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# Treatment with venlafaxine extended release for climacteric women with depression or anxiety diagnosis. An open-label study

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**Introduction.** The objective of this observational study was to assess under real clinical practice conditions the effectiveness and safety of venlafaxine extended release in anxiety-depressed and hormone-related symptoms in climacteric women with anxiety or depressive disorders.

**Methodology.** Observational, prospective, open-label, multicenter, 24-week study, carried out in Spain. A sample of 45 outpatients, adult women between 45 and 55 years of age, diagnosed of depressive disorder, generalized anxiety disorder or social anxiety disorder were analyzed. Venlafaxine extended release was administered for 24 weeks at doses according to the investigator's clinical criteria.

**Results.** Of the total of 45 patients who were included in the study, 43 (95.6%) completed it. The patients' age range was of 47 to 55 years old, median of 50 and mean of 50.82. The clinical condition evolution was assessed with the evaluation scales scores: Blatt-Kuppermann Menopausal Index, Hamilton Depression Rating Scale, Hamilton Anxiety Scale and Clinical Global Impression. During the 24-week period, a significant decrease in the different scales scores showed a clinical improvement.

**Conclusions.** The results achieved show that treatment with venlafaxine extended release significantly improved the clinical condition of climacteric patients with anxiety or depressive disorder. If these results are confirmed with placebo-controlled clinical trials, they will support the utility of Venlafaxine extended release in this kind of patients.

**Key words:**  
 Depression. Open-label. Perimenopause. Climacteric. Venlafaxine extended release. Women.

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## Tratamiento con venlafaxina clorhidrato de mujeres climatéricas con diagnóstico de ansiedad o depresión. Estudio abierto

**Introducción.** El objetivo de este estudio observacional fue evaluar, bajo condiciones reales de práctica clínica, la efectividad y seguridad de venlafaxina clorhidrato en síntomas de ansiedad-depresión y síntomas hormonales en mujeres climatéricas con trastorno de ansiedad o depresivo.

**Metodología.** Estudio observacional, prospectivo, abierto y multicéntrico, de 24 semanas de duración, llevado a cabo en España. Se analizó una muestra de 45 pacientes ambulatorios mujeres de entre 45 y 55 años con diagnóstico de episodio depresivo, trastorno de ansiedad generalizada o trastorno de ansiedad social. Se administró venlafaxina clorhidrato durante 24 semanas a dosis según criterio clínico del investigador.

**Resultados.** De las 45 pacientes que iniciaron el estudio, 43 (95.6%) finalizaron el mismo. El rango de edad fue de 47 a 55 años, una mediana de 50 años y una media 50,82 años. La evolución de la situación clínica fue mesurada por la puntuación de las escalas de evaluación: Índice Menopáusico de Blatt-Kuppermann; Escala de Hamilton para la Depresión; Escala de Hamilton de Ansiedad e Impresión Clínica Global. Durante las 24 semanas se observó una mejoría clínica demostrada por una disminución significativa de las puntuaciones de las distintas escalas.

**Conclusiones.** Los resultados obtenidos indican que el tratamiento con venlafaxina clorhidrato mejoró significativamente la situación clínica de las pacientes climatéricas con trastorno de ansiedad o trastorno depresivo. En el caso de confirmarse mediante ensayos controlados con placebo, estos resultados avalarían la utilidad de la venlafaxina clorhidrato en este tipo de pacientes.

**Palabras clave:**  
 Depresión. Estudio abierto. Perimenopausia. Climaterio. Venlafaxina clorhidrato. Mujeres.

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## INTRODUCTION

According to the World Health Organization definition, the term «climacteric» includes «transition to menopause»: a period of time prior to the last menstruation in which the variability in the menstruation cycle normally increases as well as an undetermined time after the last menstruation.<sup>1</sup> The endocrine changes produced in this period (withdrawal of estradiol and initiation of a prolonged hypogonadism) may be associated with greater susceptibility to develop depressive disorders in some women.<sup>2-5</sup>

