Review

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Cost-effectiveness of venlafaxine for the treatment of depression and anxiety. Bibliographic review

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Objective. To compare the efficiency of the treatment of major depressive disorder (MDD) and generalized anxiety disorder (GAD) with venlafaxine in comparison with tricyclic antidepressants (TCA) and selective serotonin reuptake inhibitors (SSRI).

Methods. A bibliographic systematic review of the published pharmacoeconomic studies in which one of the treatments was venlafaxine (immediate or extended-release) was conducted for MDD or GAD indications.

Results. Nine studies for immediate-release venlafaxine and seven with extended-release in MDD were published, two with Spanish data. In the more extended Spanish model (1 year treatment), in depressive disorder, 106, 97 and 99 depression symptom free days (SFD) were achieved by venlafaxine, TCA and SSRI respectively, with annual costs of 6,791, 7,116 and 7,029 €. Similar results were obtained in the second Spanish 6 month study. Regarding GAD, after the treatment of elderly patients during 8 weeks, 17 and 5 SFD were obtained with venlafaxine and placebo, with a cost per SFD of 22.94 and 65.40 €, respectively.

Conclusions. According to the available studies, venlafaxine generates lower total costs (due to the reduction of treatment failure costs) than SSRI and TCA for the treatment of MDD. Venlafaxine is cost-effective in comparison with no treatment for GAD.

Key words:
Pharmacoeconomy. Cost-effectivity. Venlafaxine. Depression. Anxiety.

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Coste-efectividad de venlafaxina en el tratamiento de la depresión y de la ansiedad. Revisión bibliográfica

Objetivo. Comparar la eficiencia del tratamiento del trastorno depresivo mayor (TDM) y del trastorno de ansiedad generalizada (TAG) con venlafaxina en comparación con los antidepresivos tricíclicos (ATC) y los inhibidores selectivos de la recaptación de serotonina (ISRS).

Métodos. Revisión bibliográfica sistemática de los estudios de farmacoeconomía publicados en los que uno de los tratamientos comparados fuera venlafaxina de liberación inmediata o sostenida (retard), en las indicaciones de TDM o TAG.

Resultados. Se han publicado nueve estudios con venlafaxina de liberación inmediata y siete estudios con venlafaxina retard en TDM; dos de ellos realizados en España. En el modelo español de mayor duración (1 año de tratamiento) en el trastorno depresivo se obtuvieron 106, 97 y 99 días sin síntomas (DSS) de depresión para venlafaxina, ATC e ISRS, respectivamente, y unos costes anuales de 6.791, 7.116 y 7.029 €. En el segundo estudio español, de 6 meses, se obtuvieron similares resultados. En el TAG en ancianos tratados durante 8 semanas se produjeron 17 y 5 DSS con venlafaxina y placebo con un coste por DSS ganado de 22,94 y 65,40 €, respectivamente.

Conclusiones. Según los estudios disponibles, venlafaxina es un tratamiento que genera menos costes totales (debido a la reducción de los costes por fracasos terapéuticos) que el tratamiento con los ISRS y los ATC en el TDM y coste-efectivo en comparación con el no tratamiento en el TAG.

Palabras clave:
Farmacoeconomía. Coste-efectividad. Venlafaxina. Depresión. Ansiedad.

INTRODUCTION

In recent years, economic reasoning has begun to form a part of the health field because its premises are totally applicable to that occurring in the health care systems of our setting at present. In the first place, the resources are limited. Although more and more is being spent on health, the need tends to be unlimited. Furthermore, the healthier the society, the greater the demand for medical health care

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and the greater the medical progress reached, the greater the cost of obtaining additional improvements. In the second place, when the resources are limited, it must be decided which is the best way to spend them: priorities must be given. Finally, when the resources are used in a specific way, the option of using them in another is lost. Precisely, pharmacoeconomic evaluation tries to assure that the benefits obtained when selecting a certain drug are greater than those that would be obtained with other alternatives[1].

It is efficient from the technical point of view in the health care scope when the maximum level of health based on given resources is achieved. When comparing alternatives that produce the same result, it is also efficient when the least costly is chosen. Efficiency is thus a relative concept. To determine which is the most efficient option, benefits obtained with different interventions and costs necessary to achieve these benefits must be compared[1].

