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The current challenges of the treatment of depression: venlafaxine extended release and remission outcomes in real-world clinical practice

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Introduction. This study aimed to assess the utility of venlafaxine XR for the current challenges of treatment of depression (remission and response) in real-world clinical practice.

Method. Observational, prospective, multicenter, cross-national, sixteen-week treatment study including out-patients seen in psychiatry with mild to moderate depressive (HAM-D ≤ 29) and anxiety symptoms (HAM-A > 7) to whom venlafaxine extended release (XR) was prescribed in real-world clinical practice. Remission of symptoms (HAM-D_{17} ≤ 7 and HAM-A ≤ 5) was assessed in 2,071 (ITT analysis) and 1,500 patients (per protocol analysis).

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Results. At 4 months of treatment, ITT remission rate after treatment with venlafaxine XR was 66.3% (1,372/2,070) for depression symptoms and 57% (1,180/2,071) for anxiety symptoms, whereas PP remission rate was 76.1% and 66%, respectively (median dose of venlafaxine XR: 150 mg/day). Of the total number of patients, 19.2% abandoned the study, but only 4.1% withdrew due to adverse events, the most common of them being nausea (3.87%), headache (2.18%) and constipation (2.06%).

Conclusions. Venlafaxine XR showed a high remission rate of either depressive or anxiety symptoms in out-patients with depression, as well as a good tolerability profile, in real-world clinical practice.

Key words:
Venlafaxine XR. Depression. Remission. Response. Clinical practice.

Actas Esp Psiquiatr 2005;33(3):165-172

Retos actuales del tratamiento de la depresión: venlafaxina retard y datos de remisión en la práctica clínica habitual

Introducción. El presente estudio persigue confrontar la utilidad de venlafaxina retard frente a los retos actuales del tratamiento de la depresión en la práctica clínica habitual (remisión y respuesta).

Métodos. Estudio observacional prospectivo, multicéntrico, de ámbito nacional, de 16 semanas de tratamiento con venlafaxina retard, en pacientes ambulatorios atendidos en consultas de psiquiatría con depresión leve o moderada (HAM-D ≤ 29) y síntomas de ansiedad asociados (HAM-A > 7). Se evaluó la remisión de síntomas ($HAM\text{-}D_{17} \leq 7$ y HAM-A ≤ 5) en 2.071 y 1.500 pacientes (de 2.515 reclutados) valorables para análisis de efectividad ITT y PP.

Resultados. A los 4 meses de tratamiento con venlafaxina retard (dosis mediana final: 150 mg/día), la tasa de remisión de síntomas de depresión y ansiedad asociados fue del 66,3% (1.372/2.070) y del 57% (1.180/2.071), respectivamente, en el análisis ITT (76,1 y 66%, respectivamente, en el análisis PP). Del total de pacientes, el 19,2% abandonaron el estudio y sólo el 4,1% lo abandonaron por tolerabilidad, siendo las reacciones adversas más frecuentes náuseas (3,87%), cefalea (2,18%) y estreñimiento (2,06%).

Conclusiones. Venlafaxina retard ofrece una elevada tasa de remisión de síntomas de depresión y ansiedad asociados en pacientes ambulatorios con depresión, así como un muy buen perfil de tolerabilidad en la práctica clínica habitual.

Palabras clave:
Venlafaxina. Depresión. Remisión. Respuesta. Práctica clínica habitual.

INTRODUCTION

Depressive disorders in Spain affect about 2.6% of the population (in Europe 8.5%), prevalence being greater among women[1]. The World Health Organization has estimated that unipolar depression will be the second cause of disability/incapacity in the year 2020[2]. The greater social-occupation involvement that these patients have should be stressed: they must spend more days in bed due to the disease, these disorders are a cause of greater work absenteeism, they have worse work performance and they account for greater health care cost[3,4].

