Comparison of the effectiveness of venlafaxine in peri- and postmenopausal patients with major depressive disorder

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Introduction: This study examines the difference in the efficacy and tolerability of a norepinephrine and serotonin reuptake inhibitor (NERI) antidepressant on the physical and psychological symptoms of climacteric patients diagnosed of major depressive disorder, comparing the therapeutic response between perimenopausal and postmenopausal patients.

Methods: A 24-week observational, prospective, open-label, multicenter study was made. The sample consisted of women between 45 and 55 years, diagnosed of major depressive disorder who were treated as outpatients. The study drug was venlafaxine extended release at doses according to the investigator's clinical criteria. Efficacy regarding depressive symptoms was evaluated by repeated measures of the values obtained with the scales: Hamilton Depression Rating Scale and Blatt-Kupperman Menopausal Index.

Results: 36 depressed women were enrolled in the study and 35 completed it. The patients' ages ranged from 47 to 55 years old (mean 50.8 years). Throughout the 24 weeks of the study, significant clinical improvement in depressive and hormonal symptoms was seen. The comparison of the pattern of improvement, according to the menstrual status of the patients, showed no significant differences between pre- and postmenopausal patients. Perimenopausal women reported a higher rate of adverse events.

Conclusion: V-XR was effective in treating depressive and hormonal symptoms regardless of the menstrual status of climacteric patients with a slightly worse tolerance in perimenopause women.

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Key words:
Depression, menopause, climacteric, venlafaxine extended release, women.

Comparación de la efectividad de venlafaxina en pacientes deprimidas peri y postmenopáusicas

Introducción: el presente trabajo estudia la diferencia en la eficacia y tolerabilidad de un antidepresivo inhibidor de la recaptación de noradrenalina y serotonina –IRNS- sobre los síntomas psico-físicos de pacientes climatéricas con trastorno depresivo mayor, comparando la respuesta del grupo de pacientes perimenopáusicas con la de las postmenopáusicas.

Metodología: Estudio observacional, prospectivo, abierto y multicéntrico. Se estudió una muestra de mujeres entre 45 y 55 años, diagnosticadas de trastorno depresivo mayor, y tratadas ambulatoriamente. Como fármaco de estudio se utilizó la Venlafaxina clorhidrato a las dosis consideradas adecuadas por el investigador. La eficacia sobre los síntomas depresivos se valoró mediante medidas repetidas de los valores obtenidos en la escala de Hamilton de Depresión (Ham-D) y la valoración de los síntomas menopáusicos mediante la administración del Índice Menopáusico de Blatt-Kupperman (IMB).

Resultados: iniciaron el estudio 36 mujeres de las que 35 finalizaron el mismo. El rango de edad fue de 47 a 55 años y la media de 50,8 años. Durante las 24 semanas de duración del estudio, se observó una mejoría clínica significativa, tanto en los síntomas depresivos como en

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los climatéricos. Cuando se comparó el patrón de mejoría según la situación menstrual de las pacientes no se observaron diferencias significativas entre las pacientes perimenopáusicas y postmenopáusicas. La única diferencia encontrada fue una tasa de efectos adversos mayor en las perimenopáusicas.

Conclusión: La Venlafaxina fue eficaz en el tratamiento de síntomas depresivos y climatéricos independientemente de la situación menstrual de las pacientes con una tolerancia ligeramente peor en perimenopáusicas.

Palabras clave:
Depresión, menopausia, climaterio, Venlafaxina, mujer

INTRODUCTION

Menopause is defined as "the permanent cessation of menstruation due to loss of ovarian follicular activity." Perimenopause includes a period immediately prior to menopause and the year following it. The term climacteric is more non-specific than the previous and includes the menopausal transition and a non-specified period after the menstrual period.[1] Climacteric is a period in the life of the woman with different stages marked by hormone changes that go from great variability in the levels of reproductive hormones in perimenopause,[2] to estrogen deprivation characteristic of the post-menopausal condition. The hormonal changes (decrease of estradiol and hypogonadism) produce dynamic alterations in both the reproductive and non-reproductive tissues that are associated with alterations in the psycho-physical health status of women.[3-6] Although there is some degree of controversy, it is assumed that perimenopause is a period in the life of the women with high depressive vulnerability.[7]

Clinical investigations have shown that there is an association between reproductive hormones and response to antidepressants, so that the modifications in the reproductive hormone levels induce acute deterioration of the depressive conditions and decrease the efficacy of antidepressant treatments.[7-10] The persistence of residual symptoms after a treatment with selective serotonin reuptake inhibitors (SSRI) is significantly more frequent in postmenopausal women,[11, 12] and estrogens at low doses may potentiate the effect of the SSRIs in depressed perimenopausal women.[13, 14] The involvement of estrogens in the physiological modifications produced on the central nervous system and the interactions existing between the reproductive hormones and the principal neurotransmission systems[15] could at least partially explain this dissociation.