There are basically four types of economic evaluation (table 1): cost-effectiveness analysis, in which the health care results are expressed as commonly used units in the medical practice (for example, reduction of blood pressure, cures achieved, complications avoided, lives saved, years of life gains, etc.); cost-utility analysis, a special type of cost-effectiveness analysis in which health care results are measured as Years of Life Adjusted by Quality (YLAQ); cost-benefit analysis, when both costs and health care results are measured in monetary units; and finally, cost minimization analysis, the easiest type of analysis, that is used when, regardless of the units in which the health care results are measured, these are equal in the different options compared[1]. Other pharmacoeconomy terms mentioned during the article are shown in an Appendix at the end of it[2,3].

Table 1 Types of analyses used in an economic evaluation[1]

Type of analysis	Cost measurement	Measurement of results
Minimization of cost	Monetary units	There are no differences in the results
Cost-effectiveness	Monetary units	Usual clinical units (for example, cures achieved, complications avoided, years of life gained)
Cost-utility	Monetary units	Amount and quality of life (years of life adjusted by quality [YLAQ])
Cost-benefit	Monetary units	Monetary units

Role of pharmacoeconomy in the study of depression and anxiety

Major depressive disorder (MDD) is an entity that has depressive episodes with tendency to recurrence, with symptom free periods. MDD has a prevalence of 2 %-3 % in men and 5 %-9 % in women in the general population[4]. It has been estimated that costs of depression in Spain could exceed 757 millions of € per year[5,6]. Generalized anxiety disorder (GAD) is characterized by an excessive, overwhelming and uncontrollable concern, with psychic symptoms that include irritability, restlessness and concentration problems[7]. Prevalence of GAD is estimated at between 1.6 % and 5.1 %[7]. This may be the cause of 50 % of the sick leaves in the European Union, with an estimated cost of about 20,000 million € per year[8]. Data suggested over the last two decades have shown that antidepressants may be as effective as anxiolytics to treat GAD. They may also be beneficial because GAD has a high rate of comorbidity with the MDD (62 %) and dysthymia (37 %)[7].

OBJECTIVES

One of the criteria to consider when choosing an antidepressant is the efficiency data[9]. Its importance is manifested, for example, if we consider that 447 articles on pharmacoeconomy related with depression were published between 1975 and 2004 (until September) according to a bibliographic review done in PubMed.

This present study aims to review the efficiency of treatment with MDD and GAD with venlafaxine, serotonin and noradrenaline reuptake inhibitor (SNRI) inhibitor basically in comparison with tricyclic antidepressants TCA) and selective serotonin reuptake inhibitors (SSRI).

METHODS

A systematic review was done to try to identify all the pharmacoeconomy studies done with venlafaxine that have been published. To do so, a bibliographic search (without limitations) was done in PubMed until September 2004[10]. The data bases of three health care technology evaluation agencies were reviewed (Cochrane Library1[11], Canadian Coordinating Office for Health Technology Assessment [CCOHTA][12], NHS Health Technology Assessment Programme of the United Kingdom[13]). Finally, the data base of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) publications was reviewed[14].

All the pharmacoeconomy studies published having the following characteristics were included: *a)* analysis of costs, costs and consequences, minimization of costs, cost-effectiveness, cost-utility or cost-benefit; *b)* in those in which one of the treatments compared was venlafaxine (immediate or extended release, called «extended re-

lease» in the rest of the article); *c)* in the MDD or GAD indications.

The following data were collected for each study: type of analysis (cost-effectiveness, cost-utility, etc.); type of patients (by age and type of depression or anxiety); country to which the results can be applied; health care scope of the study (out-patient and/or hospital); effectiveness parameter used (for example, number of depression symptom or anxiety free days or success rates obtained with the treatments); types of costs considered (direct and/or indirect); time periods of the study (that is, the period for which the costs and treatment effectiveness were calculated); antidepressant drugs compared in the analysis; effectiveness results; cost results (all the costs published in currency other than the euro were transformed to year 2004 €); cost-effectiveness results (incremental or not).

RESULTS

Pharmacoeconomy of venlafaxine in depression (MDD)

Tables 2 and 3 provide the pharmacoeconomic analysis of venlafaxine in MDD. Nine studies have been published with immediate release venlafaxine (table 2)[15-23] and seven studies with venlafaxine extended release (table 3)[9,24-29]. There were done in 11 countries: Spain, Germany, Canada, the United States, Holland, Italy, Poland, United Kingdom, Sweden, Switzerland and Venezuela.

