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Gender differences in clinical profile, response and remission of depressive patients treated with venlafaxine extended release

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Introduction. The primary objectives of this study are to evaluate gender-specific differences in the clinical profile of primary care depressive patients as well as in the clinical response and remission to venlafaxine extended release.

Methods. We have analyzed a sample of 6,719 adult outpatients (1,713 men and 4,925 women) with diagnosis of depressive syndrome with associated anxiety symptoms included in an observational, prospective, multicenter and open study. Venlafaxine extended release was administered for 24 weeks at a dosage of 75-225 mg/day.

Results. In this study, we have not found overall differences regarding the baseline severity of the depressive episode, as assessed by means of the HAM-D_{17} and Clinical Global Impression Scale of Severity (CGI-S). However, women showed higher scores on items of the HAM-D_{17} and HAM-A scales related with anxious and somatic complaints at baseline and endpoint. The percentage of remission on the HAM-D_{17} scale reached 75.4% for men and 74.3% for women (p = 0.4339) at week 24. In the case of HAM-A: 84.1% vs. 80.6% (men vs. women, p = 0.004).

Conclusions. We did not observe baseline differences in the mean score of the HAM-D_{17} nor the remission rates between women and men (HAM-D_{17}) at the final visit. Women showed lower anxiety remission rates (HAM-A) and maintained more anxious and somatic complaints throughout the study.

Key words:
Depression. Gender. Somatic symptoms. Venlafaxine extended release. Primary Care.

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Diferencias de género en el perfil clínico, respuesta y remisión de pacientes depresivos tratados con venlafaxina retard

Introducción. El objetivo principal de este estudio es evaluar las diferencias específicas de género en el perfil clínico de pacientes depresivos tratados en atención primaria, así como en la respuesta y remisión clínica a venlafaxina retard.

Métodos. Se ha analizado una muestra de 6.719 pacientes ambulatorios adultos (1.713 hombres y 4.925 mujeres) con diagnóstico de síndrome depresivo con síntomas asociados de ansiedad incluidos en un estudio observacional, abierto, prospectivo y multicéntrico. Se administró venlafaxina de liberación retardada durante 24 semanas a dosis de 75-225 mg/día.

Resultados. No se han encontrado en este estudio diferencias globales en cuanto a la gravedad basal del episodio depresivo, según las evaluaciones de la HAM-D_{17} y escala de Impresión Clínica Global de Severidad (ICG-S). No obstante, las mujeres presentaron puntuaciones más altas en ítems de las escalas HAM-D_{17} y HAM-A relacionados con quejas somáticas y de ansiedad en las visitas basal y final. El porcentaje de remisión en la escala HAM-D_{17} fue del 75,4% en hombres y 74,3% en mujeres (p= 0,4339) en la semana 24. En el caso de la HAM-A fue 84,1 frente a 80,6 % (hombres frente a mujeres, p = 0,004).

Conclusiones. No se observaron diferencias basales en la puntuación media de la HAM-D_{17} ni en las tasas de remisión entre hombres y mujeres (HAM-D_{17}) en la visita final. Las mujeres presentaron tasas de remisión de ansiedad más bajas (HAM-A) y conservaron más quejas somáticas y de ansiedad a lo largo del estudio.

Palabras clave:
Depresión. Género. Síntomas somáticos. Venlafaxina retard. Atención primaria.

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INTRODUCTION

Depressive disorders were estimated to be one of the leading causes of disability in the world in 1990, accounting for

10.7 % of total YLD (years lived with disability)[1]. A decade later, unipolar depressive disorders remained one of the leading causes of total DALYs (disability adjusted life years)[2]. Despite the high frequency use of antidepressant drugs, depressive disorders place an enormous burden on patients and society.

Gender is widely recognized as a significant differentiation factor in depressive disorders. A gender ratio, women-men, of 2:1, has been constantly reported in epidemiological studies[3-6]. Several theories have tried to explain the gender bias of depression. Thus, genetic factors and involvement of estrogens and circadian systems[7,8], seasonality[9], differences regarding neurotransmitter functions and environmental factors[10-12] have been reported. There are data supporting that gender differences can result in a higher severity of the disease and a more severe functional impairment, in the case of women[13,14]. Atypical depression, characterized by dysphoria and pronounced anxiety predominates in some clinical samples in women[15].