Most of the efficacy data on antidepressants for the treatment of depressive disorders in climacteric women are focused on the postmenopausal period, there being little data regarding the perimenopausal one.[16-18] Only one study has evaluated the impact of the "menopausal status" on response to an SSRI[11] and another study that has used fluvoxamine (SSRI) and milnacipran (antidepressant serotonin norepinephrine uptake inhibitor - SNRI) compares the antidepressive effectiveness of both products between a group of women under 45 years and another group equal or older than 45 years.[19]

The present work studies the difference in efficacy and tolerability of venlafaxine extended-release (V-XR), a SNRI antidepressant, on the psycho-physical symptoms of climacteric patients with major depressive disorder, comparing the therapeutic response in peri- and postmenopausal patients.

MATERIAL AND METHODS

This is a 24-week observational, prospective, open label and multicenter study. The study was approved by the reference Hospital Ethics Committee, there being no external financing for its conduction. Women receiving outpatient psychiatric treatment who complied with the following criteria were included: being between 45 and 55 years of age, having menstrual irregularities or having had their last menstrual period within the last 5 years and having a score greater than 15 on the "Blatt-Kupperman Menopausal Index" (BKMI) scale.[20] Other inclusion criteria were: having a clinical diagnosis of depressive disorder according to the DSM-IV which, in the opinion of the investigator, could benefit from treatment with V-XR, not having taken any antidepressant during the last month, not being treated with hormone replacement therapy, not having had any modifications in any other of the central treatments received in the 3 months prior to inclusion. Exclusion criteria were considered as: pregnancy or lactation, menstrual disorders due to non-physiological causes, psychotherapy initiated in the last 3 months, severe physical or mental diseases, risk of suicide and previous treatment or intolerability known to V-XR.

After enrollment, treatment was begun with V-XR, open labeled style, according to the recommended dose on the data sheet. The dose could be modified according to the criterion of the investigator at any time in the study. Evaluations were conducted in the initial visit (the day in which treatment with V-XR was initiated) and at weeks 12 and 24 of the study. The results were measured with the Hamilton Depression scale ($Ham\text{-}D_{17}$) [21, 22] and the BKMI. A systematic evaluation was made of the side effects at each study visit by means of collection and evaluation of the adverse events reported and the withdrawals or dropouts from the study.

All the patients who, having met the inclusions/exclusions criteria, had signed the informed consent and

Table 1 Evolution of the clinical condition of depressed climacteric patients (n=36), evaluated with the BKMI and HamD$_{17}$ scale

	BKMI		Ham-D$_{17}$	
Score	Mean	CI (95%)	Mean	CI (95%)
Baseline	27.31	24.3-30.2	22.0	19.0-24.9
Month 3	16.34	13.7-18.9	9.7	7.9-11.6
Month 6	12.34	9.7-14.9	7.02	5.4-8.5

Table 2 Descriptive statistics in the comparison of means of symptomatic level in the different evaluations according to the scorer of: Blatt Kuppermann Menopausal Index (BKMI) and Hamilton Depression scale (Ham-D$_{17}$)

	Postmenopausal (n=23)		Perimenopausal (n=13)		
	Mean	CI (95%)	Mean	CI (95%)	P
	Score on the Blatt-Kupperman Menopausal Index				
Baseline	29.82	25.7-33.9	22.92	20.4-25.3	0.018
Month 3	18.09	14.3-21.8	13.38	10.6-16.1	0.072
Month 6	13.0	9.2-16.7	11.23	8-14.4	0.5
	Scores on the Ham-D$_{17}$ scale				
Baseline	23.00	19.1-26.8	19.62	15-24.2	0.26
Month 3	10.31	7.8-12.7	8.84	5.6-12.0	0.44
Month 6	6.86	5.0-8.6	7.30	4-10.5	0.78

had received at least one dose of the study medication, were included in the statistical analyses by intention to treat. Descriptive data for all the variables, both qualitative (absolute and relative frequencies) as well as quantitative (mean, standard deviation and confidence intervals if they followed a normal distribution or, in the contrary, median, minimum, maximum and interquartile range) were obtained. The analysis of the evolution of the score on the evaluation scales at different points in time was conducted using the one-way (time) repeated measurement ANOVA with 3 levels (baseline visit, month 3 and month 6) and two dependent variables (BKMI and Ham-D$_{17}$ scores). The SPSS 12.0 for Windows (SPSS Inc) statistical program was used.