The characteristics of the studies reviewed as those indicated in tables 2 and 3. The following should be stressed: *a)* most of the studies were cost-effectiveness analyses, modeled by decision trees or analysis; *b)* both the hospital and out-patient setting were considered; *c)* the study perspective was mostly that of the National Health Care System, therefore, generally only direct health care costs were included (although the indirect ones were also estimated in some studies), and *d)* time period of the studies was generally 6 months or 1 year.

Cost-effectiveness of venlafaxine in the MDD

Both in its immediate and extended release form, venlafaxine was the «dominant» treatment in most of the studies in comparison with the tricyclic antidepressants (TCA) and selective serotonin reuptake inhibitors (SSRI). This means that venlafaxine was an effective treatment generating lower costs than the TCAs and SSRIs (tables 2 and 3).

Special mention should be given to the two cost-effectiveness analyses conducted with Spanish data that compared efficiency of MDD treatment with venlafaxine extended release, TCAs and SSRIs[24,26] (table 3). In the first model, the depression symptom free days (SFD) during the 1 year period was used as effectiveness parameter. Using a clinical trial meta-analysis, 106, 97 and 99 SFD were obtained with venlafaxine extended release, TCAs and SSRIs, respectively. Yearly costs per patient were less with venlafaxine than with the antidepressants compared, around 6,791, 7,116 and 7,029 €, respectively Consequently, treatment with venlafaxine extended release dominated the other treatments24. In the second study, modeled by a decision analysis with 6 months of follow-up (fig. 1), the success rate, also estimated by a clinical trial meta-analysis, was greater with venlafaxine extended release than with the TCAs and SSRIs (table 4). Thus, there was dominance again of venlafaxine, both in out-patients (results shown) as in the hospitalized ones[26].

Cost of therapeutic failure in the MDD

How is it possible that treatment with MDD with venlafaxine extended release is, as we have seen, more cost-effective than the SSRIs and TCAs, whose acquisition cost is lower? As has been commented, there are two reasons: *a)* the cost of the disease is less with venlafaxine extended release, because of its lower cost due to therapeutic failure, and *b)* this is a consequence of its elevated efficacy.

Efficacy of venlafaxine was evaluated in a meta-analysis of clinical trials, conducted by Einarson et al. in 1999[30]. The drugs included in the meta-analysis were venlafaxine extended release, the SSRIs citalopram, fluoxetine, fluvoxamine, paroxetine and sertraline, and the TCAs amitriptyline, imipramine, desipramine and nortriptyline. Therapeutic success was defined as a 50 % reduction in the HAM-D or MADRS scale scores, calculating the mean weighted percentages of successes for each drug class, using a random effects model. In all, 44 randomized clinical trials, including 4,033 patients with depression, were included. The percentage of therapeutic success in out-patients treated with venlafaxine extended release was 73.7 %, with SSRI 61.4 % and with TCA 59.3 %. The other results in hospitalized patients and in both groups were equally favorable for venlafaxine extended release (table 4)[30]. As can be observed, the drop-out rate due to adverse reactions was less with venlafaxine (10.9 %) than with SSRI (17.4 %) and TCA (23.1 %). In addition, the drop-out rate due to absence of efficacy was 4.8 % with venlafaxine extended release, 8.4 % with SSRI and 6.8 % with the TCAs (table 4).

This extreme has been confirmed in another more recent meta-analysis, that was used to make the estimation of the depression symptom free days (SFD) in young adult individuals (< 60 years) and in the elderly (≥ 60 years) with MDD[31]. The results of 31 randomized, double blind clinical trials of at least 8 weeks duration in which 7,031 patients with MDD —3,078 with venlafaxine immediate or extended release, 3,025 with SSRI (fluovoxamine, paroxetine, sertraline, citalopram, fluvoxamine) and 982 with placebo— were

Table 2 **Pharmacoeconomy studies conducted with venlafaxine normal release in depression**

