical environment (Warner and Hutton 1980). The need to establish some type of priority when allocating resources is becoming more and more important in the healthcare field, for three basic reasons (Vos et al. 2005):

- The growing amount of evidence pointing to the fact that the present use of resources is far from optimal.
- The constant growth in mental health expenses, both in absolute terms and percentage-wise.
- The desire to avoid the possibility that government resource-allocation decisions will not cover their intended social objectives.

In a scenario marked by a drive to minimise the resources used, a method for deciding which clinical interventions can be implemented as efficiently as possible given this situation is becoming more and more necessary. Cost-effectiveness analyses can be a useful tool for such a purpose. The goal of any cost-effectiveness analysis can be defined either as the maximization, for a given level of available resources, of the aggregate health benefits to be achieved with them, or the minimization, given a total level of health benefits defined as a target, of the costs involved in achieving this target (Weinstein and Stason 1977).

The technique used in cost-effectiveness analysis provides the link between the cost and effectiveness of a certain intervention. The former is quantified in monetary units. To calculate costs adequately, one must take into account that health expenses and health benefits usually occur at different times, with a certain time lapse between them. Such a situation makes it advisable for analysts to apply a specific discount rate to costs associated with previous years to account for the loss of value experienced by the monetary unit during the interval being considered. This loss of value is due to two basic factors: first, inflation (one dollar in 1999, for instance, could buy more goods and services than that same dollar in 2000), and second, the fact that at the present time, if the dollars allocated to costs had not been spent, they could have been invested productively, yielding interest to be earned in the future. Although widespread consensus appears to exist among economists with regard

to the need to apply discount rates when estimating costs, certain discrepancies exist when it comes to defining *how* they should be estimated (Weinstein and Stason 1977). Moreover, in addition to direct costs (e.g., the cost of drugs applied in the intervention), it is possible to take indirect costs (or earnings) into consideration, such as the possible effect of the intervention on patients' ability to perform their work (Drummond et al. 1997).

Effectiveness can be measured in natural units—e.g, life years, the likelihood of surviving five years after a cancer treatment, loss of weight after an intervention to eliminate obesity (Eddy 1992b)—or through some sort of scale that takes into account various clinically significant dimensions. Weinstein and Stason recommend orienting the estimation of effectiveness based on life prognosis estimates, assessing it in terms of QoL or total years lived, underscoring the need to contemplate subjective values (Weinstein and Stason 1977). David M. Eddy identifies three particularly complex properties that should meet measures of effectiveness in this type of analysis: being able to capture all the necessary information on the nature, frequency and desirability for the patient of all the significant treatment results, including any additional treatment characteristics that may affect its desirability to the patient; and being additive (it should be possible to add the "health units" associated with different patients in order to obtain overall sums) (Eddy 1992c). A measure of effectiveness that has been proposed with notable success is the so-called health-status index. A system of weights (generally ranging from 0 to 1) is used to assess the possible health status of an individual at a given point in time. By multiplying each of these rates by the number of years lived in each status by the individual, we reach an estimate of the total number of years lived in full health by the subject (Weinstein and Stason 1977). QALYs are one of these measures of effectiveness based on health indices (Torrance and Feeny 1989). They assume the existence of two basic dimensions for summarising the result of a treatment: its effect on the duration of the patient's life, and its effect on the patient's QoL. The purpose of the QALY measure is to unify both dimensions and combine them into a single dimension, which can be defined as an "equivalent life duration", in which years lived are weighted as a function of the QoL achieved by the patient. The underlying idea of this measure is that individuals would accept losing a certain number of life years in exchange for living the remainder of their years with a better QoL, which would enable the translation of QoL measures into equivalent time measures (years) (Eddy 1992c). Other units suggesting the same philosophy are DALYs, which the World Bank proposed as a measure of the burden associated with a specific disease (World Bank 1993). These types of measures have the advantage of making it possible to compare a wide range of diseases. An important question that all analysts should ask if they seek to draw general conclusions from their analysis (e.g., when deciding the allocation of resources) is whether all significant interventions have been examined (Drummond et al. 1997).

In short, we can conclude by saying that measures of effectiveness should try to "capture" all the necessary information about the significant dimensions of the results of a treatment (basically, the likelihood of recovery, relative mortality and morbidity, and QoL following treatment). However, in order to be useful, a cost-effectiveness analysis does not have to be absolutely inclusive and consider all the possible dimensions associated with the result of an intervention. On occasion, it is enough to consider a small number of significant dimensions (or even a single dimension), since adding others would make the study more complicated and less comprehensible, depending on the specific case to which it is being applied and the objectives set by the analysts (Eddy 1992c).

Both effectiveness and considered costs are marginal in nature; that is, it is a matter of quantifying the differential effectiveness and cost of one intervention over another (or over a specific situation: a null scenario where no intervention has been applied, the current context of interventions implemented at the present time, etc.). Cost-effectiveness is estimated by means of a ratio that expresses the cost per unit of effectiveness gained by applying the considered intervention. Let's assume we wish to compare a certain intervention (*New Strategy*) with a reference or benchmark intervention (*Benchmark Strategy*). The relevant cost-effectiveness ratio would be calculated as follows:

$$\text{Cost-effectiveness ratio} = \frac{Cost_{\text{New Strategy}} - Cost_{\text{Benchmark Strategy}}}{Effectiveness_{\text{New Strategy}} - Effectiveness_{\text{Benchmark Strategy}}}$$

TABLE 1: Types of decisions where a cost-effectiveness analysis is relevant

Costs / Effectiveness	New, MORE costly strategy	New, LESS costly strategy
New, MORE effective strategy	The application of a cost-effectiveness analysis is RELEVANT	The new strategy DOMINATES the previously implemented one
New, LESS effective strategy	The new strategy IS DOMINATED by the previously implemented one	The application of a cost-effectiveness analysis is RELEVANT

The lower the magnitude of the ratio obtained through this calculation, the more cost-effective the *New Strategy* will be. The technique could be applied to compare other alternative interventions against the benchmark. The strategy with the lowest cost-effectiveness ratio would be the *most cost-effective* strategy. Individual ratios can also be calculated for each intervention by dividing their associated cost by their effectiveness. Moreover, the cost-effectiveness analysis can also be used in absolute terms if we set a few benchmarks and thresholds for comparison. For instance, if the magnitude of the ratios obtained is below a certain predetermined threshold, then we can say that the strategy is *cost-effective*. Different studies can have different thresholds defined by their authors, so the application of the term *cost-effective* would depend on the context (Azimi and Welch 1998). The ratios obtained can also be ordered by magnitude, establishing a classification of the interventions from the lowest to the highest cost per unit of effectiveness, so that the people in charge of implementing interventions can select them sequentially until available resources are depleted.

Given the above explanation, it is easy to deduce in which situations a cost-effectiveness analysis becomes a relevant decision-making tool. If it can demonstrate clearly, when assessing a new intervention, that it is more effective and less costly than the one currently being implemented, then no additional analyses would be required (in such cases, this intervention is said to be *dominant*). The choice would be equally clear if the new intervention were associated with higher costs and less effectiveness (in which case, the intervention would be considered a *dominated* intervention). However, there is a grey area covering those cases where both the cost and the effectiveness of the new intervention are higher or lower than the intervention that is being considered as a benchmark for comparison. In such situations, the cost-effectiveness analysis represents a tool that can shed light on the decision-making process.

Table 1 shows those contexts where the application of a cost-effectiveness analysis is relevant. Table 2 (O'Brien et al. 1997) is slightly more complex than table 1, as it adds the concept of *strong dominance* (when one of the interventions is better than another in terms of both cost and effectiveness, boxes 1-2) and *weak dominance* (either the cost or the effectiveness of both interventions can be considered equivalent, boxes 3-6). Boxes 7-9 indicate those cases where no type of dominance can be determined, and therefore they would require additional information such as that which might be provided by a cost-effectiveness analysis.

The applicability of the results obtained in a cost-effectiveness analysis when making clinically significant decisions in a specific scenario will depend on two questions: To what extent can we expect the effectiveness of the intervention to be similar in both cases—which, in turn, will depend on the extent to which patients considered in the study can be likened to patients affected by the decision that is going to be made, and the extent to which the description of the clinical scenario of the study (interventions considered, way of managing their application, etc.) can be likened to local practices (O'Brien et al. 1997)—and to what extent can we expect costs to be similar in both cases? Hence the need to have specific studies for different countries, and the difficulty of extrapolating the results of cost-effectiveness analyses to other scenarios.

The published literature often identifies the "*cost-effectiveness analysis*" concept with the concept of "*cost-benefit analysis*" or "*cost-utility analysis*". However, there are differences in nuance between these three approximations which should be clarified.

In a *cost-benefit analysis*, effectiveness is always assessed in economic terms, whereas in a cost-effectiveness analysis, it is not necessary to translate clinical measures into monetary units. Adopting the cost-effectiveness analysis perspective therefore

TABLE 2: Nine possible results of comparing two interventions in terms of cost and effectiveness

BOXES **Strong Dominance**: 1 = Accept intervention. 2 = Refuse intervention. **Weak Dominance**: 3, 6 = Accept intervention. 4, 5 = Refuse intervention. No obvious decision: 7 = Does increased effectiveness make up for the increased cost? 8 = Is the reduction in effectiveness acceptable in exchange for the reduction in cost? 9 = Neutrality regarding cost and effectiveness. Are there any other reasons to accept or refuse the intervention?	**Incremental effectiveness of an intervention vs. control**		
Incremental effectiveness of an intervention vs. control	**Higher**	**Equal**	**Lower**
Higher	7	**4**	**2**
Equal	**3**	9	**5**
Lower	**1**	**6**	8

Source: O'Brien et al. (1997).

implies transforming measures such as life years or QoL into economic quantities, for which a basic strategy has traditionally been proposed: taking the annual earnings of a worker as the economic value of one productive life year. However, this approximation has been criticised for not paying attention to the more subjective aspects of health, so the alternative of assessing the individual's willingness to pay in order to reduce the chance of death or disability, or receive compensation for performing hazardous work, has been proposed (Weinstein and Stason 1977). In any case, once the effectiveness of the intervention is quantified in economic terms, it is enough to calculate the difference between this figure and the total costs allocated to it to determine its feasibility. The reduction of subjective measures, or even human lives, to a strictly economic plane is doubtless a restrictive and complex measure which has aroused the suspicion of many decision-makers (Leplege 1992). Therefore, cost-effectiveness analysis, by enabling the use of units of measure of effectiveness encompassing different dimensions, is usually the preferred strategy for decision-makers and analysts. However, it should not be overlooked that any cost-effectiveness analysis implicitly establishes a "price" per unit of health achieved (Eddy 1992b).

The expression *cost-effectiveness analysis*, on the other hand, will identify a specific case or variant of the cost-effectiveness analysis: namely, that in which different measures of the course of the disease are combined in weighted fashion to give rise to a complex index, such as QALYs or equivalent healthy life years (Drummond et al. 1997).

According to Weinstein and Stason, we can affirm that the main advantage of the cost-effectiveness analysis in the health field lies in the fact that values underpinning the allocation of resources are laid bare (Weinstein and Stason 1977), thus facilitating the discussion when it comes down to making decisions. Moreover, the methodology appears flexible enough to address different types of approximation, from a societal perspective, which is inherent to more general policy decisions, to more specific areas (hospitals, specific institutions, etc.). In spite of the multiple advantages described above, the cost-effectiveness analysis method is still far from solving all the problems related to resource allocation.

A large part of the drawbacks associated with the application of these analyses is due as much to methodological faults as to the lack of accuracy in the data input. In order to address the possible effects of this lack of accuracy, the use of sensitivity analyses (techniques that, in short, could be described as the study of the variation in the results of cost-effectiveness analyses when some of the input parameters are changed in a controlled fashion) has become popular. In any case, the precise definition of the treatments to be considered in the analysis avoids many ambiguities and enables a more accurate measurement of both costs and health benefits (Eddy 1992c).

Not all the limitations of cost-effectiveness analyses are attributable to the inaccuracy of the information being processed. Sometimes, these drawbacks arise due to a poor interpretation of the

cost-effectiveness analysis concept itself. Doubilet, Weinstein and McNeil identify two common problem situations (Doubilet, Weinstein and McNeil 1986). The first refers to the use of the expression "cost-effective" in papers where no explicit information is provided about the interventions under discussion, so that one simply tries to justify the affirmation by appealing to qualitative rationales. The second refers to the diversity of meanings that can be attributed to the expression "cost-effectiveness". The authors, providing abundant examples from medical literature, find up to four possible meanings for the expression, namely:

1) *"Cost-effectiveness" as a synonym of cost savings.* According to this criterion, a strategy will only be considered cost-effective if it saves money with regard to those to which it is compared. These types of decisions may be appropriate in an economic or administrative setting, but they are less satisfactory when applied to a clinical setting, where not all the major dimensions to be considered can be reduced without ambiguity to monetary values.
2) *"Cost-effectiveness" as a synonym of effectiveness.* According to this criterion, a strategy will be considered cost-effective if it is more effective in terms of health benefits than those to which it is compared. This is a mistaken use of the term, since adding "cost" to "effectiveness" implies that some form of economic analysis was required.
3) *"Cost-effectiveness" as cost savings with equal (or better) health results.* This criterion is used rather frequently in literature, and interventions that meet it are obviously desirable. However, it becomes an exceedingly restrictive condition when applied to clinical decisions. It would exclude more effective strategies that do not produce cost savings or those that increase effectiveness only marginally while achieving a considerable reduction in costs.
4) *"Cost-effectiveness" as obtaining an added health benefit that makes up for the added cost.* According to this criterion, a strategy is viewed as being "more cost-effective" than another one if it meets one of these three conditions:

   a) It is less costly, and at least as effective, as the other one.
   b) It is more effective and more costly than the other one, and its added benefit makes up for the extra cost.
   c) It is less effective and costly, but the added benefit from the alternative strategy does not make up for the extra cost.

According to the authors, this fourth interpretation is the best suited to the true purpose of a cost-effectiveness analysis. On the other hand, it is the hardest to apply in practice, as it requires complex value judgments from decision-makers when none of the interventions is less costly and more effective than the rest of the alternatives. Doubilet et al. propose the use of the expression "cost-effective" without providing any type of additional clarifications only in those cases that meet condition *a* of the three conditions proposed under criterion *4.* For those others that meet conditions *b* or *c*, they recommend adding some form of clarifying remark referring to the decision-maker's *willingness to pay*, thus qualifying the results obtained (example cited by the authors: "Strategy X is cost-effective provided one is willing to pay at least $30,000 per life year gained").

Finally, Doubilet et al. discuss two mistaken concepts commonly associated with the cost-effectiveness analysis methodology. The first is enunciated as follows: "The strategy with the best (i.e., the lowest) cost-effectiveness ratio is the most cost-effective, and therefore the one that should be adopted." In their opinion, the affirmation conceals two shortcomings. In the first place, it would be necessary to indicate at which cut-off value the strategy becomes cost-effective, or regarding which interventions. In the second, there are no theoretical grounds to justify that the most cost-effective option should be the one that is finally implemented in practice. The authors offer a hypothetical example. Imagine a disease that, if left untreated, causes death within one week. However, if treated with intervention A (which costs $100), life expectancy is one year, and if treated with intervention B (which costs $1,000), life expectancy increases to five years. If we compare intervention B to intervention A, we find that it is less cost-effective, obtaining an incremental ratio of $225 per life year gained: ($1,000 – $100) / (5 years – 1 year). The ratio in this case does not allow the most desirable strategy from a clinical standpoint to be selected, since complex values (prolonging life as one of medicine's

basic goals) come into play in the final decision. As for the second mistaken conception regarding cost-effectiveness analysis pointed out by Doubilet et al., it is formulated thus: "When choosing the most cost-effective alternative among available strategies, it is not necessary to 'make trade-offs' between patients' health and monetary costs." Unless one option is clearly more effective and less costly than the others, this type of discussion is inevitable, so the final decision will inevitably pose a problem that is not only strictly clinical, but also ethical.

In addition to considering the conceptual misinterpretations of the cost-effectiveness methodology, some authors have also recommended that we pay attention to possible biases in the analyses (especially in those sponsored by the pharmaceutical industry) (Hillman et al. 1991; Kassirer and Angell 1994; Azimi and Welch 1998). In drawing up the policy guidelines of *The New England Journal of Medicine*, Kassirer and Angell indicate that cost-effectiveness analyses present a certain hybrid nature that places them halfway between original scientific articles and reviews, participating partially in the characteristics of both. Like the former, they explicitly set out the methods and data used, and the conclusions are based on the results obtained. Like the latter, they allow the use of assumptions when choosing models or selecting collected data that, in the authors' opinion, would be permeable to biases (particularly with regard to the economic side of analyses) (Kassirer and Angell 1994). However, it would not be fair to attribute this risk exclusively to cost-effectiveness analyses; rather, it should be said that they are inherent to clinical research in general (Steinberg 1995).

In a series of articles where reviewing a number of fundamental questions regarding cost-effectiveness analyses, David M. Eddy—under the peculiar guise of a conversation with his father, Maxon H. Eddy, who was also a physician but was sceptical about the benefits of applying this tool—identifies some factors that, in his opinion, would explain the controversy that has sometimes been sparked by the use of this methodology (Eddy 1992a; Eddy 1992b; Eddy 1992c; Eddy 1992d). Eddy establishes four basic categories of factors, which would be as follows:

1) *Clinical reasons.* Many health professionals do not feel very comfortable with the cost-effectiveness methodology. From the clinician's viewpoint, the results obtained from such analyses can sometimes be anti-intuitive, as it is possible for treatments with proven effectiveness not to be cost-effective. The recommendations of a cost-effectiveness analysis, therefore, can sometimes run contrary to the judgment of clinicians, since while clinicians seek to achieve the maximum benefit in terms of health for a single patient or a small group of patients, the recommendations usually seek to maximise the benefit at a population level with limited resources. For the clinician, the priority of each treatment would be determined by the degree of benefit produced in a specific patient (e.g., a life-saving operation would be more important than eliminating cavities). The application of a cost-effectiveness analysis means shifting from the health professional's perspective to that of society as a whole, which would require clinicians to make two assumptions:

   a) Adopting a broad perspective covering a large number of patients, not only those assigned to him.
   b) Thinking in terms of the total volume of different treatments that can be applied with a fixed set of resources.

   Moreover, there is a widespread belief that a global perspective is associated with biases detrimental to those diseases less prevalent among the public. However, in actuality, the measure is independent from the epidemiology: since the numerator and denominator of the cost-effectiveness ratio depend on the number of patients, their possible effects would be cancelled out in the quotient.
2) *Methodological reasons.* We have already spoken of the difficulty in obtaining accurate measures of the costs and benefits in terms of health. Most treatments present benefits (or side effects) that affect different dimensions of health; all of these must be measured and ultimately integrated. In addition, cost-effectiveness analysis relies on the assumption that the health benefits to different individuals are accrued (e.g., a gain of 10 "health units" for a single subject would be assumed to equal a gain of 5 "health units" for two different subjects, something that is, at the very least, debatable: following the example

given earlier, eliminating the risk of death in a small group of patients can be more important than reducing the risk of cavities in a large percentage of the population). Therefore, it is advisable to compare interventions of similar importance using the mentioned cost-effectiveness methodology.

3) *Psychological reasons.* Any novel technique, like cost-effectiveness analysis in the medical field, is usually received with certain scepticism by professionals. This effect is aggravated by the fact that the methodology implies abstract concepts, both mathematical and economic, with which clinicians do not seem to be very familiar (although it could be argued that cost-effectiveness analysis principles have been implicitly applied to traditional medical practice for some time). In many cases, the abstruseness of the results obtained using this technique make it difficult for them to be verified in practice. It is necessary in many cases to have specialists (e.g., statisticians, mathematicians, and economists) interpret the resulting data and determine the priorities, which some clinicians can view as interference. These types of problems would not be exclusive to cost-effectiveness analyses, as they could extend to a long list of multidisciplinary techniques that seek to facilitate decision-making processes in various fields of healthcare (Salvador-Carulla, Haro and Ayuso-Mateos 2006). In addition, a classification of treatments according to their cost-effectiveness can turn some of them into "winners" and others into "losers". It is very likely that clinicians specialising in treatments that are not judged to be cost-effective would, understandably, be wary of the methodology.
4) *Philosophical and political reasons.* These imply personal and social values, which are often mismatched. We have already referred in point 1, by way of example, to the possible conflicts arising between the clinician's viewpoint and a population-based perspective. Besides, political factors subject to public debate can influence decisions deriving from cost-effectiveness analyses. For instance, the technique is useful only if we consider a scenario in which resources are limited. However, if we assume that health outlays can be increased indefinitely, the concept of cost-effectiveness would lose its supposed usefulness.

Another type of controversy refers to the matter of whether the cost-effectiveness method is a useful means of achieving the objectives for which it was proposed. For example, Azimi and Welch question the hypothesis that the application of this technique leads to savings in total health expenditures (Azimi and Welch 1998). Revising 109 articles published between 1990 and 1996 in which a cost-effectiveness ratio was mentioned explicitly, they find that the authors' conclusions for 58 of them (53%) recommended strategies whose implementation required additional investment. As Azimi and Welch themselves acknowledge, the reduction of overall costs is not in itself the main goal of cost-effectiveness analyses; rather, it is more related to the efficient allocation of limited resources (often by establishing a classification of interventions according to their cost-effectiveness, such that those regarded as more cost-effective are applied with preference over those deemed less cost-effective). Even so, the authors note a number of drawbacks that should be taken into account, including the difficulty in accurately determining the total usable budget (i.e., the resources that can be allocated) and the impossibility of providing cost-effectiveness ratios for all the available interventions. In the face of this criticism, it should be noted that the cost-effectiveness study is simply an analytical tool (Eddy 1992b), whose aim is none other than to provide information. It is possible that this information is not always used to achieve the same goals, as the end-goals to be achieved are not always laid out by the analysis methodology, but rather attuned to the specific interests of the decision-maker who will assess its results.

Another type of limitation is inherent to the approach of cost-effectiveness studies. For example, the costs and accrued effects are assessed for a group of individuals (or even entire populations) from the perspective of this methodology, disregarding the study of individual cases (or of cases of highly specific groups of individuals, e.g. marginal minorities) (Weinstein and Stason 1977). Therefore, such fundamental aspects when making decisions like ensuring fairness in the distribution of therapeutic interventions among the members of a population lie beyond the reach of this type of analysis. Their results can be considered as providing orientation in economic terms, but there are also other types of values that determine the final decision.

The well-known Oregon case is a good example of the drawbacks of using cost-effectiveness analyses as the sole criterion when allocating resources. In a bid to optimise the investment provided by a limited Medicaid public health budget, which is geared toward meeting the health needs of the low-income segments of the American population, the Oregon Health Services Commission implemented a priority system based on the application of cost-effectiveness ratios from 1990 to 1996. The proposed resource allocation policy generated such a controversy that it finally had to be withdrawn. In reply to the criticism received, the Commission finally established a selection process where priorities were assigned according to 13 different factors, including—not as the main factor, but as one among the 13—the cost-effectiveness of the interventions. Other factors included by the Commission referred to key issues, such as fairness or the benefit of the majority. Therefore, it would be a mistake to consider that the function of all cost-effectiveness analyses is to determine the allocation of resources by itself, excluding all other criteria. Rather, they should be viewed as a tool providing supplementary information for the decision-making process that should be taken into account, together with other different considerations. The main contribution of these types of techniques is to provide standardised quantitative estimates to facilitate the comparison between interventions (Russell et al. 1996).