It has been reported that gender can have an influence on pharmacokinetic and pharmacodynamic processes[16-18]. Due to the potential differences in antidepressant pharmacokinetics, some authors have recommended a dosage adjustment for women to ensure favorable drug response, compliance and decrease of adverse events[19]. Nevertheless, despite the U.S. Food and Drug Administration guidelines in 1993 encouraging the inclusion of women in early medication testing[20], scarce studies have investigated the potential impact of these differences in the clinical efficacy of antidepressants, especially in the primary care setting. Whether gender differences are clinically relevant in the treatment of depressed patients remains to be established[17,18,21-23].

Some studies have found inhibited responses to tricycles and selective norepinephrine reuptake inhibitors with enhanced response to selective serotonine reuptake inhibitors (SSRIs), mainly in premenopausal women[8,23-25]. Whereas Kornstein et al. (2000) reported better response to sertraline in premenopausal women, other authors did not find differences[26]. A meta-analysis of original data from 8 comparable double-blind, active-controlled, randomized clinical trials showed venlafaxine exhibited a more rapid onset and a greater likelihood of remission than SSRI, regardless of age or gender[27].

In this article we analyze gender-specific differences in the clinical profile of the depressive disorder, as well as in the clinical response to venlafaxine extended release, a dual serotonine and noradrenaline reuptake inhibitor, in a population of depressive patients with associated anxiety included in an observational study carried out in the primary care setting. The observational design of the study has allowed us to determine the clinical effects of the antidepressant treatment accordingly to the use in the daily clinical practice.

METHODS

Study population

We have analyzed a sample made up of a total of 6,719 adult outpatients treated for 24 weeks with venlafaxine extended release who were included in an observational, prospective, multicenter, open study performed in Spain in 2003-2004[28]. A total of 2,119 primary care physicians were involved. The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinky and its amendments, and that are consistent with the Good Clinical Practice (GCP) and other applicable regulatory requirements for the performance of clinical trials in humans. The study protocol was presented to the Spanish Agency for Drug Evaluation. Written informed consent was obtained prior to inclusion in the study, assuring data confidentiality.

Inclusion/exclusion criteria

Subjects included in the study were older than 18 years and were diagnosed of depressive syndrome with associated anxiety symptoms, susceptible of receiving treatment according to investigators' criteria. Inclusion criteria included minimum scores of 17 and 10 in the Hamilton for Depression (HAM-D_{17}) and Anxiety (HAM-A) rating scales, respectively. Exclusion criteria were, among others: known hypersensitivity to venlafaxine, use of psychoactive drugs on the week prior to the onset of the study and presence of a serious cardiovascular, hepatic, renal disease or non-pharmacologically controlled hypertension. The use of non-benzodiazepinic hypnotics as concomitant treatments was permitted throughout the study.

Treatment and clinical assesments

Treatment with venlafaxine extended release (VXR) started at recommended doses of 75 mg/day, which could be increased following the investigator's criteria, according to clinical response and tolerability, up to 225 mg/day. Treatment with venlafaxine extended release lasted for 24 weeks. Three follow-up visits were performed at weeks 4, 12 and 24.

Intensity of depressive-anxious symptoms and their evolution was assessed using Spanish validated versions of the HAM-D_{17}[29-31] and HAM-A scales[32,33]. The remission rate for depression and associated anxiety was considered as the primary treatment effectiveness variable. Remission for depression and anxiety was defined as a score lower or equal to 7 on the HAM-D_{17} and HAM-A scales, respectively[34]. As secondary effectiveness variable, CGI-S and Clinical Global Impression Scale of Improvement (CGI-I)[35] assessed baseline severity of the disease and its evolution along the study. Tolerability and safety measures included collection of adverse

events, reasons for discontinuation and effect of treatment on physical variables as weight, arterial pressure and heart rate.

Statistical analysis

Numerical variables were described using mean and standard deviations and superior and inferior ranges. Absolute and relative frequencies, in percentage, were used for categorical variables (nominal or ordinal). Evolution during the study in HAM-D_{17} and HAM-A scales (total scores for associated and individual items) was assessed with repeated measures analysis (ANOVA) or Mann-Whitney's U test, using the Student's *t* test for comparisons between sub-groups. Categorical variables were assessed using chi-square test, Fisher's exact test or McNemar's test, as considered appropriated. WHODRUG v.2003 and MedDra v.5.0 systems were used to codify adverse events and concomitant diseases. All comparisons were two-sided, considering values significant when $p \leq 0.05$. The analyses were performed with the SAS v.6.12 (SAS Institute Inc., Cary, NC, USA) statistical package.