The use of antidepressants in the climacteric period is justified by the alteration that estrogen deprivation would produce on the use of brain tryptophan for 5HT syntheses and its relationship with gonadotropin release.<sup>6</sup> However, some data that has been questioning the importance of serotonin in the pathogenesis climacteric of affective disorders must also be considered. Among these are the finding that menopausal women who have recently recovered from a major depressive disorder do not experience mood deterioration when they are subjected to tryptophan depletion in spite of the clinical risk of relapses<sup>7</sup> and the variability of the efficacy data of Selective Serotonin Reuptake Inhibitors (SSRI) in the treatment of menopausal patients<sup>8</sup> (positive for citalopram<sup>9</sup> and negative or changing based on the characteristics of the patients for sertraline).<sup>8,10</sup>

The role of norepinephrine in the climacteric period would be supported by the study of the differential effect of the different types of antidepressants in women that show that SSRIs would be more effective in younger women than in older women while the Serotonin-Norepinephrine reuptake inhibitors (SNRIs) would be effective regardless of age.<sup>11</sup> The observational study data suggest that treatment with SNRI improves overall well-being and reduces depressive and vasomotor symptoms in perimenopausal depressive patients.<sup>12,13</sup> Some clinical trials<sup>14-17</sup> and systematic reviews<sup>18,19</sup> have also demonstrated that venlafaxine may be effective in the treatment of vasomotor symptoms in hypoestrogenic women.

The observational study aimed to evaluate the effectivity and safety of venlafaxine hydrochloride in anxiety-depression symptoms and hormonal symptoms in climacteric women with depressive disorder or generalized or social anxiety disorder under real clinical practice conditions.

## METHODOLOGY

This is an observational, prospective, open label and multicenter 24-week long study carried out in Spain during the year 2006 with the participation of 10 investigators who were specialists in psychiatry. The study was approved by the Ethics Committee of the reference Hospital and did not receive any external financing for its conduction. Out-patient treated women were included in the study when they

fulfilled the following criteria: they were between 45 and 55 years of age, had irregular menstruation or had had the last menstruation in the last 5 years and had a score greater than 15 on the Blatt-Kupperman Menopausal Index scale<sup>20</sup>. Other inclusion criteria were those who had DSM-IV clinical diagnoses of Depressive Disorder, Generalized Anxiety Disorder or Social Anxiety Disorder which, in the opinion of the investigator, could be benefited by treatment with venlafaxine hydrochloride (VXR); who had not taken any antidepressant during the last month, who were not being treated with hormone replacement therapy and who had not had any modifications in any other of the treatments received in the last 3 months. The exclusion criteria were pregnancy or breast-feeding, menstruation disorder due to non-physiological causes, psychotherapy initiated in the last 3 months, physical or severe mental diseases, suicide risk in previous treatment or known intolerance to VXR.

After verifying the adequacy of the patients selected, treatment was begun with VXR, in an open-label study, according to be dosage recommended on the data sheet, which could be modified according to the clinical criteria at any time of the study. Evaluations were made in the initial visit (prior to the initiation of treatment with VXR) and at weeks 12 and 24 of the study. The instruments used in the evaluation were the 17-item Hamilton for depression scale (HAM-D17),<sup>21,22</sup> Hamilton anxiety scale (HAM-A),<sup>23,24</sup> Blatt-Kupperman menopausal index (BMI),<sup>20</sup> and the Clinical Global Impression Scale (CGI).<sup>25</sup> The BMI is a scale designed to measure the severity of the menopausal symptom. It evaluated 11 symptoms (hot flashes, paresthesia, insomnia, nervousness, melancholia, vertigo, weakness, arthralgia-myalgia, headache, palpitations, and dysesthesias) that were scored according to the following criteria: 0 = none; 1 = mild; 2 = moderate; and 3 = severe. Each one of the symptoms were given a certain weight (conversion index) which when multiplied by the score observed gave us the corrected score of the symptoms. The BMI makes it possible to quantify the symptomatic severity of the menopausal syndrome, considering mild (< 15), moderate (15-20) and severe (> 20).

The primary variable of efficacy was the magnitude of the reduction of the score in the evaluation scales of HAM-D<sub>17</sub>, HAM-A and BMI. As secondary variable of effectivity, the baseline severity of the clinical picture and its evolution in time were evaluated. The data obtained by the administration of CGI scale were used to evaluate it. A systematic evaluation was made of the side effects in each study visit by the collection and evaluation of the adverse events reported and of the reasons for withdrawals and drop-outs.