Indeed, the disparity of methods used by cost-effectiveness analyses is one of the biggest downsides of this methodology (Udvarhelyi et al. 1992). Various solutions have been proposed to address these controversies and ensure the standardization and comparability of the results. For instance, national guidelines have been developed for cost-effectiveness studies in countries like Canada (Canadian Coordinating Office for Health Technology Assessment 1994) and the UK (Joint Strategy Group of the Government and the Association of the British Pharmaceutical Industry 1994), advising the use of sensitivity analyses. The efforts in America by a panel of cost-effectiveness experts (the Panel on Cost-Effectiveness in Health and Medicine) convened by the US Public Health Service (PHS) are worthy of note. After a consensus process that spread out over 11 meetings and two-and-a-half years involving PHS personnel and methodologists from federal agencies, the panel drew up the conclusions of the discussion in the form of a set of guidelines referring to different aspects of cost-effectiveness analyses (Russell et al. 1996; Weinstein et al. 1996; Siegel et al. 1996):

1) *Nature and limits of the cost-effectiveness analysis.* The panel of experts reflected on some issues relating to cost-effectiveness analyses which we have referred to earlier: the possible perspectives to be adopted (individual or society-centred) and the auxiliary nature of the information provided by this type of methodology to the decision-making process involving the allocation of resources, notwithstanding that other dimensions (ethical, social, etc.) should also be considered. The authors indicate that no single study can provide, by itself, all the information required to compare health services in a wide range of conditions and interventions, so it is vital to ensure the possibility of comparing the different analyses. Hence the advisability of determining certain standards to which the individual studies should be subjected.
2) *Components pertaining to the numerator and denominator in a cost-effectiveness ratio.* By convention, the numerator of the ratio should reflect the changes in the use of resources associated with the application of a given intervention, and the denominator should reflect the resulting health improvements. However, the question is open to certain ambiguity in some cases, like quantifying intervals of time. The authors recommend considering the time individuals invest in finding healthcare or being subjected to treatment as one more component of the intervention that should be assessed in monetary terms as part of the numerator. The time elapsed while the individual suffers from the disease (the period of morbidity), however, would be viewed as a measure of the effect on the patient's health of applying the intervention being considered, and therefore should be included in the denominator.
3) *Measure of numerator terms (costs) in a cost-effectiveness ratio.* The authors underscore the need to assess variations in the use of resources consigned in the numerator of the ratio according to opportunity costs; i.e., in reference to the value that the resources could have produced if they had been invested in the best possible way among the possible alternatives. In addition, the use of constant monetary measures (referring to

a specific year) is recommended to avoid the distortion introduced by inflation. Another matter that can commonly give rise to ambiguity is the quantification of the costs associated with the work force to which individuals pertain. In other words, the common solution of considering a worker's salary to estimate the opportunity cost is hailed by the authors as being appropriate, although they advise that estimates of salary according to the composition of the population by gender and age should be taken into account. Another important issue refers to the inclusion of what the authors call "induced costs" concept, which encompass five different main categories:

- Costs originated by diseases related with the intervention that appear in the life years that would have been lived anyway if the intervention had not been applied (e.g., the cost or savings in treating heart attacks by applying an intervention to control hypertension). Costs originated by diseases not related to the intervention that appear in the life years that would have been lived anyway if the intervention had not been applied.
- Costs related directly to health originated by diseases related to the intervention that appear in the life years added (or subtracted) as a result of applying the intervention.
- Costs related directly to health originated by diseases not related to the intervention that appear in the life years added (or subtracted) as a result of applying the intervention.
- Costs not related directly to health yet linked to the provision of services (food, board, etc.) that occur in the life years added (or subtracted) as a result of applying the intervention.

The authors recommend including the costs associated with diseases related to the intervention, while leaving at the discretion of the analyst the decision of whether or not to consider the costs produced by diseases not related to the intervention. As for costs not directly related to health, the panel of experts does not recommend their inclusion.

4) *Assessment of the health consequences in the denominator of a cost-effectiveness ratio.* The panel of experts recommends the use of measures based on weights according to preferences, like DALYs, but acknowledging at the same time that their application can generate some controversy on an ethical or social plane. These same authors cite the following example: an intervention that would lengthen the life of 80-year-old patients could appear to be "less cost-effective" than an identically effective intervention applied to a group of subjects in their twenties, not only due to the lower number of years gained but also because the QoL of years gained would be lower in the former case.
5) *Estimation of the effectiveness of interventions.* It is possible to obtain valid effectiveness data from different sources: controlled randomised trials, observational studies, uncontrolled experiments or series of descriptions. The authors also recognise that the use of models can constitute a valid and necessary scientific process to estimate these measures, bearing in mind that the models should always be viewed as complementary and not as substitutes for empirical data.
6) *Time preference and discount.* The panel of experts proposes the use of discounts to reflect the regular preference of individuals toward receiving benefits as quickly as they become available. Moreover, they also point out that the empirical evidence seems to demonstrate that this discount rate would hover around 3%, the figure recommended by the authors for cost-effectiveness analyses, although they underscore the convenience of performing sensitivity analyses accounting for the effects on results of a variation in the discount percentage.
7) *Handling uncertainty in cost-effectiveness studies.* Even acknowledging the unit of application of one-way sensitivity analyses, where the value of a single parameter varies each time, the authors point to the convenience of also performing multiway sensibility analyses where the value of several significant parameters is varied simultaneously, thus enabling correlations between them to be uncovered.
8) *Recommendations for presenting results.* For an optimum use of the results of cost-effectiveness analyses, these should be presented according to standardised procedures. The differences in the presentation of results of different analyses could hamper the interpretation and comparison of the information provided.

Although initially the application of the cost-effectiveness analysis technique was characterised by a certain methodological heterogeneity, the appearance of guidelines and standards has vastly improved the possibilities of comparing between studies and their rigor, and therefore their practical usefulness. The following paragraph, taken from the panel of experts from the US Public Health Service, can provide a good summary of the situation by way of conclusion:

> If researchers endeavour to follow a standard set of methods in CEA [cost-effectiveness analysis] and to obtain the required inputs for their studies, much will have been accomplished toward improving the utility of this form of analysis. It is hoped that the recommendations contained here will stimulate rapid progress toward availability of the necessary data and tools, so that the practice of CEA can soon become as established as many other forms of scientific enquiry (Weinstein et al. 1996).

THE WHO-CHOICE PROGRAMME

The functions of the World Health Organization include giving advice to the persons responsible for healthcare policy in each country so that they can have information on which to base priorities for a more efficient allocation of resources. With this purpose in mind, the WHO designed the WHO-CHOICE *(CHOosing Interventions that are Cost-Effective)* programme, which started to be developed in 1998. This programme's basic goals include collecting regional databases on cost, the health impact on the population, and the cost-effectiveness analyses of the main interventions against various diseases (Tan Torres, Baltussen and Adam 2003).

The WHO-CHOICE programme has adopted a *sector-based perspective* regarding the development of cost-effectiveness studies. Thus, for each analysis it has attempted to assess all the possible alternative uses for the available resources in order to offer the authorities in charge of allocation a classification or league table of such alternatives, ordered according to their cost-effectiveness (Hutubessy et al. 2001) and including uncertainty analyses (Baltussen et al. 2002). In this regard the programme can be considered ground-breaking, since until its launch there were very few published analyses adopting such a broad perspective, in spite of the fact that the World Bank had already carried out cost-effectiveness comparisons at the international level to identify priorities in controlling diseases in developing countries (Jamison et al. 1993) and care programmes for nations with different levels of economic development (World Bank 1993). The analyses developed by the Oregon Health Services Commission (Dixon and Welch 1991) and the Harvard Life Saving Project (Tengs et al. 1995) are also worthy of note.

In particular, through the WHO-CHOICE programme the WHO attempted to solve some of the difficulties traditionally faced by authorities in charge of allocating resources in various countries, which can essentially be summarised as follows (Hutubessy, Chisholm and Edejer 2003):

1. *Methodological inconsistencies*. The heterogeneous nature of the methods used until now to assess costs has been a drawback, regarding both the interpretation and the comparison of the results of different studies.
2. *Lack of data*. Of note is the absence of information that has regularly affected certain services and populations (especially in developing countries).
3. *Lack of generalization*. The results of specific cost-effectiveness studies have rarely been presented in a way that can easily be transferred to other scenarios and systems.
4. *Limited technical or implementation capability*. In addition to the shortage of expert personnel capable of performing economic assessments in some settings (developing countries), there are also limited possibilities and (sometimes) interest when it comes to translating the results of the analyses into decisions regarding the allocation of healthcare resources.

Some of these problems could be due to the regular adoption of an incremental perspective when performing cost-effectiveness studies. Incremental cost-effectiveness analyses start off with the present situation in a specific scenario (i.e., considering the alternatives that have been put into practice at the present time) in order to take this context as the point of reference for determining the cost and differential effectiveness associated

with adding or replacing an intervention compared to the alternatives already in place. This approach involves, among others, the following pitfalls (Hutubessy et al. 2002):

- The incremental approach is appropriate when allocation decisions are restricted by the measures already in place (i.e., when it comes to changing them). However, this type of analysis is not helpful in planning long-term policies, and tells us nothing about whether the currently applied interventions are cost-effective or not.
- By taking the interventions already being applied in certain scenarios as the starting point, the use of the incremental analysis is limited to those scenarios, because the alternatives applied to other scenarios do not necessarily have to be the same, thus hindering any generalization.
- The incremental approach does not consider the synergy effect that can arise between different interventions.

In a bid to overcome these obstacles, commonly associated with sector-based studies, the WHO-CHOICE programme adopted the *generalised cost-effectiveness analysis* perspective. The novelty of such a perspective is the consideration of a "null scenario", which would reflect the situation where no type of intervention is applied. The introduction of this null (or "counterfactual") scenario makes it possible to establish a standard with which the different interventions may be compared. The fact that alternative interventions are assessed in relation to the non-intervention situation does not necessarily hamper a hypothetical decision to reallocate resources in the short term (which, *a priori*, would be simpler if based on an incremental analysis; i.e., estimating the marginal variations caused by a change in the intervention currently being implemented in terms of cost and effectiveness). Suffice it to consider the present intervention as one more alternative to be assessed in relation to the null scenario, thus making it possible to establish differential comparisons between the cost-effectiveness of the rest of the operations and the one currently being implemented. Furthermore, a generalised perspective distinguishes the possibility of grouping different interventions that interact in terms of cost-effectiveness (that is, those interventions whose costs or effectiveness changes when applied simultaneously, so that they cannot be considered additive or accruable) with the purpose of assessing not only the cost-effectiveness of individual alternatives, but also the cost-effectiveness of combinations of the various alternatives (Hutubessy, Baltussen, Torres-Edejer and Evans 2002; Hutubessy, Chisholm and Edejer 2003). The WHO-CHOICE programme has developed its own guidelines for applying generalised cost-effectiveness analysis (Murray et al. 2000) and for reducing variability when estimating costs (Adam, Koopmanschap and Evans 2003).

Thus, in addition to the main goal acknowledged by the WHO-CHOICE programme (the search for an efficient allocation of resources), other goals include the need to generalise results and the consideration of long-term effects (Hutubessy, Bendib and Evans 2001). To achieve its objectives, the WHO-CHOICE programme has implemented a series of strategies (Hutubessy, Chisholm and Edejer 2003). These include the development of a set of analytical tools enabling the comparison of studies performed with different methodologies. The *CostIt* (Costing Intervention Templates) software was designed for the purpose of storing and analysing cost data. Its main function is to automatically calculate the economic expense of considered interventions. It consists of a set of templates where costs are consigned at different levels: hospital, service provider, family, and also programme costs—that is, costs generated at the administrative level and not directly linked to the application of healthcare resources to beneficiaries. These costs have regularly been dodged by cost-effectiveness studies thus far (Johns, Baltussen and Hutubessy 2003). *CostIt* uses macros to perform complex calculations, such as automatically converting the costs measured in any year to costs in the base year selected by the analyst, or adjusting costs to different levels of use. The *PopMod* application was designed to model diseases according to different stages of transition, making it possible to simulate the evolution of different cohorts (by age and gender) after applying a given intervention (Lauer et al. 2003).

The WHO-CHOICE programme chose to assess the efficacy of interventions based on the savings they generate in terms of DALYs. One of the advantages of using DALYs as a unit of efficacy is that it enables the analyst to express gains at the population level as a proportion of the current burden of dis-

ease (which is likewise assessed in DALYs). An added advantage is the simplicity of cataloguing an intervention as either cost-effective or not cost-effective. The WHO-CHOICE programme applies the criterion suggested by the WHO Commission on Macroeconomics and Health (Commission on Macroeconomics and Health 2001), which can be summarised as follows:

- If the cost per DALY saved is lower than the annual per capita income of the region or country being considered, the intervention is assumed to be *"highly cost-effective"*.
- If the cost per DALY saved is lower than three times the annual per capita income of the region or country being considered, the intervention is assumed to be *"cost-effective"*.
- If the cost per DALY saved is higher than three times the annual per capita income of the region or country being considered, the intervention is assumed to be *"not cost-effective"*.

The WHO-CHOICE programme established a division of the world's population into 14 epidemiological subregions. The choice of the "subregion" as the geographic unit for carrying out each analysis owes its existence to a compromise between the general and the specific. On one hand, the need to overcome the global approaches used in the past was taken into account, since these approaches provided scant information for decision-making in specific national contexts. On the other hand, the unfeasibility of performing specific studies focusing on each one of the 192 WHO member countries (an objective that is doubtless desirable, yet impossible in the short term) is also assumed.

Based on this philosophy, the WHO-CHOICE programme has promoted global or regional cost-effectiveness studies on different health-related interventions and preventive measures: policies for the safe and adequate administration of injections to avoid the hypothetical spread of lethal pathologies, such as hepatitis or the HIV virus (Dziekan et al. 2003), proposals to reduce the risk of cardiovascular diseases through the reduction of systolic pressure and cholesterol levels (Murray et al. 2003), measures to stem air pollution caused by the use of solid fuels in indoor spaces (Mehta and Shahpar 2004), anti-smoking policies (Shibuya et al. 2003), interventions aimed at reducing iron deficiency (Baltussen, Knai and Sharan 2004), different cataract surgical procedures (Baltussen, Sylla and Mariotti 2004), strategies for reducing the global burden associated with alcohol abuse (Chisholm et al. 2004a), measures for controlling trachoma (Baltussen et al. 2005), and interventions targeting breast cancer (Groot et al. 2006).

The subregional studies of the WHO-CHOICE programme use international dollars as cost units. Therefore, cost-effectiveness estimates are measured in terms of international dollars per DALY saved. The international dollar is a hypothetical currency given the same buying power that a US dollar would have in the United States at a given point in time. Conversion of the local currency to international dollars is not done according to traditional currency exchange rules, but rather according to the purchasing power parity criterion introduced in the 1990s by the International Monetary Fund. It allows one to realistically compare living standards in different countries, taking into account price variations, and is insensitive to the "monetary illusion" caused by possible appreciations or devaluations of the local currency. Obviously, the use of the international dollar seeks to streamline cost comparisons between the different regions.

In short, the WHO-CHOICE programme has already applied generalised cost-effectiveness studies in the 14 worldwide subregions it established, and has already generated a substantial amount of significant information for a wide number of diseases and risk factors (World Health Organization 2002). The results have made it possible to establish comparisons between the different subregions, but this does not mean that their conclusions are easily exportable for application in health-related policies and decisions at the national level. Moreover, implementing detailed studies focusing on specific countries is unfeasible. The need to find methods for adapting the available information to more specific environmental, political, economic and social contexts seems inevitable (Paalman et al. 1998). The WHO-CHOICE programme has proposed the use of population and disease models that can be adapted to the specific scenario of each country. The software tools mentioned earlier were designed taking into account the possibility of applying national data (economic, population, epidemiological, etc.) and thus obtaining specific results that would help

local health authorities in their decision-making tasks. The methodology seeking to transfer the results of cost-effectiveness studies obtained in more general studies to the national level would be structured into a series of phases. The proposed steps are summarised as follows:

1) *Election of interventions.* This includes the description of the interventions (attending not only to technical or clinical characteristics, but also to organizational aspects) and their possible grouping into combinations.
2) *Contextualization of the effectiveness of interventions.* In order to adequately estimate the DALYs saved at the national level, it is necessary to have a number of readily available key parameters: demographic structure of the population, epidemiological figures (incidence, prevalence, case fatality, mortality) and health status assessments relating to the disease under consideration. Moreover, the efficacy of the intervention would be measured according to coverage and adherence levels associated with each intervention.
3) *Contextualization of intervention costs.* It would be advisable to have information available regarding the national costs for each individual country. Contrary to the use of the international dollar in the regional studies, the unit of measure to be used in studies at the national level should be the local currency, which would make it easier to obtain information and for the hypothetical decision-making authority to better assess the results. For those cases where no local information on unit costs exists, the WHO-CHOICE programme proposes its own estimation methodology based on data culled from more general contexts (Adam, Evans and Murray 2003).
4) *Contextualization for different specific scenarios at the national level.* WHO-CHOICE proposes the implementation of three different options:

    a) To assume that the different interventions are applied in a technically efficient manner.
    b) To assume that there are certain local restrictions preventing a completely efficient implementation (e.g., if a shortfall in healthcare staff is assumed).
    c) To assume that the interventions are carried out at the current level of resource use and that there are local limitations in terms of the availability of infrastructure.

It is necessary to consider that the determination of the most cost-effective interventions in no way marks the end of the decision-making process; rather, it constitutes a key input—but not the sole one—in any task involving the setting of priorities (Hutubessy, Chisholm and Edejer 2003). As mentioned earlier, a wide range of values—political, ethical, and social—comes into play in decisions of such import. For instance, in many places the concern for reducing inequalities in access to medical services is an overriding one compared to the objective of a more efficient distribution of resources, so in such cases the alternatives that will most benefit an underprivileged populace will take precedence over all others.

Indeed, the ability to transfer information from a global or regional level to specific population-based contexts has made it possible to extend cost-effectiveness studies to developing countries, overcoming the traditional drawback of a lack of available information.

The objectives of the WHO-CHOICE programme are perfectly aligned with the United Nations Millennium Declaration of September 2000 (United Nations 2000), which, among other points, recognised the need to fight against the main causes of disease in poor countries: poor childbirth and perinatal conditions, childhood diseases, and communicable diseases. The WHO-CHOICE methodology is a valuable decision-making aid in the health field, making it possible to use resources in developing countries more efficiently, making comparisons possible between different individual interventions and groups of interventions, and permitting the extrapolation of regional or population-based data for cases where more specific information is not available (Evans et al. 2005a; Evans et al. 2005b; Evans et al. 2005c). Recent years have seen the publication of studies that, adopting the WHO-CHOICE methodology, have analysed the main strategies for achieving the Millennium Declaration's goals for developing countries: promoting children's health (Edejer et al. 2005), guaranteeing maternal and perinatal health (Adam et al. 2005), reducing infant mortality (Darmstadt et al. 2005), and fighting specific diseases—HIV/AIDS (Hogan et al. 2005), tuberculosis (Baltussen, Floyd and Dye 2005) and malaria (Morel, Lauer and Evans 2005).

More recently, the work of the WHO-CHOICE programme has focused essentially on obtaining results at the national level and applying them to establish health policies based on them.

APPLICATION OF WHO-CHOICE IN MENTAL HEALTH

Given the growing consensus attributing a large proportion of the Global Burden of Disease (GBD) to mental disorders (World Health Organization 2001), it is small wonder that mental health is one of the areas where the WHO-CHOICE programme has developed greater research activity. Three basic criteria have guided the selection of disorders to be analysed (Chisholm 2005a):

- Public health burden and importance of disorders.
- Availability of efficient and potentially cost-effective interventions.
- Availability of data on epidemiology, clinical effectiveness, use of resources and costs.

In keeping with the first guideline, schizophrenia, bipolar disorder, depression (unipolar) and obsessive-compulsive disorder (OCD) should be considered pathologies of choice, since all of them are among the top ten in the list of causes of disability throughout the world (World Health Organization 2001). A set of specific interventions (including drug as well as psychosocial treatment) was defined for each of these disorders, and their efficacy was estimated by means of reviewing the available literature. Sufficiently robust tests were found to determine the effectiveness of treatments associated with three of the pathologies in question, but not for OCD, so it was replaced by panic disorder as a prototypical example representing anxiety disorders. The results of the global cost-effectiveness analysis of these pathologies show, among other conclusions, the following:

1) The most effective interventions for treating common mental disorders (depression and panic) can be considered *highly cost-effective* (in accordance with the aforementioned criterion by the WHO Commission on Macroeconomics and Health, i.e., the cost per DALY saved is lower than the annual per capita income of the region under consideration).
2) Community-based interventions for more severe mental disorders (typical antipsychotics and mood stabilisers for schizophrenia and bipolar disorder) meet the cost-effectiveness criterion (cost per DALY saved lower than three times the annual per capita income).

Analyses dedicated to depression and bipolar disorder have been published in independent articles. With regard to depression (Chisholm et al. 2004b), the considered treatment alternatives—old antidepressants (tricyclic), new antidepressants (selective serotonin reuptake inhibitors), short-term psychotherapy, old antidepressants plus short-term psychotherapy, new antidepressants plus short-term psychotherapy, proactive care combined with old antidepressants, proactive care and new antidepressants—all gave signs of clear potential for reducing the world burden associated with the disorder (specifically, by 10–30 %). It was estimated that the strategies involving the use of tricyclics (with or without proactive care) were more cost-effective than those based on the administration of selective serotonin reuptake inhibitors, especially in developing regions. Effective interventions in primary care were "highly cost-effective" according to the WHO's criterion, underscoring the priority nature of such interventions when addressing depression (Ayuso-Mateos 2004). As a fundamental conclusion, the need to increase the coverage of interventions as a priority measure to reduce the world burden of depression was indicated. As for bipolar disorder (Chisholm et al. 2005), the results point to treatment with lithium and psychosocial care as the most cost-effective of the alternatives under study (lithium, valproic acid, lithium plus psychosocial treatment, valproic acid plus psychosocial treatment; all of these considered within a community treatment model as well as within a model based only on hospital services). The community interventions showed more effectiveness than those based on hospital services, moving within the range that runs from "cost-effective" to "highly cost-effective" according to the WHO criterion. Finally, in the case of schizophrenia, the WHO-CHOICE programme considered four interventions: traditional antipsychotics (neuroleptics), new antipsychotics (atypical), traditional antipsychotics with psychosocial treatment, and new antipsychotics with psychosocial treatment.

The work of the WHO-CHOICE programme has also been extended to the neurological field, including both the analysis of specific pathologies—epilepsy (Chisholm 2005b)—and the use of resources (Ferri et al. 2004), in both cases for developing countries. Compared with the results obtained for other mental disorders, the results for schizophrenia are characterised by the modest effectiveness of available treatments, even assuming a high coverage. The most cost-effective intervention would be that which involves the administration of typical antipsychotropic drugs plus the application of a psychosocial treatment. The high price of atypical drugs would account for their lower cost-effectiveness, making their application in developing countries, for instance, questionable. However, the appearance of generic drugs could considerably alter this perspective (Chisholm 2005a). A recent study that applies the WHO-CHOICE methodology specifically to analyse the treatment of schizophrenia in the developing world (both at the inter-regional and multinational level) repeats these conclusions (Chisholm et al. 2006).

These results provide new and significant information for preparing health policies and can guide the first steps to allocating resources more efficiently, thus reducing the burden associated with mental disorders. However, once again, it is important to note that the results obtained for regions defined with a high degree of aggregation do not guarantee that the possible guidelines resulting from them can be put into practice at the national level. Therefore, it is necessary to propose attempts at contextualising the estimates for large regions at the national level, since many of the factors determining the results of a cost-effectiveness analysis can vary considerably from one local scenario to another (epidemiological data, potential effective population coverage level, availability of resources, local prices, etc.). The change in the level of analysis would impose minor methodological variations with regard to the study's approach. For instance, costs calculated by the WHO-CHOICE programme at the level of world regions are expressed in international dollars, because this makes it possible to compare different areas. However, in an analysis at the national level, it would be more appropriate to express costs according to the local currency.

Several papers have been published regarding the cost of mental disorders in Spain (Haro et al. 1998; Salvador-Carulla et al. 1999), but these were limited to collecting information about healthcare outlays resulting from current care levels for these pathologies in our setting, with the healthcare coverage currently in existence. No impact or cost-effectiveness study of a broad number of interventions in mental health in our setting has been performed to date.

