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# Economic and epidemiologic aspects of generalized anxiety disorder: a review of the literature

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**Introduction.** The objective is to assess the prevalence and treatment patterns of generalized anxiety disorder (GAD) in Spain as well as the cost associated to this disorder in different countries.

**Methods.** A search in the literature of health and economics databases was conducted.

**Results.** In regards to the 32 references selected, 6 studies had data on the prevalence of GAD and 3 on treatment patterns in Spain and 11 studies on the costs associated to the disease on an international level. The remaining 20 studies were of general interest for methodological or contextual reasons.

**Conclusions.** GAD is a mental disorder with high prevalence. According to some authors, it is probably underdiagnosed. No appropriate long term treatment is available. High health care and social costs are associated to GAD. The frequent presence of comorbidity, different definitions and methodologies used in the studies limits the comparability and synthesis of the results. It also makes it difficult to obtain valid estimations of prevalence and costs.

**Key words:**

Anxiety disorders. Prevalence. Therapeutics. Cost of illness.

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## Aspectos económicos y epidemiológicos de los trastornos de ansiedad generalizada: una revisión de la literatura

**Introducción.** El objetivo es determinar la prevalencia estimada, las pautas de tratamiento más utilizadas en el trastorno de ansiedad generalizada (TAG) en España y los costes asociados a este trastorno en diversos países.

**Métodos.** Búsqueda en bases de datos especializadas en economía y salud.

**Resultados.** De 32 referencias seleccionadas, 6 estudios tienen datos sobre prevalencia y 3 de pautas de trata-

miento en España; 11 estudios de costes asociados a la enfermedad a nivel internacional y los 20 artículos restantes tienen un interés general por razones de contexto o metodología.

**Conclusiones.** El TAG es un trastorno mental con alta prevalencia. Según algunos autores, infradiagnosticado. No se dispone de un tratamiento satisfactorio a largo plazo. Genera elevados costes sanitarios y humanos. La frecuente comorbilidad, las diferentes definiciones y las metodologías utilizadas limitan la comparabilidad, la síntesis de los resultados y dificulta las estimaciones válidas de prevalencia y costes.

**Palabras clave:**

Trastornos de ansiedad. Prevalencia. Tratamiento. Coste la enfermedad.

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## INTRODUCTION

Anxiety is a natural emotion present in all humans. An adaptive function is attributed to it since it alerts the individual to a possible threat. However, there are times when, and especially when the anxiety is very intense, it sometimes determines that the individual perceives somatic changes, has loss of control over normal behavior and functioning deterioration.

Serious and chronic anxiety disorder<sup>1</sup> is characterized by being «generalized and persistent anxiety, that is not limited nor even predominates in any specific environmental circumstances (that is, it is "free floating anxiety")». It makes up a medical entity called generalized anxiety disorder (GAD) that is defined in the 10<sup>th</sup> edition of the International Classification of Diseases (ICD-10) of the World Health Organization, Spanish edition, chapter F (V) «Mental and behavioral disorders», GAD code: F41.1. and in the Diagnostic and Statistical Manual of Mental Disorder of the American Psychiatric Association DSM IV, code 300.02.

GAD is, together with substance abuse disorder, the most frequent psychiatric disorder in both Europe and the United States, with a prevalence of 2%<sup>1</sup> and 5%<sup>2</sup>, respectively. The ESEMeD study (European Study of the Epidemiology of

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Mental Disorders), conducted in six European countries, found that 14% of the Europeans develop an anxiety disorder at some time in their life<sup>3</sup>.

GAD has an early onset, it frequently appearing before 25 years of age and the incidence is greater in the female gender (ratio 2:1). Generally, its course is chronic, with low rates of remission and moderate ones of recurrence. It is related with multiple risk factors, such as family background, background of physical or emotional trauma, increased stress, or even with the smoking habit, since evidence exists that the frequency of TAG among smokers is five to six times higher<sup>2</sup>. Several factors have been proposed in the study of the search for the origin of anxiety: genetic variants and predisposition, environmental expositions and even structural and molecular alterations.