All the patients who met the inclusion/exclusion criteria, who had signed the informed consent and who had received at least one study medication dose were included in the statistical analysis for intention to treat and were evaluated for effectivity, safety and tolerability. Descriptive analyses were made of all the qualitative and quantitative

variables. The qualitative variables were analyzed by absolute and relative frequencies, while the quantitative ones were studied through the mean, standard deviation and confidence interval if they followed a normal distribution or, if not, through the median, minimum, maximum and interquartile range. The analysis of the evolution of the scores on the evaluation scales was made with the repeated measures ANOVA. All the comparisons were paired, considering a value of  $p \leq 0.05$  as significant. The statistical program of SAS v.6.12 (SAS Institute Inc., Cary, NC, USA) was used.

## RESULTS

Of the 45 patients who initiated the study, 43 (95.6%) completed it properly. The reasons for abandoning the study of the patients were loss to follow-up in one case and poor therapeutic compliance in the other. The 45 patients studied presented an age range of 47 to 55 years, with a median of 50 years and a mean of 50.82 years ( $CI_{95\%} = [50.11-51.53]$ ). A total of 82.2% of the women were married, 8.9% widows and the rest were single or separated. In addition, 37.8% had completed primary studies, 35.6% secondary studies, 22.2% had a middle upper university degree and 4.4% had no studies. Of the patients, 57.8% were dedicated to housework, 22.2% had temporary work incapacity, 15.6% were active workers and the remaining 4.4% were retired or on a pension. Regarding women, 19.3% (5) had no children, 72.3% had 1 or 2 children and the rest (13.85) 3 or more. In regards to their medical background, 12 patients (26.6%) stated they had had 1 physical disease during their lifetime, 5 (11.1%), 2, and 28 (62.24%) stated they had not had any significant physical problem. A total of 55.6% of the patients had not had any mental disease prior to the current episodes and in regards in the episode, 80% of the patients had a depressive disorder and the rest an anxiety disorder (table 1). Seven patient had already received treatment for the current episode with drugs: 6 of them (13.3%) with antidepressants SSRIs that had been withdrawn at some point in the course prior to one month before being included in the study and 1 (2.2%) with pregabalin (these drugs had been withdrawn at some point in the evolution of the episode due to lack of efficacy, a datum that was obtained by the investigators from the clinical records). At the onset of the study, 32 patients (71.1%) were taking benzodiazepines, this percentage decreasing to 39.5% at the end of the study ( $p = 0.0001$ ). Some clinical aspects collected in the baseline evaluation, regarding the menstrual status of the patients, the clinical background and the drug treatments are shown in table 2.

The evolution of the clinical status measured by the score of the evaluation scales (BMI, HAM-D17 and HAM-A) during the study can be observed in table 3. During the 24-weeks of follow-up, an improvement was observed in the hormonal and psychic symptoms, evidenced by a significant decrease of the scores of the different scales, so that the scores obtained in visit 2 were significantly better than the

baseline and the scores of visit 3 were significantly better than those of visit 2 (Table 4). In the initial visit, the mean of the clinical global impression scale was 4.14 ( $SD = 0.86$ ), at month 3, it was 2.16 ( $SD = 0.75$ ) and at the final visit, it was 2.07 ( $SD = 1.07$ ), the difference between the final and initial clinical status being statistically significant ( $p < 0.0001$ ).

| Table 1   | Diagnoses of current psychiatric episode |       |
|---|--|-------|
| Clinical Diagnoses  | n  | %     |
| Mild depressive episode                                     | 3  | 6.7   |
| Moderate depressive episode                                 | 17                                       | 37.8  |
| Severe depressive episode without psychotic symptoms        | 1  | 2.2   |
| Recurrent depressive disorder with mild current episode     | 3  | 6.7   |
| Recurrent depressive disorder with moderate current episode | 2  | 4.4   |
| Returned depressive order with severe current episode       | 1  | 2.2   |
| Dysthymia   | 9  | 20.0  |
| Mixed anxious-depressive disorder                           | 4  | 8.9   |
| Unspecified anxiety disorder                                | 5  | 11.1  |
| Total   | 45                                       | 100.0 |