RESULTS

Of the 36 patients included in the study, 35 (97.2%) completed it. One female patient was withdrawn due to loss to follow-up. Age range of the participants was 47 to 55 years, with medium of 50 years and mean 50.83 years (95% CI=[50.03-51.63]). A total of 86.1% lived with their own family, and 55.6% dedicated their time to housework. Regarding their medical history, 14 patients (51.9%) stated they had no significant physical problem and 23 (63.9%) had had no mental problems prior to the current depressive episode. Thirteen patients (36.1%) were in the premenopausal period and 23 patients (63.9%) in the postmenopausal one (their last period had been more than one year prior to enrolment in the study). Mean time from the last menstruation in the menopausal patients was 2.3 years (SD = 1.86; range= 1-8 years) and mean time after initiation of menstrual irregularities in the perimenopausic was 1.91 years (SD=1.88; range= 4 months-7 years). Five patients (13.9%) had been treated for the current episode with SSRI antidepressants, which had been withdrawn due to lack of efficacy at some point of the evolution more than one month prior to enrollment in the study. This information was obtained by the investigators retrospectively based on the notes in the clinical history. Use of benzodiazepines was permitted. Their use decreased significantly (chi^2= 13.2; p=0.001) from the onset of the study, at which time they were taken by 25 patients (69.4%), until its completion when 21 patients (58.3%) took them. Mean doses of V-XR used were: 139.2 mg/d (SD=51.9) in the initial visit, 163.2 mg/d (SD=91.3) at month 3 and 167.6 mg/d at month 6. Although the doses used in perimenopausal patients were greater than

those used in postmenopausal ones, the differences were not statistically significant.

The evolution of the primary efficacy variables (Ham-D_{17} and BKMI) in the complete group of patients studied can be seen in Table 1. Table 2 and Figures 1 and 2 show the comparative data of the peri- and post-menopausal patients. Post-menopausal women had a significantly higher score of hormone symptoms (BKMI) at the onset and middle phase of the study then the peri-menopausal patients ($p<0.038$). Regarding the depressive symptoms, the differences between both groups were not statistically significant. During the 24 weeks of the study, a specific clinical improvement in the significant decrease of the scores of both scales used was observed. In this way, the scores for visit 2 were significantly lower than the baseline and the scores of visit 3 were significantly lower than those of visit 2 (Table 3). When the improvement pattern was compared according to menopausal status, no significant differences were observed between the 2 groups studied.

Four patients (11.1%) reported adverse events (3 having mild intensity and one moderate, that were: decreased libido (n=1), constipation (n=1), exanthema (n=1) and nausea (n=1). The proportion of adverse events was significantly different according to the menstrual status of the patients (p=0.005). Thus, while the adverse event rate in the group of postmenopausal women was 0%, it was 30.8% in the perimenopausal group.

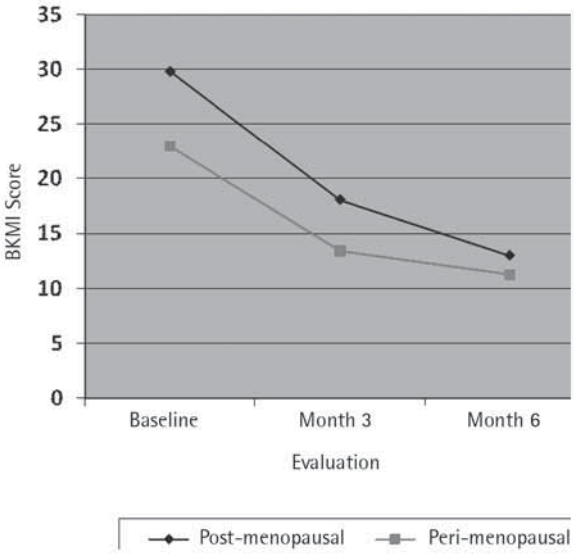

Figure 1 Profile of the clinical situation, measured with the BKMI in the 3 study evaluation periods, separating the patients according to menstrual status