GAD is characterized by having high comorbidity<sup>4</sup>, and it coexists with diseases such as major depression, which is the most frequent association, diabetes mellitus, substance abuse disorders and panic attack, among others. Thus, the diagnosis of anxiety is an exclusion diagnosis, in which the medical professional should previously rule out other medical disorders.

The effects of GAD go beyond their medical implications. Decrease in the quality of life of the persons affected and thus the gradual loss of psychosocial functionality of them is currently observed<sup>1</sup>. Thus, clinical research has focused towards studies not only on the drug but also on the psychological treatment of this disorder.

The costs of GAD include both direct costs (that go from the primary health care and specialized visit to the need for care in the emergency services and hospitalization) as well as indirect costs, such as decrease in productivity and sick leaves.

This review of the literature aims to identify the principal characteristics of the treatment of generalized anxiety disorders as well as the use of associated health care resources and social burden of the disease. The specific objective of the bibliographic review has been to obtain epidemiological data (prevalence of generalized anxiety disorders) in Spain, information on the usual medical practices for the treatment of the anxiety disorders in Spain and estimations of the costs of the disease and its treatment on an international level.

## MATERIAL AND METHODS

A bibliographic search was conducted for the period 1995–2005 in three databases: Medline-Pubmed (National Library of Medicine), OHE-HEED (Office of Health Economics-Health Economic Evaluation Database) and NHS EED (National Health System Economic Evaluation Database). The last two databases are specialized in financial evalua-

tion studies on an international level and the articles are previously selected by a group of experts on the subject who elaborate a standardized datasheet with an extensive summary of the works.

The search strategy was divided into two parts:

- For the epidemiological and treatment information: this was done in the database of Pubmed with the key words: «anxiety», «epidemiology» «prevalence» «pharmacotherapy/treatment» and «Spain». The articles that mentioned generalized anxiety disorder were chosen from these.
- For information on cost and cost-effectiveness, the databases of OHE-HEED and NHS EED were used with the key words: «anxiety» and «cost».

For the cost and cost-effectiveness studies, the following selection criteria were used:

- Those works that had been conducted with patients who had been diagnosed of «anxiety» or GAD as principal diagnosis or as secondary diagnosis, but in whom the results of the costs were attributable specifically to anxiety in either of the two cases, were included.
- Works that did not differentiate the costs of the anxiety with other comorbidities, such as depression, were excluded.
- In addition, opinion and review articles were excluded.

## RESULTS

A total of 354 references were obtained from the search. Those references which were duplicated and not relevant were discarded (table 1). Eleven articles coincided from the search with OHE-HEED and NHS-EED. Finally, according to the interest of the contents of the summaries, 44 articles were preselected in order to read the complete text or the datasheets from the databases of the OHE-HEED and NHS EED. In addition, 20 references identified in previous works of the authors, that did not appear in the previously described search, were reviewed. The 44 articles indicated were read by a reviewer who decided to rule out 32 because they were not relevant for the purposes of the research or based on the exclusion criteria (annex 1).

The total number of references finally included in this review were 32 articles. They can be classified into the following subjects: financial costs and evaluation (11 articles), epidemiology (11 articles) and drugs (10 articles). Of these, those that contributed relevant information for Spain are included in tables 2, 3 and 4 that present a summary of the results of *a*) the studies regarding the prevalence of anxiety in Spain<sup>3,5-9</sup>; *b*) the studies with diagnostic and treatment criteria of anxiety in Spain<sup>9-11</sup>, and *c*) cost and cost-effective studies of anxiety in Spain on an international level<sup>12-22</sup>.

Table 1		Number of articles found		
Database	Search term	No. of references found in the search	No. of references reviewed	No. of references included
NHS Economic Evaluation				
Database (York)	Anxiety AND cost	287	29	6
OHE-HEED	Anxiety, cost	17	12	3
Medline-Pubmed	Anxiety disorder, epidemiology/prevalence, Spain	32	2	2
Medline-Pubmed	Pharmacotherapy/treatment, anxiety disorder, Spain	18	1	1
Others		0	0	20
Total		354	44	32

### Prevalence of generalized anxiety disorders in Spain

The prevalence data of the different mental diseases of the population obtained from the studies for Spain are collected in table 2<sup>3,5-9</sup>.