Traditionally, there are basically two families of antidepressive drugs: monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants. Very briefly, their therapeutic possibilities can be summarized, stating that the MAOIs and tricyclic antidepressants were potent and effective, but with considerable tolerability problems[5]. After, introduction of selective serotonin reuptake inhibitors (SSRI) motivated a renewed interest in antidepressive therapy after some years in which there had been no interesting new contributions[6] because they had already produced better tolerability and safety. After this, serotonin reuptake inhibitors and noradrenaline (SRIN) accounted for the most recent contribution in antidepressive treatment, adding greater efficacy than the SSRIs, whose tolerability is, at least, comparable to them.

The present main challenges of depression treatment for the psychiatrist are found in achieving complete remission[7-9]. In the presence of these challenges, venlafaxine extended release, an antidepressant having dual action on serotonin reuptake inhibition and noradrenaline (SRIN), has been shown to have superior efficacy to that obtained with other antidepressants[10,11]. One outstanding characteristic is that it has a lineal type dose-response relationships that makes it possible to obtain more efficacy when increasing the dose, with good tolerability[12]. Furthermore, venlafaxine has demonstrated its efficacy in the relief of anxiety that frequently accompanies depression[13].

The performance of the DAFNE study (observational study in patients with mild to moderate intensity depression and anxiety symptoms to evaluate effectiveness and tolerability of treatment with venlafaxine extended release), carried out in Spain and whose results are presented in this article, is found within this framework. Specifically, this study aims to compare the utility of venlafaxine extended release to the present challenges of treatment of depression in the common clinical practice (remission and response).

METHOD

Investigators and patients

The study was performed between March 2002 and January 2003. In all, 365 psychiatrists distributed throughout the Spanish geography participated in the enrollment.

Included in the study were out-patients seen in the psychiatry clinic with clinical diagnosis of depressive disorder according to the DSM-IV criteria, including major depressive disorder, dysthymic disorder or other non-specific depressive disorder included as such according to DSM-IV criteria, with mild or moderate depression (HAM-D ≤ 29) and associated anxiety symptoms (HAM-A > 7), in whom, according to the physician, treatment with venlafaxine extended release was indicated. Exclusion criteria included the presence of another psychiatric disorder as principal diagnosis or as priority motive of treatment (including psychotic, bipolar and dementia disorders) and pregnancy or possibility of becoming pregnant, breast-feeding, serious organic, incapacitating diseases or those with life risk. Furthermore, those patients who had contraindications to treatment with venlafaxine extended release described in its data sheet (background of hypersensitivity to the active ingredient or to some of the non-active ingredients, concomitant treatment with MAOIs) were excluded. In keeping with the recommendations of the Spanish Health Care Authorities on existing post-authorization studies (Spanish Drug Agency)[14], the study design and protocol were agreed on by a scientific committee created for such objective and subjected to the consideration of the Pharmacoepidemiology Division of the Spanish Drug Agency.

Study design

This is an observational, post-authorization, follow-up, multicenter, prospective and single cohort study with a four month follow-up period, conducted under conditions of common clinical practice. A total of five visits necessary for the study were established in the four months of follow-up: one baseline or patient inclusion and four during the follow-up after 2 weeks and at months 1, 2 and 4 after the onset of the follow-up, respectively. As this was an observational study, the investigator was free to establish any other follow-up or control visit considered necessary.

Besides the sociodemographic and baseline clinical data of the patients, effectiveness and tolerability variables that are described in the following section were collected in each follow-up visit. The investigator was free to prescribe, change or continue the treatments necessary for the concomitant diseases (or for the depression and anxiety disorder) that the patient included in the study could have according to his/her clinical opinion, as long as these treatments had no contraindication with the study drug according to its data sheet, and to withdraw a patient from the study when he/she considered it adequate or in the patient's best interest. The physician should record any treatment administered other than that of the study on the corresponding CRF sheet. Patients who were receiving concomitant treatment with benzodiazepines at the moment of their inclusion could be included. Furthermore, given the naturalistic design of the study, administration of any concomitant treatment which, according to clinical opinion was required during the study, an aspect that was considered in the later statistical analysis, was accepted. The Anatomic-Therapeutic-Chemical Classification System (2001 ATC Classification) of the World Health Organization was used to classify the pharmacological treatments collected.