RESULTS

A total of 6,719 adult outpatients, 1,713 [26 %] men and 4,925 [74 %]) women were included in the analysis. The men age was 50.4 ± 14.4 years (age range: 16-89 years, and median of 50 years) for women and 49.6 ± 13.7 years (age range: 17-90 years, and median of 49 years) for men ($p < 0.05$). A significant number of women when compared with men presented medical diseases (50.7 % vs. 45.3 %) or received concomitant medications (53 % vs. 45.5 %) ($p = 0.000$, both comparisons). Musculoskeletical and cardiovascular disorders were among the diseases most frequently diagnosed in women when compared with men (32.1 % vs. 17 % and 18.5 % vs. 15.9 %, respectively) ($p < 0.05$, both comparisons). Besides, men reported more respiratory and genitourinary complaints (8.5 % vs. 4.9 % and 8.7 % vs. 5.7 %, respectively) ($p = 0.000$, both comparisons).

At baseline, women received significantly lower daily doses of venlafaxine extended release than men ($p = 0.028$). Thus, a total of 88 % of women started treatment at 75 mg/day doses, 11.6 % received 150 mg/day doses and the remaining 0.4 % received other doses. In the case of men, 85.7 % started treatment at 75 mg/day doses, 14.0 % received 150 mg/day doses and the remaining 0.1 % required other doses. Study's final visit the majority of patients continued receiving a single daily dose of 75 mg of VXR (71.7 % for women and 68.9 % for men), while 26.1 % of women and 29.2 % of men required 150 mg/day doses and 2.2 % of women and 1.9 % of men received other doses, with no significant gender differences observed ($p = 0.115$).

Baseline intensity of depressive-anxious symptoms

The mean baseline score on the HAM-D_{17} scale was 22.6 ± 4.7 for woman and 22.6 ± 4.9 for men, with no gender differences ($p = 0.771$). The analysis of individual items of this scale related with somatic and anxious complaints showed that, compared with men, a significantly lower percentage of women scored «absent/mild» on items 10 (psychic anxiety: 25.4 % vs. 30.4 %) ($p = 0.000$) and item 11 (somatic anxiety: 31.2 % vs. 36.8 %) ($p = 0.000$) and «absent» on item 13 (general somatic symptoms: 3.5 % vs. 5.3 %) ($p = 0.002$).

The mean baseline score on the HAM-A scale was significantly higher for women when compared with men: 22.6 ± 6.8 and 21.5 ± 6.8, respectively (women vs. men; $p = 0.001$). The analysis of individual items of this scale showed that a significantly higher percentage of women scored «intense/extreme» on items 2, 3, 7, 8, 9 10 and 13, when compared with men ($p = 0.05$, all comparisons).

Evolution of the intensity of depressive-anxious symptoms

The total mean score in the HAM-D_{17} scale at week 24 was 5.6 ± 4.5 for women and 5.4 ± 4.3 for men, without significant gender differences ($p = 0.164$) ($p = 0.001$ vs. baseline, both comparisons). The analysis of individual items of this scale shows no differences in the reduction of the intensity between men and women, excepting for items 11 and 13. At the final visit, a significantly lower percentage of women scored «absent/mild» in items 11 ($p = 0.003$) and «absent» in item 13 ($p = 0.000$). Table 1 summarizes mean total scores at baseline and week 24, as well as the mean total score decrease throughout the study, for men and women, on the HAM-D_{17}, while figures 1 and 2 summarize the evolution of the scores obtained by either men or women on items 11 and 13 on the HAM-D_{17} scale.

Women maintained higher scores than men throughout the study, on the HAM-A scale. At week 24, mean total score on this scale was 4.9 ± 4.5 for women and 4.4 ± 4.0 for men ($p = 0.001$) ($p < 0.001$ vs. baseline, both comparisons). Despite this, women showed higher decreases in the total score along the study ($p = 0.0216$). Table 1 summarizes mean scores at baseline and week 24, as well as the mean score decrease throughout the study, for men and women, on the HAM-A, while figure 3 shows the comparative evolution on this scale's score. Regarding items 2, 3, 7, 8, 9, 10 and 13 of the HAM-A scale, a significantly lower percentage of women scored «absent/mild» at the final visit (table 2). No gender differences were observed in the case of other HAM-A scale related items at the final visit.

