Quality of life, in depressed patients in Primary Health Care setting. Effectiveness and safety of venlafaxine extended release

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Calidad de vida en pacientes con depresión tratados en Atención Primaria. Efectividad y seguridad de la venlafaxina retard

Summary

Introduction. *The aim of this observational study was to evaluate effectiveness, tolerability and impact on quality of life of treatment with venlafaxine extended release at a dose of 75 to 150 mg/day, in depressed outpatients treated in Primary Health Care.*

Methods. *Observational, prospective, open-labeled study, carried out by 882 Primary Health Care physicians. Outpatients, between 18 and 70 years of age with depressive symptomatology susceptible of treatment, with a Hamilton Depression Scale (HAM-D_{17}) score ≥ 14 were included. Daily doses of 75 or 150 mg of venlafaxine extended release were administered orally for 24 weeks. Antidepressant effectiveness was assessed using the HAM-D_{17} scale and quality of life with the Quality of Life in Depression Scale (QLDS), Spanish version.*

Results. *4,747 patients were recruited, of which 4,320 were included in a intention to treat effectiveness analysis and 4,557 patients in a safety analysis. HAM-D_{17} and QLDS mean score significantly decreased from week 4 to the end of study. 86,2% of the patients were responders and 73.8% achieved remission of the symptoms. Likewise, 95% reported absence or mild somatic and psychic anxiety on the final visit. Tolerability was considered good or excellent for 98.7% subjects. 191 patients (4.2%) reported adverse events.*

Conclusions. *Venlafaxine extended release is a safe and effective drug that reduces depressive symptoms of Primary Health Care patients and improves their quality of life.*

Key words: *Depression. Quality of life. Venlafaxine extended release. Primary Care. Observational study.*

Resumen

Introducción. *Los objetivos del estudio observacional han sido evaluar la efectividad, tolerabilidad y el impacto sobre la calidad de vida del tratamiento con venlafaxina retard a dosis de 75 a 150 mg/día en pacientes ambulatorios con depresión tratados en Atención Primaria.*

Métodos. *Estudio abierto, observacional, prospectivo, realizado por 882 médicos de Atención Primaria. Se incluyeron pacientes con edad entre 18 y 70 años y sintomatología depresiva susceptible de tratamiento, con una puntuación mínima en la Escala de Hamilton para la depresión con 17 ítems (HAM-D_{17}) de 14. La venlafaxina retard se administró a dosis de 75 o 150 mg/día durante 24 semanas. La efectividad antidepresiva se evaluó mediante la HAM-D_{17} y la calidad de vida mediante la Escala de calidad de vida de depresión (ECVD) validada, versión española.*

Resultados. *Se incluyeron 4.747 pacientes, de los cuales 4.320 pacientes fueron evaluables por intención de tratar para efectividad y 4.557 para seguridad. Se redujeron significativamente la puntuación media de la HAM-D_{17} y la de la ECVD desde la cuarta semana hasta el final del estudio. El 86,2 % de los pacientes mostró respuesta y un 73,8 % presentó remisión de los síntomas. Asimismo, el 95% mostró ausencia de ansiedad o ansiedad ligera, tanto somática como psíquica, en la visita final. La tolerancia fue considerada buena o excelente en el 98,7% de los sujetos. Ciento noventa y un pacientes (4,2%) presentaron algún acontecimiento adverso.*

Conclusiones. *La venlafaxina retard es un fármaco efectivo y seguro que reduce los síntomas depresivos de pacientes tratados en Atención Primaria y mejora su calidad de vida.*

Palabras clave: *Depresión. Calidad de vida. Venlafaxina retard. Atención Primaria. Estudio observacional.*

INTRODUCTION

At present, there are different drugs available for the treatment of depression in the medical armamentarium of primary health care (PHC), among them venlafaxine extended release. This is an appropriate agent, due to its pharmocokinetic and pharmacodynamic characteristics, for single daily administration[1,2], and has been shown to be an effective and safe antidepressant in the treatment

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of different psychiatric disorders in different studies[3-7]. venlafaxine extended release has demonstrated its efficacy in depressive disorder[8,9], in generalized anxiety disorder (GAD)[10,11], in depression with GAD[12] and in depression with associated symptoms of anxiety[13-15].