The epidemiologic information found in the studies regarding Spain is very diverse due to the different diagnostic criteria used in each one of the studies (DSM-III, DSM-III-R, DSM-IV, ICD-9, ICD-10). On the other hand, the prevalence is reported both in terms of prevalence-life as well as prevalence-year and prevalence-punctual. These results are similar to those found in international level studies<sup>1,3-4,6-9,23-24</sup>.

It is difficult to draw reliable conclusions on the prevalence of the GAD due to the variety of information and elevated comorbidity it has. Different studies<sup>9,25</sup> conclude that the GADs present a high comorbidity with other psychic disorders. According to the ESEMedD project (European Study of the Epidemiology of Mental Disorders), 69.4% of the patients who suffer a generalized anxiety disorder had had at least one other mental disorder during the last 12 months: major depression (OR: 33.7; 95% CI: 23.2-49.1), agoraphobia (OR: 25.7; 95% CI: 12.9-51.0), panic disorders (OR: 20.3; 95% CI: 11.4-36.0) among others<sup>26</sup>. On the other hand, the GAD has a high comorbidity index with the major depressive disorder (62%) and dysthymia (37%) in the review of the Cochrane review «Antidepressants for generalized anxiety disorder»<sup>27</sup>.

It can be added to these difficulties that the data on the anxiety disorders are not broken down into their different manifestations and the studies refer to different population groups, such as general population, primary health care patients and secondary care patients. Thus, the reasons explained above do not make it possible to determine the prevalence rate of GAD precisely and reliably for Spain or for other countries. With these limitations, life prevalence can provisionally be placed at about 5%-13% of the population.

### Drug treatment guidelines of generalized anxiety disorders in Spain

The generalized anxiety disorder generally has a chronic course of 5 to 15 years or more<sup>25</sup>. Benzodiazepines and non-benzodiazepinic anxiolytics have generally been the axis of the drug treatment in the last decade<sup>27</sup>. These alternatives have problems due to the need for prolonged periods of drug treatment, risk of abuse and dependence (benzodiazepines) and a limited efficacy spectrum and late onset of the action in the base of buspirone<sup>28</sup>. In addition, long half life benzodiazepines may induce elevated sedation and lack of psychomotor coordination that have been associated with the increase of risks of hip fractures<sup>29</sup> and traffic accidents<sup>30</sup>. The shorter life benzodiazepines, on their part, are associated with more psychiatric type adverse reactions and with rebound phenomena.

The drugs used most in Spain to treat generalized anxiety disorders are benzodiazepines, other anxiolytics and antidepressants (table 3). A study on the use of drugs conducted in Spain in a primary care center reports that 21% of those who come to a primary care physician take some type of psychodrugs<sup>31</sup>. Vedia Urgell et al., in a study on prescription-indication, found that 43% of the psychodrugs prescribed were antidepressants (AD) and 57% anxiolytics/hypnotics (A/H). Those prescribed the most are the selective serotonin reuptake inhibitors (SSRI) (31.6%) and short half life benzodiazepines (BZD) (32.9%) and long half life BZD (19.8%). The primary reasons for prescription are major depression or dysthymia (60.2%) for AD and generalized anxiety (33.3%) and insomnia (22.9%) for the A/H<sup>10</sup>. García del Pozo et al. found that the use of the anxiolytics and hypnotics grew from 39.7 to 62.0 daily defined dose per 1,000 inhabitants/day during the period of the years 1995-2002<sup>9</sup>.

In a review of the Cochrane «Antidepressants for generalized anxiety disorder», Kapczinsk et al. found that imipramine, venlafaxine and paroxetine were superior to the placebo in the treatment of GAD<sup>27</sup>. The reviews found on drug treatment of GAD consider that the BDZ are the alternative