Remission of depressive-anxious symptoms

Treatment with venlafaxine extended release was associated with a significant increase of remission rates of depressive

Table 1 Gender comparisons in the intensity and severity of depressive and anxious symptoms. Mean scores in HAM-D_{17} and HAM-A scales, baseline and week 24 and mean decreases along the study

Assessment scales	Mean (DS)	Range	p* values
Mean scores HAM- D_{17} scale: women			
Baseline	22.6 (4.7)	15-51	0.771
Visit 4 (week 24)	5.6 (4.5)	0-34	0.164
Mean scores HAM- D_{17} scale: men			
Baseline	22.6 (4.9)	17-56	
Visit 4 (week 24)	5.4 (4.3)	0-26	
Mean decreases in the mean score HAM-D_{17} scale: week 24 vs. baseline			
Women	–17.7 (7.1)	–50-11	0.229
Men	–17.2 (7.2)	–48-9	
Mean scores HAM-A scale: women			
Baseline	22.6 (6.8)	10-52	0.001
Visit 4 (week 24)	4.9 (4.5)	0-44	0.001
Mean scores HAM-A scale: men			
Baseline	21.5 (6.8)	10-52	
Visit 4 (week 24)	4.4 (4.0)	0-32	
Mean decreases in the mean score HAM-A scale: week 24 vs. baseline			
Women	–17.7 (7.1)	–50-11	0.0216
Men	–17.2 (7.2)	–48-9	

HAM-D_{17}: Hamilton Depression Rating scale. HAM-A: Hamilton Anxiety Rating scale. SD: standard deviation. * Women vs. men. Student's *t* and ANOVA tests.

and anxious symptoms. At week 24, the percentage of remission on the HAM- D_{17} scale reached 75.4% for men and 74.3% for women, with no significant differences between genders at the final visit (p = 0.4339 (p < 0.05 vs baseline, both comparisons). A significantly higher percentage of men achieved remission, compared with women, on the HAM-A scale. Rates of remission on that scale at week 24 were 84.1% for men and 80,6% for women (p = 0.004) (p < 0.05 vs. baseline, both comparisons). Table 3 shows gender related rates of remission on the HAM-D_{17} and HAM-A scales achieved in the study.

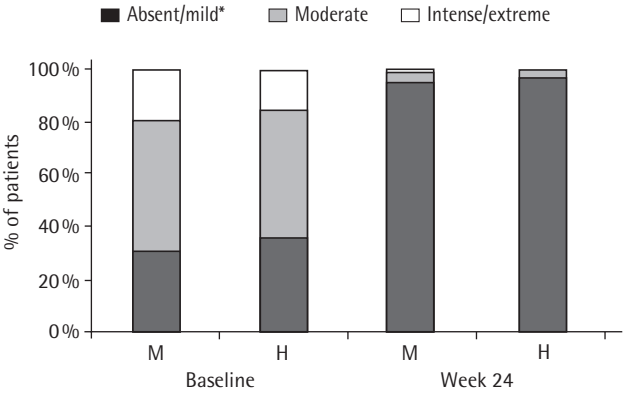

Figure 1 *Evolution of scores achieved by women (W) and men (M) on item 11 of the HAM-D_{17} scale. Baseline and week 24. HAM-D_{17}: Hamilton Depression Rating scale. * p = 0.003, women vs. men, week 24. Chi-square test.*

At baseline, 93.5 of women and 92.2 % of men rated as moderate/severely ill as assessed by the CGI-S scale, with no significant differences between groups (p = 0.525). At the final visit and according to investigators' criteria, 97.8 % of women and 98.1 % of men rated as «improved», as assessed by the CGI-I scale. These percentages were 96.9 % and 97.6 % (women and men, respectively) according to patients' criteria. No differences between genders were observed during the study (p = 0.816, week 12; p = 0.694, week 24).