A single treatment cohort with venlafaxine extended release with the doses established by clinical criterion (respecting, in any case, the establishment of the therapeutic dose indicated in the product's data sheet) was contemplated in the study design.

Effectiveness measures

The main effectiveness endpoints were the following:

- Remission rate according to the HAM-D_{17} and HAM-A scales. It was defined in terms of a total score of the HAM-D_{17} ≤ 7 scale and a total score of the HAM-A ≤ 5 scale[15,16], respectively.
- Response rate according to the HAM-D_{17} and HAM-A scales. It was defined after a decrease of the total score ≥ 50% regarding the baseline visit.

Calculation of the total scores and by dimensions of the HAM-D_{17} and HAM-A scales and the score of the GCI scales of severity and change, variables that were considered to define the patient sample and evaluable visits, was included among the secondary variables.

Assessment of tolerability and safety

This was evaluated by the recording of adverse reactions reported spontaneously by the patient or detected by the investigator that appeared or deteriorated during the study. For each adverse reaction detected, the following had to be detailed: date of appearance, end date, intensity (mild, moderate, severe), action taken by the physician and its resolution. The adverse reactions reported were coded and classified by body systems according to the WHO-ART World Health Organization criteria[17].

Statistical analysis

A sample «by intention to treat» (ITT) was used to analyze tolerability and safety. It included all the patients who had initiated treated with venlafaxine extended release and returned for at least one visit. A sample «by intention to treat» (ITT) was also used for the effectiveness analysis. It included all the patients from the tolerability analysis except those in whom there was no baseline effectiveness data (HAM-D_{17}, HAM-A, GCI severity scales) or in whom there was baseline effectiveness data but these were not found again in any of the following visits. This analysis was performed by carrying the last observation forward (LOCF). In addition, an effectiveness analysis was perform-

ed in a sample defined «per complete protocol» (PP) in which all the patients of the effectiveness analysis «by intention to treat» were included except those who had not finished the 4 months of follow-up planned or who had not provided effectiveness data of some of the visits. This analysis was performed by taking the available data in each visit (visit wise).

Once the study data were listed and quality control performed, the results were analyzed with the SPSS statistical program version 11.5.1. The mean, standard deviations, range for quantitative variables and frequency and percentage of patients in each category for the qualitative variables were estimated in the descriptive analysis. Friedman's nonparametric test was used for the analysis of the evolution of the scores of the effectiveness scales. This was complemented with comparisons regarding baseline values of the values in each visit with the Wilcoxon test. Cochran's and McNemar's tests were used in the case of dichotomic variables (response and remission rates).

The *p* values referenced in this manuscript correspond to the two tailed test of statistical significance. Values inferior to or equal to 0.05 were considered statistically significant.

RESULTS

Evaluable patients

Figure 1 shows the follow-up of the patient sample studied, with details of the patients enrolled, evaluable and excluded for the three different analyses that were conducted, and specifying the exclusion motives.

A total of 2,515 patients were enrolled by 365 investigating physicians participating in the study. Of these 2,515 patients, 87, 444 and 1,015 patients were excluded for the analysis of tolerability and for the analysis of effectiveness «by intention to treat» (ITT) and «per protocol» (PP), a total of 2,428, 2,071 and 1,500 evaluable patients remaining for each one of these analyses, respectively. Of these, 466 (19.2%) and 354 (17.1%) discontinued early before finishing the 4 months of study follow-up in the samples of tolerability and effectiveness «by intention to treat» (ITT), respectively.