We propose a comparative cost-effectiveness analysis of mental health interventions in Spain focusing on two pathologies, depression and schizophrenia, for the following reasons: importance from a public health perspective, due to their being prevalent pathologies that are responsible for a significant percentage of the global burden of disease in Europe-wide estimates (World Health Organization 2001; Ayuso-Mateos 2002); the availability of effective and potentially cost-effective interventions that can be applied in a generalised way in our country; and, finally, the availability of data on epidemiology, clinical effectiveness of the interventions, use of services, and their cost in Spain.

PART 1

Comparative Analysis at the Population Level of the Cost-Effectiveness of Therapeutic Interventions in Depression

1 Introduction to Part 1

1.1 DEPRESSION IN GLOBAL BURDEN OF DISEASE STUDIES

The findings of the first study on the Global Burden of Disease (GBD) (Murray and Lopez 1996), published in 1991, were conducted at the Harvard School of Public Health and funded by the World Bank and the World Health Organization (WHO). This study provided a set of summarised indicators and measures that assessed the fatal and disabling consequences of diseases and injuries in the different regions of the world. To ensure the rationality of epidemiological estimates, the GBD study developed internally consistent calculations for data on incidence, prevalence, duration and lethality used to assess 107 health problems, and 483 incapacitating consequences associated with them. As a result, a broad and consistent series of mortality and morbidity estimates by age, gender and region were generated, which in turn served to introduce and calculate a new way of measuring the burden of disease: Disability-Adjusted Life Years (DALYs). The use of DALYs makes it possible to combine, in a single indicator, the Years of Life Lost (YLLs) due to premature death and the Years of Life Lost due to Disability (YLDs), weighted according to severity. This was without a doubt one of the most salient findings of the study, as the assessment of disability together with mortality made it possible to include mental disorders, which are highly incapacitating but rarely mortal, among the major causes of the burden of disease in the world. The GBD study thus revealed the true magnitude of the impact of mental health problems, which had traditionally been underestimated. When disability is included in the assessment of the consequences of diseases, mental disorders become as important as cardiovascular or respiratory diseases, and more important than malignant tumours or HIV. The GBD study showed that unipolar depression causes a tremendous burden of disease, to such a degree that it ranks fourth worldwide, accounting for 3.7% of total DALYs and 10.7% of total YLDs. Projections by the WHO within the GBD study to 2020 indicate that the relative importance of mental disease will reach 15% of the total, due primarily to greater life expectancy of the population and a lowering of the burden attributable to infectious diseases. Hence, by 2020 depression will be second only to ischemic cardiopathy as a major cause of DALYs worldwide (Murray and Lopez 1997).

The WHO has conducted a new GBD study, this time for the year 2000 (GBD 2000), including the same goals as the first study and a review of the original methodology (Mathers et al. 2002). The GBD 2000 working group identified the need to revise and update the epidemiological prevalence and incidence estimates used to calculate the DALYs. A decade after the first GBD study (World Health Organization 2001; World Health Organization 2002), depressive disorders continue to be one of the main causes of DALYs throughout the world. Globally, they account for 4.46% of total DALYs and 12.1% of YLDs. Perinatal diseases, lower respiratory tract infections, AIDS and HIV, and unipolar depression constitute the four main causes of DALYs for both sexes combined. A gender difference exists in depression, which is the fourth-ranked cause of DALYs in women and the seventh-ranked among men (5.6% versus 3.4% of total DALYs, respectively) (Ustun et al. 2004). There are also marked differences in epidemiological patterns

between the world's rich and poor regions. In developed countries, the proportion of the burden of disease due to sexually transmitted, maternal, perinatal and nutritional diseases hovers around 5%, while in Africa it ranges from 70% to 75%. Depression contributed 1.2% to the total burden of disease in Africa, while accounting for 8% of the GBD in the Americas. Globally, the burden of disease in high per capita income countries reached 8.9%, while it reached only 4.1% of total DALYs in low and medium per capita income countries.

1.2 DEPRESSION IN SPAIN

Depression is also the most prevalent mental disorder in Spain, although European comparative studies reflect lower rates of depression among the general population than in other European countries (Ayuso-Mateos et al. 2001). In recent years, several epidemiological studies using comparable methodologies and diagnostic criteria to those applied in the most salient international studies have been completed in our country. It is estimated that 5% to 10% of the population suffers from a depressive episode over the course of their lives.

The degree of clinical severity is lower in patients with depression as measured against the general population than among those in contact with healthcare resources. However, depression is associated with significantly lower levels of perceived health among the general population (Ayuso-Mateos et al. 1999). Mortality rates due to depression obtained from death certificates are very low, with an annual average risk estimated at 3 per 1,000 (Harris and Barraclough 1998), although death by suicide can affect up to 15% of people suffering from depression (World Health Organization 2002). Nevertheless, studies in which verbal autopsies (interviews with relatives and primary care physicians of the deceased) are performed reveal that depression is the main background factor in 30%-45% of successful suicides. As a result, a large part of deaths by suicide should be counted as attributable to depression. In Spain, depression is being increasingly recognised as a cause of death.

In addition to bearing a significant social burden stemming both from the suffering of patients and relatives and from the premature deaths by suicide, depressive disorders also have a high social impact, due to the costs associated with their morbidity and care. The total cost of depression in Spain varies depending on the source, but some papers have set the figure at 745 million euros per year (Ofisalud 1998), 535 million of which are accounted for by direct costs arising from patient management and treatment, and the rest is attributed to loss of productivity generated by the attending temporary job disability. Only 15.9% of the direct costs are ascribable to drug treatment (Alonso et al. 1997), with the biggest direct cost component being that linked to outpatient care and monitoring. Hospitalization due to depression also accounts for a relatively small percentage of expenses stemming from the disorder (15.9%).

1.3 COMPARATIVE COST-EFFECTIVENESS ANALYSIS OF INTERVENTIONS FOR DEPRESSION

As mentioned in the introduction, the WHO-CHOICE (*CHOosing Interventions that are Cost-Effective*) project is a WHO initiative developed in 1998 to provide evidence helping health policy-makers to decide which interventions and programmes to implement in order to achieve the best possible effectiveness with the available resources. The specific objectives of the WHO-CHOICE programme include developing a standardised method of cost-effectiveness analysis that can be applied to different interventions in different scenarios, and developing the required tools to assess the costs and the impact of the interventions on the population.

Public health systems have multiple objectives, but the fundamental reason for their existence is doubtless to improve the health of the population. However, such an improvement cannot be viewed as a linear function of expenses allocated to achieving it, as healthcare systems with similar per capital cost levels exhibit dramatic variations in results. Some of the differences can be due to factors that are unrelated to the health sphere, such as the educational level of the population. But others could be explained by an inefficient allocation of resources (devoting excessive resources to expensive interventions with small effects on the population,

not implementing enough low-cost interventions that would potentially generate more benefits).

Cost-Effectiveness Analysis (CEA), as mentioned in the introduction, constitutes a tool that healthcare system decision-makers can use to assess and improve performance. It indicates which interventions make the most of the investments made and helps choose the programmes that maximise health in keeping with the available resources.

Cost-effectiveness analyses constitute the basis of the WHO-CHOICE programme. Its specific methodology makes it possible to compare existing interventions and new interventions at the same time. Until it was developed, cost-effectiveness analyses had been basically limited to assessing the efficacy of a single intervention added to the currently existing scenario, or with a view to replacing an existing intervention with another alternative. Thanks to the methodology provided by the WHO-CHOICE programme, analysts are no longer constrained by the implemented scenario of interventions that have already been applied. The WHO-CHOICE methodology makes it possible to compare currently existing interventions as well as interventions whose implementation is still being considered. Decision-makers can even revise choices made in the past if necessary, obtaining rational criteria enabling them to distribute resources among the various options and thus achieve the proposed objectives.

When applying this methodology to the analysis of mental health interventions in Spain, we initially intended to conduct work on depression for the following reasons, which have already been mentioned in the introduction: importance from a public health perspective due to it being a prevalent pathology which is responsible for a significant percentage of the GBD in Europe-wide estimates (World Health Organization 2001; Ayuso-Mateos 2002; Ustun et al. 2004); the availability of effective and potentially cost-effective interventions that can be applied in a generalised way in our country; and, finally, the availability of data on epidemiology, clinical effectiveness of the interventions, use of services, and their cost in Spain. Epidemiological data on depressive disorders were available through recent studies conducted by members of the research team. There is evidence of the effectiveness of drug, psychological and health-care organizational interventions applicable to our current health-care system (Dowrick et al. 2000; Serrano-Blanco et al. 2006).

1.4 DIFFERENTIATED OBJECTIVES

This research set for itself the following differentiated objectives:

- Quantification of DALYs associated with depressive disorders in Spain in the year 2000.
- Comparative study of the cost-effectiveness of different interventions aimed at managing depressive disorders in our setting.
- Application to our health system of the new methodology developed by the World Health Organization within the WHO-CHOICE project to analyse the impact of therapeutic interventions at the population level.

2
Research Methodology

2.1 POPULATION

The study was carried out taking the Spanish population in the year 2000 as a benchmark. The demographic data needed for our research (the general population in Spain in the year 2000 and its distribution by gender and age groups) were obtained from census figures drawn up by the National Statistics Institute (INE). These census figures are publicly accessible and can be consulted at the INE's website (www.ine.es). In addition, the epidemiological studies that will be used to obtain prevalence and incidence parameters were carried out around the same date.

2.2 METHODOLOGY FOR ESTIMATING THE BURDEN OF DISEASE

Different types of measures were proposed to assess the estimated burden of a disease in a population. In our study we will use DALYs, whose calculation method is described below. This methodology is common to any type of pathology, so its validity also extends to analyses focusing on schizophrenia, which makes up the second part of this report.

■ Disability-Adjusted Life Years (DALYs)

The number of DALYs associated with a given disease is calculated as the sum of the life years lost due to premature death (YLLs) and the life years lost due to disability (YLDs).

$$\text{DALYs} = \text{YLLs} + \text{YLDs}$$

■ Years of Life Lost due to Premature Death (YLLs)

The *Years of Life Lost* (YLL) concept reflects the difference between the age of death and an age limit (established according to the life expectancy at the age of death, which can be obtained by means of standard low-mortality life charts) for each death attributable to the disease being considered. In burden of disease studies, the sum of the YLLs corresponding to the deaths attributable to the disease being considered within a given period of time would determine the premature mortality associated with the disease.

The years of life lost due to premature death are estimated according to the following formula:

$$\text{Years of Life Lost (YLL)} = \sum_{x=0}^{x=l} d_x \, e_x$$

where: e_x = standard life expectancy for each age, d_x = number of deaths at each age, l = last age group.

Therefore, the variables needed to calculate the YLLs would be as follows:

- Mortality of the Spanish population during the relevant year, broken down according to cause of death and to age groups and gender.
- Life expectancy at each age and for each gender, using the West level 26 standard low-mortality life table for women (with a life expectancy at birth of 82.5 years) and the West level 25 standard low-mortality life table for men (with a life expectancy at birth of 80 years).

Years of Life Lost due to Disability (YLDs)

The consequences of living in conditions below that of a perfect state of health are assessed according to the time spent in each state and its severity. Without applying discount rates or weighing by age, the value of each year of life lost due to disability would be calculated applying the following formula:

$$\text{AVD} = (\text{YLL}) = \sum_{0}^{1} N_i \times I_i \times T_i \times D$$

where: N_i = population in each age group, I_i = incidence at each age group, T_i = average duration of disease at each age, D = level of disability (0 = perfect health; 1 = death).

To calculate the *Years of Life Lost due to Disability* (YLDs), the following variables are required:

- Incidence, by age groups and gender, of the different diseases and injuries.
- Average duration of each of the diseases for the different age groups and genders.
- Average age of onset of each disease for each age group and gender.
- Severity of the disability on a scale of 0 (perfect health) to 1 (death).

Mathematical Calculation of DALYs

The calculation of the DALYs regularly includes two types of social assessments:

1) *Weight by ages*. The value of each year of life lost can be weighted by a factor expressing the relative importance that is socially accorded to the different ages. A year lost during youth is not assessed the same as a year lost in old age. The formula proposed by the WHO to calculate these weights is as follows:

$$\text{Weight} = Cxe^{-\beta x}$$

where: x = age for each year of life lost, C = 0.1658, β = 0.04.

This function can be adjusted by introducing a constant to change the weighting by age (K):

$$\text{Weight} = KCxe^{-\beta x} + (1 - K)$$

If = 0 each year of life lost has the same value, and if = 1 the value of each year increases from birth (value = 0) up to a maximum at age 25, and then gradually declines at more advanced ages.

2) *Time discount.* Represents the relative value for individuals of a gain in health today compared to a gain in health in the future. The discount percentage applied in the DALY formula is 3%. Each year lost would be assessed according to the following continuous discount formula:

$$\text{Discount function} = e^{-r\,(x-a)}$$

where: r = discount rate, set at 0.03; x = age; a = year of onset of disability.

Formulas for Calculating DALYs

As mentioned before, DALYs are the sum of *Years of Life Lost* (YLLs) and *Years of Life Lost due to Disability* (YLDs):

$$\text{DALYs} = \text{YLLs} + \text{YLDs}$$

YLLs due to premature death are estimated according to the following formula:

$$\text{YLL} = \frac{KCe^{ra}}{(r+\beta)^2}\left[e^{-(r+\beta)(L+a)} [-(r+\beta)(L+a) - 1] - e^{-(r+\beta)a} [-(r+\beta)a - 1]\right] + \frac{1-K}{r}(1 - e^{-rL})$$

where: K = 1, C = 0.1658, r = 0.03, a = age of death (modified West 26 table), b = 0.04, L = life expectancy at age of death (modified West 26 table).

YLDs are estimated according to the following formula:

$$\text{YLD} = D\left\{\frac{KCe^{ra}}{(r+\beta)^2}\left[e^{-(r+\beta)(L+a)} [-(r+\beta)(L+a) - 1] - e^{-(r+\beta)a} [-(r+\beta)a - 1]\right] + \frac{1-K}{r}(1 - e^{-rL})\right\}$$

where: D = weighted value of the disability (between 0 and 1), K = 1, C = 0.1658, r = 0.03, a = age at onset of disability (modified West 26 table), β = 0.04, L = duration of disability.

Both formulas are valid provided that the discount rate is applied.

The indicated formula makes it possible for the weighting of years to be varied according to age by changing the value of *K* (between 0 and 1) and the values of *r* (discount rate) and observing the variations in the results.

All calculations were made using the *GesMor* software application developed at the National Health School's International Health Department. The programme automatically calculates YLLs and YLDs. A rate of discount of 3% and weighting by ages ($r = 0.03$ and $K = 1$) were applied.

TABLE 2.1: Levels of health in the general population by age range

Age group	Health level (men)	Health level (women)
0-5	0.970	0.972
5-15	0.983	0.984
15-30	0.957	0.952
30-45	0.941	0.934
45-60	0.903	0.901
60-70	0.826	0.838
70-80	0.731	0.756
80+	0.642	0.635

The method for estimating DALYs used for the Spanish population follows the one proposed in the WHO's Global Burden of Disease (GBD) study (Murray and Lopez 1996; World Health Organization 2001) with the application of the disease models developed as part of the WHO project for depression. We participated in the development of these models, which can be consulted at the following link: http://www.who.int/evidence/bod.

In order to calculate the DALYs of a given pathology, it is necessary to know its incidence and duration, as well as the disability it causes and its mortality. Community psychiatric epidemiological studies provide data concerning prevalence. The rest of the variables we need can be derived from these data using the DISMOD programme provided by the WHO. This programme assesses the internal consistency of estimates of incidence, remission, prevalence, duration and lethality. With the use of this programme we will obtain the incidence parameters per age and gender ranges based on prevalence information available in databases of community epidemiological studies carried out recently by our group. The calculation of the disability weights that assess the level of disability—from 0 (perfect health) to 1 (death), which we mentioned in the description of the DALY calculation—uses values recently developed by the WHO in the Global Burden of Disease study estimates for 2000 (http://www.who.int/evidence/bod), which include baseline values for the healthy general population (see table 2.1, the data reflect the defined health level as the value complementary to the disability weight, 1-DW) as values for the different episodes of depression (see table 2.2).

The epidemiological information used part of the analysis from two population studies conducted recently in Spain by our group: the ODIN study and the ESEMeD-MHEDEA España study. The ODIN (*Outcome of Depression International Network*)

TABLE 2.2: Disability weights for the depressive episode

Severity	Disability weight	Description of health condition
Mild depressive state	0.140	Gloomy mood, loss of interest and enjoyment, fatigue. Distress and some difficulty continuing with regular activity and social relations, but without fully ceasing functioning
Moderate depressive state	0.350	Marked sadness, loss of pleasure in some activities, loss of energy and appetite, some difficulty thinking. As a result of symptoms, considerable difficulty continuing work and household activity, as well as social relations
Severe depressive state	0.760	Intense sadness, loss of energy and anhedonia. Often associated with slowing of motor skills or agitation, crying, negative thoughts about oneself or one's surroundings, death wishes, sleep and eating disorders. Incapable of continuing regular activity

study, conducted with the participation of five European academic institutions and funded by the European Union under its 1995 BIOMED-2 programme (PL 951681), sought to provide reliable and valid data on the epidemiology and assessment of depressive disease (in the rural and urban setting) through a representative epidemiological sample, and to assess the impact on the evolution of depression of an approach with a low-cost preventive intervention focusing on the individual. In Spain, the epidemiological study was carried out in the northern city of Santander. The prevalence data have already been published (Ayuso-Mateos et al. 2001). In addition to information about the prevalence of depressive disorders in the general population, the database provides data on the level of clinical severity and healthcare coverage of subjects with depression in the general population.

ESEMeD-MHEDEA España is an epidemiological study on mental disorders in Spain, and it is integrated into the WHO's World Mental Health Survey Initiative. In the study, a representative sample of the non-institutionalised Spanish population was interviewed. The project's objectives were:

1) To assess and quantify the prevalence of the different psychiatric disorders in the Spanish general population and associated risk factors.
2) To assess the QoL, disabilities and handicaps of people suffering from these disorders.
3) To assess healthcare needs and the use of services and treatment received by people with psychiatric disorders.

A total of 5,500 personal interviews were conducted with a representative sample of the non-institutionalised Spanish population aged 18-64, obtained through a multistage stratified design. The individuals were interviewed using Spanish-language versions of various tools (CIDI, WHO-DAS II, EuroQol-5D and SF-36) plus a general questionnaire on socio-demographic variables. A trained clinician re-interviewed a sample of some 200 individuals out of the above population using the SCID questionnaire.

The DALYs for the Spanish population can be generated based on incidence, duration and disability estimates with the use of the GesMor software application developed by the Carlos III Health Institute's International Health Department.

2.3 COST-EFFECTIVENESS ANALYSIS METHODOLOGY, MEASURED IN DALYS, OF DEPRESSION INTERVENTIONS IN SPAIN

2.3.1 SELECTED INTERVENTIONS FOR THE COST-EFFECTIVENESS STUDY

We assessed the expected impact at the population level of several interventions (individual or combined) that can be implemented in our healthcare system to improve depressive disorders. Information about their efficacy in controlled clinical trials is available for all of them. The impact at the population level of seven interventions to be developed in the primary care field was assessed:

1) Tricyclic antidepressants (imipramine).
2) SSRIs (fluoxetine).
3) Psychotherapy: short-term cognitive therapy, interpersonal therapy for depression, problem-solving therapy.
4) TCAs + psychotherapy.
5) SSRIs + psychotherapy.
6) Proactive collaboration management with TCAs (management protocol that includes diverse simultaneous strategies with the goal of achieving adherence to protocols for treatment of depression, patient education and increased primary-care medical support for the management of these conditions).
7) Proactive collaboration management with SSRIs.

2.3.2 IMPACT OF INTERVENTIONS AT THE POPULATION LEVEL

The impact of interventions in the Spanish population was assessed through the analysis of population models provided by the *PopMod* programme, which enables the development of a population to be established taking into account births, mortality and the disease being studied.

The programme model distinguishes between the male and female population and includes segmentation by age ranges of one year. According to this model, the susceptible population (i.e., individuals not depressed at the moment being considered) produces new cases at an instantaneous transition rate of *i* (incidence, including recurrence); individu-

als suffering a depressive episode become susceptible again at a remission rate of *r*; depressive cases are subject to a specific instantaneous mortality rate of *f*; both susceptible individuals and cases are subject to a general mortality rate of *m*.

In addition, the model includes information on the disability weights associated with each disease—on a scale of 0 to 1, where 1 equals a complete state of health and 0 equals death—for the time elapsed both while in the depression and susceptible states. The programme also makes it possible to obtain models for a situation where no intervention for the disease is implemented and compare the results with those of the alternative model generated by the implementation of the proposed therapeutic interventions among the study population in a 10-year period. The difference between the two models would represent the gain at the population level linked to the intervention under study (measured as a reduction of DALYs).

As their main therapeutic effect, the considered interventions cause a reduction in the depressive episode that can be likened to an increase in the remission rate (which, in turn, translates into changes in the disability weights with respect to a situation of untreated depression). These changes can be modelled according to the methodology described by Andrews et al. (2000) which makes it possible to transform the effect sizes estimated in clinical trials (standardised difference between the intervention group mean and the control group mean) into changes in the disability weight. Estimates of the efficacy of different interventions were obtained from data relating to the natural history of the disease (Ayuso-Mateos 2002) and from the analysis of information available in the literature regarding the effect of the different interventions on the duration of the depressive episode, remission rates achieved with the treatment, and, for the case of collaborative management strategies, their effect on the incidence of successive depressive episodes (Simon, Katon and VonKorff 2001; Chisholm et al. 2004b).

2.3.3 ANALYSIS OF INTERVENTION COSTS

When considering costs, our study takes on the financier's perspective, without considering costs associated with the patient's and his/her relatives' perspective (e.g., lost production capacity). The cost of interventions was established at the patient level and at the level of the programme implementation cost. Costs at the programme level include central administration and training (2 or 3 days were estimated for training primary care physicians and depression case handlers, while 10 days of training and 2 days of supervision were considered necessary for psychosocial interventions) (Dowrick et al. 2000). The use of services at the patient level during the 6-month treatment period was estimated for each of the clinical severity categories of depression based on service usage data in depressive patients from the ESEMeD-MHEDEA España project (Alonso et al. 2002) and on the opinion of experts from the research team. Depending on each intervention model, the healthcare usage components included estimates of drug dosage and frequency (e.g., 20 mg of fluoxetine daily), the duration of short-term psychotherapy (8 sessions), the number of contacts in collaborative case management (6 contacts); the number of primary care contacts (6 visits), the number of visits to outpatient mental health services (4-6 visits in 33% of cases) and psychiatric admissions (5% of moderate and severe cases during one or two weeks).

We used the units of cost available for our healthcare system that were developed according to preliminary studies by the PSICOST group, and which have already been used previously by members of the research team in economic analyses of mental health interventions in Spain (Haro et al. 1998; Salvador-Carulla et al. 1999; Saldivia et al. 2005). The healthcare costs used were not estimated on the basis of prices, but rather on the basis of estimated actual costs. The SOIKOS (Soikos 2001) unit cost database was used to determine the cost for the rest of the healthcare services used. As for antidepressant medication costs, the costs of the lowest-priced generic presentation of the two agents included in our study, imipramine and fluoxetine, were considered.

The average cost per episode was multiplied by the average number of episodes treated in the Spanish population in the year 2000, considering a healthcare coverage of 50%. The healthcare coverage of the Spanish population suffering from depression was obtained from analysing the ESEMeD-MHEDEA España study. Thus, a total healthcare cost for depression over a year of implementation was calcu-

lated. A 3% discount was applied to all the baseline analyses during the 10-year implementation period considered in our model. The final economic values were expressed in euros.