**Table 2** Summary of studies of prevalence data in Spain

Year of publication	Reference	Study title	Number of persons	Prevalence
1987, Spain	Vázquez Barquero et al. <sup>6</sup>	Depression and anxiety: differential sociodemographic profile in the general population	1,250	Anxiety: 4.47%
1988, Spain	Lobo et al. <sup>7</sup>	Psychiatric morbidity among medical out-patients in Spain: a case for new methods of classification	250	Psychiatric disorders: 46.9%. Most of the cases were depression or anxiety. Anxiety states: 14%
1995, Spain	Chocrón et al. <sup>5</sup>	Prevalence of psychopathology in a primary health care site	400	Patients with psychopathology: 38.8% (IC: 34.05-43.55): Major depression: 6% Dysthymia: 4.3% Adaptive disorder: 9.5% Anxiety 13.8% Anxiety disorders: GAD: 7.3% Panic disorders: 3% Obsessive-compulsive disorders: 3%
1998, Spain	Torras Bernáldez, et al. <sup>8</sup>	Prevalence of mixed anxiety-depressive syndrome in a population of a care unit of a health care site	1,950	Anxious-depressive syndrome mixed type: 6.7% (with distribution by gender of 32-68%)
2004, six countries of Europe	Alonso et al. <sup>3</sup>	Prevalence of mental disorders in Europe: results from the European Study of the Epidemiology of Mental Disorders (ESEMeD) project	21,425	Life prevalence % (IC 95%): Some mental disorder: 25 Mood state disorders: 14 Some anxiety disorder: 13.6 GAD: 2.8 In the last year % (IC 95%): Some mental disorder: 9.6 Mood state disorders: 2.8 Some anxiety disorder: 3.8 GAD: 1.0
2004, Spain	García del Pozo et al. <sup>9</sup>	Use of anxiolytics and hypnotics in Spain	3,247	Anxiety disorders: 13.8%. The most frequent types are the GAD: 65%

of choice for the treatment of acute symptoms while buspirone and the new antidepressants are options to consider for patients who required long-term treatment<sup>32</sup>.

### Financial studies of generalized anxiety disorders

Of the studies chosen (table 4), 10 have been conducted in the US and one in Sweden<sup>14</sup>. The analytic approaches vary greatly. Two of the works<sup>13, 15</sup> adopt the approach of cost of the prevalence, that is, they try to estimate the total costs of the disease at one year and the specific country based on the sum of the values from official registries and popu-

lational surveys. Six studies<sup>12,16,18-21</sup> are grouped into the category of costs of the incidence, that estimate the costs of a cohort or sample of subjects from the follow-up studies or from administrative databases. Two studies<sup>17,22</sup> use multivariate statistical analyses to determine the factors responsible for the cost variations of the anxiety. Finally, one of the articles is a cost-effectiveness analysis of a treatment for pregnancies with anxiety<sup>14</sup>.

Most of the studies, with a single exception<sup>12</sup>, apply retrospective approaches, using administrative databases as source of basic information. The duration periods of the different studies go from 12 months to 3 years.

**Table 3** Summary of the studies with diagnostic and drug treatment criteria conducted in Spain

Reference, year of publication and country	Study title	Diagnostic criteria	Drug treatment
Vega Alonso et al. <sup>11</sup> , 1999, Spain	Anxiety disorders Variability and conditioners of therapeutic attitude of primary health care means	Not available	Daily use of anxiolytics and hypnotics grew from 39.71 daily defined dose (DDD) per 1,000 inhabitants and day in 1995 to 62.02 in 2002 Greater growth for the intermediate half life benzodiazepines, especially lorazepam, alprazolam and lormetazepam Active with greater decrease: flunitrazepam
García del Pozo et al. <sup>9</sup> , 2004, Spain	Use of anxiolytics and hypnotics in Spain	Anxiety disorders were those coded as F40 and F41 according to ICD-10 Lack of a common pattern in the anxiety disorders hinder its diagnosis in the primary care setting. In many cases, this leads to a decrease in therapeutic treatment. The frequent somatization and association with chronic diseases are some of the reasons that hinder the diagnosis and lead the doctors to consider a physical cause for this problem in the first place	Antipsychotics with or without antidepressant anxiolytics Antidepressants with anxiolytics and/or antipsychotics
Vedia Urgell et al. <sup>10</sup> , 2005, Spain	Study of use of psychopharmaceutics in primary health care	Epidemiological, observational, cross-sectional study of prescription-indication	Profile of use of antidepressants (AD) and anxiolytics/hypnotics (AH) in primary health care in Catalonia

The types of costs considered in the disease vary from one article to another. Rice and Millar<sup>15</sup> establish the most extensive definition of both direct and indirect costs. According to these authors, the direct costs include:

- Costs of primary consultation.
- Costs of the medications.
- Laboratory costs.
- Costs of the consultation to medical specialist.
- Costs of treating adverse effects.