Tolerability and safety of venlafaxine extended release

A similar number of women (91.4 %) and men (90.7 %) completed the study, with no differences observed between

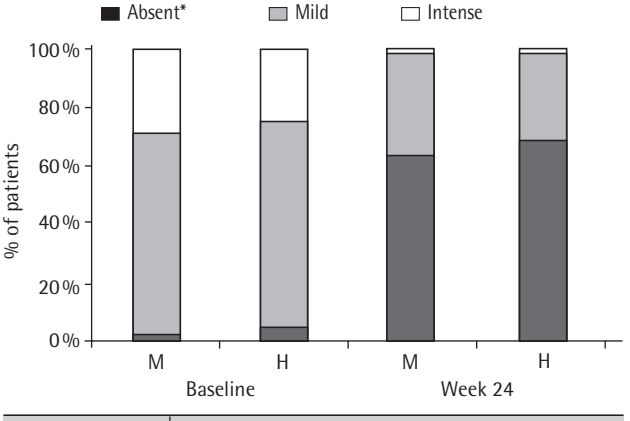

Figure 2 *Evolution of scores achieved by women (W) and men (M) on item 13 of the HAM-D_{17} scale. Baseline and week 24. HAM-D_{17}: Hamilton Depression Rating scale. * p = 0.003, women vs. men, week 24. Chi-square test.*

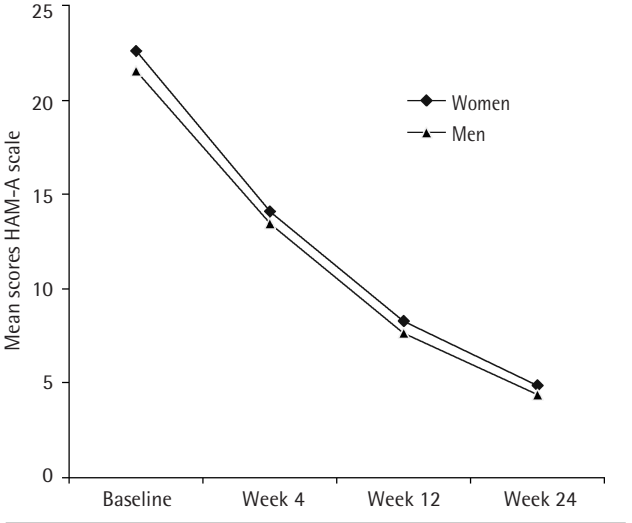

Figure 3 *Mean evolution of total scores and mean decreases compared with baseline obtained throughout the study by men and women on the HAM-A scale. HAM-A: Hamilton Anxiety Rating scale. p < 0001 (mean scores weeks 4, 12 and 24 vs. baseline; both genders); Student's* t *test. p = 0.021 (mean score decrease week 24 vs. baseline; women vs. men); ANOVA test.*

groups for overall rates of dropouts or withdrawals along the study (p=0.631). Nevertheless and compared with men, a significant percentage of women discontinued the study due to adverse events (2.0% vs. 1.2%, woman and men, respectively; p = 0.044). Besides, a higher percentage of men discontinued the study due to loss to follow-up (3.7% vs. 2.3%, men and women, respectively; p = 0.001) and concomitant diseases (1.2% vs. 0.5%, men and women, respectively; p=0.002). A similar percentage of women (334: 6.8%) and men (93: 5.4%) reported adverse events. The number of patients who reported severe adverse events was 17 (2.9% overall patients reporting adverse events) in the case of women and 5 (3.4% overall patients reporting adverse events) in the case of men, with no significant differences between groups. The most frequently reported adverse events were nausea (13.2% overall reported adverse events) and dizziness (7.8% overall reported adverse events). Mean systolic and diastolic blood pressure, as well as heart rate, remained stable without gender differences observed during the study (data not shown).

CONCLUSIONS

Observational studies on differences on the symptomatic profile of the depressive disorder and treatment response differences for women when compared with men can add valuable information to the treatment of depressed patients. Epidemiological studies suggest that vulnerability to depression may be gender related. Nevertheless, whether this fact has a clear impact on the response to antidepressant treatments has been not extensively investigated.