| Table 2   | Clinical condition at baseline evaluation |        |       |
|---|---|--------|-------|
| Parameters  | n   | Mean   | SD    |
| Age   | 44  | 50.82  | 2.33  |
| Age of last period (in menopausal subjects)                               | 30  | 48.73  | 2.65  |
| Age of onset of menstrual irregularities (in non-menopausal subjects)     | 15  | 48.87  | 2.29  |
| Difference between the chronological age and age of menopause             | 29  | 2.17   | 1.71  |
| Difference between a chronological age and age of onset of irregularities | 15  | 1.86   | 1.72  |
| Age at first diagnosis of mental disorder                                 | 43  | 46.42  | 6.44  |
| Age at first psychiatric treatment  | 44  | 43.68  | 7.50  |
| Age of onset of treatment due to current psychiatric condition            | 44  | 49.00  | 4.35  |
| Dose of venlafaxine hydrochloride at baseline visit*                      | 44  | 136.36 | 49.25 |
| Dose of venlafaxine hydrochloride at months 3*                            | 43  | 156.97 | 87.85 |
| Dose of venlafaxine hydrochloride at months 6*                            | 43  | 163.95 | 92.95 |

SD: standard deviation. \*Mean dose in mg/day.

| Table 3    |       | Descriptive statistics of the symptoms evaluated by: Blatt Kuppermann menopausal index (BMI) and the Hamilton anxiety and depression scales (HAM-A and HAM-D <sub>17</sub> ) |       |      |                     |      |  |
|------------|-------|--|-------|------|---------------------|------|--|
| Evaluation | BMI   |  | HAM-A |      | HAM-D <sub>17</sub> |      |  |
|            | Mean  | SD   | Mean  | SD   | Mean                | SD   |  |
| Baseline   | 27.41 | 8.40   | 25.72 | 8.89 | 21.26               | 8.04 |  |
| Month 3    | 16.51 | 7.35   | 13.00 | 7.52 | 9.58                | 5.10 |  |
| Month 6    | 12.74 | 7.52   | 9.60  | 7.22 | 7.02                | 4.35 |  |

SD: standard deviation.

Five patients (11.1%) reported adverse events that consisted in decreased libido (n=1), dyspepsia (n = 1), constipation (n = 1), exanthema (n = 1) and nausea (n = 1). A total of 60% of the adverse events reported were of mild severity and 40% were moderate. The relationship with the drug was considered likely or very likely in 80% of the cases and possible in the remaining 20%. A total of 40% (n = 2) of the adverse events were resolved during the study while the remaining 60% (n = 3) persisted at the end of it. The clinician never took any specific measure to resolve them.

## DISCUSSION

In spite of the high prevalence of the affective disorders in women during the climacteric period and the frequent use of antidepressants for their treatment, there are little data that study the overall effect of these drugs on the clinical condition of these patients. The existing data come from studies that generally test the efficacy of antidepressants, generally SSRI, on the vasomotor symptoms of women with physiological menopause or menopause induced after the diagnoses of breast cancer, overlooking the consideration of climacteric period as an era in which, in addition to the va-

somotor symptoms, depressive and anxious symptoms are generally present.<sup>26,27</sup> The SNRI antidepressants have been studied little in this group of patients. After a systematic review of the literature, 4 placebo- controlled or active substance clinical trials were found in which Venlafaxine showed efficacy in the control of hot flashes<sup>14-17</sup> in patients with physiological menopause or menopause induced due to having breast cancer. The duration of the trials was short (between 4 and 12 weeks) and a dose of up to 150 mg/d was used in them. There is also a naturalistic study that investigated the effectivity of venlafaxine hydrochloride in patients with physiological menopause in depression whose duration was short (8 weeks) and with the maximum dose of VXR of 225 mg/day.<sup>12</sup> Another open label naturalistic study conducted with duloxetine in 30 postmenopausal patients with depression and vegetative symptoms<sup>13</sup> shows that this drug produces improvement in both depressive and vasomotor symptoms. The studies conducted have focused on depressive symptoms, and we had no knowledge at the time of the present study of the existence of any study that included climacteric women diagnosed of anxiety disorder.