2.3.4 SENSITIVITY AND UNCERTAINTY ANALYSES

Cost-effectiveness analyses rely on a large amount of data input from various sources. In many cases, it is complicated to perform an adequate sampling to calculate costs or estimate the associated effectiveness. One way of ensuring more robust results from such analyses consists of assuming a certain variability of the input and verifying to what extent this affects the final estimated cost-effectiveness values. Therefore, the best-suited approach would be to replace the estimates for certain parameters (costs, efficacy measures, etc.) with a range of values.

Two possible strategies can be used to this end. The first, traditionally known as sensitivity analysis, consists of replacing the specific initially considered estimate with various deterministic values established by the researchers.

However, the methodology associated with any sensitivity analysis presents certain constraints that should be considered. Firstly, it is the researcher's responsibility to decide which alternative values are assigned to the selected variables to which the analysis is going to be applied. Secondly, the interpretation of the results is necessarily arbitrary, as there are no established guidelines or standards determining under what conditions the analysis can be considered to be robust. Finally, varying different parameters separately presents the drawback of overlooking the possible effects of interaction.

A second type of methodology, the uncertainty analysis, which is probabilistic rather than deterministic, was applied to avoid these constraints. It consists of assuming that the values assigned to the parameters whose influence in the final results we seek to determine are but momentary "walks" of a random distribution. Monte Carlo simulations were used in our research to carry out the uncertainty analysis of the results, and we assumed a cost and effectiveness behaviour according to random distributions, of which a high number of momentary "walks" were taken so as to obtain a distribution (in the form of a cluster of points that can be graphically depicted) of the final values of the cost-effectiveness ratios associated with each of the interventions.

However, these results are not without difficulties in interpretation. The results of the uncertainty analysis can be depicted in the form of point clusters, and it is simple to order the final cost-effectiveness results according to the position of these clusters if they do not overlap. However, there is no recommended interpretation when different clusters overlap.

It would be desirable for uncertainty analyses to provide results in the form of classification tables where the different interventions appear ordered according to cost-effectiveness ratios associated with each of them. In a deterministic analysis, it is assumed that decision-makers will begin by considering the first intervention on the list (the most cost-effective) and then go down the list until they stop when the funds are depleted. Adding an element of uncertainty to such an analysis allows for a more realistic approach by considering intervals of possible cost-effectiveness ratio values, but difficulties would appear when determining the ordering of interventions when the different intervals overlap. It would simply be assumed that a decision over which alternative would be the most efficient cannot not be reached.

To overcome these difficulties, a different uncertainty analysis method was proposed. This method shows the information to decision-makers in the form of "stochastic league tables". The idea is to present the probability with which each of the alternatives would be included in the optimal distribution of interventions for different levels of available resources, taking into account the uncertainty associated with costs and measures of efficacy. The construction of stochastic league tables requires four steps.

1) In the first place, the use of Monte Carlo simulations to provide "random walks" for cost and efficacy values. This first step would be common with the probabilistic uncertainty analysis described above.
2) In the second place, the determination of the optimum assignment of interventions for differ-

ent levels of resource availability following the procedure for choosing between independent and mutually exclusive alternatives described by Murray et al. (2000). The most cost-effective intervention is assessed according to its average cost-effectiveness ratio (as against not applying any intervention), while the ratios of the other mutually exclusive alternatives are incrementally assessed, comparing them to the most efficient intervention.

3) Thirdly, this process is repeated a high number of times to obtain as many estimates of the optimum distribution in the way interventions are assigned. If P represents the number of times an intervention has been included in the optimum distribution, P divided by the number of simulations will represent the probability that the intervention will be included in the optimum distribution.
4) The fourth step involves repeating the previous process assuming different levels of resource availability, obtaining a distribution (or "*expansion path*" of resources) showing the probability that each intervention is included in the optimum distribution for each resource availability level.

To perform this type of simulation, the WHO-CHOICE programme provides a tool, the Monte Carlo League (MC League) software application, which generates stochastic league tables. This application makes it possible to consider the existence of covariance between the costs and results of the analysis, for which it simulates different values (use of health services, proportion of individuals using secondary services and treatment effectiveness—efficacy and adherence). MC League provides its output data in the form of stochastic decision tables and graphs depicting the probability of inclusion of each of the mutually exclusive alternatives in the optimum distribution of interventions for the different resource availability levels.

2.3.5 CONSTRAINTS

Some of the estimations under this analysis have a degree of uncertainty inherent to the measure of the parameter in question. These include, for instance, epidemiological prevalence estimates, cost units (medication costs, number of visits in psychotherapeutic interventions, proportion of cases using healthcare services not included in the intervention) and, finally, those linked to the effect of the intervention. In order to mitigate some of these constraints, an uncertainty analysis was conducted according to the methodology described in the previous section.

In addition, to offset some of the constraints inherent to an analysis that quantifies efficacy by means of a synthetic measure, the DALYs, which include information about operation as well as about the relative mortality associated with the disorder, a second analysis in which efficacy was assessed by QoL units (*Quality-Adjusted Life Years*, or QALYs) was performed, as described in the following section.

2.4 COST-EFFECTIVENESS ANALYSIS METHODOLOGY, MEASURED IN QALYS, OF DEPRESSION INTERVENTIONS IN SPAIN

In recent years, the clinical relevance of QoL measures has been gaining recognition in the health research field. The improved QoL of patients obtained thanks to a reduction in clinical symptoms is starting to be taken into account in treating depression. With this in mind, our work includes a second cost-effectiveness analysis of depression interventions in Spain in which the improved QoL of patients, assessed in QALYs, was chosen as a measure of efficacy.

QALYs can be estimated using the scores obtained with the EQ-5D (*EuroQol-5 Dimensions*) tool (Williams 1990). The EQ-5D was designed to be a generic, simple, self-administered tool with a low cognitive burden for the individual and preference-based, whose purpose is to describe and assess QoL related to health, obtaining a descriptive health profile on one hand, and a general health index on the other. The questionnaire comprises four parts. The first part contains a description by the patient of his/her own state of health using 5 dimensions (mobility, personal care, day-to-day activities, pain/discomfort, and anxiety/depression), with 3 levels of severity for each (1 = no problem, 2 = a few problems, 3 = lots of problems). The individual must mark the problem level for each dimension that best describes his/her state of health at the moment. The

state of health is determined by the combination of the degree of severity in each of its dimensions. This combination of 5 dimensions and 3 levels of severity gives rise to 243 different states of health. The second part consists of a vertical Visual Analogue Scale (VAS) measuring 20 cm, marked off by millimetres, with two clearly defined end points: *the best state of health imaginable*, with a point value of 100, and *the worst state of health imaginable*, with a point value of 0. The individual is asked to assess his/her state of health *on the day of assessment* by drawing a line from the lowest point in the scale (0) to the point that, in his/her opinion, indicates how good his/her state of health is. The third part of the questionnaire is designed to obtain individual values that represent the preferences for, or usefulness of, the states of health of the descriptive system of the EQ-5D, in addition to the *unconscious* and *death* states that cannot be defined by the descriptive system. The individual assessment is presented on two consecutive pages, each of which contains a VAS in its central portion with eight states of health described in boxes on both sides of the scale. The interview subjects are asked to imagine that they find themselves at each state of health, and to draw lines between the boxes containing the state of health and a value in the VAS, thus indicating their preference for each of the states of health. Once the values are assigned to the states of health on both pages, the interview subjects are asked to assign a value to *death* on the same VAS on both pages. Based on the values obtained for the states of health in this exercise, and using regression models, an index value can be obtained for each of the 243 states of health in the EQ-5D. Finally, the fourth part contains information about the interview subject, including: age, gender, disease experience (own, family members or other people), difficulty filling in the questionnaire, and experience completing similar questionnaires.

The QALY methodology seeks to include the quantitative increase in life years resulting from a health improvement by weighting this increase according to the quality of the life years gained. An assessment of the quality of the various states of health involved in the decision is required. To this end there are several basic techniques, each of which in turn has been subjected to different applications and interpretations. Each of these techniques provides different results, since a detailed examination of the techniques reveals differences in terms of subject matter, instructions, decision-making framework and description of the issues. The three techniques with the broadest-based theoretical and practical grounds are the Standard Gamble (SG), the Time Trade-off (TTO) and the Person Trade-off (PTO). Health status values based on two scale techniques were used in this project: the Visual Analogue Scale, which is the scale used by the EQ-5D questionnaire and provides the health status values described by the interview subjects, and the Time Trade-off (TTO) technique.

A recent study performed by the DAPGA *(Depressió en Atenció Primaria de Gavà*—Depression in Primary Care in Gavà) research group was used as a source of data for a representative assessment of the QoL of the Spanish population with depressive disorders, the purpose of this choice being to overcome some of the constraints that are inherent to randomised clinical trials with antidepressant drugs (exceedingly restrictive criteria, exceedingly specific results) and that hinder the generalization of their results to clinical practice. This study, which adopts a naturalistic perspective, focused on the comparison of two drugs (fluoxetine and imipramine) with a sample of 103 depressive patients in three primary healthcare centres in the metropolitan area of Barcelona, which were tracked for a period of sixth months (Serrano-Blanco et al. 2006).

Since only the application of drug therapy was taken into account (i.e., psychosocial interventions were disregarded), our study on the QoL impact focused only on the two alternative interventions mentioned earlier: fluoxetine and imipramine. The baseline sample value was taken as a measure of the QoL of individuals with depression before they received any form of treatment. The average EQ-5D scores by age range and gender obtained from the Spanish sample of the ESEMeD / MHEDEA 2000 study (Alonso et al. 2002) were taken as measures of the QoL for the Spanish population. The effectiveness of the two compared interventions was estimated based on the variation in the EQ-5D scores after the sixth-month tracking period (see table 2.3).

The same software tools provided by the WHO-CHOICE programme for the cost-effectiveness analysis with DALYs can be used on this input data.

TABLE 2.3: EQ-5D scores (baseline and after 6 months of tracking)

Drug	Measure	N	Median	Average	Standard deviation
Fluoxetine	*Baseline*	49	0.46	0.48	0.30
	Six months	42	0.83	0.74	0.27
Imipramine	*Baseline*	45	0.54	0.57	0.25
	Six months	37	0.88	0.82	0.22

In the results obtained here, the effectiveness at the population level reflects the variation in Quality-Adjusted Life Years (QALYs). As for the costs associated with the interventions, the same that were considered for the analysis in terms of DALYs were assumed.

3
Results

3.1 BURDEN OF DISEASE FOR DEPRESSION IN SPAIN IN THE YEAR 2000

The burden of disease associated with depression in Spain for 2000 is estimated at 301,697.06 DALYs—108,130.14 in men and 193,566.92 in women—which means a raw rate per 100,000 inhabitants of 553.44 (men) and 949.34 (women).

By age group, the greatest number of DALYs corresponds to the 15-59 age range in both sexes (see tables 3.1 and 3.2).

According to severity, the greatest burden of disease, percentage-wise, is caused by moderate depressive episodes (42.5%), followed by severe episodes (39.66%) and mild episodes (17.84%) (see the details differentiated by sex in tables 3.3 and 3.4).

TABLE 3.1: Burden of disease outcome for depression in Spain. Men

Age group	YLDs due to depression	YLLs due to depression	DALYs	DALYs per 100,000 inhabitants
0-4	0.00	0.00	0.00	0.00
5-14	8,833.14	0.00	8,833.14	425.67
15-44	72,905.76	0.00	72,905.76	780.14
45-59	18,044.84	29.16	18,074.00	526.34
60+	8,268.83	48.41	8,317.24	223.31
TOTAL	108,052.58	77.56	108,130.14	553.44

YLDs: Years of Life Lost due to Disability; YLLs: Years of Life Lost due to Death; DALYs: Disability-Adjusted Life Years.

TABLE 3.2: Burden of disease outcome for depression in Spain. Women

Age group	YLDs due to depression	YLLs due to depression	DALYs	DALYs per 100,000 inhabitants
0-4	0.00	0.00	0.00	0.00
5-14	8,400.81	0.00	8,400.81	429.11
15-44	132,496.89	0.00	132,496.89	1,459.38
45-59	38,917.65	43.97	38,961.62	1,102.81
60+	13,566.29	141.30	13,707.59	278.79
TOTAL	193,381.64	185.27	193,566.92	949.34

YLDs: Years of Life Lost due to Disability; YLLs: Years of Life Lost due to Death; DALYs: Disability-Adjusted Life Years.

TABLE 3.3: Distribution of the burden of disease of depressive episodes according to level of severity. Men

	Mild depression	Moderate depression	Severe depression	Total
Percentage	17.84	42.50	39.66	100
0-4	0.00	0.00	0.00	0.00
5-14	1,576.27	3,754.51	3,503.3	8,834.07
15-44	13,010.01	30,988.43	28,915.0	72,913.40
45-59	3,220.10	7,669.92	7,156.7	18,075.89
60+	1,475.57	3,514.65	3,279.5	8,318.10
TOTAL	19,281.95	45,927.51	42,854.4	108,141.47

TABLE 3.4: Distribution of the burden of disease of depressive episodes according to level of severity. Women

	Mild depression	Moderate depression	Severe depression	Total
Percentage	17.84	42.50	39.66	100
0-4	0.00	0.00	0.00	0.00
5-14	1,499.12	3,570.75	3,331.82	8,401.69
15-44	23,644.03	56,317.51	52,549.24	132,510.78
45-59	6,944.84	16,541.86	15,435.02	38,965.69
60+	2,420.90	5,766.32	5,380.49	13,709.02
TOTAL	19,281.95	82,196.44	76,696.57	193,587.18

Tables 3.5 and 3.6 show the burden of disease expressed in DALYs for depressive episodes, lung cancer in men and breast cancer in women. Unlike depression, these last two diseases cause a significant number of deaths. However, their proportion of YLDs is minimal, both for lung cancer (9,336.09 YLDs versus 134,023.5 YLLs) and for breast cancer (28,919.12 YLDs versus 56,587.79 YLLs). That is to say, YLDs account for 6.5% of DALYs for lung cancer and 33.8% for breast cancer, while in the case of depression, YLDs account for nearly 100% of the DALYs.

3.2 COST-EFFECTIVENESS ANALYSIS, MEASURED IN DALYS, OF DEPRESSION INTERVENTIONS IN SPAIN

3.2.1 EFFECTIVENESS OF INTERVENTIONS AND AVOIDED DEPRESSION

"Proactive" collaborative interventions have a greater impact on the health of the population, basically due to the added beneficial effects by avoiding a considerable proportion of recurring depressive episodes. Thus, they manage to double the number of DALYs avoided when antidepressant therapy and psychotherapy are administered separately. The total gains over the health of the population can be expressed in terms of the proportion of the global burden that is alleviated with each of the interventions. Table 3.7 shows the effectiveness of each considered treatment, estimated in DALYs avoided per year.

3.2.2 CONTEXTUALIZATION AND COST-EFFECTIVENESS OF INTERVENTIONS

The costs per treated episode are shown in table 3.8. The total application costs associated with each intervention are shown in table 3.9. As anticipated, there is a considerable variation in the cost of the interventions. The lowest costs are those for tricyclic antidepressants (332 euros). At the other end of this variable is the cost of implementing the proactive collaborative programme (1,401 euros). Development costs for this programme account for

TABLE 3.5: Comparison of depression with lung cancer. Men

	Depressive episode		Lung cancer	
Age groups	DALYs	DALYs per 100,000 inhabitants	DALYs	DALYs per 100,000 inhabitants
0-4	0.0	0.0	0.0	0.0
5-14	8,833.1	425.7	0.0	0.0
15-44	72,905.8	780.1	11,193.0	119.8
45-59	18,074.0	526.3	50,628.3	1,474.4
60+	8,317.2	223.3	81,538.3	2,189.3
TOTAL	108,130.1	553.4	143,359.6	733.8

TABLE 3.6: Comparison of depression with breast cancer. Women

	Depressive episode		Breast cancer	
Age groups	DALYs	DALYs per 100,000 inhabitants	DALYs	DALYs per 100,000 inhabitants
0-4	0.0	0.0	0.0	0.0
5-14	8,400.8	429.1	0.0	0.0
15-44	132,496.9	1,459.4	19,337.2	213.0
45-59	38,961.6	1,102.8	29,820.4	844.1
60+	13,707.6	278.8	36,349.3	739.3
TOTAL	193,566.9	949.3	85,506.9	419.4

TABLE 3.7: Efficacy associated with the proposed interventions

Interventions	Incremental ratios (DALYs avoided per year)
Tricyclic antidepressants (imipramine)	35,719
SSRIs (fluoxetine)	37,602
Psychotherapy	37,286
TCAs + psychotherapy	44,516
SSRIs + psychotherapy	44,516
Proactive collaboration management with TCAs	72,234
Proactive collaboration management with SSRIs	72,234

a very low percentage of total costs. The highest costs are those linked to the programme that are based on psychotherapy, due to the higher cost of training.

The concept of average costs per avoided DALY makes it possible to perform comparisons from the perspective of the cost-effectiveness of interventions (see figure 3.1). Of all of these, the use of tricyclic antidepressants is the most cost-effective option. Moreover, table 3.10 shows the incremental ratios, defined as the quotient of the incremen-

TABLE 3.8: Costs per treated episode (in euros)

Intervention	Cost in international dollars	Cost in euros
Tricyclic antidepressants (imipramine)	391.16	332.41
SSRIs (fluoxetine)	416.75	405.07
Psychotherapy	611.15	413.01
TCAs + psychotherapy	681.76	537.62
SSRIs + psychotherapy	709.76	610.28
Proactive collaboration management with TCAs	655.56	1,133.74
Proactive collaboration management with SSRIs	685.77	1,401.67

TABLE 3.9: Total application costs
(in euros)

Intervention	Patient	Programme	Training	Total
Tricyclic antidepressants (imipramine)	106,903,389	2,438,261	3,537,948	112,879,598
SSRIs (fluoxetine)	131,577,853	2,438,261	3,537,948	137,554,061
Psychotherapy	130,169,198	2,438,261	7,643,079	140,250,537
TCAs + psychotherapy	168,943,655	2,438,261	11,181,026	182,562,942
SSRIs + psychotherapy	193,618,118	2,438,261	11,181,026	207,237,405
Proactive collaboration management with TCAs	372,174,776	2,438,261	10,379,454	384,992,490
Proactive collaboration management with SSRIs	463,678,558	2,438,261	9,861,473	475,978,291

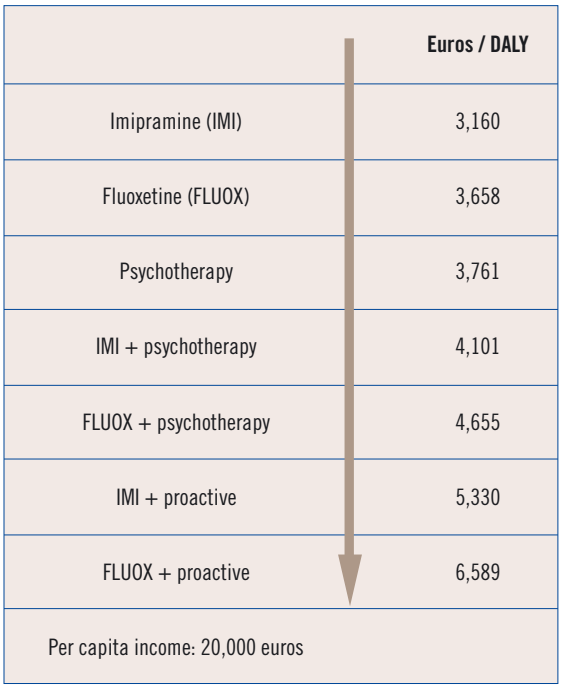

Figure 3.1 Cost-effectiveness of interventions

TABLE 3.10: Incremental cost-effectiveness ratios associated with the proposed interventions (DALYs)

Interventions	Incremental ratios (euros per DALY avoided)
Tricyclic antidepressants (imipramine)	3,160
SSRIs (fluoxetine)	Dominated
Psychotherapy	Dominated
TCAs + psychotherapy	Dominated
SSRIs + psychotherapy	Dominated
Proactive collaboration management with TCAs	7,542
Proactive collaboration management with SSRIs	Dominated

tal change in costs divided by the incremental change in effectiveness between interventions. They indicate the interventions that would be elected (if we apply only a cost-effectiveness criterion) if available resources were to increase. They start with the most cost-effective intervention, then the next one, and so on. The term *dominated* denotes those interventions that are more costly and less effective than others, and therefore they are not included in the expansion path of the most cost-effective strategies.

3.2.3 UNCERTAINTY ANALYSIS

Figures 3.2 and 3.3 show the results of the uncertainty analysis. These were obtained using the *MC League* software application, which involved 1,000 "walks" assuming a normal global truncated distribution of total costs. The first graph below shows the point clusters associated with each of the interventions. The second shows the results in the form of a stochastic league table.

The most notable phenomenon that can be seen in figure 3.2 is the overlap along the effectiveness axis of the clusters associated with baseline interventions in pharmacotherapy and psychotherapy without collaborative management, on one hand, and of the clusters associated with interventions including proactive collaborative management, on the other. However, no overlap appears between both groups of interventions; the distance in terms of efficacy between them can be explained by the addition of proactive intervention.

Of special interest as well is the stochastic league table obtained in our uncertainty analysis (figure

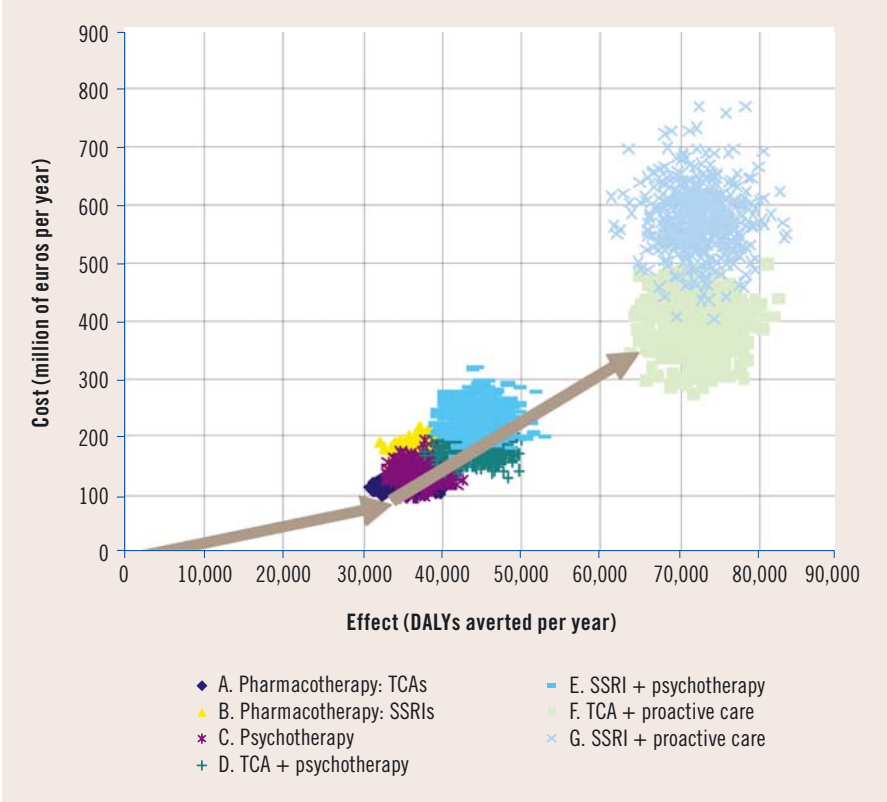

Figure 3.2 Uncertainty analysis results - cluster graph

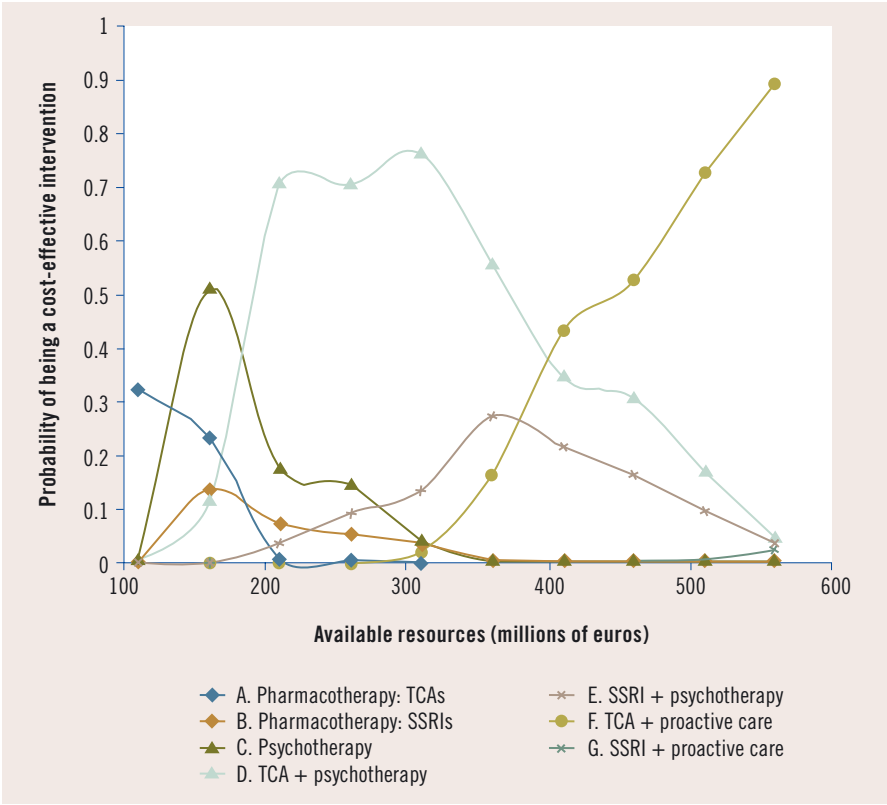

Figure 3.3 Uncertainty analysis results - stochastic league table

TABLE 3.11: Cost-effectiveness ratios associated with the proposed interventions (QALYs)

Intervention	Average cost per QALY gained (in euros)
Imipramine	2,244
Fluoxetine	3,040

3.3). According to the estimated results, with available resources of more than 400 million euros per year, the most widely applied intervention of choice would be that based on the administration of tricyclics with proactive management. With resources ranging from 200 to 400 million euros, the intervention based on tricyclic antidepressants plus psychotherapy would present the greatest possibility of being cost-effective. At under 200 million euros, the top choice would be the application of psychotherapy alone, while under 125 million euros, it would be the administration of tricyclic antidepressants alone.