Characteristics of the patients

Table 1 describes the baseline demographic data of the patients of the tolerability sample. Most of the patients were

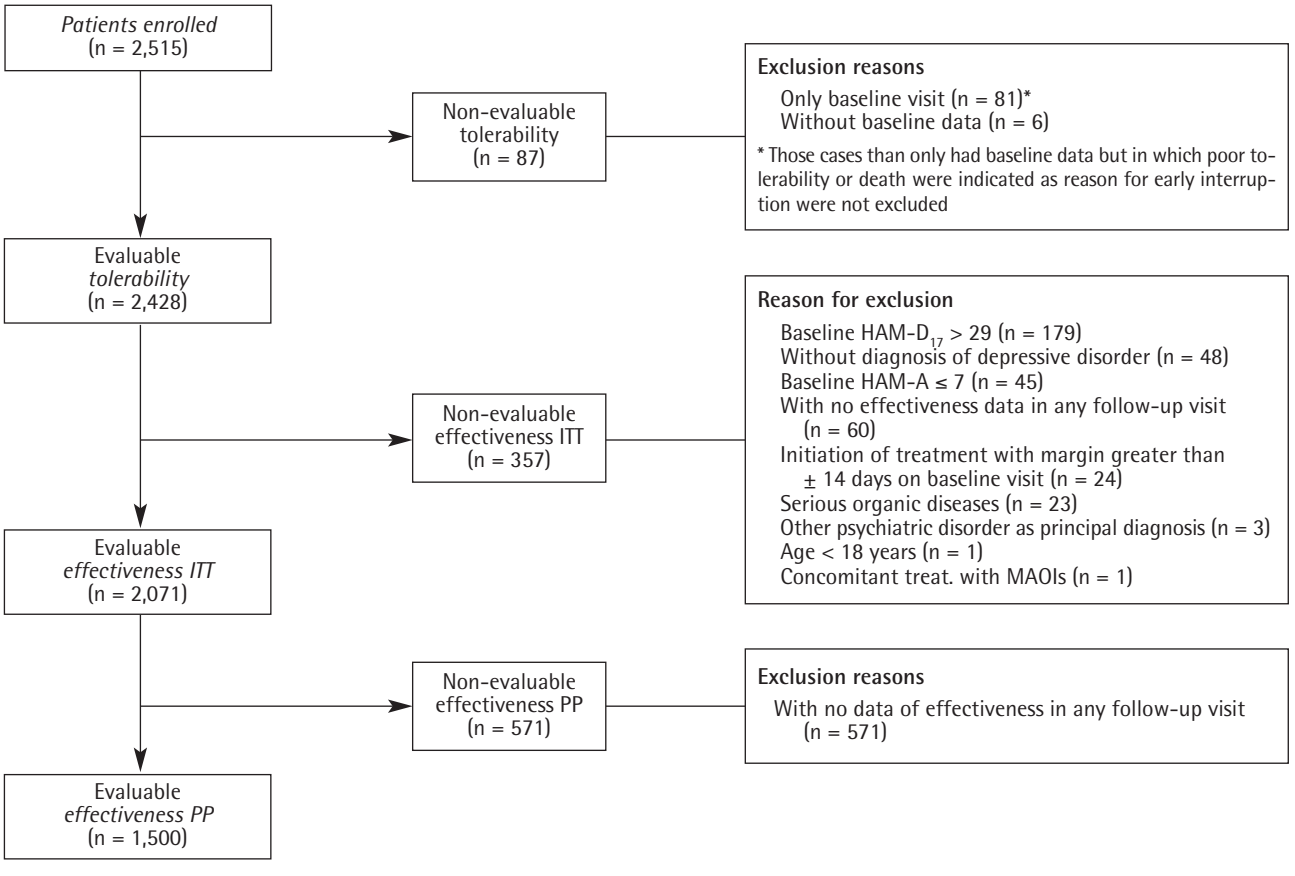

Figure 1 *Diagram of evaluable patients.*

Table 1 Biodemographic characteristics of the patients (tolerability sample)