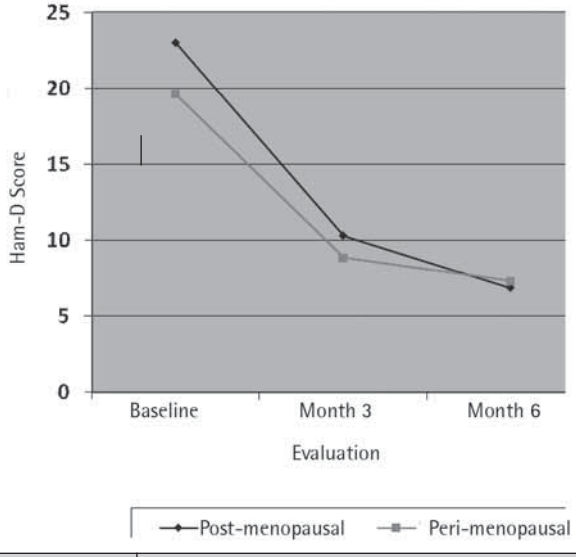

Figure 2 Profile of the clinical situation, and measured with the Ham-D17 in this 3 study evaluation periods, separating the patients according to menstrual status

DISCUSSION

The characteristics of our sample coincide with most of the previous data in regards to climacteric symptoms,[9, 23, 24] since the postmenopausal women on enrollment had more climacteric symptoms than the perimenopausal ones. However, contrary to what could be expected, we did not find any differences in the intensity of the depressive symptoms. This poses the question of the possibility of biases in the sample, which may be due to: age range included, the small sample size and lack of control on aspects that could influence the general clinical conditions such as social situation, styles of life, and intensity of the vasomotor symptoms.[4, 10]

In regards to efficacy, we did not find differences in the response pattern to V-XR in perimenopausal patients compared with postmenopausal ones or in the hormone or affective symptoms. Although the results of the previous studies do not coincide totally, the data suggest that selective serotoninergic antidepressants would lose effectiveness after the hormonal changes that take place in climacteric women,[25, 26] it being necessary to use an estrogen supplement to maintain the level of efficacy obtained in premenopausal women.[27, 28] The rationale for this fact would be provided by the data from the *in vivo* and *in vitro* studies on the reciprocal relationship between estrogens and serotoninergic neurotransmission.[29] Estrogens increase the tryptophan-hydroxylase production[30] (limiting enzyme for serotonin production from the tryptophan), increasing the serotonin concentration,[31] and they also inhibit the serotonin

Table 3 Two-sided comparisons of the symptom level using the BKMI, HAM-D_{17} scales in different evaluations

Evaluation	Comparison evaluation	Difference between means	Standard error	p
BKMI				
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
Ham-D_{17}				
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

transporter gene expression (SERT), increasing the time for which serotonin is available in the synapsis and interstitial spaces.[32]

Regarding the SNRI antidepressants, they have shown a lower dependence on hormone aspects. Similar efficacy has been demonstrated in men and women.[33] In addition, when the treatments are specifically studied in women, data are found that suggest that the antidepressant efficacy of the SNRIs is maintained independently of the menopausal status,[19] also showing effectiveness in the treatment of the vasomotor symptoms associated to menopause.[34, 35] The explanation for this differential fact is not easy, since the estrogens increase the activity of norepinephrine in the brain, by means of decrease of the reuptake and inhibition of the MAO and COMT enzymes.[36] However, it can be hypothesized that the decrease in efficacy of the noradrenergic agents produced by the hypoestrogenism would be less than that of the serotoninergic antidepressants because, on the contrary to that which occurs with serotonin, the estrogens only potentiate the noradrenergic action through the inhibition of the reuptake and metabolism of norepinephrine, without affecting their production, while in the case of serotonin, estrogens affect both metabolism and production.

The worst tolerance found by us in perimenopausal women coincides with data in a previous study in which imipramine was used and could be due to the situation of hormonal fluctuations produced during this period.[25] This circumstance has clinical implications, due to the high rate of dropouts from antidepressive treatment and should lead us to consider perimenopausal women as the risk group in which measures should be increased to prevent adverse effects. However, the tolerability data should be evaluated carefully for the possibility that the adverse effects would be confused with climacteric symptoms.[37]

The present study has methodological limitations because of its open label character and lack of control group. Added to this is the impossibility of controlling the effects of the passage of time that may be a factor which, by itself, modifies the symptoms being studied,[38] and the exclusively clinical evaluation of the adverse effects. The use of clinical criteria for the diagnoses of menopause would be justified by the nonspecificity of the laboratory tests available.[6, 39]

In conclusion, the present work shows that V-XR is effective in treatment both for depressive symptoms as well as vasomotor ones in climacteric patients diagnosed with major depressive disorder. No differences were found in the pattern of efficacy based on menstrual status (peri- or postmenopausal). The data also revealed that tolerability, being good in both groups, was worse in perimenopausal patients.

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