On the other hand, in recent times, growing interest has been observed in the evaluation of quality of life related with health (QLRH), especially in patients with chronic diseases[16]. Quality of life can be defined as the subjective evaluation by the person of their vital situation or, alternatively, as the «goodness of life» measured objectively or subjectively[17]. At present, QLRH is reflected in an extension of the treatment goals of prolonging life, relieving disease symptoms and maximizing satisfaction of the individual for life[18]. The quality of life of the patient is a parameter having incalculable value, since it gathers the point of view of the patient and provides help in the assessment of the real clinical utility of a drug. In our setting, the McKenna et al. quality of life of depression scale (QLDS) for patients with depressive symptoms, whose cultural adaptation process was performed by Cervera et al. in 1999, was validated recently[19]. This scale is simple and easy to administer in any health care level, including that of Primary Health Care, thus enabling it to be introduced routinely, both in the common medical practice as well as in observational studies, besides in traditional clinical trials, in which it is aimed to assess the impact of existing antidepressive pharmacotherapy on the quality of life of the patient with depressive disorders.

Although there are long duration open studies in which the safety of this antidepressant agent has been assessed in the long term[4], even on the primary health care level[20], in our setting, there are no observational studies having sufficient duration, which, besides assessing effectiveness and tolerability of venlafaxine extended release in a wide sample of patients, evaluate the impact of the therapy with this drug on the quality of life of the patient with depressive disorders in common medical practice conditions in the primary health care level.

For these reasons, the main objectives of this study have been to make an observational assessment of effectiveness and tolerability of oral treatment with venlafaxine extended release, at a dose of 75 to 150 mg/day, in out-patients with depression treated in primary health care. Furthermore, the impact of the drug treatment on the quality of life of these patients has been evaluated. The observational character of the study has made it possible, on the other hand, to analyze the results obtained from a naturist perspective, given that the follow-up was proposed in agreement with the way it is generally performed in the primary health care setting.

METHODS

Open, observational, prospective, multicenter study performed by 882 PHC physicians from the entire national territory, during the years 2000 to 2001 to evaluate effectiveness, tolerability and impact on the quality of life of the administration of venlafaxine extended release in out-patients with depressive symptoms diagnosed in PHC. Given the expected variability of response on the Hamilton depression rating scale (HAM-D_{17}) and on the quality of life of depression scale, validated in Spanish (QLDS) as well as the possible loss to follow-up of patients during the study, an enrollment of approximately 5,000 patients was established to guarantee that the size of the sample would be evaluable.

Patients were included according to the following inclusion criteria: out-patients of both genders with depressive signs and symptoms susceptible to treatment according to clinical observation and age ranging from 18 to 70 years; a minimum score of 14 on the HAM-D_{17} scale; negative beta-HCG pregnancy test before entering in the study, use of adequate contraceptive protection in the case of childbearing aged women; and written informed consent of the patient. The following exclusion criteria for the study were considered: previous treatment without success of venlafaxine or venlafaxine extended release; participation in another clinical study within the 3 months prior to the onset of this study; known hypersensitivity to venlafaxine; convulsive disorders other than a simple febrile convulsive episode in childhood; any mental disorder due to general medication; suicidal ideas that require establishment of preventive measures; having suffered myocardial infarction in the 6 months prior to the onset of the study; disorders in the cardiac rhythm or conduction; mania or any psychotic disorder not associated to depression; organic mental disorders, hepatic or renal diseases that are clinically relevant that could affect the study or that could be harmful for the patient; drug or alcohol dependence in the last year, as defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV); pregnant women or those who are breast-feeding; positivity for human immunodeficiency virus (HIV) or hepatitis B virus infection; clinically relevant abnormalities at the onset of the study; uncontrolled hypertension, with or without drug treatment; use of any investigational drug, antipsychotic drugs, electroconvulsive therapy (ECT) or sumatriptan, in the 30 days prior to the onset of the screening; use of monoamine-oxidase inhibitors or Hypericum Perforatum in the 14 days prior to enrollment; anxiolytic drugs or sedative/hypnotic agents (except lorazepam or oxazepam) in the 7 days prior to the baseline visit and use of any non-psychodrug in the 7 days prior to the baseline visit which, according to the investigator's opinion, could have psychotropic effects, unless the dose has remained stable for at least 30 days prior to the baseline visit.

Venlafaxine extended release was administered at the dose of 75 mg/day, it being possible to increase this dose to 15 mg/day according to the opinion of each participating investigator. As concomitant treatments, the use of up to 4 mg/day of lorazepam, or up to 30 mg/day of oxacepam as well as psychotherapy in case of being established prior to the study, were permitted. Treatment duration with venlafaxine extended release was continued for 24 weeks.