3.3 COST-EFFECTIVENESS ANALYSIS, MEASURED IN QALYS, OF DEPRESSION INTERVENTIONS IN SPAIN

When the same cost-effectiveness analysis methodology as above is applied to the two selected interventions (fluoxetine and imipramine), but considering the effect on the variation in the subjects QoL (measured by means of QALYs) rather than the variation in disability (DALYs), treatment with imipramine (cost per QALY gained: 2,244 euros) is a more cost-effective option than the administration of fluoxetine (cost per QALY gained: 3,040 euros) according to the population model used (table 3.11).

4 Discussion

4.1 DEPRESSION, A PRIORITY THAT CAN BE DEALT WITH

Basically, in a cost-effectiveness analysis one determines numerically the relationship between the costs of a given intervention and its consequences, with the particularity that the consequences are measured with the same natural units that can be used in regular clinical practice (e.g., life years gained, number of lives saved) (Prieto et al. 2004). The methodology of burden of disease studies enables us to have the same unit of effectiveness (in this case, DALYs) to compare the different interventions for a given process and compare in terms of cost-effectiveness the result of different interventions involving different pathologies. The results obtained for the Spanish population show that the most effective interventions for depression are highly cost-effective in relative terms if we compare them to other therapeutic strategies used in medicine. The most cost-effective alternative was the generalised application of imipramine, while the application of fluoxetine plus a collaborative model was situated at the opposite side of the spectrum. The low cost of interventions based on tricyclic antidepressants explains why they are ultimately more cost-effective than those based on selective serotonin reuptake inhibitors. This difference appears not only in the DALY-based analysis, but also in the QALY-based one.

Beyond comparisons between intervention alternatives for a single disease, it is possible to make comparisons between interventions addressing different health problems. For the purpose of comparison, if we consider other health interventions assessed to date as part of the WHO-CHOICE programme, depression-related interventions have a higher cost per DALY avoided than primary prevention strategies against infant malnutrition, but are similar in cost to treatments aimed at reducing hypertension and cholesterol levels (World Health Organization 2002; Murray et al. 2003). Interestingly, in all the regions of the world that were studied using this analysis, the cost of avoiding a DALY in depression was lower than the annual per capita income value. This is the cost level established by experts to consider health interventions as cost-effective (Commission on Macroeconomics and Health 2001). This is also the case for the analysis we conducted in Spain, where all interventions have a lower cost per DALY than the annual per capita income (20,000 euros).

This type of information can be useful when presenting an argument in favour of the advantages of investing in depression treatment to the health authorities in charge of allocating healthcare resources. On one hand, it allows us to place the results of mental health assessments in a broader context, and on the other, it serves as a tool to make informed decisions about the distribution of healthcare resources between alternative programmes or interventions that compete against each other for such resources.

4.2 ADDRESSING DEPRESSION IN THE COMMUNITY: THE RESEARCH AGENDA

The analysis of the burden of disease and the impact of the various interventions on the analysis

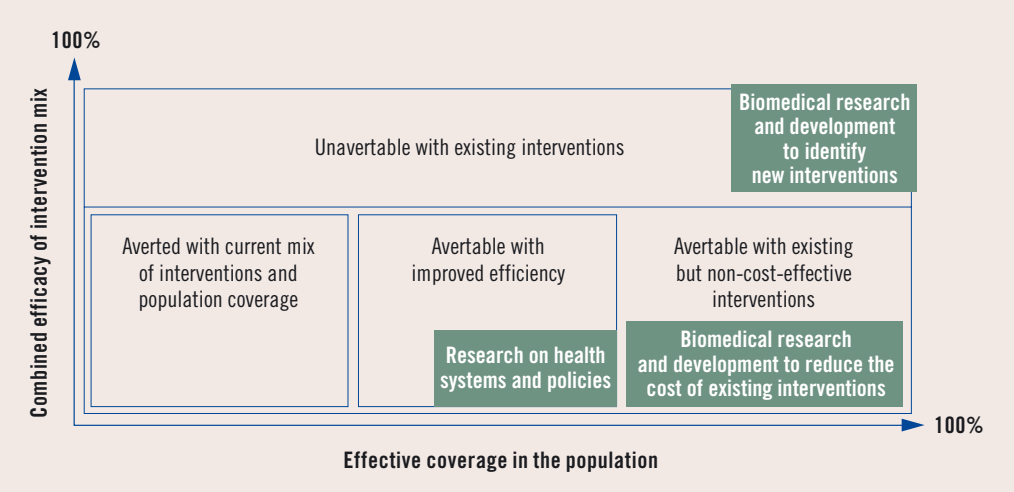

Figure 4.1 Model for identifying research needs through the analysis of the burden of disease

allow us to identify what the limits of the available therapeutic strategies are at the present time, and can help us to identify different research and development needs in the field of depressive disorders from a population perspective (see figure 4.1).

Thus, there is a proportion of the burden of depression that is adequately addressed with the intervention strategies currently in use in our health system. There is also a part of the burden of depression that could be avoided with the available treatment strategies if the efficiency of health systems were increased. Thus, for example, we know that a significant percentage of patients with depression consulting with primary care physicians are not adequately diagnosed. This lack of recognition of depressive disorders from a primary care perspective is due to many factors, the most important of which is the form of clinical presentation of depressive disorders in primary care, where somatic symptoms typically prevail (Bair, Robinson and Katon 2003). The development and generalised application of instruments for quickly assessing the presence of depressive disorders in patients with unexplained somatic symptoms could be a way of improving the quality of care in depression in these resources.

In many other cases, patients are prescribed an adequate treatment, but fail to experience the therapeutic effects due to a lack of compliance. As a result, they cannot benefit from available interventions that are effective against this pathology and can be covered by the existing healthcare budget. The type of research required to act on this level focuses on implementing training programmes in primary care that are centred not only on acquiring diagnostic and therapeutic skills, but also on developing strategies that favour therapeutic compliance.

A significant part of the burden of disease is avoidable with treatment strategies that already exist but are not cost-effective at the present time. The type of research required at this level should be focused on reducing the cost of interventions. Thus, for example, our health system could not shoulder the burden of referring all depression-related contacts to specialised care resources so as to receive a drug treatment supplemented by a psychotherapeutic approach. One objective of research could focus on developing cost-effective intervention models in primary care that would allow depression to be efficiently addressed at this level with a protocol for intervention in resistant cases and referral to specialised care in a very small number of cases (Simon, Katon and VonKorff 2001).

Finally, there is a very significant proportion of the total global burden of depression that cannot be addressed adequately with any of the currently existing interventions. Research at this level should be geared towards developing new intervention strategies. This would justify, for example, invest-

ing in the development of new treatments that would reduce the time of onset of the therapeutic response, and also in the development of drugs that could reduce the number of depressions resistant to the first antidepressant agent and the development of new drugs for efficiently treating the residual symptoms of depression. Research at this level should not be exclusively biological. It is well known that a significant percentage of individuals suffering from depression among the general population do not contact the healthcare resources or seek out consultation for this disease. This would justify investing research resources in the development of population intervention techniques to urge subjects with this disorder to consult the healthcare resources and thus benefit from available therapeutic interventions.

4.3 CONCLUSION

When considering the analysis of the health of populations in terms of disability, depressive disorders are among the processes accounting for the highest burden of disease in the world, in spite of their low mortality. This significant contribution to the burden of disease is due to a combination of high prevalence of depression, its major influence on functioning and its onset at early stages of life, with a highly recurrent course.

Until very recently, mortality statistics were the central element in the identification of public healthcare priorities and in the monitoring of the success or failure of interventions in healthcare. Today, with the development of new synthetic measures to describe the state of health of populations, such as the DALYs, we can assess the impact on the population of a wide range of interventions, simultaneously taking into account their effect on mortality and morbidity. We thus have a common metric to identify priorities and assess interventions that is usable in many diverse processes and makes comparisons in cost-effectiveness terms possible. This has enabled us to demonstrate that interventions for depression are cost-effective. However, the total burden of disease for depression that cannot be addressed using the currently available treatment strategies is very large. Even in countries like Spain, with a high level of development of healthcare services and coverage, the total burden due to depression that could be avoided with the implementation of currently developed treatment strategies is very limited. Therefore, there is a wide margin for research in this field and enough scientific evidence to advocate the development of healthcare policies that take these data into account when allocating healthcare resources in a manner that is proportional to the magnitude of the problem, and that recognise the need to implement adequate intervention programmes, basically at the primary care level.

PART 2

Comparative Analysis at the Population Level of the Cost-Effectiveness of Therapeutic Interventions in Schizophrenia

5
Introduction to Part 2

5.1 SCHIZOPHRENIA AND GLOBAL BURDEN OF DISEASE STUDIES

Schizophrenia is a severe disorder, which typically appears during adolescence or early adulthood. A classic study carried out by the World Health Organization in the early 1980s to estimate the incidence of schizophrenia analysed the presence of the disorder in ten different countries. Using a restrictive definition of schizophrenia, the study found an average incidence of approximately 10 per 100,000 inhabitants per year (Jablensky et al. 1992). The WHO's Global Burden of Disease (GBD) project reports a worldwide prevalence of schizophrenia of 0.4% (World Health Organization 2001). A recent study on disability associated with physical and mental condition, conducted in 14 countries, found that the positive symptoms of schizophrenia (active psychosis) ranked third among the most incapacitating conditions for the general population, ahead of such conditions as paraplegia or blindness (Ustun et al. 1999). In the GBD study, schizophrenia accounted for 1.1% of the world population's DALYs and 2.8% of the YLDs. The economic cost of schizophrenia to society is high. It was estimated that the total cost associated with schizophrenia in the United States in 1991 amounted to 19 billion dollars in direct costs, plus an additional $46 billion due to the effect of productivity losses (World Health Organization 2001). However, burden of disease data alone, whether expressed in epidemiological or economic terms, are not grounds enough to allocate resources and establish action priorities. The cost-effectiveness analysis of current intervention strategies, including the estimate of the amount of burden that can be avoided, could provide additional information useful in the decision-making process. Different studies have focused on the differences in cost-effectiveness of interventions applied to certain populations (Knapp 2000; Palmer et al. 2002; Andrews et al. 2003; Basu 2004; Magnus et al. 2005). However, our study considers, for the first time, a cost-effectiveness comparison between the different schizophrenia interventions applied to the Spanish population.

5.1.1 DISABILITY AND FUNCTIONING IN SCHIZOPHRENIA

Psychiatric research has traditionally focused on the study of clinical symptoms. However, the ascertainment of other idiosyncratic problems of undoubted risk for schizophrenics has opened up new pathways for exploration. The discovery that an improvement in psychopathological terms squares up only moderately with subjects' adequate social and functional integration into their environment has given rise to the inclusion of alternative recovery measures (criteria of functioning, employment, rehospitalization, QoL, social adjustment, etc.). However, the World Health Organization's guidelines remain faithful to criteria based on signs and symptoms, establishing that psychosocial indicators do not constitute measures of the course of the disorder, but rather consequences of it (*International Classification of Impairments, Disabilities, and Handicaps*, WHO, 1980).

As part of our research, we reviewed the literature on the course and prognosis of schizophrenia published in the last five years. This involved a keyword search on the MEDLINE database. The differ-

ent measures of course that we considered are reflected in the titles of the following subsections, which describe the results obtained. This review illustrates the difficulty of finding a single criterion that could make possible a truly functional prognosis for schizophrenic disorder. It is true that significant progress has been made in recent years with the addition of functional assessments to efficacy measures in the more traditional therapeutic (symptom-based) interventions. However, we still need to devote more attention to prognosis scales centred on the patient's functioning, and create new tools that include multidimensional criteria that would allow us to go beyond the heterogeneous results that exist today.

■ Measures of Functioning and Social Disability

In recent years, the assessment of how individuals diagnosed with schizophrenia function and adjust socially has spurred great interest, both as an object of study in itself and in relation to other measures. For example, Loebel et al. (2004), in a reanalysis that tracks 270 patients treated with ziprasidone, found that cognitive function, assessed using the PANSS (*Positive and Negative Syndrome Scale*) subscales, is a significant predictor of social functioning.

In analysing the results of the WHO ISoS study (Hopper and Wanderling 2000), Harrison et al. (Harrison et al. 2001) use two favourable course measures regarding functioning and disability: a score above 60 on the GAF (*Global Assessment of Functioning*, adopted from DSM-III-R) scale, and a final grade of "excellent" or "good" (<2) on the the WHO-DAS (*Disability Assessment Schedule*) tool. Table 5.1 shows the percentages of subjects who met these criteria at the end of the tracking period.

TABLE 5.1: Percentage of subjects diagnosed with schizophrenia with good social-functional course according to scores using the DAS and GAF-D tools following tracking in the ISoS sample

	Incidence samples	Prevalence samples
DAS	33.4	47.7
GAF-D	50.7	60.3

Source: Harrison et al. (2001)

Ganev (2000) addresses the problem of the course of social disability in a sample (part of the aforementioned ISoS study by the WHO) of 60 Bulgarian patients with recent onset (at the most, 2 years before the start of the study) of non-affective psychosis diagnosed between 1978 and 1980 (ICD-9), who were tracked over a period of 16 years. Three assessments were made (using functioning measurement tools, such as the DAS scale), and the authors analysed whether the course improved, worsened, or remained stable. Results showed that 29.1% of the subjects tended towards improvement, whereas 45.5% got worse.

Ruggeri et al. (2004) used their work on the GAF scale to analyse the overall functioning of a sample of 107 Italian subjects diagnosed with schizophrenia (ICD-10 diagnosis). The overall results were not very positive, since the assessed subjects presented poor functioning at the baseline, and on average tended to worsen after 3 years of tracking. However, this drop in the average score of the sample is not so great as to be statistically significant. Analysing individual by individual, the figures also reflect functional deterioration: almost half the subjects worsened (47%), although 30% improved their score, and 23% remained stable.

In a recent article, Häfner et al. (2003) reviewed the results they had published previously (Häfner et al. 1999), assessing the social disability (measured by the DAS) of 115 individuals diagnosed with schizophrenia over a tracking period of 5 years. There were significant differences in the course of the illness between men and women (more favourable for the latter). Male subjects scored approximately 2.75 at the time of their inclusion, and after applying treatment (1 year later), they stabilised at around 2 (threshold value for social disability according to the DAS scale) throughout the tracking period. Female subjects, on the other hand, scored slightly above 1.5 (hence lower than the social disability threshold), which remained stable (declining slightly) throughout the tracking period.

In their comprehensive study of a group of 65 subjects diagnosed with schizophrenia (from 1976 to 1987) with onset before age 18 (according to ICD-9 criteria) and a tracking period of ten years, Lay et al. (2000), using the DAS, found an absence or minimal level of dysfunction in a relatively small

proportion (no dysfunction, 12.5%; minimal, 14.1%), whereas almost two-thirds of the sample suffered from severe dysfunction (severe, 29.7%; very severe, 31.3%; maximum, 4.7%). The authors' report also included a logistical regression analysis of the possible predictive factors of long-term social disability, with significant findings in the following: degree of symptoms at discharge (OR = 1.46), level of social competence at discharge (OR = 0.87), and having suffered more than two episodes requiring admission (OR = 10.69).

The social functioning of the subgroup of patients presenting onset during childhood or adolescence was also examined by Hollis (2000) in a study that compared 51 individuals diagnosed with schizophrenia with a control group of 42 individuals with another type of diagnosed psychosis (in both cases with early onset). In this case, the GAF (disability scale) was used as an assessment measure. The author concluded that there are significant differences between the two groups, which are clearly unfavourable towards those diagnosed with schizophrenia. The average score for this group was 42.6, whereas the control group scored 59.7 on average.

The use of qualitative measures and less restrictive criteria could give more positive results on social functioning for subjects diagnosed as having schizophrenia. For instance, in a recent article, Haro et al. (2005) reported more optimistic results after analysing the sample of more than 10,000 outpatients with a schizophrenia diagnosis in ten European Union countries (SOHO study, *European Schizophrenia Outpatient Health Outcomes*). By assessing the percentage of "socially active" subjects (subjects who have maintained some form of social contact in the 4 weeks prior to the assessment are given this consideration) at the time of starting or changing treatment with antipsychotics, and after 6 months of monitoring, a clear increase can be seen regardless of the type of antipsychotic prescribed (see table 5.2).

TABLE 5.2: Increased percentage of "socially active" patients diagnosed as having schizophrenia according to the treatment followed after 6 months of monitoring

Treatment	Baseline	After 6 months monitoring
Olanzapine	66.5	84.6
Risperidone	69.7	82.4
Quetiapine	67.4	78.9
Amisulpride	69.8	82.2
Clozapine	64.6	81.6
Typical antipsychotics (oral)	70.2	80.3
Typical antipsychotics (*depot*)	66.9	78.3
More than one antipsychotic	61.2	84.8
Total	67.3	83.0

Source: Haro et al. (2004).

■ Employment Integration

According to the information compiled from the incidence sample of the ISoS study by Harrison et al. (2001b), 56.8% of the subjects diagnosed with schizophrenia had performed a job over most of the two years prior to the assessment. Prevalence rates show a slightly higher outcome of 69.2%. However, the definition of employment used by Harrison et al. is too broad, since it encompasses both financially remunerated work and household chores. The application of a more restrictive criterion—i.e., only a remunerated job is considered employment—reduces the percentages to about 65% of the initial values: 37.0% (incidence samples) and 46.2% (prevalence samples). In addition, a significant difference in gender can be seen, favouring men, probably due to job market conditions in the less developed countries included in the study (unfortunately, the authors do not analyse the effect of the country's degree of economic progress in their final results): 45.4% men with remunerated work, compared with only 28.4% in the incidence samples, and the gap widens even more in the prevalence samples (64.8% and 18.8%, respectively).

The differences between developed and developing countries in the ISoS study are addressed by Hopper and Wanderling (2000), who use the same definition of employment (including both paid work and household chores, over the last two years), obtaining percentages that differ significantly, depending on the countries being considered: 46% (developed) versus 73% (developing). Unfortunately, these percentages are not broken down by gender or by type of work performed (paid work or housework). If we extrapolate the data obtained by Harrison et al., we can assume that approximately 65% of these subjects will earn a salary for their work, so the gross proportion of employees in de-

veloped countries would be close to one out of every three subjects diagnosed with schizophrenia (approximately 30%).

Some articles published since show less favourable results regarding the ability of subjects diagnosed with schizophrenia to adapt to the job market. Resnick et al. (2004), working with a sample of 825 patients assessed in the PORT (*Schizophrenia Patient Outcomes Research Team*) study, found that only 15.9% of the subjects worked in exchange for a salary. However, 78.6% of the subjects reported having earned income during the previous month in excess of $300 (50.2% from $300 to $900, 28.4% more than $900). This reveals the need to consider, before drawing any conclusions, the system of public aid provided to disabled subjects in each country. A strong monetary outlay in the form of disability-related pensions and furloughs or leave could halt their integration into the labour market, and since such forms of aid are more common in affluent countries, it could be a factor to bear in mind when explaining the difference in percentages observed by Hopper and Wanderling, clearly in favour of developing countries.

In relation to the sample of the SOHO study, Haro et al. (2005), based on two assessments (one before switching antipsychotic treatments or starting antipsychotic treatment for the first time, and the other six months later), find that 20.7% of the subjects were gainfully employed at the baseline, and 22.9% had paying jobs at the end of the monitoring period. Given this outcome, it could be deduced that, at least in the short term, treatment does not significantly favour the job prospects of subjects diagnosed with schizophrenia. In their research on the course of the disorder, Di Michele and Bolino (2004) found that only 22.5% of the sample patients had a job. However, the relatively small number of subjects in the sample can be a disadvantage for the generalizability of the outcomes with regard to the studies mentioned above. Using the aforementioned sample of 65 patients with onset during adolescence, Lay et al. (2000) found that 24.6% (26.3% in men, 22.2% in women) had sources of income that depended on themselves (the remaining percentage was divided between public assistance [36.9%] and family care [parents or spouse—38.5%]). In addition, they found that 29% of the subjects had unprotected jobs at the time of the assessment, 23% had protected jobs outside the clinical sphere, 23% were employed within the clinical sphere with little or no remuneration, and 25% lacked employment of any kind. It is interesting to note that gender-based differences were smaller compared with those reported by Harrison et al., which seems to corroborate that these were due to the weight of underdeveloped countries in the total percentages. Researchers also paid attention to the subjects' educational and occupational disability: 18.5% did not present any disability, 24.6% showed slight disability, with 20% moderate, 18% severe and 9.2% complete. Using a logistical regression analysis, it was found that the two main predictors of educational/occupational disability were the duration of hospitalization during the first episode (OR = 1.25) and having experienced more than two episodes requiring admission (OR = 15.11). However, a certain pessimistic bias in these outcomes should be considered due to the early age of onset (age of first admission between 11 and 18), which implies serious limitations in terms of the subjects' academic and professional training that undoubtedly complicate their entry in the job market. Therefore, in overall terms, the actual percentage of subjects diagnosed with schizophrenia can be expected to be considerably higher than that provided by Lay et al. (2000).