Characteristic		
Gender (n, %)	2,416	100
Men	830	34.4
Women	1,586	65.6
Age (m, SD) (in years) (n = 2,416)	45.5	13.6
Height (m, SD) (in cm) (n = 2,211)	166.1	8.1
Weight (m, SD) (in kg) (n = 2,210)	68.8	11.7
BMI (m, SD) (in kg/m^2) (n = 2,190)	24.9	3.8

m: mean; SD: standard deviation.

women (65.6 %), whose ages were mostly around 45 years (m: 45.5 years; SD: 13.6), with mean body mass index (BMI) of 24.9 kg/m2 (SD: 3.8).

Table 2 describes the characteristics of the depressive disorder of the patients, using the tolerability sample as reference. Eighty percent of the patients are observed with diagnosis of depressive disorder and the rest with dysthymia diagnosis.

Table 2 Characteristics of depressive disorder (tolerability sample)

	n	%
Diagnosis	2,387	100
Major depressive disorder, single episode	712	29.8
Major depressive disorder, recurrent	712	29.8
Disthymic disorder	472	19.8
Non-specified depressive disorder	491	20.6
First depressive episode	2,413	100
Without previous depressive episodes	1,086	45
With some previous depressive episode*	1,327	55
Number of previous episodes*	998	100
1 episode	253	25.4
2 episodes	213	21.3
3 episodes	191	19.1
4 episodes	103	10.3
5 episodes	67	6.7
More than 5 episodes	171	17.1
	m	**SD**
Age of first episode (years)*	34.8	12.3
Number of previous episodes*	3.6	3.3
Time from first episode (years)*	13.6	10.1
Duration present episode in weeks	16.8	29.8

* Of the patients with some previous depressive episode.

Effectiveness

The results obtained in the main endpoints of effectiveness used in this study are shown in figures 2 and 3. Of these, the following results at 4 months of treatment with venlafaxine extended release (final median dose: 150 mg/day) stand out:

– A remission rate of associated depression and anxiety symptoms (defined according to a final score ≤ 7 and ≤ 5 on the HAM-D_{17} and HAM-A scales, respectively)