Evaluation of the evolution of the depressive symptoms was performed with the 17 item Hamilton depres-

sion rating scale (HAM-D_{17}) and the quality of life for depression scale, validated Spanish version (QLDS), was used for the assessment of antidepressive treatment on the quality of life. These scales were performed on the initial visit and at 4, 8, and 24 weeks of treatment. Assessment of the state of the patient by the physician was also used in all the patients as an additional measure of effectiveness of the study treatment. Treatment effectiveness parameters were considered to be response to treatment (considering a reduction greater than or equal to 50% in the symptoms score of the HAM-D_{17} scale as positive response) and the proportion of patients in whom remission of the symptoms occurred (score on the HAM-D_{17} scale $\leqq 7$). In addition, specific evaluation was made of the responses to items 10, 11 and 13 of the HAM-D_{17} scale to determine the effect of the treatment on psychic anxiety, somatic anxiety and somatic symptoms, respectively of the patients. Furthermore, variation in the QLDS scale and in the assessment of the patient's condition was determined by the physician in each one of the study visits. In addition, safety of the study treatment was analyzed by the monitoring of the possible adverse reactions in all the follow-up visits; intensity was assessed as mild (it does not require treatment or drug withdrawal), moderate (it is very uncomfortable and may require treatment, but does not require drug withdrawal), serious (it is not controlled with treatment, requiring the withdrawal of the drug) and very serious (it requires drug withdrawal and use of emergency treatment, with or without hospitalization). The number and cause of the treatment withdrawals were counted.

The study was performed at all times in agreement with the existing guidelines for post-authorization observational studies and international rules for clinical studies in humans were respected (Helsinki Declaration and other rules in force). In agreement with the good clinical practice (GCP) rules, telephone monitoring of the study was performed for all the participating centers and in real presence in 5% of the centers, carrying out a specific follow-up at all times of the possible adverse events to establish their intensity, severity and causal relationship with the study treatment.

Statistical methodology

The study endpoints were described using the mean and standard deviation for numeric endpoints and absolute and relative frequencies, in percentages, for the categorical endpoints (nominal or ordinal). Evolution during the study was evaluated by the variance analysis (ANOVA) for repeated measurements, using the Student's *t* test for comparison of subgroups (gender, etc.). The relationship between nominal and ordinal endpoints was established by means of the Pearson's association test or the Fisher's exact test. Correlation between the score on the quality of life scale and the HAM-D_{17} scale score was evaluated with the Spearman correlation index. All the contrasts were bilateral, considering values of $p \leq 0.05$ as significant. All the tests were performed with the SPSS v. 9.0 statistical program.

RESULTS

A total of 4,747 patients were selected. Of all the patients, 190 (4%) were excluded from the study: 122 (2.6%) because they exceeded the maximum age established and 68 (1.4%) because their score was below 14 on the HAM-D_{17}. Two hundred thirty seven (5.2%) withdrew from the study after the inclusion visit. Safety analysis was performed on 4,557 patients (95.9%; the totality of the subjects initially enrolled except for those who presented some reason for exclusion). Although 3,716 patients completed the study (after the withdrawal of 157 patients after the 4th week and 447 after the 8th week), the statistical evaluation of efficacy was performed on a sample of 4,320 patients (91%).

Table 1 summarizes the main demographic and clinical characteristics of the patients included in the study. Mean age of the patients was 49 ± 12 years and age range went from 18 to 70 years; age median was 50 years. The

TABLE 1. Demographic and clinical characteristics of the patients included in the study before initiating treatment with venlafaxine extended release

Endpoint	*Venlafaxine extended release (n = 4,320)*
Age (years)	
Mean ± SD	49 ± 12*
Median	50
Range	18-70
Gender (women)	71.2%
Weight (kg)	70.1 ± 14.1*
BMI (kg/m^2)	25.8 ± 3.9*
SBP (mmHg)	131 ± 14.9*
DBP (mmHg)	78.1 ± 9.1*
HR (beat/min)	75.5 ± 8.2*
Score on HAM-D_{17} score	
Mean ± SD	21.6 ± 5.1*
Median	21
Range	14-52
Psychiatric anxiety (question 10)	Median: 2
Somatic anxiety (question 11)	Median: 2
Quality of life scale	24.8 ± 6.5
Overall assessment of the physician	
Excellent	0.1%
Very good	0.7%
Good	8.4%
Fair	46.7%
Bad	39.1%
Unstable	4.9%
Initial dose venlafaxine extended release	
75 mg	95.8%
150 mg	4.2%