Häfner et al. (2003) considered the early course of schizophrenia as the period of study, defining it as the period of time elapsed from the onset of the first signs of mental disorder up to the first admission. The outcomes: a 33% employment rate at the time of the first pathological sign (average age: 24), rising to 44% on first contact with healthcare resources (average age: 30). The data are limited by the relatively low number of subjects, but the study has in its favour the use of a paired control group of healthy individuals, making it possible to infer the employment rate among the population with no psychiatric disorders (42% and 58% at ages 24 and 30, respectively). The comparison between both groups only shows significant differences between subjects diagnosed with schizophrenia and healthy ones at the time of the first admission, which seems to indicate that the employment problems of the diagnosed group appeared before they are diagnosed, and not as an effect of their being "labelled" as mentally ill. The article can be interpreted as a warning regarding how dangerous a

TABLE 5.3: Percentage of subjects diagnosed with schizophrenia who are employed

Study	Year	Country	Subjects (N)	Age	Diagnosis	Diagnosed subjects with jobs
Hopper and Wanderling	2000	Several	319 (developed countries)	Adults	ICD-10	46 *
Hopper and Wanderling	2000	Several	183 (developing countries)	Adults	ICD-10	73 *
Lay et al.	2000	Germany	65	Onset between ages 11-18	CIE-9	29 **
Harrison et al.	2001	Several	502 (ISoS incidence samples)	Adults	ICD-10	37.0
Harrison et al.	2001	Several	142 (ISoS prevalence samples)	Adults	ICD-10	46.2
Häfner et al.	2003	Germany	57 (first symptom of disorder)	Adults	CIE-9	33
Häfner et al.	2003	Germany	57 (first admission)	Adults	CIE-9	44
Di Michele and Bolino	2004	Italy	40	Adults	ICD-10, DSM-IV	22.5
Resnick, Rosenheck and Lehman	2004	United States	825	Adults	Data from the PORT study	15.9
Haro et al.	2005	Ten EU countries	10,972 outpatients	Adults		21.2

* The percentage includes both gainfully employed subjects and subjects who perform household chores.
** Excludes the percentage of individuals with specially protected employment arrangements.

mere analysis of percentages in absolute terms can be, without taking into consideration the general employment trends that would overlap the effect of the disorder. To avoid these problems, it would be advisable to use measures relating the percentage of mentally ill subjects to employment, and the equivalent figure among the healthy population (odds ratios, standardised ratios, etc.).

An approach that sets itself apart from the rest is that of Samele et al. (2001), who looked into the relationship of socioeconomic status with various prognosis measures of psychoses. The authors found significant differences between the two extreme groups (white-collar workers and the unemployed) in negative symptom course, functioning and unmet needs, while no differences were found in days of hospitalization, other symptoms, QoL, and dissatisfaction with health services.

In conclusion, the literature (table 5.3) seems to tend to confirm the results obtained in the WHO's ISoS study, situating the percentage of subjects diagnosed with schizophrenia in the 20-40% range. However, the information obtained is far from being conclusive. New research taking into consideration temporary socioeconomic factors, such as the level of economic protection provided by the state to subjects with disability, or general employment data from the study area, is needed.

■ Quality of Life

Quality of Life (QoL) is an increasingly important concept in recent research on schizophrenia, especially as a complement to symptomatic and functioning measures when establishing a complete prognosis of the course of the disorder. However, given the difficulty in operationally defining the concept universally, the research developed thus far has been characterised by a high degree of heterogeneity with regard to concepts (objective versus subjective assessment of QoL, assessed by the subject or by the professional, etc.), methodology (use of a great diversity of tools), and outcomes.

In addition to the other prognosis measures considered in earlier sections, the study by Ruggeri et al. (2004) also includes an analysis of the subjective assessment of QoL on the part of the patients. In monitoring 107 subjects diagnosed with schizophrenia over 2 years, the researchers did not note any significant differences in the average value obtained by the sample using the LQoLP (*Lancashire QoL Profile*) tool, while an analysis of the percentages reveals that approximately half of the individuals kept a stable perceived QoL against the rest, which was divided into virtually equal parts between those who considered that their QoL had improved and those who judged that it had worsened. This

TABLE 5.4: Improvement in the QoL score (EQ-5D tool, 0 [worst] to 100 [best]) after 6 months' monitoring in the SOHO study

Treatment	Baseline	After 6 months monitoring
Olanzapine	45.7	63.2
Risperidone	46.9	61.2
Quetiapine	47.2	59.9
Amisulpride	45.7	59.5
Clozapine	42.2	61.0
Typical antipsychotics (oral)	47.4	58.8
Typical antipsychotics *(depot)*	48.5	59.4
More than one antipsychotic	43.0	61.4
Total	46.1	61.9

Source: Haro et al. (2004).

strong trend towards maintaining the same outcomes after monitoring was also seen when considering the profile subdomains: only the emotional balance scale and the "religion" dimension showed a significant reduction in score, while the rest remained approximately constant (dimensions included overall well-being, work, leisure activities, financial status, life, safety and legal status, family relations, social relations, health and the self-esteem scale). Moreover, Ruggeri et al. (2001), in a previous longitudinal study, made use of the same tool to assess the changes in subjective QoL in a sample of 183 subjects diagnosed with schizophrenia who were tracked over a period of two years. The outcomes were relatively uniform on the different scales: approximately one third of the subjects improved their assessment, another third worsened it, and the remainder kept it constant.

In recent years, various lines of research have sought to link the QoL concept to other clinically significant dimensions. One matter of special interest is the influence of the type of treatment. The SOHO study is doubtless one of the greatest research efforts in recent years concerning the QoL concept applied to the prognosis of schizophrenia. The study focused on the effect of antipsychotic treatment on a sample of more than 10,000 outpatients in 10 countries of the European Union. In a recent article, Haro et al. (2005) analysed the results after 6 months of prospective monitoring of the sample, considering, among other dimensions, the patients' subjective QoL. This was assessed using the EQ-5D (*EuroQuol-5 Dimensions*) questionnaire, validated in the population of the ten countries considered (Prieto et al. 2002), which consist of five independent dimensions: mobility, self-care, regular activities, pain and anxiety/depression. The outcomes are moderately optimistic: all patients, regardless of the treatment followed, experienced increases in their QoL scores (see table 5.4).

The authors also performed a preliminary assessment 3 months into the course of the treatment. Most of the rise in scores had already taken place by this early stage, remaining approximately constant over the next 3-month period (rising slightly). As for the differential behaviour of the different treatments, the researchers, based on a multivariate analysis taking as reference the application of olanzapine, calculated different odds ratios (>1 indicates a diminished response). Olanzapine obtained better scores in EQ-5D than the rest of the antipsychotics (odds ratios: risperidone, 2.3; quetiapine, 3.0; etc.), except clozapine (odds ratio: 0.5). The authors link these outcomes to good psychopathological evolution, affirming that improved symptoms (basically negative ones) and cognitive function may be responsible for the enhanced QoL. However, they warn that more research is still required to determine the differential impact of antipsychotics on the patients' QoL.

Some researchers (Hellewell 2002) have noted that the subjective well-being and QoL perceived by patients diagnosed with schizophrenia could influence their adherence to medication, thus influencing the prognosis. The relationship could well be two-way, since the absence of secondary effects and improved symptoms could be associated with a more positive subjective feeling. Along this line, various studies have addressed the effect of different types of treatment, some focusing on the results of specific drugs—such as Nasrallah et al. (2004), who reported a significant improvement in QoL relative to health in a group treated with risperidone as compared to the placebo group, and Beasley et al. (2003), who found analogous results for olanzapine—and others comparing two different antipsychotics, such as Gureje et al. (2003), who report better results in treatment with olanzapine than by applying risperidone, or Hertling et al. (2003), who did not discover significant differences

in QoL comparing the application of flupentixol and risperidone.

One hypothesis that enjoys certain acceptance grants a preponderant role to the influence of the secondary effects of antipsychotics on the self-perception of QoL. Miller et al. (2000) considered the adverse effects of akathisia on patients' well-being. Hofer et al. (2004), after applying a multiple linear regression analysis to the scores obtained from a sample of 80 outpatients diagnosed with schizophrenia on scales for measuring QoL and the secondary effects caused by antipsychotic medication, concluded that parkinsonism, an after-effect primarily associated with typical neuroleptics, was the only side-effect that had an impact on subjects' general satisfaction and self-esteem. The effects of late-generation drugs, sedation or weight gain were shown to have little influence on QoL. These affirmations align the authors with those who advocate the hypothesis of improved QoL related to the switch from typical to atypical medication. In addition to these general conclusions drawn from regression analysis, researchers have also found negative links between some of the side effects and specific domains of QoL, e.g. between akathisia and self-esteem, between erectile dysfunction and affection and self-esteem, and between depression and general satisfaction, affection and self-esteem. Ritsner et al. (2002) addressed the problem in-depth with their analysis of 161 Israeli patients diagnosed with schizophrenia (Ohayon 1997). In spite of finding a correlation between the adverse effects of medication and QoL, the authors defended the idea that this influence appears to be mediated by a subjective discomfort factor (i.e., how the subject perceives these adverse consequences). Using a multiple regression analysis, they concluded that adverse effects would only explain 3.2% of the QoL variance, which would be determined primarily by psychosocial factors (20.9%) and clinical symptoms and associated discomfort (World Health Organization 1992).

Furthermore, the link between pathological measures and QoL has been addressed abundantly by various researchers. In a recent 3-year study tracking a group of 25 American patients diagnosed with schizophrenia or schizoaffective disorder who underwent a switch from typical to atypical antipsychotic medication, Zhang et al. (2004) found a marked improvement in self-assessed QoL, which rose throughout the treatment monitoring period. The perceived evolution of symptoms also presented improvements over time, although more qualified than in the case of QoL. The authors point to a lack of sensitivity of the instrument used in the self-assessment of symptoms (the Saint Louis Symptom Scale or SLSS, empirically developed by the University of Missouri), as a possible explanation of the scant correlation between the two measures. However, other studies published in the last five years indicate the lack of a significant relationship between symptom and QoL measures, including Lambert et al. (2004), who concluded, after analysing a sample of 150 diagnosed subjects treated with atypical antipsychotics, that psychopathological measures have only a very slight influence on subjective QoL assessments. In a recent article, Naber et al. (2005) compared the use of olanzapine and clozapine in samples of patients with schizophrenia and assessed the subjective impact of treatment using two tools: the SWN (Subjective Well-being under Neuroleptic Treatment) scale, which assesses subjective well-being, and the MLDL (Munich QOL Dimension List), which focuses on QoL. The authors found a notable increase in both measures after 26 weeks of treatment in groups of 50 patients, but without significant differences depending on the drug (average SWN score of 132.6 to 154.5 with olanzapine, and of 138.7 to 152.4 with clozapine; average MLDL score of 4.7 to 6.0 with olanzapine, and of 4.5 to 5.8 with clozapine), whose results seem to indicate that the perception patients have of their own situation improves when they benefit from the advantages of medication. However, they found a moderate correlation of these subjective measures with clinical measures assessed by psychiatrists (correlation between the change of SWN and PANSS, $r = -0.45$, correlation between changes in MLDL and PANSS, $r = -0.16$), figures that approach those obtained by the same authors in a previous study (Naber et al. 2001), which they interpret as a sign that patients and psychiatrists do not share the same perception regarding symptom improvements.

Finally, the importance of the differential cultural influence of each society is reflected in the study by Gaite et al. (2002), who found significant differences in the data from five European countries with regard to some QoL domains (such as life situ-

ation and family relations). They attribute this discrepancy to cultural differences: subjects in southern European centres (Santander, Spain and Verona, Italy), for instance, give more importance to family relations and less to health services (socially, the family plays the role of the subject's primary care provider), establishing significant differences with the rest of the centres considered in the study (Copenhagen, London, and Amsterdam).

5.1.2 MORTALITY AND SCHIZOPHRENIA

It is generally accepted that all severe mental disorders increase the risk of premature death to those suffering from them. Schizophrenia is not an exception, particularly when it comes to the risk of death due to non-natural causes (Harris and Barraclough 1998). Studies on general mortality in subjects with schizophrenia appear to show that it is two to three times higher than among the normal population (Miles 1977; Tsuang and Woolson 1977; Black and Fisher 1992). In their comprehensive analysis as part of the ISoS study (Hopper and Wanderling 2000), Harrison et al. (2001) obtained standard mortality ratios ranging from 1.04 to 8.88. The authors found that when going from non-industrialised countries to industrialised ones, the proportion of non-natural deaths (especially suicide) jumps dramatically, and the ratios obtained rise.

Suicide deserves special attention within the study of mortality among schizophrenia subjects as the main cause of non-natural death. The differences established between the population with schizophrenia and the population that does not suffer from the disorder would be qualitative (greater number of previous attempts, more serious and more lethal in the case of subjects with schizophrenia, to the extent that the disorder itself could be considered a risk factor) as well as quantitative (published literature on the matter seems to coincide on the fact that the risk of suicide among diagnosed subjects is about ten times higher than the general population; for instance, a review published in 2002 [Meltzer 2002] places it between 8 and 13 times higher). These figures are alarming enough to consider the incidence of suicide in schizophrenic populations as a priority research objective. In a bid to shed more light on the possible ways of increasing prevention, various predictors and risk factors have been pointed out, including youth, male gender, lack of a partner, good premorbid functioning, having suffered a recent loss or rejection, limited social support, high intelligence, high expectations, chronic course of the disorder, or the presence of despair. Pompili et al. (2004) point to a possible link between suicide and symptoms: two positive symptoms, suspicion and delirium, seem to increase the risk (which would explain a higher percentage of suicides in the paranoid subtype), whereas some prominent negative symptoms seem to constitute a protective factor. In their review, the same authors explored published data on the preventive effect of drug treatment, which seems to be more favourable in the case of atypical antipsychotics, especially clozapine, although the evidence is not conclusive. Although factors associated with treatment with typical neuroleptics—e.g., certain side effects and slight induced depression—have traditionally been thought to be able to have an indirect impact on increased risk of suicide, Meltzer's review (2002) questioned the validity of such a claim. Its conclusions do provide evidence, however, of the greater efficacy of clozapine in reducing the risk of suicide. However, the existence of other studies that do *not* show a significant reduction in the risk of suicide among patients treated with clozapine (Sernyak et al. 2001) underscores the need for more research in order to reach definitive conclusions.

The complexity of the phenomenon, both conceptually (the suicide study is markedly multidimensional, encompassing psychological, social and even physiological approaches) and methodologically (the need to work with large samples and have mortality data concerning the general population), can account for the traditional lack of studies on the matter. However, research has increased constantly in recent years. It is to be hoped that this increase will ultimately be translated into more effective prevention measures.

5.2 SCHIZOPHRENIA IN SPAIN

Very few studies on the epidemiology of schizophrenia have been conducted in Spain, and in most cases they focus their attention on highly localised areas with a small number of cases. One of the

most important contributions to this field of research is the study by Vázquez Barquero et al. (1995) on first episodes in the population of Cantabria, a northern region of Spain. The authors take into consideration all the subjects in Cantabria who contacted a psychiatrist for the first time and were diagnosed as having schizophrenia (DSM-III-R or ICD-9) over a 2-year period (the study began in 1989). The conclusions reached by this group of researchers with regard to the incidence of the disorder in Cantabria are consistent with the data from international studies: there is an estimated incidence of 19 per 100,000 (18.8 for males, 19.3 for females) for the population at risk (defined by the authors as the population group aged between 15 and 54). If the total population were considered instead of this group, the incidence would drop to 8.0 per 100,000 (8.4 for males, 8.0 for females). The figure is also estimated when the diagnosis used is the S+ diagnosis of the CATEGO tool. For the population at risk, the incidence value obtained is 13 per 100,000 (12.7 for men, 14.4 for women). One detail to be noted is that the authors found no significant differences regarding the distribution of the disorder by gender. They did find differences between the sexes, however, in relation to the type of environment: in rural settings, significantly more women develop the disorder than men. Vázquez Barquero et al.'s research also provided the average age of the 96 subjects that make up the study. Since having suffered from the onset of the disorder within the previous year was one of the requirements for inclusion in the study, the figures can be taken as an approximation to the age at onset, although it is slightly overestimated. The average age obtained is 26, with an earlier onset in males (24 among men versus 27 among women).

The growing number of case records in Spain arising in recent years provides new perspectives for epidemiological research and makes it possible to more reliably estimate the actual figures relating to schizophrenic disorders in the country. However, at least for now, there is no record encompassing the entire national territory. Annual prevalence figures for 1998 compiled from the records of different Spanish provinces are consistent with regularly assumed worldwide prevalence values, ranging approximately from 2 to 4.5 per 1,000 (Moreno Küstner et al. 2005) (see table 5.5).

TABLE 5.5: Annual prevalence of schizophrenia and related disorders according to Spanish case records, 1998

Psychiatric case records, by regions	Prevalence (per 1,000 inhabitants)
Alava	1.98
Asturias	2.16
Granada-South	2.40
Navarre	2.70
La Rioja	3.10
Guipuzcoa	3.22
Biscay	4.51

Source: Moreno Küstner et al. (2005).

As for the evolution of the disorder's epidemiology over time in Spain, Iglesias García (Iglesias García, 2001), using data collected by the Cumulative Record of Psychiatric Cases in Asturias (*Registro Acumulativo de Casos Psiquiátricos de Asturias*—RACPAS) from 1987 to 1997 (which includes information about new cases aged 15-64—ICD-9 diagnosis—in all the public hospitals and clinics of the northwestern region of Asturias), found that the annual incidence tended to decline among the population of Asturias during the period under consideration. The administrative incidence of the disorder declined from 3.60 per 10,000 (1987) to 1.81 per 10,000 (1997). Although the decline in the total population is statistically significant, differential results appear when this information is broken down into age groups. The declining incidence affects all ages except the 15-24 age group. The author views the hypothesis of genetic anticipation and higher consumption of psychotropic drugs among younger individuals as possible explanations, as they could inflate the schizophrenic incidence figure due to overinclusion in this diagnosis of psychotic episodes due to intoxication. The downward trend can also be seen both in the subsample of men and women. Iglesias García observed that the total number of men diagnosed with schizophrenia virtually doubles the figure for women (63.1% versus 36.9%).

In spite of the relative dearth of epidemiological studies performed in Spain, the existent research does seem to point to the fact that no significant differences exist compared with other developed countries.

5.3 COMPARATIVE COST-EFFECTIVENESS ANALYSIS OF INTERVENTIONS FOR SCHIZOPHRENIA

In previous sections we have already described the basics of this methodology with the objectives and approaches of the WHO-CHOICE programme. Following this philosophy, our study seeks to perform a cost-effectiveness analysis of interventions capable of reducing the burden of schizophrenia disorder in the Spanish population. The purpose of this analysis is to assign a relative position to each of the interventions in an order of priority of application. This information is particularly useful when the level of analysis is that of a national population.

Mood disorders and psychoses have taken the lion's share of the cost-effectiveness analyses that have appeared in the mental health field. Several studies have analysed the differential cost-effectiveness associated with various schizophrenia interventions in different countries, such as Australia (Andrews et al. 2003; Andrews et al. 2004; Magnus et al. 2005), Mexico (Palmer et al. 2002), and even Spain (Sacristan, Gomez and Salvador-Carulla 1997). However, we should note with regard to the Spanish study that the criterion for measuring effectiveness chosen by the authors was different from the one applied in our research. Since the methodology for cost-effectiveness analysis in the WHO's Global Burden of Disease (GBD) study had not been developed at the time of the study's appearance, these authors were unable, obviously, to consider the amount of DALYs avoided taking as a reference unit the number of months elapsed with partial remission. Until our study, this methodology had not been applied to any study of the Spanish population.

5.4 DIFFERENTIATED OBJECTIVES

This research set for itself the following differentiated objectives:

- Quantification of DALYs associated with schizophrenia in Spain in the year 2000.
- Comparative study of the cost-effectiveness of different interventions for handling schizophrenia in our setting, using DALYs and QALYs as measures of effectiveness.
- Application to the Spanish health system of the new methodology developed by the World Health Organization within the WHO-CHOICE project to analyse the impact of therapeutic interventions at the population level.

6
Research Methodology

6.1 POPULATION

The demographic data needed for our research (the general population in Spain in the year 2000 and its distribution by gender and age group) were obtained from census figures drawn up by the National Statistics Institute (INE). These census figures are publicly accessible and can be consulted at the INE's website (www.ine.es).

6.2 METHODOLOGY FOR ESTIMATING THE BURDEN OF DISEASE

The applied methodology for estimating the DALYs is identical to the one considered in estimating the burden of depression, which we discussed in the relevant section.

6.3 METHODOLOGY FOR ESTIMATING THE PREVALENCE AND INCIDENCE OF SCHIZOPHRENIA IN SPAIN

The epidemiology of schizophrenia can be addressed through prevalence as well as incidence studies. Since the total number of cases in a population is partially determined by the number of new cases, an obvious link is established between prevalence and incidence values, or, what is in essence the same, the rate of prevalence can be estimated through the incidence and vice-versa. The calculation of the prevalence or incidence rate involves different methodological approaches. Incidence studies focus on cases involving the first episode of the disorder. Such an assumption can involve certain practical restrictions, but in exchange, it provides additional advantages, such as the ability to estimate the age of onset. The methodological rigour of most incidence studies accounts for the consistency of their results. In order to benefit from this advantage, for our research we estimated the prevalence of schizophrenia in the Spanish population based on the data from an incidence study. To calculate one starting with the other, a disease model was used that applies the specific methodology of the WHO's GBD study and assumes a causal link between prevalence and incidence. This assumption is of a causal but not a linear link, since the competitive effect of other diseases is taken into consideration, thus arriving at a more realistic model. These types of models have already been successfully applied to the study of various diseases, including some subtypes of cancer (Kruijshaar, Barendregt and Hoeymans 2002; Kruijshaar, Barendregt and Van De Poll-Franse 2003) or non-insulin-dependent diabetes mellitus (Barendregt, Baan and Bonneux 2000). However, they had not been used until now in mental health.

The model was implemented using a software application called DISMOD, designed by Barendregt et al. within the WHO's Global Programme on Evidence for Policy (GPE) (Barendregt et al. 2003). DISMOD was designed to provide consistent estimates of incidence, duration and mortality rates in burden of disease studies. It uses an approach based on mortality tables to monitor an initially healthy cohort over time, applying to this cohort the risks associated with a specific disease (e.g., incidence, remission, rate of lethality) as well as the

risk associated with the competitive presence of other diseases, represented by general mortality. The model takes the distribution by age of a given population to obtain epidemiological measures that are consistent with the assumed levels of incidence, remission and lethality. Therefore, the estimates of such values must be entered as input parameters, namely:

1) Rate of incidence.
2) Rate of remission.
3) Rate of lethality or relative mortality risk (i.e., the excess general mortality attributable to the disease).

The rates of incidence, remission and lethality considered are instantaneous, calculated in yearly units. However, in the real world, a susceptible population is continuously exposed to the risk posed by a disease, not at the end of discrete time intervals. DISMOD simulates this phenomenon by means of a decreasing exponential function. In other words, the size of the susceptible population declines continuously, while the disease continues its course in the individuals. The model assigned a rate *i* to the likelihood of appearance of the disease or disorder in the susceptible population and a rate *m* for general mortality. Cases of disease would remit at a rate *r*, with death by general causes at the same rate as the susceptible population (*m*) to which a specific mortality rate *f* would be added (see figure 6.1).

If we assume that these rates are approximately constant during a short interval of time, we can define a set of differential equations that would characterise the transitions between the three conditions mentioned earlier: susceptibility, disease and death. This is, in essence, the model underlying the operation of the DISMOD tool. For each age cohort, the DISMOD application calculates the relative percentage of individuals who will develop, recover from, or die from a disease; the percentage of individuals who will die from other causes of mortality; and the percentage of individuals who will continue living free of the disease.