The indirect costs, in turn, include:

- Morbidity costs:
  - Lost of productivity of patients per days not worked.
  - Lost of productivity of patients in order to attend therapies.

- Costs of travel to attend therapies
- Mortality costs.
- Other associated costs (prison, costs of caretaker, etc.).

All the studies consider the direct medical costs, but only some include the indirect ones. Five of the studies chosen<sup>12,14,18-20,22</sup> only consider the direct medical costs. In addition, the studies frequently differ regarding specific concepts included in each category. The studies also apply different discount rates.

The variability of approaches, analytic methodologies and cost categories considered make it difficult to compare the results and obtain reliable conclusions. In general lines, it can be stated that the groups with diagnosis of anxiety, compared with the control group, have a greater likelihood of using health care services and have more absenteeism and temporal work incapacity<sup>18</sup>.

Table 4 Summary of cost studies of anxiety on an international level (continuation)

Reference, year of publication and country	Approach	Reference population	Types of data and information source	Total annual cost	Direct costs	Indirect costs
Simon et al. <sup>12</sup> , 1995, USA	Cost of incidence in primary health care	327 patients with anxiety disorders (206 with data of complete costs) of a sample of 2,110 consecutive patients from primary health care	Prospective study The 12-question general health questionnaire was administered to 1,962 patients A stratified sample of 615 patients was chosen for a subsequent diagnosis, 373 of these completed the Composite International Diagnostic Interview and this was re-administered to 328 one year later. The costs were obtained from the registries at approximately 6 months of the baseline survey and 6 more months of the second questionnaire	Patients in baseline survey with: DSM-III-R anxiety or depressive disorders: \$2,390 Patients without anxiety disorder: \$1,397. The differences of costs persisted after adjustment for medical morbidity The differences of costs are due more to an increase of use of services than to more expensive mental treatments	Only the direct medical costs were included	They were not included
DuPont et al. <sup>13</sup> , 1996, USA	Cost of prevalence	Total population	Retrospective study Survey of use of resources, official statistics on cost and income	Total cost of the anxiety disorders: \$46.6 billions (compared to \$147.8 thousand billions for all the mental diseases)	\$10.7 thousand billion (of which approximately 50% correspond residences)	Mortality: \$1.3 thousand billion Morbidity: \$34.2 thousand billion Others: < 1% of the total They were not included
Sjogren and Thomasson <sup>14</sup> , 1997, Sweden	Cost-effectiveness analysis of psychological and obstetric support treatment to patients with anxiety	68 pregnant women diagnosed of anxiety who received psychotherapy 100 women in control group	Retrospective study of costs in a clinical trial	Cost of psychotherapy for all the krona currency group 446,660 Cost saved due to potential cesareans avoided for the whole group: krona currency 570,000 Net savings: krona currency 123,340	Only the direct medical costs were included	They were not included

Summary of cost studies of anxiety on an international level (continuation)						
Reference, year of publication and country	Approach	Reference population	Types of data and information source	Total annual cost	Direct costs	Indirect costs
Rice y Miller <sup>15</sup> , 1998, USA	Cost of prevalence	All of the USA population	Retrospective study The direct costs were obtained from the national survey of the homes and of supplier surveys The indirect costs estimated were: Morbidity costs (cost per loss of earnings linked to reduction or loss of productivity) Costs per premature death and other related costs A discount rate of 6% was used	Mental disorders: \$147.8 thousand billions in 1990 Anxiety: \$46.6 thousand billions (31.5% of the total) Anxiety has the highest costs of all the mental disorders	Mental disorders: \$67 thousand billions Anxiety: \$10 thousand billions	Mental disorders (thousand billions) Costs of morbidity: \$63 Costs of mortality: \$11.8 Other costs: \$6 Anxiety (in thousand billions): Morbidity costs: \$35 Mortality costs: \$1 Other costs: \$0.3
Goetzl et al. <sup>16</sup> , 1999, USA	Cost of the incidence based on the definition of episodes	347,799 employees of 6 large companies	Retrospective review of the data of sick leaves and temporary incapacity linked to the health data found in the medical and pharmaceutical registries. The data comes from the subgroup HPM (Health and Productivity Management) of the administrative database MarketScan	Mean cost association to anxiety episode: \$13.20	Medical costs: \$6.74	Costs per sick leave: \$4.24 Cost for temporary incapacity: \$2.22 (49% of the total costs)