*Values expressed as mean ± standard deviation. BMI: body mass index; SD: standard deviation; SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate; HAM-D_{17}: 17 item Hamilton depression rating scale.

proportion of women in the sample (71.2 %) exceeded that of men (28.8 %) by more than twofold. A total of 38.5 % of the patients reported some concomitant disease and 48.1 % took some medication for the concomitant disease or for the treatment of their depressive disorder. The most frequent concomitant diseases were: arterial hypertension (493 patients; 11.4 % of all the cases), arthrosis (291 patients; 6.7 % of all the cases), dyslipidemias (233 patients; 5.4 % of all the cases) and diabetes mellitus (161 patients; 3.7 % of all the cases). Mean age of the patients with concomitant diseases was significantly greater than in those who did not present them (54.7 ± 11.5 vs 45.4 ± 11.4, respectively; $p < 0.0001$). The proportion of women with concomitant diseases was slightly greater than that of men, although statistically significant (39.6 % vs 35.7 %, respectively; $p = 0.016$) (data not shown). The patients presented depressive symptoms susceptible to drug treatment according to clinical observation, with a mean baseline score on the HAM-D_{17} scale of 22 ± 5 points (minimum of 14 points and maximum of 52 points) and a median of 21 points. A total of 95.8 % of the patients initiated treatment with venlafaxine extended release at a dose of 75 mg/day and the remaining 4.1 % required a dose of 150 mg/day. Those patients who initiated treatment with the higher dose showed a greater score on the HAM-D_{17} depression rating scale on the baseline visit (data not shown).

Treatment with venlafaxine extended release significantly reduced the score on the HAM-D17 depression rating scale in each one of the study visits in relationship to each preceding visit (fig. 1). A total of 86.2 % of the patients showed an antidepressive response to treatment (reduction ≥ 50 % of the score on the HAM-D17 scale in the baseline visit) and 73.8 % presented remission of the depressive symptoms (HAM-$D_{17} \leq 7$) at the end of the 24 week study follow-up (table 2). The percentage of patients who showed antidepressive response or remission of the depressive symptoms increased significantly after the 4th week, in comparison with the weeks of previous treatment. These increases were independent of the presence or absence of concomitant diseases, although the patients with concomitant diseases showed significantly greater mean scores than those that did not present them during the study, although without clinical relevance (data not shown). When the score of the item 10 questions (psychic anxiety) and item 11 ones (somatic anxiety) on the HAM-D_{17} scale was specifically analyzed, a progressive and statistically significant evolution was observed during the study, reaching absence of anxiety or mild anxiety (figs. 2 and 3, respectively). While 67.8 % of the patients reported «moderate», «intense» or «extreme» psychic anxiety and 60.9 % of the patients reported «moderate», «intense» or «extreme» grade somatic anxiety in the baseline visit, 95 % of the patients showed absence of anxiety or mild anxiety, both somatically as well as psychically, at week 24 of treatment. In regards to the score on question 13 (general somatic symptoms, with reference to fatigability, limb heaviness, back, head and muscle pain, among others) in the HAM-D_{17} scale, a significant reduction was observed in the score from the first visit, while 71.5 % of the patients scored as «mild» and 22.3 % as «intense» in the first visit, 66.1 % of the patients scored

TABLE 2. Rate (%) of patients who reach positive response (decrease ≥ 50 % of the HAM-D_{17} scale score) and remission of depressive symptoms (HAM-D_{17} scale score ≤ 7 pts) according to week of treatment

	Treatment week		
	4	*8*	*24*
Response (↓ ≥ 50% HAM-D_{17})	26.9 %	70.8%*	86.2%*
Remission (HAM-$D_{17} \leq 7$ pts)	11.7 %	47.8%*	73.8%*

* $p < 0.0001$ regarding the previous week of treatment. Mcnemar and Cochran test.