First author (year)[reference]	Type of study	Patients	Country scope	Effectiveness parameter	Costs included	Time period	Treatments compared	Results: effectiveness	Results: costs (euros, €)[a]	Results: incremental cost-effectiveness (euros, €)[a,b]
Gross (1994)[15]	Costs	Adults MDD	France HOSP	–	Direct and indirect	NA	Venlafaxine Fluoxetine	–	4,868 5,486	-
Einarson (1995)[16]	CEA Decision analysis	Adults MDD	USA HOSP OP	Symptom free days (SFD)	Direct health care	1 year		HOSP:	HOSP:	HOSP:
							Venlafaxine	219 SFD	12,201	-
							TCA	173 SFD	12,513	Venlafaxine dominates[c]
							HCA	189 SFD	11,492	23 with venlafaxine
							SSRI	150 SFD	11,864	5 with venlafaxine
								OP:	OP:	OP:
							Venlafaxine	186 SFD	2,401	–
							TCA	172 SFD	3,061	Venlafaxine dominates[c]
							HCA	191 SFD	1,896	HCA dominate[c]
							SSRI	189 SFD	2,412	3.6 with SSRI
Einarson (1997)[17]	CEA Decision analysis	Adults MDD	Canada HOSP OP	Symptom free days (SFD)	Direct health care	6 months		HOSP:	HOSP:	–
							Venlafaxine	99.1 SFD	21,948	Venlafaxine dominates[c]
							TCA	88.7 SFD	23,544	Venlafaxine dominates
							SSRI	88.4 SFD	24,149	
								OP:	OP:	
							Venlafaxine	103.8 SFD	8,300	–
							TCA	87.4 SFD	10,786	Venlafaxine dominates[c]
							SSRI	98.2 SFD	8,825	Venlafaxine dominates
Crown (1999)[18]	Observational prospective costs	Adults MDD	Spain OP	–	Direct and indirect	6 months	Venlafaxine	–	1,247	–
							Fluoxetine	–	1,063	–
							Fluvoxamine	–	1,353	–
							Sertraline	–	1,211	–
							Paroxetine	–	1,542	–
Griffiths (1999)[19]	Retrospective costs Data base	Adults MDD	USA HOSP OP	–	Direct health care	1 year	Venlafaxine	–	6,543	–
							TCA	–	8,073	–
Freeman (2000)[20]	CEA Decision analysis	Adults MDD	United K OP	Efficacy rate	Direct health care	6 months	Venlafaxine	73.7 %	NA	7.16 €/SFD[d]
							TCA	59.3 %	NA	10.55 €/SFD
							SSRI	61.4 %	NA	9.00 €/SFD
Sullivan (2000)[21,e]	Retrospective costs Data base	Adults MDD	USA HOSP OP	–	Direct health care	1 year	Venlafaxine	–	6,945	–
							TCA	–	7,925	–
							SSRI	–	7,237	–
Doyle (2001)[22]	CEA Decision analysis Multinational	Adults MDD	Spain and (nine other countries) HOSP OP	Efficacy rate	Direct health care	6 months	Venlafaxine	HOSP:	HOSP:	HOSP:
							TCA	76.7 %	7,686	–
							SSRI	71.7 %	8,053	Venlafaxine dominates[c]
								72.8 %	7,955	Venlafaxine dominates
							Venlafaxine	OP:	OP:	OP:
							TCA	80.0 %	1,408	–
							SSRI	73.0 %	1,539	Venlafaxine dominates[c]
								74.1 %	1,552	Venlafaxine dominates
Francois (2002)[23]	CEA Decision analysis	Adults MDD	Sweden HOSP OP	YLAQ	Direct and indirect	6 months	Venlafaxine	0.365	4,101	–
							Escitalopram	0.370	3,909	Escitalopram dominates[c]
							Citalopram	0.360	4,539	Venlafaxine dominates
							Fluoxetine	0.360	4,572	Venlafaxine dominates

[a] Cost per patient in period indicated (conversion of original currency into 2004 euros). [b] Cost of gaining an additional unit of effectiveness with most effective treatment in comparison with venlafaxine. [c] One treatment dominates another when it is more effective and generates less cost than it. [d] Cost/effectiveness ratio of each treatment. [e] Study continuation of that of Griffiths [19]. CEA: cost-effectiveness analysis; OP: out-patient; YLAQ: years of life adjusted by quality; SFD: depression symptom free days; USA: United States of America; HCA: heterocyclic antidepressants; HOSP: hospital; NA: not available; TCA: tricyclic antidepressants; SSRI: selective serotonin reuptake inhibitors; MDD: major depressive disorder.