Summary of cost studies of anxiety on an international level (continuation)						
Reference, year of publication and country	Approach	Reference population	Types of data and information source	Total annual cost	Direct costs	Indirect costs
Greenberg et al. <sup>17</sup> , 1999, USA	Multiple regression analysis	Total population in USA	Retrospective study To calculate the costs of anxiety in USA, the data were extrapolated from the National Comorbidity Study to the whole of the population The data were adjusted, considering the demographic characteristics and existence of comorbidity. Health care costs were obtained partially from a large health care organization and the economic ones form a human capital model	Anxiety disorders: \$42.3 thousand billions in 1990 \$1,542 per patient	Non-psychiatric medical treatment: 54% Psychiatric treatment: 31% Drug costs: 2%	Indirect costs linked to work: 10% Loss of productivity: 88% Absenteeism: 12% Costs linked to mortality: 3%
Berndt et al. <sup>18</sup> , 2000, USA	Cost of the incidence	2,222 employees of different productive sites. Subjects with anxiety: 96 Subjects with GAD: 20	Retrospective study The health care costs were calculated based on payments made by the insurance companies. The data on daily productivity of the employees were obtained from an insurance company	Mean annual cost: Anxiety: Hospital: \$2,665 Outpatient: \$2,853 Prescription: \$429 GAD: Hospital: \$3,204 Outpatient: \$3,089 Prescriptions: \$504	Mean annual cost: Anxiety: Hospital: \$2,665 Outpatient: \$2,853 Prescription: \$429 GAD: Hospital: \$3,204 Outpatient: \$3,089 Prescriptions: \$504	



Table 4 Summary of cost studies of anxiety on an international level (continuation)						
Reference, year of publication and country	Approach	Reference population	Types of data and information source	Total annual cost	Direct costs	Indirect costs
Wan et al. <sup>19</sup> , 2002, USA	Cost of incidence	9,093 subjects with depression diagnosis 468 treated with Venlafaxine, 276 of whom had depression with anxiety and 192 depression without anxiety	Retrospective study. The data comes from the administrative database MarketScan, 1994–1999. Differences between payments for psychiatric and non-psychiatric services and those subdivided into outpatient, hospital and pharmaceutical	Patients with depression and anxiety (with venlafaxine: \$3,468; with SSRI: \$3,637) Patients with depression and without anxiety (with Venlafaxine: \$2,279; with SSRI: \$4,890) (Costs of a 6-month period)	Only the direct medical costs are included	They are not included
Pesa y Lage <sup>20</sup> , 2004, USA	Cost of incidence	190 individuals with anxiety and depression of a cohort of 11,332 patients with migraine	Retrospective study Database of 45 large companies of the United States	The total annual cost of treatment (hospitalization, outpatient and medications) in patients with migraine and anxiety was \$12,642 versus \$5,179 for those that only had migraine	Only the direct medical costs were included	They were not included

**Table 4** Summary of cost studies of anxiety on an international level (continuation)

Reference, year of publication and country	Approach	Reference population	Types of data and information source	Total annual cost	Direct costs	Indirect costs
Marciniak et al. <sup>21</sup> , 2004, USA	Cost of incidence	Subjects with anxiety: 1,917 Without anxiety but with similar patterns of age, gender, residence and type of insurance coverage: 1,917	Retrospective study of control case The data comes from the subgroup HPM (Health and Productivity Management) of the administrative database MarketScan To estimate the direct and indirect costs better, comorbidity were identified both in the anxiety group as well in the control one	Total costs: Population with anxiety: \$12,432 Population without anxiety: \$8,211 Total adjusted costs, considering comorbidities: Population with anxiety: \$11,782 Population without anxiety: \$8,861 (The costs correspond to a 5-month follow-up period)	Health care costs: Population with anxiety: \$4,755 Population without anxiety: \$2,467	Productivity costs: Population with anxiety: \$7,676 Population without anxiety: \$5,744
Marciniak et al. <sup>22</sup> , 2005, USA	Multivariate statistical analysis of cost	6,497 patients diagnosed of anxiety at least once	Retrospective study The data comes from the subgroup HPM (Health and Productivity Management) of the administrative database MarketScan	\$6,475	Only the direct medical costs were included	They were not included