Table 2 Scores obtained by women and men on items 2, 3, 7, 8, 9, 10 and 13 on the HAM-A. Baseline and week 24

Items HAM-A scale	Women (%)	Men (%)	p value*
Item 2: tension			
Baseline			
Absent	15.4	23.3	0.000
Moderate	48.0	50.0	0.154
Intense/extreme	36.6	26.7	0.000
Week 24			
Absent/mild	95.5	97.3	0.003
Moderate	4.2	3.4	0.006
Intense/extreme	0.5	0.3	0.302
Item 3: fears			
Baseline			
Absent/mild	60.9	67.8	0.000
Moderate	27.5	23.0	0.000
Intense/extreme	11.5	9.3	0.000
Week 24			
Absent/mild	97.8	99.0	0.004
Moderate	1.9	0.9	0.008
Intense/extreme	0.3	0.1	0.319
Item 7: general muscular somatic symptoms			
Baseline			
Absent/mild	46.5	55.2	0.000
Moderate	36.5	33.4	0.021
Intense/extreme	17.0	11.4	0.000
Week 24			
Absent/mild	96.2	98.1	0.001
Moderate	3.1	1.8	0.010
Intense/extreme	0.7	0.1	0.007
Item 8: general sensorial somatic symptoms			
Baseline			
Absent/mild	64.1	69.4	0.000
Moderate	27.5	24.4	0.011
Intense/extreme	8.4	6.2	0.005
Week 24			
Absent/mild	98.1	99.0	0.021
Moderate	1.8	0.9	0.019
Intense/extreme	0.2	0.1	0.800
Item 9: cardiovascular symptoms			
Baseline			
Absent/mild	60.9	66.5	0.000
Moderate	28.7	25.4	0.008
Intense/extreme	10.4	8.2	0.009
Week 24			
Absent/mild	98.5	99.3	0.029
Moderate	1.3	0.7	0.067
Intense/extreme	0.2	0.0	0.147
Item 10: respiratory symptoms			
Baseline			
Absent/mild	58.3	64.3	0.000
Moderate	30.6	28.2	0.065
Intense/extreme	11.1	7.5	0.000
Week 24			
Absent/mild	98.3	99.2	0.016
Moderate	1.5	0.8	0.043
Intense/extreme	0.2	0.0	0.117
Item 13: autonomical symptoms			
Baseline			
Absent/mild	59.8	68.1	0.000
Moderate	30.5	25.4	0.000
Intense/extreme	9.8	6.6	0.000
Week 24			
Absent/mild	98.0	99.2	0.003
Moderate	1.7	0.7	0.009
Intense/extreme	0.3	0.1	0.133

HAM-A: Hamilton Anxiety Rating scale. *Women vs. men. Chi-square test.

Table 3 Gender comparisons in remission rates. HAM-D_{17} and HAM-A scales: follow-up visits

Assesment scales	Women (%)	Men (%)	p*
Remission in depression: mean score HAM-D_{17} ≤ 7			
Visit 2 (week 4)	9.5 (427)	9.1 (145)	0.700
Visit 3 (week 12)	43.0 (1.822)	43.7 (646)	0.661
Visit 4 (week 24)	74.3 (2.986)	75.4 (1.056)	0.433
Remission in anxiety: mean score HAM-D_{17} ≤ 7			
Visit 2 (week 4)	15.9 (717)	16.3 (259)	0.689
Visit 3 (week 12)	53.7 (2.267)	57.3 (849)	0.016
Visit 4 (week 24)	80.6 (3.235)	84.1 (1.177)	0.004

HAM-D17: Hamilton Depression Rating scale. HAM-A: Hamilton Anxiety Rating scale.
* Women vs. men. Chi-square test.

Gender differences in the clinical profile of the depressive episode

Psychomotor retardation and neurasthenic symptomathology have been reported to be more common in men, whereas women are more frequently rated as anxious[21,26,36]. In spite of these findings, some authors have failed to find significant differences regarding the diagnostic spectrum, duration and severity of depression or its associated functional impairment[21,26,37]. Other researchers have reported higher severity ratings in assessment scales and greater impairment in depressed women[13,14,24].

We have not found overall differences regarding the baseline severity of the depressive episode, as assessed by means of the HAM-D_{17} and CGI-S scales, in this study. Nevertheless, our findings indicate women have significantly higher scores on items of the HAM-D_{17} and HAM-A scales related with somatic complaints. Baseline mean total score on the HAM-A scale, as well as mean scores in 7 out of 14 items of that scale, were significantly higher in women. Our finding of depressed women reporting more somatic and anxious complaints is consistent with other research. Women consulting general practitioners tend to have more mood, anxiety, somatoform disorders and psychiatric comorbidity than men[38,39]. Indeed, physical symptoms are 50 % or more likely to be reported by women in the primary care setting[40].