Table 3 Phamacoeconomy studies conducted with venlafaxine extended release in depression

First author (year)[reference]	Type of study	Patients	Country scope	Effectiveness parameter	Costs included	Time period	Treatments compared	Results: effectiveness	Results: costs (euros, €)[a]	Results: incremental cost-effectiveness (euros, €)[a,b]
Baca (1999)[24]	CEA Decision analysis	Adults MDD	Spain HOSP OP	Symptom free days (SFD)	Direct health care	1 year		HOSP:	HOSP:	HOSP:
							Venlafaxine	106 SFD	6.791	–
							TCA	97 SFD	7.116	Venlafaxine dominates[c]
							SSRI	99 SFD	7.029	Venlafaxine dominates
								OP:	OP:	OP:
							Venlafaxine	117 SFD	1.155	–
							TCA	99 SFD	1.361	Venlafaxine dominates[c]
							SSRI	102 SFD	1.372	Venlafaxine dominates
Casciano (1999)[25]	CEA Decision analysis	Adults MDD	Italy HOSP OP	Symptom free days (SFD)	Direct health care	6 months		HOSP:	HOSP:	HOSP:
							Venlafaxine	100 SFD	7.967	–
							TCA	91 SFD	8.435	Venlafaxine dominates[c]
							SSRI	93 SFD	8.287	Venlafaxine dominates
								OP:	OP:	OP:
							Venlafaxine	110 SFD	814	–
							TCA	91 SFD	824	Venlafaxine dominates[c]
							SSRI	94 SFD	863	Venlafaxine dominates
Casciano (2002)[7]	CEA Decision analysis	Adults MDD	Spain HOSP OP	Success rate	Direct health care	6 months		HOSP:	HOSP:	
							Venlafaxine	62.3%	ND	21.474 €/success[d]
							TCA	58.2%	ND	25.882 €/success
							SSRI	58.6%	ND	25.224 €/success
								AMB:	OP:	
							Venlafaxine	73.7%	ND	3.732 €/success[d]
							TCA	59.3%	ND	5.893 €/success
							SSRI	61.4%	ND	5.981 €/success
Casciano (2001)[26]	CEA Decision analysis Multinational	Adults MDD	USA (and nine other countries) HOSP OP	Efficacy rate	Direct health care	6 months		HOSP:	HOSP:	HOSP:
							Venlafaxine	75.8%	7.686	–
							TCA	70.9%	8.053	Venlafaxine dominates[c]
							SSRI	71.8%	7.955	Venlafaxine dominates
								AMB:	OP:	AMB:
							Venlafaxine	82.9%	1.307	–
							TCA	73.0%	1.539	Venlafaxine dominates[c]
							SSRI	74.1%	1.552	Venlafaxine dominates
Wan (2002)[27]	Retrospective costs Data base	Adults MDD	Spain HOSP	–	Hospitalization	6 months	Venlafaxine	–	206	–
							SSRI	–	472	–
					Total health care	6 months	Venlafaxine	–	There were no differences	–
							SSRI	–		–
Lenox-Smith (2004)[28]	CEA Decision analysis	Adults MDD	United K. HOSP OP	Symptom free days (SFD)	Direct health care	6 months	Venlafaxine	60–61 SFD	1.885-1.894	–
							TCA	42–44 SFD	2.006-2.066	Venlafaxine dominates[c]
							SSRI	50–53 SFD	1.956-2.009	Venlafaxine dominates
Trivedi (2004)[29]	CEA Decision analysis	Adults MDD	USA HOSP	Symptom free days (SFD)	Direct health care	2 months	Venlafaxine	23	1.304[d]	–
							SSRI	19	1.515[d]	Venlafaxine dominates[c]

[a] Cost per patient in period indicated (conversion of original currency into 2004 euros). [b] Cost of gaining an additional unit of effectiveness with most effective treatment in comparison with venlafaxine. [c] One treatment dominates another when it is more effective and generates less cost than it. [d] Cost/effectiveness ratio of each treatment. CEA: cost-effectiveness analysis; OP: out-patient; YLAQ: years of life adjusted by quality; SFD: depression symptom free days; USA: United States of America; HCA: heterocyclic antidepressants; HOSP: hospital; ND: not available; TCA: tricyclic antidepressants; SSRI: selective serotonin reuptake inhibitors; MDD: major depressive disorder.