In a prevalence cost study<sup>15</sup> it was estimated that the costs of anxiety in the USA account for 31.5% of the total costs attributed to mental disorders. This makes anxiety one of the most expensive mental diseases. A common result in the studies on cost of anxiety is the significant weight regarding indirect costs (loss of productivity) associated to morbidity in relationship to direct medical costs. The indirect cost/direct cost ratio is greater than 3:1 in the prevalence cost studies. However, the relative importance of the indirect costs is substantially reduced in the studies that apply an incidence approach, possibly because they do not consider or they underestimate some of the indirect costs that are included in the direct costs.

## DISCUSSION

As generally occurs in the reviews of epidemiological and economic studies of diseases, the heterogeneity of the methods and instruments of quantification limit the comparability of the results and the possibility of obtaining reliable estimations of the effects with greater accuracy than the order of magnitude.

One of the principal objectives of the cost studies of the disease is to sensitize the authorities and the public in general on the social and economic relevance of a certain disease. The authors and sponsors of the studies thus generally believe they are better the higher the costs. This generates the possibility of biases upwards, both intentional and involuntary, in the estimations. On the other hand, the cost values of the disease, in regards to the criterion to indicate the relative importance of a disease, can only be interpreted in comparative terms. In this sense, it would be desirable to have greater standardization of the methodology, that would go from the definition and precise limits of the disease and from the concepts of prevalence and costs to their measurements. Lacking methodological standards that assure comparability of the results, it is desirable to conduct simultaneous cost studies for several diseases, for example, for all the mental diseases. This would assure that the results would be comparable and valid, at least in relative terms.

A general problem of the disease cost studies, especially relevant in the case of anxiety, is comorbidity. This is true especially when it is not possible to establish an unidirectional relationship of causality between the diseases involved, as occurs, for example, in the case of the complications of diabetes. In the case of anxiety, this situation is very clear in relationship with depression. If no cost distribution can be made between the different causes of morbidity, it must be admitted that a certain upward bias is being introduced. Thus, the sum of the costs of depression and the costs of anxiety made independently would lead to a higher value than a study that jointly estimates the costs of the two diseases.

Another methodological limitation present in most of the cost studies of the disease, which in this case introduced a bias of the results downwards, is the lack of a control

group. Patients with anxiety may consume resources due to said disease that are diagnosed for other diseases. If they are only considered as costs for the anxiety, the resources that are associated to said diagnosis may be producing an underestimation of their importance. The most correct method to account for the costs of anxiety in an observational study is to subtract the total costs of a population with similar characteristics who do not have said diagnosis from the total health care costs generated by the patients with anxiety. Among the cost studies of anxiety focused on incidence, Pesa et al.<sup>20</sup> and Simon et al.<sup>12</sup> used a control group. Bernd et al.<sup>18</sup> used multivariate regression analysis to estimate the effect of different comorbidities. Finally, Goetzel et al.<sup>16</sup> developed a new methodology that created disease episodes based on the diagnoses of administrative databases which, in spite of the interest and originality of the approach, did not take possible costs attributable to anxiety associated to a different diagnosis into account.

Finally, it should be stated that the cost studies of the disease, which have been of a majority in the review of economic studies of anxiety, have limited utility for decision making. This is because they only make it possible to obtain an idea of the magnitude of the disease impact while the efficient allotment of resources requires complete financial evaluations of interventions that indicate their efficiency. This is, the relationship between the resources used and the results in terms of health or well being is needed. That is why future efforts should be focused on economic research of GAD in this second line of analysis.

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