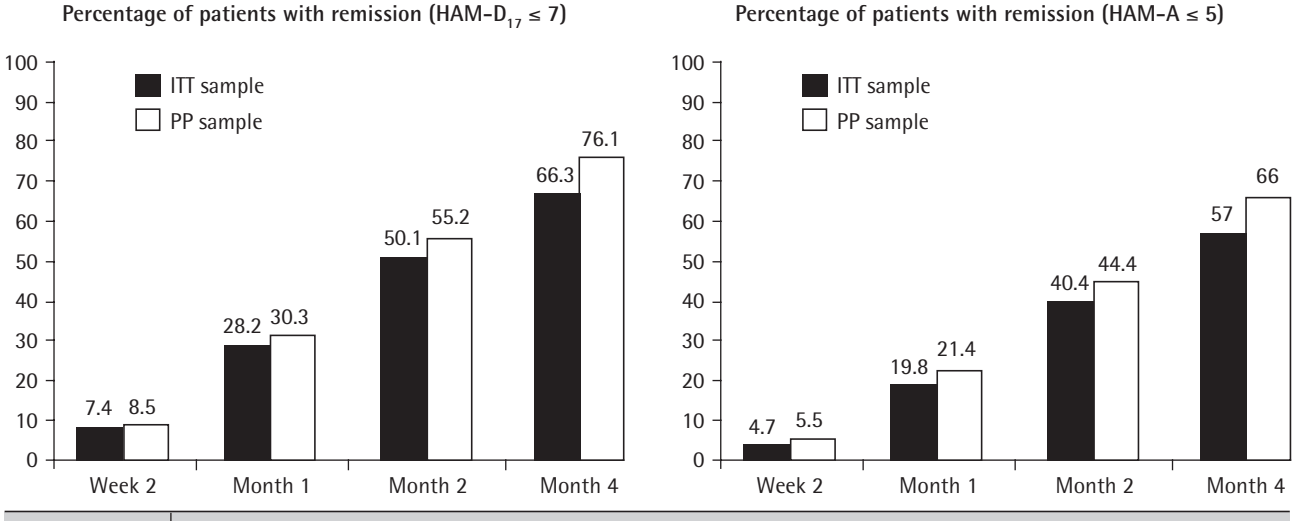

Figure 2 *Remission rate.*

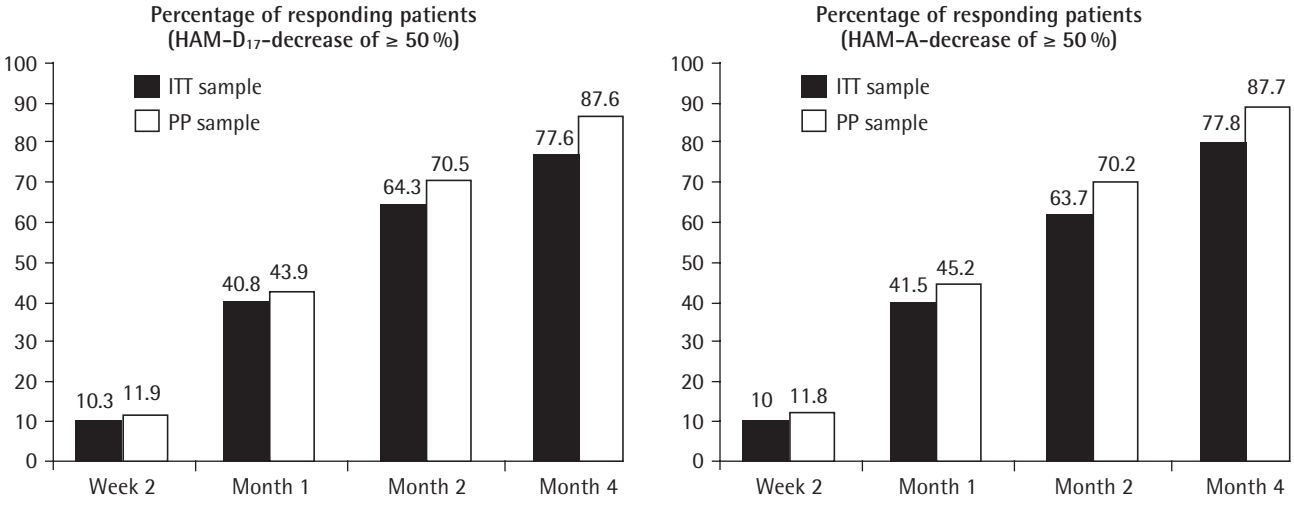

Figure 3 *Response rate.*

of 66.3 % (depression) and 57 % (anxiety) in the ITT analysis, results that were even greater in the PP analysis (76.1 % for depression and 66 % for anxiety).

— A rate of responding patients (defined according to a decrease ≥ 50 % on the HAM-D_{17} and HAM-A scales) that was greater than 75 % in the two effectiveness analyses conducted (ITT and PP), this being even higher in the PP analysis.

Table 3 also describes the detailed evolution of the scores on the HAM-D, HAM-A and GCI scales of severity, in which a statistically significant decrease is observed in all of them (Friedman; $p < 0{,}001$).

Tolerability

In all, 382 patients were recorded with adverse reactions (15.73 %) for the sample of 2,428 patients evaluable for the tolerability analysis. The most frequent adverse reactions were nausea (3.87 %). After these, the most frequent adverse reactions were headache (2.18 %), constipation (2.06 %), mouth dryness (1.81 %), nervousness (1.28 %), increased sweating (1.19 %) and dizziness (1.15 %). Almost all the reactions had moderate (37.2 %, n = 260) or mild (48.9 %, n = 342) intensity, there being 73 reactions having severe intensity (10.4 %). Two cases of serious adverse reaction due to hypertensive episode were observed. Most of the adverse reactions had mild or moderate intensity (86.12 %).