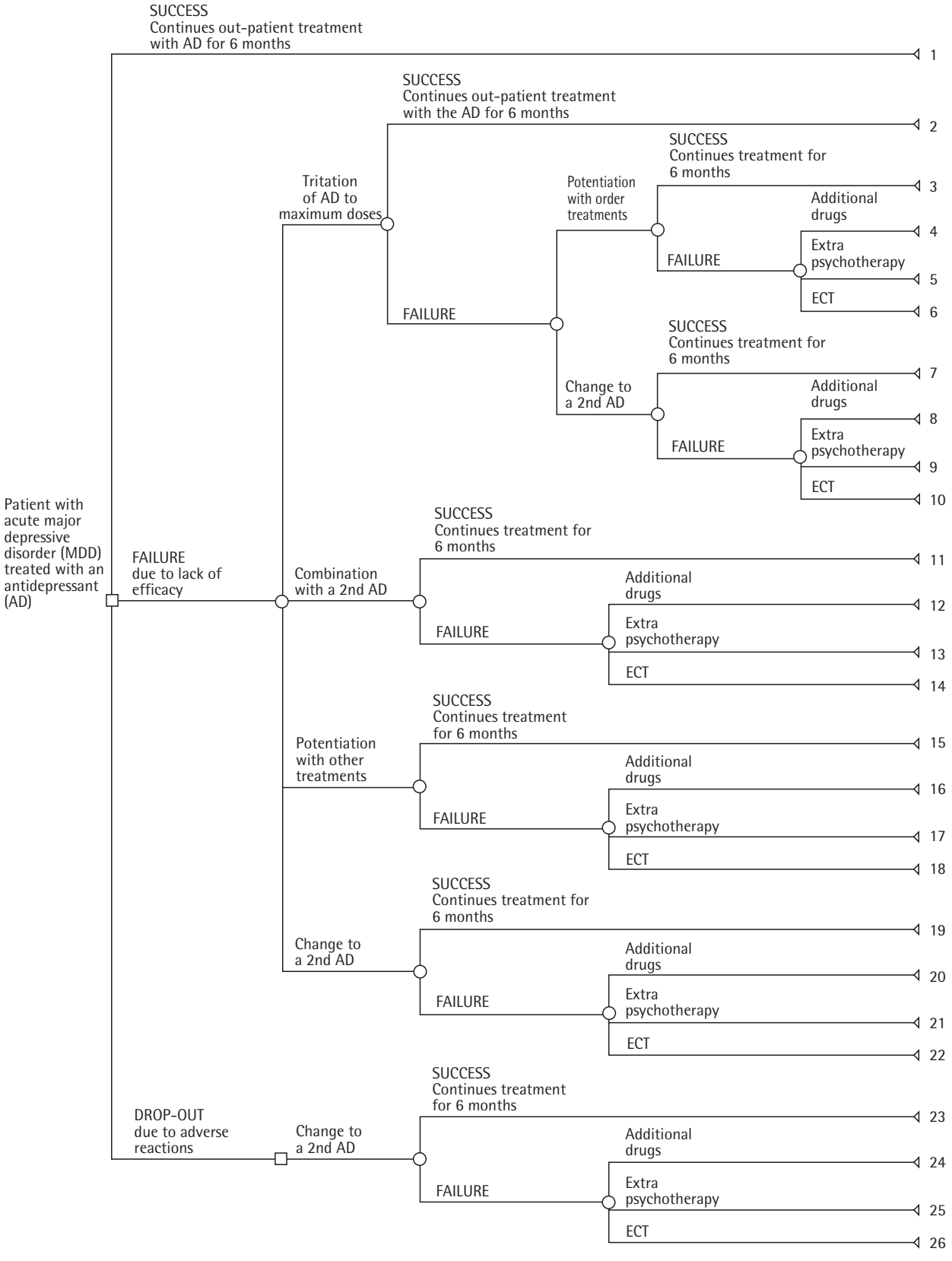

Figure 1 *Decision tree of treatment of major depressive disorders. AD: antidepressant; ECT: electroconvulsive therapy[24,26].*