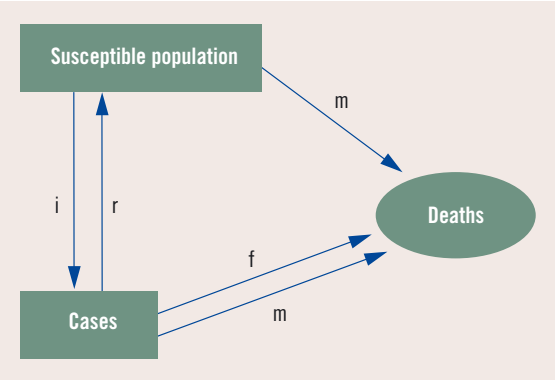

Figure 6.1 Condition transition model used by DISMOD

6.3.1. INCIDENCE FIGURES

Our primary source for estimating the incidence of schizophrenia in Spain was the comprehensive monitoring study mentioned earlier, conducted by Vázquez Barquero et al. on the population of Cantabria, Spain (1995). The study selected patients suffering from a first episode of schizophrenia who, over a period of two years, established first contact with any of the public mental health services in Cantabria. The strategies adopted by the study (basically, including not only admissions but also any contact with the mental health services, and assuming a prospective approach of patients with the first episode instead of the regular retrospective approach with chronic patients) rendered considerably more accurate results than previous epidemiological studies. The incidence estimates calculated by the authors (0.80 per 10,000 inhabitants per year—0.84 for men and 0.80 for women—for the general population, 1.9 per 10,000 inhabitants per year—1.88 for men and 1.93 for women—for the considered age range) seem to be consistent with the figures obtained by other Spanish epidemiological studies on schizophrenia focusing on the population of other regions: for example, from 1.2 to 2.4 per 10,000 inhabitants in Navarre (Mata et al. 2000)—incidence for the general population—or 1.81 per 10,000 inhabitants in Asturias (Iglesias García 2001). The epidemiological estimates by Vázquez-Barquero et al. also seem to be consistent with international data. Our review of the articles published between 2000 and 2005 (using a keyword search on the MEDLINE database) found that the different incidence estimates hovered at around 10 per 100,000 inhabitants per year. These data are also consistent with previous estimates, such as those provided by the classic incidence study carried out by the WHO in the 1980s, which also determined an average inci-

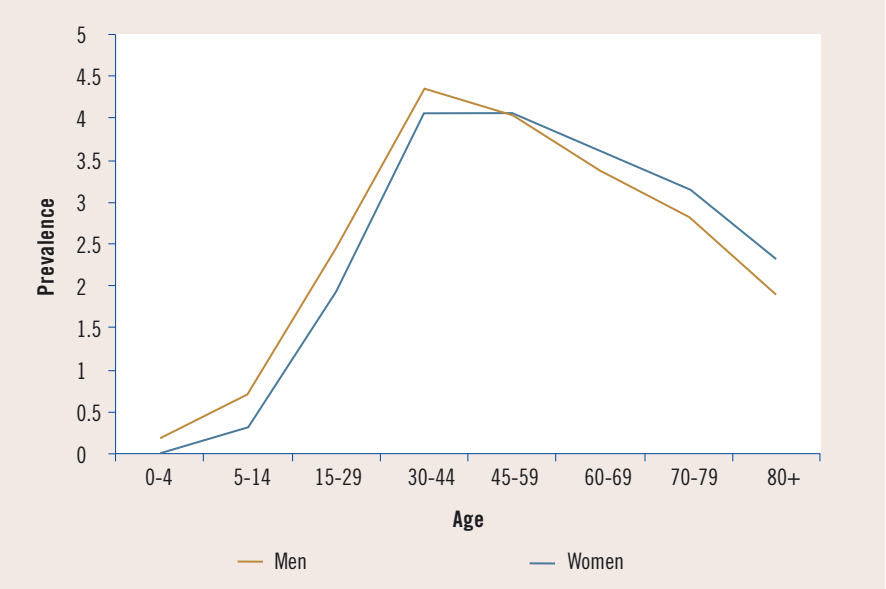

Figure 6.2 Estimated prevalence for the Spanish population in 2000 by age

dence of schizophrenia for European countries of approximately 10 per 100,000 inhabitants/year.

6.3.2. RELATIVE MORTALITY RISK

To estimate the relative risk of mortality (which should be entered as an input parameter in the DISMOD tool to achieve the estimate sought for prevalence figures), the results provided by the WHO GBD study in 2000, based on meta-analyses (Harris and Barraclough 1998; Inskip, Harris and Barraclough 1998), were accepted given the lack of studies focusing on the Spanish population. The value taken as the relative mortality risk associated with schizophrenia was 1.4. Our own review of international publications on the issue appearing from 1998 (the year in which the meta-analyses taken as reference by the GBD study appeared) to 2004 (using the MEDLINE database) provided a range of outcomes that varied between 1.54 (for men) and 1.62 (for women) (Kelly et al. 1998) and 4.41 (Enger et al. 2004). However, since none of the articles found in our review involved a meta-analysis, we decided to take 1.4 as a valid input parameter.

6.3.3. REMISSION

Remission (another of the input parameters needed to estimate the prevalence values) in developed countries was estimated using the WHO GBD study, placing it at 10% of cases over a period of 11.5 years, which in turn corresponds to an instantaneous rate per person of 1 per 100 (the GBD considers remission the fact that the subject stops being treated as a case and goes back to forming part of the "susceptible population"). Our review of the literature on the subject between 2000 and 2004 (once again, availing ourselves of a MEDLINE keyword search) provided heterogeneous results, none of which contradicted the GBD estimate.

6.3.4. PREVALENCE FIGURES

The prevalence figure was estimated using the DISMOD tool described earlier. We assumed a relative mortality risk of 1.4 (except for the 0-4 and 5-14 age groups, for which we respectively assumed a rate of 0 [they are not considered schizophrenia cases] and 1 [same mortality as in the general population]) and a remission rate of 10 per 1,000 (except in the 0-4 age group, for which no schizophrenia cases were considered to exist) as input parameters. The prevalence figures obtained per age group are shown in figure 6.2 for both men (brown line) and women (blue line).

The estimated average prevalence was 3.00 per 1,000 inhabitants per year in the case of men, and slightly lower in the case of women: 2.86 per 1,000. The average age at onset of the disorder (24.04 for men, 27.00 for women) and the output values obtained for incidence (0.084 per 1,000 for

men and 0.079 per 1,000 for women) exactly match the outcomes observed by Vázquez Barquero et al. (age at onset of first episode: 24 for men, 27 for women; incidence of 0.84 per 10,000 for men and 0.80 per 10,000 for women).

6.4 COST-EFFECTIVENESS ANALYSIS METHODOLOGY, MEASURED IN DALYS, OF SCHIZOPHRENIA INTERVENTIONS IN SPAIN

6.4.1. SELECTED INTERVENTIONS FOR THE COST-EFFECTIVENESS STUDY

Our analysis considered several possible interventions at the population level for the treatment of schizophrenia in Spain. The different interventions were defined according to the treatment administered to five subdivisions of the total population of subjects diagnosed with schizophrenia: 1) subjects with complete remission after the first episode (20% of the total); 2) subjects with incomplete remission after the first episode (25% of the total); 3) subjects with an episodic course, remitting between episodes (30% of the total); 4) subjects with an episodic course, with progressive or stable deficit (15% of the total); 5) subjects with an ongoing course (10% of the total).

In turn, six different types of alternatives were considered:

1) Typical antipsychotics administered individually.
2) Atypical antipsychotics administered individually.
3) Typical antipsychotics plus psychosocial treatment.
4) Atypical antipsychotics plus psychosocial treatment.
5) Typical antipsychotics plus psychosocial treatment and ongoing care programmes.
6) Atypical antipsychotics plus psychosocial treatment and ongoing care programmes.

To simplify our analysis, a single type of typical antipsychotic, risperidone (the first second-generation antipsychotic widely used in Spain) was taken

TABLE 6.1: Assumed distribution for the current scenario

DRUG	Haloperidol		Risperidone		Fluphenazine decanoate		Olanzapine		Zuclopentixol	
Drug type	Typical antipsychotic		Atypical antipsychotic		Depot		Atypical antipsychotic		Depot	
	Percentage	Dose (mg)	Percentage	Dose (mg)	Percentage	Dose (mg)	Percentage	Dose (mg)	Percentage	Dose (mg)
Complete remission after one episode	39	3	29	0.4	0	0	15	7	0	0
Incomplete remission after one episode	39	6	29	6	0	0	15	10	0	0
Episodic course, remitting between episodes	39	10	29	4	23	25	15	10	6	15
Episodic course with stable or progressive deficit	39	10	29	8	23	25	15	12	6	15
Ongoing	39	10	29	8	23	25	15	15	6	15

TABLE 6.2: Assumed distribution for interventions with pharmacotherapy based on typical antipsychotics

Drug	Haloperidol		Fluphenazine decanoate	
	Percentage	Dose (mg)	Percentage	Dose (mg)
Complete remission after one episode	100	3	0	0
Incomplete remission after one episode	100	6	0	0
Episodic course, remitting between episodes	50	6	50	75
Episodic course with stable or progressive deficit	50	10	50	75
Ongoing course	50	10	50	75

into consideration. An ideal coverage of 90% was assigned for these six hypothetical interventions. In addition, the use of haloperidol and fluphenazine decanoate was assumed in the options applying pharmacotherapy based on typical neuroleptics. Tables 6.1-6.3 show the application doses considered in the study and the corresponding consumption rates for patients in the various scenarios.

These percentages reflect both public and private consumption, and were estimated from 2000 antipsychotic sales data for the Spanish population provided by IMS España (International Marketing Services). The report includes purchases (in units of each pharmaceutical speciality) from chemists' offices to laboratories and distribution warehouses. The data are based on a sample of wholesalers operating throughout the country that provide IMS with actual retailer-chemist's traffic data on a weekly or monthly basis. Moreover, the report integrates data from a stratified sample of chemist's representing direct laboratory-chemist's sales. The data were expressed in defined doses per patient/day.

6.4.2 IMPACT OF INTERVENTIONS AT THE POPULATION LEVEL

The main therapeutic effect of the interventions considered is a reduction in psychotic symptoms, which in turn results in a decline in associated disabilities (which translates into changes in disability weight with regard to the untreated schizophrenia situation). These changes can be modelled according to the methodology described by Andrews et al. (2000) which permits the transformation of effect sizes estimated in clinical trials (standardised difference between the intervention group mean and the control group mean) into changes in the disability weight.

The estimate provided by the WHO GBD (DW = 0.627) was used as the weight value of disability associated with depression. The same figures already mentioned in the section on depression were taken as the estimates for the corresponding level of health in the general population.

A complete meta-analysis of controlled randomised trials performed by Leucht et al. (1999) estimated the efficacy and onset of extrapyramidal secondary effects of several conventional and atypical antipsychotics. The selected assessment measures were the changes after monitoring with the BPRS (Brief Psychiatric Rating Scale) and the use of anti-Parkinson's medication. The authors offer the outcomes of the meta-analysis in terms of effect sizes, which is particularly appropriate for our purposes. Leucht et al. presented the estimated effect sizes as Pearson correlation coefficients (r). Converted to Cohen coefficients, the effect size measures obtained for haloperidol and risperidone are, respectively, d = 0.465 and d = 0.495.

TABLE 6.3: Assumed distribution for interventions with pharmacotherapy based on atypical antipsychotics

Drug	Risperidone	
	Percentage	Dose (mg)
Complete remission after one episode	100	0.4
Incomplete remission after one episode	100	6
Episodic course, remitting between episodes	100	4
Episodic course with stable or progressive deficit	100	8
Ongoing course	100	8

In addition, a complete meta-analysis performed by Mojtabai et al. (2003) provides an estimate of the additive effect derived from adding a psychosocial intervention (family therapy, training in social skills and cognitive-behavioural therapy) to conventional drug treatment. The additive effect size calculated for the psychosocial intervention was d = 0.39.

Finally, our research took into account two systematic Cochrane reviews by Marshall et al. (2000), one on ongoing care programmes and the other on assertive community treatment (Marshall and Lockwood 2000). Neither of the two models shows a strong impact on clinical or social course. We estimate a minimum additional effect size of d = 0.05 on combined drug and psychosocial therapy.

6.4.3 ANALYSIS OF INTERVENTION COSTS

When considering costs, our study adopts the financier's perspective, without considering costs associated with the perspective of patients and their relatives (e.g., lost production capacity). The WHO-CHOICE methodology assumed involves an approach by "ingredients" to the cost calculation of

interventions in the health field that requires separate identification and assessment of the amount of inputs of the involved resources (e.g., healthcare personnel figures) and the unit price or cost of such resources (e.g., the salary of a healthcare professional). It assumes two categories of resource and cost inputs: costs per patient, which refer to the input of resources used or provided at the patient or supplier level (including days admitted, outpatient visits, medications, laboratory tests; the unit costs of these resource inputs at the patient level include the costs per day of hospitalization or per outpatient visit, or the price of prescribed drugs and of any test carried out by the laboratory) and programme costs, which refer to the resources used in implementing an intervention above the patient or supplier level; these resources include central planning, policy and function administration issues, as well as resources that go to training healthcare service providers and preventive programmes.

The estimates at the programme level are based on existing guidelines (e.g., regarding the duration of training). A unit cost line item was also generated for every resource item in Spain in order to estimate the total cost of activities at the programme level. Unit costs for mental healthcare were estimated by the PSICOST group (Salvador-Carulla et al. 1999; Saldivia et al. 2005). These units have been used in the financial analysis of mental health interventions in Spain (Vazquez-Polo et al. 2005). The SOIKOS unit cost database was used to determine the cost for the rest of the healthcare services used. All of these elements of the total cost are estimated and assembled in a series of templates implemented in spreadsheets (*CostIt*) designed specifically by the WHO-CHOICE programme (available at www.who.int/evidence/ceachoice). A discount of 3% was considered in all the baseline cost analyses for the 10-year implementation period. All costs were estimated in euros.

6.4.4 SENSITIVITY AND UNCERTAINTY ANALYSIS

In our study we performed three different types of sensitivity analyses. The first considered the impact of applying social preference measures in calculating DALYs on the final estimate of the cost-effectiveness ratios: age discount (i.e., granting more weight to ages that are closer to the current age of the subject and less weight to ages that are farther away) and weight by age (which weighs each age by a predetermined coefficient, granting more weight to the central life years of individuals as they are considered to be the most productive). The second sensitivity analysis looked at the variation in the price of a dose of risperidone between two possible values. Two different costs were estimated: the first considering its price as a patented drug, and the second, considering its price as a generic drug. The generic version of risperidone has recently appeared on the Spanish mental health market; it was not available in the year 2000, the date our study focuses on. However, by weighting the prices of the different versions of generic risperidone currently available on the Spanish market, we estimated a price for the year 2000 (0.63 euros per 2-mg dose, while the estimated cost for the same dose of patented risperidone was 1.76 euros). The purpose of this sensitivity analysis was to determine if the variation in the cost per dose resulting from the appearance of generic versions of atypical antipsychotic caused a significant variation in the estimated cost-effectiveness of interventions based on applying these drugs. Finally, a third sensitivity analysis was conducted, leading to a ±10% variation on the effect size of each treatment over the disability weight.

With regard to the uncertainty analysis, the methodological considerations made in the section on depression are also applied to the analysis of schizophrenia.

6.4.5 CONSTRAINTS

The constraints due to the inherent presence of uncertainty in the estimates of some parameters have already been discussed. Moreover, the uncertainty analysis applied to our outcomes in order to offset these constraints has already been described in previous sections.

Due to the lack of rigorous epidemiology studies encompassing the Spanish population at the national level, most of the data needed to calculate our estimates were extrapolated either from regional studies or from international meta-analyses. However, until it becomes feasible to have robust evidence at a truly national level, our results can be considered a valid means to approach the differences in terms of cost-effectiveness of the different schizophrenia treatments in Spain.

Among the limitations of our study, we must also mention those inherent to the methodology used. The use of models can be a useful solution when facing certain problems in epidemiological research, but any model implies assumptions and hypotheses that cannot always be verified in real-life situations. A model always represents a simplification, to a certain degree, of reality. For example, in our case it would have been enriching to assume a broader economic perspective and also contemplate indirect costs related to patients' loss of productivity, etc., instead of adopting a perspective that focused primarily on the healthcare system. It is also obvious that our model does not cover all the possible intervention alternatives that could be applied. For example, it does not contemplate the effect of a possible change in the assigned medication (e.g., patients who switch from typical to atypical antipsychotics).

The use of multidimensional and population-based measures of the burden of disease, such as DALYs, presents clear advantages (the chance of comparing the burden of different diseases of a dramatically different nature, for instance), but it also involves assumptions that are not always admissible, such as the additive nature of these measures (e.g., can it be accepted *a priori* that the sum of the burden due to several mild disorders affecting broad swathes of the population equals that caused by a severe disorder affecting a small number of individuals?). Neither do these types of measures fully cover the entire range of possibilities that can be derived from an intervention. We have already commented earlier on the need to assess other types of phenomena related to patients' lives. In the context of schizophrenia, there are important additional benefits including the reduction of the family burden, absenteeism and unemployment (with the attendant rise in productivity). In spite of the clear social focus of the WHO-CHOICE programme, challenges still remain, such as implementing measurement procedures for including cost-effectiveness analyses of productivity gains, as well as the time spent on care (both by the patient and by "informal care givers") (Tan Torres, Baltussen and Adam 2003). In an attempt to make up in part for these shortcomings, we performed an alternative analysis assessing efficacy in terms of QoL improvements according to the QALY methodology, as discussed in the following section.

In addition to the intrinsic constraints of our methodology, it is necessary to consider other restraints due to estimates of the different input parameters used as a basis for applying this methodology. One of these, for example, would be the use of international estimates given the lack of specific data for Spain. To take a case in point, our study used the disability weights proposed by the WHO GBD study instead of calculating specific values for the Spanish population. Since these reflect values that depend on subjective assessments, cultural variations could exist. However, the calculation of these weights would have exceeded the bounds of the objectives proposed in the present study.

6.5 COST-EFFECTIVENESS ANALYSIS METHODOLOGY, MEASURED IN QALYS, OF SCHIZOPHRENIA INTERVENTIONS IN SPAIN

The improved QoL of patients obtained thanks to a reduction in clinical symptoms is also one of the goals of schizophrenia treatments. Some recent studies indicate that an improvement of symptoms is correlated with improvements in QoL (Pyne et al. 2003; Saleem, Olie and Loo 2002). However, this correlation is often weak, so it would be advisable to assess the impact of treatment on the QoL of patients by means of specific and independent methods. With this in mind, our work includes a second cost-effectiveness analysis of schizophrenia interventions in Spain in which the improved QoL of patients, assessed in QALYs, which has already been described in the section on depression, was chosen as a measure of efficacy.

The SOHO (European Schizophrenia Outpatient Health Outcomes) study, which we have already mentioned in earlier sections, was taken as a source of data, the goal being to overcome some of the limitations inherent to randomised clinical trials with antipsychotic drugs (short duration of monitoring, use of selected patient samples, restrictions on generalising outcomes due to the administration of highly specific treatment regimes, absence of measures to assess QoL and social functioning) (Haro et al. 2003). The SOHO study constitutes the largest naturalist study conducted to date on antipsychotic medication. It was based on prospectively monitor-

TABLE 6.4: EQ-5D scores (baseline and after 12 months of tracking)

Drug	Measure	N	Median	Average	Standard deviation
Haloperidol	Baseline	363	0.70	0.58	0.34
	12 months	329	0.83	0.76	0.28
Risperidone	Baseline	1,830	0.70	0.60	0.32
	12 months	1,591	0.83	0.79	0.25

ing patients from ten European countries over a period of three years, during which they were administered an outpatient antipsychotic treatment.

For our analysis we have considered only the QoL measures of the Spanish sample of SOHO, assessed with the EQ-5D (*EuroQol-5 Dimensions*) tool (Williams 1990). Since only the application of drug therapy is taken into account in the SOHO study, and not psychosocial interventions, our study on QoL focused only on two alternative interventions: typical antipsychotics (haloperidol) and atypical antipsychotics (risperidone). The baseline of the Spanish sample (average EQ-5D score: 0.59) was taken as a measure of the QoL of individuals with schizophrenic disorders before they received any type of treatment. The average EQ-5D scores by age range and gender obtained from the Spanish sample of the ESEMeD / MHEDEA 2000 study (*European Study of Epidemiology of Mental Disorders*) (Alonso et al. 2002) were considered as measures of QoL in the national general population. The effectiveness of the two interventions being compared was estimated based on the variation obtained in the EQ-5D scores after 12 months of treatment (total European samples of patients treated with haloperidol and risperidone were considered as they presented a considerably higher N, thus enabling a more reliable estimate of the effect size) (see table 6.4).

The same software tools provided by the WHO-CHOICE programme for the cost-utility analysis can be used on this input data. In the results obtained here, the effectiveness reflects the variation in quality-adjusted life years (QALYs). As for the costs associated with the interventions, the same that were considered for the analysis in terms of DALYs were assumed. For risperidone, the cost of the patented version of the drug was assumed.

7 Results

7.1 BURDEN OF DISEASE FOR SCHIZOPHRENIA IN SPAIN IN THE YEAR 2000

According to our results, the burden of disease associated with schizophrenia in Spain for 2000 is estimated at 60,215.90 DALYs—30,740.49 in men and 29,475.41 in women—which means a raw rate per 100,000 inhabitants of 155.89 (men) and 143.47 (women).

By age group, the highest number of DALYs corresponds to the 15-44 age range for both sexes. Table 7.1 shows the distribution by age group of years lived with disability, years of life lost and DALYs corresponding to the male population, while table 7.2 shows the data corresponding to the female population.

7.2 COST-EFFECTIVENESS ANALYSIS, MEASURED IN DALYS, OF SCHIZOPHRENIA INTERVENTIONS IN SPAIN

7.2.1 COST OF INTERVENTIONS

The estimated annual costs for each of the considered interventions are shown in table 7.3. The total annual cost of each of the considered options was broken down into three components, namely: cost per patient, cost associated with the programme, and cost associated with the required specialised professional training. The estimated cost of the present scenario amounted to 210 million euros. Costs associated with alternative interventions ranged from 161 million euros (typical neuroleptics with a 90% rate of coverage) and 323 million euros

TABLE 7.1: Burden of disease outcome for schizophrenia in Spain. Men

Age group	YLDs due to schizophrenia	YLLs due to schizophrenia	DALYs	DALYs per 100,000 inhabitants
0-4	1,335.67	0.00	1,335.67	139.72
5-14	3,402.69	0.00	3,402.69	161.83
15-29	20,221.63	35.94	20,257.57	429.91
30-44	5,233.17	128.79	5,361.96	114.12
45-59	82.85	149.09	231.95	6.67
60-69	2.08	73.27	75.34	3.99
70-79	0.00	64.36	64.36	4.70
80 +	0.05	10.90	10.96	2.12
TOTAL	30,278.08	462.36	30,740.49	155.89

YLDs: Years of Life Lost due to Disability. YLLs: Years of Life Lost due to death. DALYs: Disability-Adjusted Life Years.

TABLE 7.2: Burden of disease outcome for schizophrenia in Spain. Women

Age group	YLDs due to schizophrenia	YLLs due to schizophrenia	DALYs	DALYs per 100,000 inhabitants
0-4	150.20	0.00	150.20	16.63
5-14	3,101.35	0.00	3,101.35	155.82
15-29	17,771.03	0.00	17,771.03	394.05
30-44	7,545.06	0.00	7,545.06	162.09
45-59	698.03	33.18	731.21	20.53
60-69	17.34	99.34	116.67	5.52
70-79	0.00	33.67	33.67	1.87
80 +	0.00	26.23	26.23	2.59
TOTAL	29,282.99	192.42	29,475.41	143.47

YLDs: Years of Life Lost due to Disability. YLLs: Years of Life Lost due to death. DALYs: Disability-Adjusted Life Years.

(risperidone and psychosocial intervention with ongoing care programme).

The differences observed between costs basically depend on the psychopharmaceutical product provided in the intervention. The options based on applying risperidone have appreciably higher associated costs than those using typical antipsychotics as the drugs of choice. However, as expected, the use of a generic drug instead of patented risperidone results in a steep decline in costs: from 291 to 193 million euros (in the option applying pharmacotherapy alone); from 307 to 208 million euros (in the option including risperidone and psychosocial intervention); and from 323 to 224 million euros (in the option combining the administration of risperidone and psychosocial intervention with the ongoing care programme).