The present study has clear methodological limitations: absence of blind design, absence of control group and a

| Table 4                   |                          | Two-by-two comparisons of the symptomatic level evaluation measured by the Blatt Kuppermann Menopausal index (BMI) and the Hamilton anxiety and depression scales (HAM-A and HAM-D <sub>17</sub> ) in the different evaluations |               |       |  |
|---------------------------|--------------------------|---|---------------|-------|--|
| Evaluation                | Evaluation of comparison | Differences between means   | Typical error | p     |  |
| <b>BMI</b>                |                          |   |               |       |  |
| Baseline                  | Month 3                  | 10.90   | 1.23          | 0.000 |  |
|                           | Month 6                  | 14.67   | 1.54          | 0.000 |  |
| Month 3                   | Month 6                  | 3.76  | 0.69          | 0.000 |  |
| <b>HAM-A</b>              |                          |   |               |       |  |
| Baseline                  | Month 3                  | 12.72   | 1.44          | 0.000 |  |
|                           | Month 6                  | 16.11   | 1.70          | 0.000 |  |
| Month 3                   | Month 6                  | 3.39  | 0.59          | 0.000 |  |
| <b>HAM-D<sub>17</sub></b> |                          |   |               |       |  |
| Baseline                  | Month 3                  | 11.58   | 1.40          | 0.000 |  |
|                           | Month 6                  | 14.14   | 1.46          | 0.000 |  |
| Month 3                   | Month 6                  | 2.55  | 0.45          | 0.000 |  |

random allotment. Added to these is the impossibility of controlling the effects due to passage of time that may be a factor which, by itself, modifies the symptoms that are the object of study.<sup>27</sup> Regarding the absence of laboratory diagnosis, although the WHO has proposed endocrinological criteria for climacteric, a recent meta-analysis concludes that the perimenopausal diagnosis should be made from the menstrual background and age, it not being necessary to base it on the results of the laboratory tests.<sup>28</sup>

One of the primary difficulties found when studying psychiatric problems in climacteric patients comes from the lack of specificity of the symptoms that are present in this period.<sup>29-31</sup> Thus, and in order to have a general view of this condition, the present study makes it possible to capture the clinical picture from different aspects and in different stages of the climacteric period, to include patients who are usually seen in the outpatient consultation, who normally have previous and current commitment treatments, depressive and anxious comorbid pathology, to use flexible dosage and to have a long observation period (24 weeks), which is important when evaluating the effect of an antidepressant drug.

The results obtained indicate that treatment with venlafaxine hydrochloride significantly improved the clinical situation of climacteric patients with anxious or depressive disorder, improving the anxious, depressive and climacteric symptoms. This is consistent with the data of previous studies obtained in postmenopausal depressive patients. If this were to be confirmed by placebo-controlled trials, these results would support the utility of venlafaxine hydrochloride in psychophysical malaise conditions of patients who are initiating or are currently changing to the menopausal condition, above all if they also have anxious or depressive disorder.

In the present study, the mean dose of venlafaxine was above 150 mg/day, requiring doses of up to 450 mg/d (higher than that used in the previous clinical trials and naturalistic studies), without increasing the level of adverse effects. In the naturalistic studies, the serious adverse effects are practically nonexistent, some mild ones (dry mouth, appetite alteration) and moderate (abdominal discomfort, insomnia, headaches or sexual dysfunction) appear with a higher frequency (between 30% and 60%).<sup>14</sup> In our case, the low prevalence of adverse effects (11.1%) stands out. The possibility that the adverse effects may be confounded with climacteric symptoms<sup>12</sup> may have resulted in the fact that fewer are reported since the climacteric symptoms are collected by means of a specific scale.

In spite of its limitations, the present study confirms the previous data of effectivity of venlafaxine hydrochloride in climacteric patients. It extends some aspects related with the clinical condition, drug doses, and duration of the evaluation and increases the rationale for the conduction of more rigorous investigations aimed at formulating the best

treatment of these psychic syndromes that appear associated to climacteric symptoms.

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