Table 4 Resultados of meta-analysis (efficacy and drop-outs) of treatment of depression with venlafaxine extended release, SSRI and TCA[30]

Drugs	Efficacy rates (95 % CI) Out-patients	Efficacy rates (95 % CI) Hospitalized patients
Venlafaxine extended retard	73.7 % (68.9-78.4)	62.3 % (49.7-74.9)
SSRI	61.4 % (55.7-67.0)	58.6 % (48.2-69.0)
TCA	59.3 % (50.1-68.6)	58.2 % (43.0-73.5)
Drugs	**Drop-out rates (95 % CI) Due to lack of efficacy**	**Drop-out rates (95 % CI) Due to adverse reactions**
Venlafaxine extended retard	4.8 % (1.8-7.8)	10.9 % (7.9-13.9)
ISRS	8.4 % (4.6-12.3)	17.4 % (17.4-21.3)
TCA	6.8 % (4.6-9.0)	23.1 % (16.2-30.0)

combined. In young adult patients, the median SFD was 22 with venlafaxine, 18 with SSRIs and 13 with placebo ($p < 0.0001$). In the elderly, the result was equally favorable to venlafaxine (20 SFD) in comparison to the SSRIs (16 SFD) and placebo (11 SFD) ($p < 0,05$). Therefore, more SFD are obtained with venlafaxine than with the SSRI[31].

Consequently, as it is clear that there are fewer failures with venlafaxine than with the SSRIs or TCAs together, we could ask about the relevance of the cost of therapeutic failure. In this respect, a study has recently been published on the economic impact of inadequate treatment of depression, understanding «inadequate» treatment as that which is abandoned due to inefficacy or for other reasons[32]. In this study conducted in the United States, a retrospective analysis was done between 1999 and 2002 with 21,632 patients. A total of 51 % of them were treated inadequately, giving rise to additional costs with successive rescue antidepressants in addition to the cost of the initial treatment that was abandoned. Logically, the greater the rate of «adequacy» of the treatments (51.3 % with venlafaxine, 37.2 % with SSRI and 16.5% with TCAs), the lower the drop-out rate. These differences in favor of venlafaxine gave rise to additional costs for each inadequate treatment that ranged from 280 € to 446 € with the SSRIs and from 9 € to 11 € with the TCAs[32]. It is clear that these values, when extrapolated to the population of depressive patients, could have a considerable impact on the National Health Service drug budget.

Second line treatment in MDD

A study conducted in the United States[21] retrospectively studied the costs of second line treatment of depression for 1 year in 981 patients (208 received venlafaxine, 332 SSRI and 191 TCA). The direct health care costs produced during 1 year were the following: 6,945 € with venlafaxine, 7,237 € with the SSRI and 7,925 € with the TCA (table 2).

Pharmacoeconomy of venlafaxine in anxiety (GAD)

In a recent study, also conducted in the United States, cost-effectiveness of treatment of generalized anxiety disorder (GAD) in the elderly (≥ 60 years) with venlafaxine extended release was estimated in comparison with placebo, from the perspective of the financing organization[33]. Costs and effectiveness that were assessed as anxiety SFD were obtained by a meta-analysis of five 8-week long clinical trials. There were 17 SFD with venlafaxine and five with placebo. The cost of a SFD was 22.94 € with venlafaxine and 65.40 € with placebo. Incremental cost-effectiveness (cost of gaining an additional SFD with venlafaxine in comparison with the placebo) was 5.25 € (with a savings of 22.08 € in the best case and a cost of 35.58 € in the worst one).

DISCUSSION

It was concluded in a recent systematic revision of cost-effectiveness of treatments of depression[34] that it was not possible to identify the most cost-effective strategy for the relief of the disease symptoms, although the SSRIs and the most recent antidepressants (as venlafaxine) in most of the patients were more efficient than the tricyclic antidepressants. This impossibility was basically due to the variability of the treatments evaluated, of the efficacy parameters used and of the perspectives considered to estimate the costs.

This variability, which is true for the overall evaluation of depression treatments, is not so true for the combined pharmacoeconomy studies conducted with venlafaxine. Cost-effectiveness of venlafaxine was compared with the SSRI in 15 studies[7,15-18,20-29], with the TCA in [87,16,17,19,24-26,28] and with the heterocyclic antidepressants in only one[16]. Efficacy was measured in most of the studies as depression symptom free days[15,17,24,25,28,29], in some cases as success rate in the resolution of the symptoms[7,20,22,26] and as years of life adjusted by quality (YLAQ) in only one study[23]. Finally, in most of the models (16), only direct health care costs were considered[7,15-29]. Indirect costs were also estimated in three studies[15,18,23] and only hospital costs were estimated in one[27].