CONCLUSIONS

The present naturalistic study verified the utility of venlafaxine extended release in the face of the present challenges of the treatment of depression in the common clinical practice (response and complete remission of symptoms). However, it can be stated that these types of studies could have some limitations, among which their uncontrolled design that could limit their external validity would stand out.

Table 3 **Evolution of scores on HAM-D, HAM-A and GCI of severity scales (ITT analysis)**

	Baseline	2 week**	Month 1**	Month 2**	Month 4**
HAM-D_{17}/total (0-50)*					
Mean	19.1	15.6	11.2	8.2	6.3
SD	4.6	5.5	5.7	5.6	5.5
HAM-D_{17}/melancholy (0-22)*					
Mean	9.7	8.1	5.9	4.4	3.3
SD	2.6	2.9	3	3	3
HAM-D_{17}/anxiety (0-10)*					
Mean	4.1	3.4	2.5	2	1.6
SD	1.6	1.6	1.5	1.4	1.4
HAM-D_{17}/sleep (0-6)*					
Mean	2.8	2.1	1.4	1	0.8
SD	1.4	1.4	1.3	1.2	1.1
HAM-A/total (0-56)*					
Mean	19.4	15.9	11.3	8.4	6.4
SD	6.6	6.8	6.6	6.3	6
GCI-G*					
Mean	4.2	3.9	3.3	2.7	2.2
SD	0.7	0.8	1	1.1	1.1

* Statistically significant differences were found during the entire study (Friedman, $p < 0{,}001$). ** Statistically significant differences were found in regards to baseline visit (Wilcoxon, $p < 0{,}001$).

However, in response to this limitation, it should be considered that this naturalistic design may be useful when trying to be able to generalize the conclusions obtained in clinical trials and overcome, to a certain degree, their already mentioned limitations, thus being able to respond to the demands of the daily clinical practice[18,19] and also to have a large sample of patients necessary to detect and obtain knowledge on rarely appearing adverse reactions.

The study results verified that the symptom remission rate of associated depression and anxiety at 4 months of treatment was high, 66.3 % (depression) and 57 % (anxiety) in the ITT analysis. These results were even greater in the PP analysis (76.1 % and 66 %, for depression and anxiety, respectively) and which are even superior to those observed in other previous studies in both cases[20,21]. This result is especially interesting, considering that it has been stated that the remission of the symptoms has been indicated as the key therapeutic objective of the antidepressive treatment in several studies[7-9], beyond the obtaining of certain response to antidepressive treatment. This is because its relationship with a minor probability of relapses and better quality of life and psychosocial functioning in general has been demonstrated[20,22]. Secondly a rate of responding patients (defined according to a decrease ≥ 50 % on the scores of the HAM-D_{17} and HAM-A scales) was observed. It was superior to 75% in the two effectiveness analyses conducted (ITT and PP). Specifically, the response rate was 77.6 % (depression) and 77.8 % (anxiety) in the ITT analysis, results that were even greater in the PP analysis (87.6 % and 87.7 %, for depression and anxiety, respectively). In addition, it was found that the scores on the depression and anxiety HAM-D_{17} and HAM-A scales, as well as on the GCI scale of severity and change showed an improvement during the visits that was already observable beginning with the second week of treatment, both in the ITT analysis and in the PP analysis that were conducted.

In regards to safety and tolerability, the present study confirms the good profile that venlafaxine extended release has, a result that coincides with that described in previous studies[21,23], including the two single cases of serious adverse reactions consisting in a hypertensive episode that was an adverse reaction already described prior to this study in the product's data sheet.

ACKNOWLEDGEMENTS

This study has been financed by Almirall, S. A., Barcelona (Spain).

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