However, the addition of psychosocial treatment or of an ongoing care programme does not give rise to an appreciable increase of total costs.

7.2.2 EFFECTIVENESS OF INTERVENTIONS (AVOIDED BURDEN)

The amount of DALYs avoided per year by applying each of the considered interventions is shown in table 7.4. If we do not take into consideration weighting by age or discounts, the intervention

TABLE 7.3: Costs associated with the proposed interventions

Description of the intervention	Costs (in millions of euros per year)			
	Patient	Programme	Training	TOTAL
Current situation	206	4	0	210
Typical antipsychotics	149	7	5	161
Risperidone (patented)	279	7	5	291
Risperidone (generic)	180	7	5	193
Typical antipsychotics + psychosocial treatment	153	7	11	171
Risperidone (patented) + psychosocial treatment	289	7	11	307
Risperidone (generic) + psychosocial treatment	190	7	11	208
Typical antipsychotics + psychosocial treatment + ongoing care programme	193	12	16	221
Risperidone (patented) + psychosocial treatment + ongoing care programme	296	12	16	323
Risperidone (generic) + psychosocial treatment + ongoing care programme	197	12	16	224

TABLE 7.4: Effectiveness associated with the proposed interventions

Description of the intervention	Effectiveness (DALYs avoided per year)		
	Weighting by age and discount	Discount only	Without weighting by age and without discount
Current situation	3,020	2,558	3,008
Typical antipsychotics	3,315	2,808	3,302
Risperidone (patented or generic)	4,033	3,416	4,018
Typical antipsychotics + psychosocial treatment	6,531	5,532	6,506
Risperidone (patented or generic) + psychosocial treatment	7,662	6,489	7,632
Typical antipsychotics + psychosocial treatment + ongoing care programme	8,296	7,027	8,264
Risperidone (patented or generic) + psychosocial treatment + ongoing care programme	8,571	7,259	8,538

modelling the current situation would avoid 3,008 DALYs and the proposed reduction alternatives would range from 3,302 (typical antipsychotics) to 8,538 DALYs (risperidone with psychosocial intervention and ongoing care programme).

The differences between the different interventions are appreciable. The use of risperidone is moderately more effective than that of typical antipsychotics (the number of DALYs avoided rises from 3,302 to 4,018, a 22% increase). The differences in the results of applying atypical and typical antipsychotics are slightly attenuated by adding psychosocial treatment (with a 17% increase in the number of DALYs avoided by replacing conventional antipsychotics with risperidone). When an ongoing care programme is also added, the discrepancy in effectiveness between the two types of drugs declines notably (the increase in saved DALYs by replacing conventional antipsychotics with risperidone is then 3%).

The greatest differences in terms of effectiveness of the various interventions are determined primarily by whether or not psychosocial treatment and ongoing care programmes are included. By adding the psychosocial treatment, the number of DALYs saved nearly doubles (97% increase when traditional antipsychotics are considered, and 90% if the administered drug is risperidone). If an ongoing care programme (including psychosocial treatment) is added, the effectiveness rises by 150% (traditional antipsychotics) and 113% (risperidone) with respect to interventions that consider only pharmacotherapy. However, the application of the ongoing care programme only leads to a slight increase in effectiveness compared to interventions that already include psychosocial treatment: 27% (typical antipsychotics) and 12% (risperidone).

The amount of DALYs avoided ranges from 2,808 to 7,259 after considering the discount. If the discount and weighting by age are considered, the figures range from 3,315 to 8,571 avoided DALYs. In either of the two cases, the relative differences between the different interventions we have commented remain roughly the same.

7.2.3 COST-EFFECTIVENESS OF INTERVENTIONS

Two interventions stand out as the most cost-effective when the effectiveness results are weighted with population costs and the relevant average costs per avoided DALY are determined: typical antipsychotics plus psychosocial treatment, with or without an ongoing care programme (which, respectively, would generate a cost per DALY avoided annually of 26,343 and 26,713 euros). At the opposite end, the least cost-effective option would be administration of risperidone alone (72,552 euros per DALY avoided). The current situation would imply a ratio of 69,816 euros per avoided DALY. The results obtained in the rest of the interventions are approximately similar. These are, expressed in euros per avoided DALY, as follows: 48,839 (only typical antipsychotics), 40,186 (risperidone and psychosocial treatment) and 37,855 (risperidone with ongoing care programme).

Replacing the patented version of risperidone with its generic equivalent causes a considerable reduc-

TABLE 7.5: Cost-effectiveness ratios associated with the proposed interventions

Description of the intervention	Average cost per DALY avoided (in euros)		
	Weighting by age and discount	Discount only	Without weighting by age and without discount
Current situation	69,546	82,108	69,816
Typical antipsychotics	48,650	57,438	48,839
Risperidone (patented)	72,272	85,326	72,552
Risperidone (generic)	47,789	56,421	47,975
Typical antipsychotics + psychosocial treatment	26,241	30,980	26,343
Risperidone (patented) + psychosocial treatment	40,031	47,261	40,186
Risperidone (generic) + psychosocial treatment	27,143	32,045	27,248
Typical antipsychotics + psychosocial treatment + ongoing care programme	26,610	31,417	26,713
Risperidone (patented) + psychosocial treatment + ongoing care programme	37,709	44,520	37,855
Risperidone (generic) + psychosocial treatment + ongoing care programme	26,188	30,918	26,289

tion in the cost per DALY saved, so that the ratios obtained are along the same lines as those estimated for interventions based on conventional antipsychotics. In fact, in this case the option that includes the administration of generic risperidone, psychosocial treatment and an ongoing care programme is the most cost-effective solution (26,289 euros per DALY avoided).

The above figures are estimates obtained when neither weighting by age nor discounts are applied. In these cases, the outcomes do not represent a substantial variation from those we have already mentioned. Table 7.5 shows all the cost-effectiveness ratios obtained. Moreover, table 7.6 shows the incremental ratios, defined as the quotient of incremental change in costs divided by the incremental change in effectiveness between interventions. They indicate the interventions that would be elected (if we apply only a cost-effectiveness criterion) if available resources were to increase. They start with the most cost-effective intervention, and then the next one, and so on. The term *dominated* denotes those interventions that are more costly and less effective than others, and therefore they are not included in the expansion path of the most cost-effective strategies. The administration of a generic version of risperidone was not contemplated when estimating the incremental ratios.

7.2.4 SENSITIVITY AND UNCERTAINTY ANALYSES

Figure 7.1 depicts the results of the sensitivity analysis. The different bars represent the percentage increase or decrease experienced by the average cost-effectiveness ratio under different assump-

TABLE 7.6: Incremental cost-effectiveness ratios associated with the proposed interventions

Description of the intervention	Incremental cost per DALY avoided (in euros)		
	Weighting by age and discount	Discount only	Without weighting by age and without discount
Current situation	Dominated	Dominated	Dominated
Typical antipsychotics	Dominated	Dominated	Dominated
Risperidone (patented)	Dominated	Dominated	Dominated
Typical antipsychotics + psychosocial treatment	26,241	30,980	26,343
Risperidone (patented) + psychosocial treatment	Dominated	Dominated	Dominated
Typical antipsychotics + psychosocial treatment + ongoing care programme	27,977	33,031	28,086
Risperidone (patented) + psychosocial treatment + ongoing care programme	Dominated	Dominated	Dominated

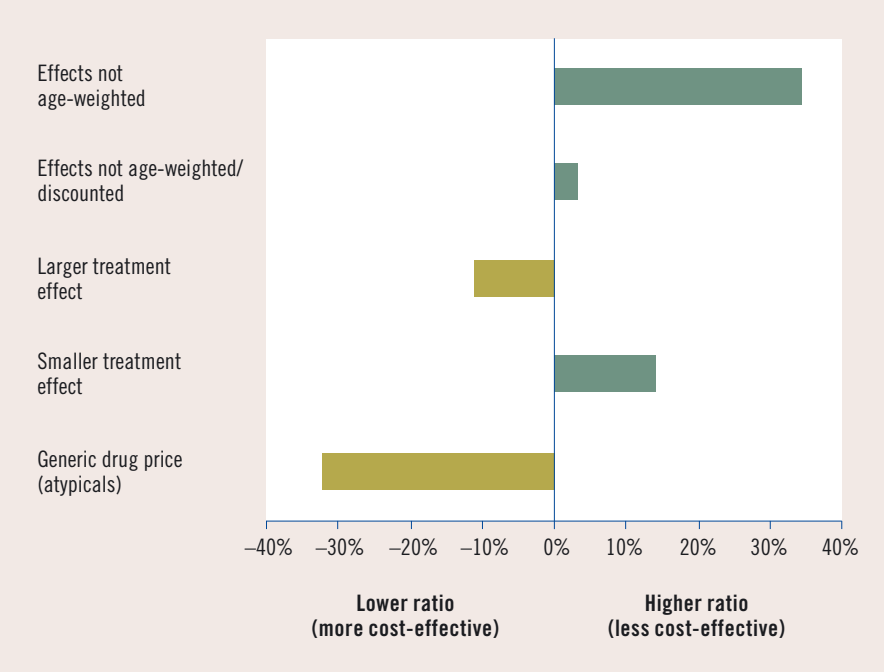

Figure 7.1 Sensitivity analysis results

tions. The first two refer to the application (or not) of age-related weights and discounts. The situation that does not consider weighting by age but does consider discounts (bar 1) as well as the situation considering neither age weight nor discount (bar 2) are compared to the situation considering both weight and discount. The next two consider the maximum and minimum effects of each treatment. Finally, the last bar reflects the variation introduced by replacing the price associated with the patented version of risperidone with the price associated with the generic version of the same drug.

In turn, figures 7.2 and 7.3 show the results of the uncertainty analysis. These were obtained using the MC League software application, which involved 1,000 "walks" assuming a normal global truncated distribution of total costs. The first graph shows the point clusters associated with each of the interventions. The second shows the results in the form of a stochastic league table.

The most notable phenomenon that can be seen in figure 7.1 is the overlap along the effectiveness axis of the clusters associated with baseline interventions in pharmacotherapy only, on one hand, and of the clusters associated with interventions including psychosocial therapy, on the other. However, no overlap appears between both groups of interventions; the gap in terms of efficacy between them can be explained by the addition of the psychosocial treatment.

Of special interest as well is the stochastic league table obtained in our uncertainty analysis (figure 7.2). According to the estimated results, with available resources of more than 250 million euros per year, the most widely applied intervention of choice would be that based on generic risperidone, psychosocial treatment and ongoing care programmes. According to the optimum distribution reflected in the table, the second-ranked intervention in percentage of application is the one based on administering typical antipsychotics, psychosocial treatment and ongoing care programmes, when available resources do not exceed 500 million euros per year. Above this amount, the intervention based on patented risperidone, psychosocial treatment and ongoing care programmes overtakes it in terms of cost-effectiveness. With available resources in the 150-250 million euro range, the most applied intervention is the one based on typical antipsychotics and psychosocial treatment. Only in the 100-150 million euro range do we find an intervention based on pharmacotherapy alone (typical antipsychotics) as the top-ranked intervention.

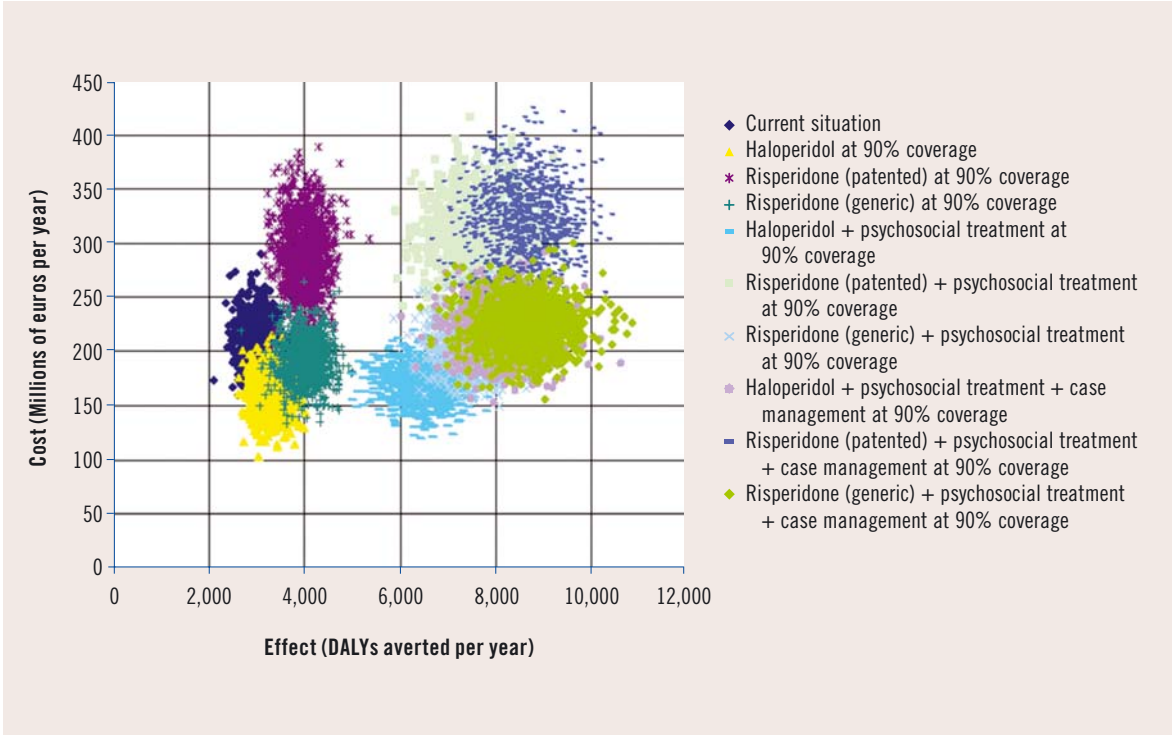

Figure 7.2 Uncertainty analysis results - cluster graph

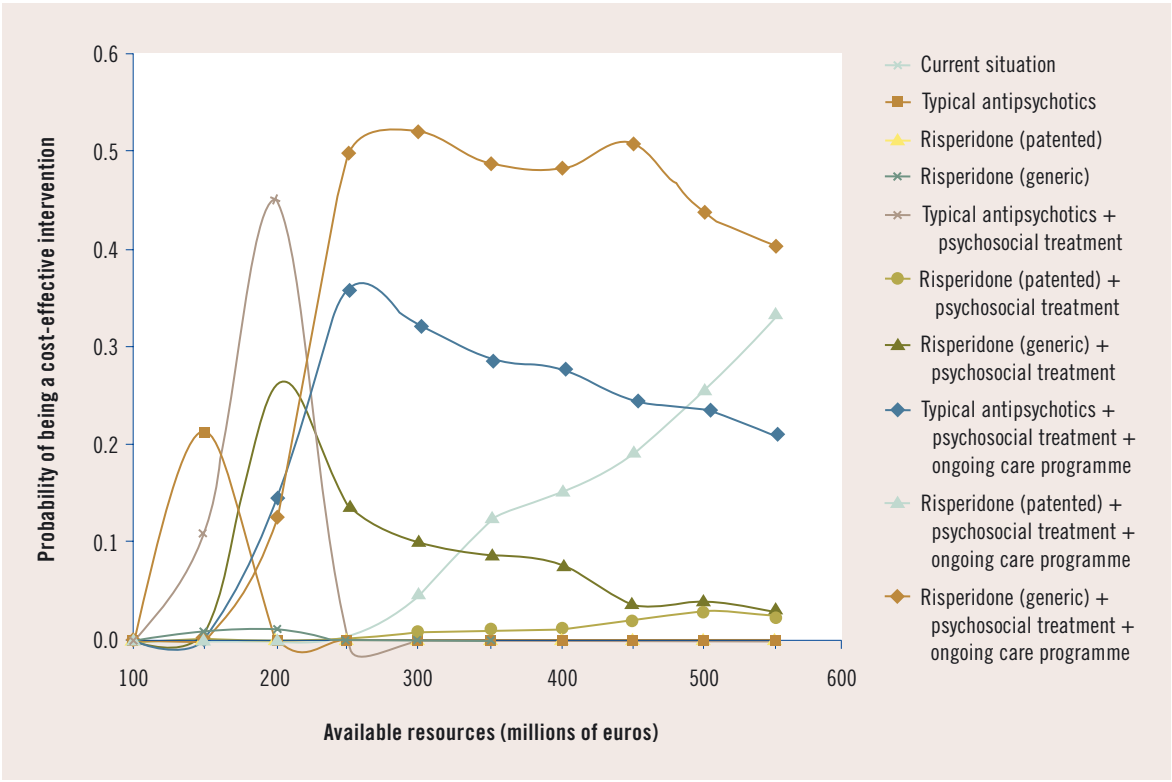

Figure 7.3 Uncertainty analysis results - stochastic league table

7.3 COST-EFFECTIVENESS ANALYSIS, MEASURED IN QALYS, OF SCHIZOPHRENIA INTERVENTIONS IN SPAIN

When the same cost-effectiveness analysis methodology as above is applied to the two selected interventions (typical neuroleptics and risperidone), but considers the effect on the variation in the subjects' QoL (measured in QALYs) rather than the variation in disability (DALYs), the treatment with typical antipsychotics (cost per QALY gained: 38,772 euros) is a more cost-effective option than administering risperidone alone (cost per QALY gained: 67,111 euros).

TABLE 7.7: Cost-effectiveness ratios associated with the proposed interventions (QALYs)

Intervention	Average cost per QALY gained (in euros)
Typical antipsychotics	38,772
Risperidone (patented)	67,111

8
Discussion

The results obtained in the cost-effectiveness analysis (measured in terms of costs per DALY saved) enable us to make three key comparisons: traditional vs. new antipsychotics (risperidone); pharmacotherapy plus psychosocial treatment vs. pharmacotherapy alone; and pharmacotherapy plus ongoing care programmes (which include psychosocial treatment) vs. pharmacotherapy alone. It is to be expected that interventions involving the administration of risperidone will be more effective, since evidence seems to indicate that, when compared to haloperidol, the use of riperidone leads more to improvements on the PANSS (Positive and Negative Symptom Scale), reduces the risk of relapse, and presents a significant reduction in the appearance of side-effects (Hunter et al. 2003).

Given the high cost of atypical antipsychotics in general (and of risperidone in particular), we have found that interventions involving the administration of antipsychotics are more cost-effective. However, when the administration of patented risperidone is replaced by a generic version of the drug, the costs become roughly equal and no differences of note are observed in terms of cost-effectiveness with regard to interventions based on the use of typical neuroleptics (however, we assumed that the drug's effectiveness is identical in its patented and generic version, an affirmation that is, of course, open to discussion).

As expected, the inclusion of psychosocial treatment together with the use of antipsychotic medication translates into an improvement of the intervention in terms of cost-effectiveness. Psychosocial therapy ensures better adherence to drug therapy and the added costs it generates are more than offset by the reduction in new hospital admissions. Finally, the inclusion of ongoing care programmes makes for more efficient use of resources and provides an improvement in terms of cost-effectiveness that is of the same order of magnitude as that obtained by adding psychosocial therapy; in some cases it is slightly less cost-effective (when the basic drug treatment consists of the administration of typical antipsychotics), and in other cases it is slightly more cost-effective (when the basic drug treatment consists of the administration of risperidone, either patented or generic).

The cost-effectiveness ratios calculated in our study range between one and three times the estimated per capita income figure (20,000 euros) for the Spanish population, except in two interventions: the option modelling the present situation, and that which contemplates the administration of risperidone alone. Therefore, most of the considered options are within the range set by the WHO's Commission on Macroeconomics and Health, which considers "cost-effective" those interventions whose cost per DALY avoided does not exceed the threshold of three times the national per capita income. The intervention based on the administration of risperidone alone, however, would be considered "not cost-effective", as it exceeds that threshold.

Comparisons with other studies that apply a national level of analysis are limited by economic and population-related constraints, as well as by the different methodological approaches used. Since international cost-effectiveness studies often quantify the effectiveness of schizophrenia interventions making use of a wide range of criteria—such as

improved score on the BPRS scale (Palmer et al. 2002), or variation in years of life lived with the disorder (Andrews et al. 2004)—our comparison should focus only on those that, like our study, offer estimates in terms of cost per DALY avoided for it to be considered valid.

A recent study on the Australian population compared the use of typical and atypical antipsychotics in terms of cost-effectiveness (Magnus et al. 2005). According to the results provided by Magnus et al., the replacement of typical neuroleptics by risperidone would imply an increase in the cost-effectiveness ratio of 48,000 Australian dollars (which would equal 36,400 international dollars if we apply the currency exchange rate in effect in 2000). According to our study, a switch in treatments would increase the cost per DALY avoided (considering discount, as Magnus et al. do) by between 11,142 euros (14,700 international dollars at the 2000 exchange rate)—if psychosocial therapy and ongoing care programmes are also applied—and 23,713 euros (31,200 international dollars) when the drug treatment alone is applied. Some of the conclusions that the same authors reached about the advantages of applying the cost-effectiveness methodology to priority decision-making in mental health (Vos et al. 2005) are consistent with those drawn from our own findings: in particular, those referring to improved cost-effectiveness achieved thanks to psychosocial treatment and the reduction of cost-effectiveness associated with the widespread use of atypical antipsychotics as the treatment of choice.

If we compare them with the strategies applied to other disorders using the WHO-CHOICE methodology, the results we obtained for interventions involving schizophrenia present a high cost in relation to the outcome achieved. Our estimated cost per avoided DALY (26,343 to 72,552 euros, or 34,662 to 95,463 in 2000 international dollars) exceeds by a factor of about five the average cost associated with bipolar disorder interventions, which amounts to between 5,487 and 21,123 international dollars for developed subregions (Chisholm et al. 2005). The disparity we found between the cost-effectiveness of interventions in schizophrenia and bipolar disorder cannot be explained as a function of the costs (between 8.4 and 17.6 million international dollars per million inhabitants in interventions involving bipolar disorder in developed subregions, and between 6 and 10.5 million international dollars per million inhabitants in interventions involving schizophrenia in the Spanish population). Rather, it is due to differences in effectiveness: the total number of DALYs avoided for schizophrenia with the alternative interventions under consideration in our study varies between 81 and 211 per million inhabitants, while interventions for bipolar disorder manage to save between 375 and 517 DALYs per million inhabitants in developed subregions. The differences are even greater when we compare our results to those for interventions for depression, since the average cost per DALY avoided by interventions involving depression based on primary care was estimated between 1,600 and 1,700 international dollars a year per million inhabitants (Chisholm et al. 2004).

In any case, the comparison between the cost-effectiveness results obtained for the three disorders is clearly limited by methodological differences: while our estimates were made taking into account a national population analysis level (Spain), the figures provided for interventions involving bipolar disorder or depression come from aggregate studies considering populations from different subregions, so a greater heterogeneity can be expected from these. It should be noted that the main objective of the present study is to compare interventions associated with the same disorder, and not to compare different disorders.

Our uncertainty analysis enables us to draw a significant conclusion for clinical practice: the addition of psychosocial treatment (whether alone or as part of an ongoing care programme) to pharmacotherapy (based on either typical or atypical antipsychotics) significantly increases the cost-effectiveness of the interventions, as reflected in the uncertainty analysis results: there is no overlap between clusters corresponding to interventions that include psychosocial treatment and those that do not; moreover, on the stochastic league table, interventions with psychosocial treatment constitute the first choice for available resource levels in excess of 150 million euros.

Consequently, our results show the advisability of implementing psychosocial strategies as a complement to current pharmacological interventions,

since the benefits resulting from their application seem to be more pronounced than those from a simple switch to atypical antipsychotics. In addition, the sensitivity analysis of our study contributes to highlighting the need to reconsider the usual controversy regarding the cost-effectiveness of interventions with typical vs. atypical antipsychotics, given the appearance on the Spanish health market of generic versions of some atypical drugs, which considerably reduces the corresponding price, making it virtually equal to that of typical antipsychotics.

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