As has been stated during the article, most of the results of the pharmacoeconomy studies available indicate that venlafaxine is a more efficient treatment of depression and anxiety than other commonly used options. However, the grade of the internal and external validity of these studies,

a determinant of their applicability to the clinical practice, could be questioned. In this regards, in the first place, it should be stressed that most of the studies published have pharmacoeconomic models, that is theoretical diagrams, generally decision analysis, that make it possible to make economic simulations of complex health care processes by estimations obtained from available or published data of efficacy, toxicity and costs of the alternatives compared[35]. Studies based on models usually generate some mistrust due to the need to use estimations and the complexity of the mathematical models sometimes used. However, the models are not only useful but also essential, especially when no pragmatic type randomized clinical trials that adequately compare the treatments are available. Furthermore, due to the high external validity, which, of course, should be preceded by internal validity, the conclusions of the models may have great importance in the health care policy decision making[35]. In the case of the venlafaxine models, the fact that the efficacy data of the different treatments compared were obtained by meta-analysis of the clinical trial, the method with a greater degree of scientific evidence, should be stressed[36]. In the case of Spain, the fact that the use of resources was estimated by a Delphi type clinical experts panel, using Spanish unit costs, should also be stressed. However, it should be mentioned that not all the studies are unanimous. In 1999, a Spanish observational, naturalistic and retrospective study was published. It compared the costs in the clinical practice of treatment for 6 months of depression with fluoxetine, fluvoxamine, sertraline, paroxetine and venlafaxine immediate release[18]. According to this study, the total daily costs of the patients treated with fluoxetine were 35 % and 37 % less than those observed with the other antidepressants. However, the study did not consider that, according to the meta-analyses of clinical trials, there were real differences of efficacy between the treatments (for example, in the number of depression symptoms free days), so that a study of costs would not be sufficient, it being necessary to conduct a cost-effectiveness analysis.

On the other hand, and although the results of the pharmacoeconomic analyses done with antidepressants in other countries cannot be directly extrapolated to Spain, the present revision of the cost-effectiveness studies of venlafaxine done in 10 other countries has clear utility: they serve to «confirm» the results obtained in the Spanish studies, given that they mostly reach the same conclusion: that venlafaxine is an effective treatment of major depressive disorder (MDD) (with greater success rates and more depression symptom free days) that generates lower total costs (due to the reduction of the costs due to therapeutic failures) than treatment with the SSRI and tricyclic antidepressants. This has been confirmed both in first line as well as second line treatment of the MDD and in the out-patient care as well as the specialized one. Venlafaxine is, therefore, a cost-effective treatment of generalized anxiety disorder (GAD) in comparison with non-treatment, with an acceptable cost for each day gained without anxiety symptoms. However, it would be necessary to perform comparative pharmacoeconomic analyses with other GAD treatments.

As conclusion and based on the available studies, venlafaxine is an effective treatment with lower total costs (due to the reduction of the costs per therapeutic failures) than treatment with the SSRI and TCA in the MDD and cost-effective in comparison with non treatment in GAD.

APPENDIX

Brief glossary of pharmacoeconomy terms[2,3]

Types of costs

Costs that are considered in the pharmacoeconomic analyses may be direct and indirect. Direct health costs are those due to health care processes or interventions, such as consultations, diagnostic tests, treatments, surgical interventions, hospital stay, etc. Non-health care direct costs are those that affect the pocket of the patients or that negatively affect the income of their relatives, as those due to transportation, domestic changes, etc. Finally, indirect costs are mainly those caused by loss or decrease of work productivity, resulting from premature morbidity or mortality due to a disease or treatment.

Incremental cost-effectiveness

It is the cost of gaining an additional unit of effectiveness (for example, 1 % of success) with the most effective treatment and it is calculated with the following formula:

$$IC = \frac{C_A - C_B}{E_A - E_B}$$

C_A and C_B being the cost and E_A and E_B the results of the treatment with two options A and B, respectively.

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