Gender differences in the response to venlafaxine extended release

Venlafaxine extended release proved to be an effective and safe treatment in this study, both for women and men. These findings are consistent with the results previously reported in a meta-analysis of original data from 8 comparable double-blind, active-controlled, randomized clinical trials of venlafaxine and SSRI. Researchers failed to detect significant age-by-treatment, gender-by-treatment or age-by-gender interactions. Regardless of age and gender, remission rates at week 8 with venlafaxine were significantly higher than with SSRI: venlafaxine, 45 % (men and women) and SSRI, 36 % for men and 34 % for women ($p < 0.05$)[27].

This is one of the few studies assessing the gender related effects of an antidepressant on individual depression and anxiety symptoms in primary care centers. We have failed to show differences during the study between women and men in the case of the HAM-D_{17} scale intensity, though women maintained significantly higher scores by week 24 in two HAM-D_{17} items related with anxiety and somatic complaints. In the case of HAM-A scale, despite women presented a higher reduction of the intensity of the anxiety symptoms throughout the study, they maintained higher total mean scores from baseline to endpoint when compared with men, with a lower percentage of women scoring «absent» at week 24 in 7 out 14 anxiety and somatic HAM-A related items. We did not observe gender differences in the remission rates between women and men in depressive symptoms, as measured by the HAM-D_{17} scale. For instance, women showed lower associated anxiety remission rate, as assessed by the HAM-A scale, probably related to higher baseline severity.

Other studies have shown gender differences in the pharmacological response to depression and anxiety associated symptoms[15,23,24] though no specific analysis of individual or subsets of symptoms were performed. A controlled, open-label, 8 weeks comparative study in 239 patients with non-melancholic depression or dysthimia showed women taking sertraline responded more highly to anxiety symptoms as measured by the HAM-A scale than those taking imipramine, whereas no differences were reported among men[23]. To our knowledge, this is the first study evaluating gender differences in somatic complaints after an antidepressant treatment course. We have found a 24 week active treatment was associated with reductions in the percentage of patients with higher scores in the somatic complaints related items. Nevertheless, a significantly higher percentage of women maintained higher scores on items related with somatic complaints at week 24.

It has been suggested that correctly diagnosed depressed patients who receive three adequate trials of antidepressant medication if unresponsive, have an approximately 90 % chance of achieving a state of remission[41]. It can be argued that antidepressants inhibiting both serotonine and noradrenaline reuptake, as is the case of venlafaxine extended release, can represent an advantage in the treatment of both psychological and physical symptoms of depression; this may lead to a higher percentage of patients achieving

remission, as it has been suggested by other authors[42,43]. In addition, venlafaxine may incur lower relapse rates than SSRI during maintenance treatment[44].

In this study, we have not found overall differences regarding the baseline severity of the depressive episode, as assessed by means of the HAM-D_{17} and CGI-S scales. However, at baseline women had higher scores on items of the HAM-D_{17} and HAM-A scales related with anxious and somatic complaints. In this study, venlafaxine extended release has resulted to be a well-tolerated, safe and effective antidepressant, both for women and men. There were no gender differences in the mean score of the HAM-D_{17} scale at final visit. We did not observe any differences in the remission rates between women and men (HAM-D_{17}). Women had lower anxiety remission rates (HAM-A) and maintained more anxious and somatic complaints throughout the study. Rates of remission at week 24 were 75.4% vs. 74.3% in the case of HAM-D_{17} and 84.1% vs. 80.6% in the case of HAM-A (men vs. women; both comparisons). No differences were observed between groups on overall rates of dropouts or withdrawals during the study. A similar number of women and men reported adverse events.

This study has two main limitations. The first and most important is inherent to its open design with no controlled placebo-arm. A second limitation is the large number of patients included in this trial that can overestimate treatment significant differences. Nevertheless, and taking into consideration the higher intensity of the anxiety symptoms and somatic complaints observed on depressed women included in our study, we suggest further long-term controlled trials are needed to investigate the clinical relevance of these gender differences in the response to antidepressants in order to optimize specific treatment courses for subtypes of patients.

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