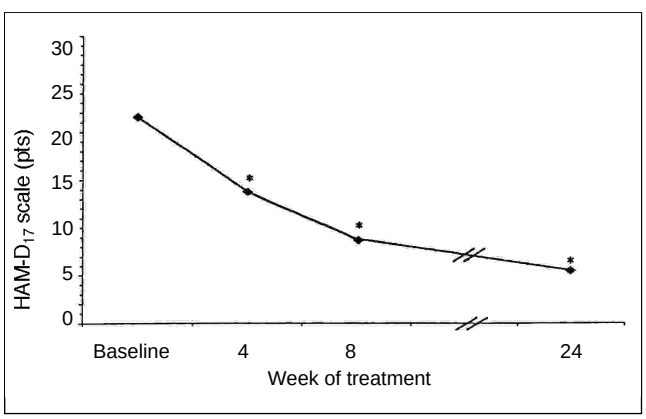

Figure 1. Evolution of mean score on the HAM-D_{17} scale during treatment with venlafaxine extended release. * $p < 0.0001$ regarding previous visit. Analysis of variance for repeated series (ANOVA).

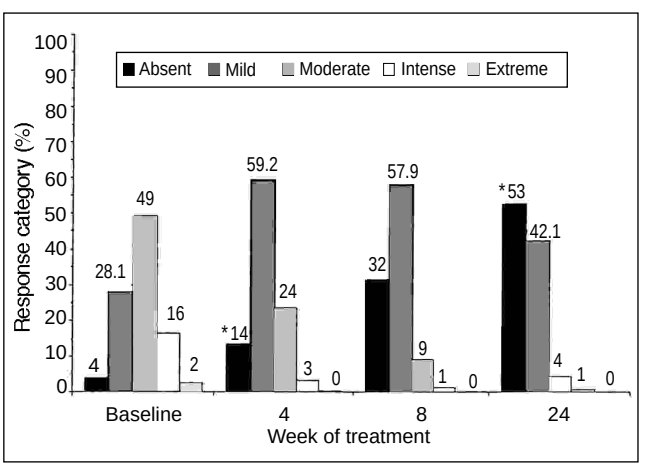

Figure 2. Evolution of the response to question 10 on the HAM-D_{17} scale (psychic anxiety) during the treatment with venlafaxine extended release. Values expressed as percentage of each response category. * $p < 0.0001$ regarding previous visit. Friedman test.

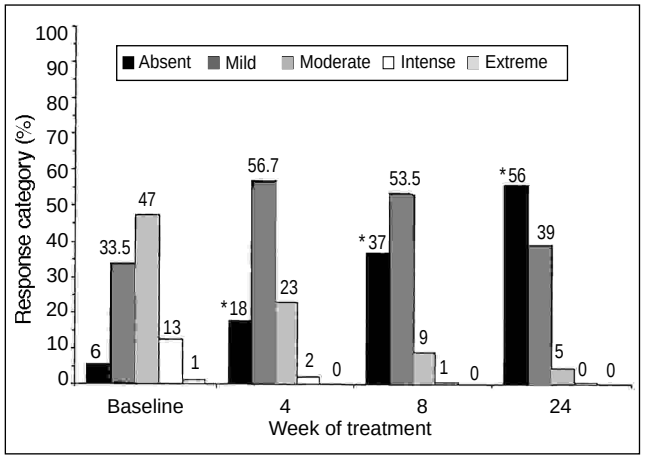

Figure 3. Evolution of the response to question 11 of the HAM-D_{17} scale (somatic anxiety) during the treatment with venlafaxine extended release. Values expressed as percentage of each response category. * $p < 0.0001$ regarding the previous visit. Friedman test.

as «absent» and 32.5 % as «mild» (data not shown) on the 4th visit.

On evaluating the effect of treatment with venlafaxine extended release in the mean score of the quality of life depression scale (QLDS), according to which a greater score is equivalent to greater negative impact on the quality of life, a significant reduction was observed in the score from the 4th week of treatment until the end of the study at 24 weeks (fig. 4). This reduction was independent of the presence or absence of concomitant diseases, although the patients with concomitant diseases showed significantly greater mean scores during the study ($p \leq 0.0001$ for visits 2, 3 and 4, there being no significant difference in visit 1) to those who did not present them, although without clinical relevance (data not shown). In the same sense, the medical assessment of the patient's condition during the treatment with venlafaxine extended release significantly improved during the study. While the patient's condition was considered as fair, bad or unstable in 91 % of the patients at the onset of the study, only 3% of them were classified in one of these categories on the final visit (data not shown). Thus, the physician considered the result of treatment in the final visit (week 24) as satisfactory in 87.3 % of the patients, acceptable in 12.4 % and null in 0.3% of the cases (data not shown).

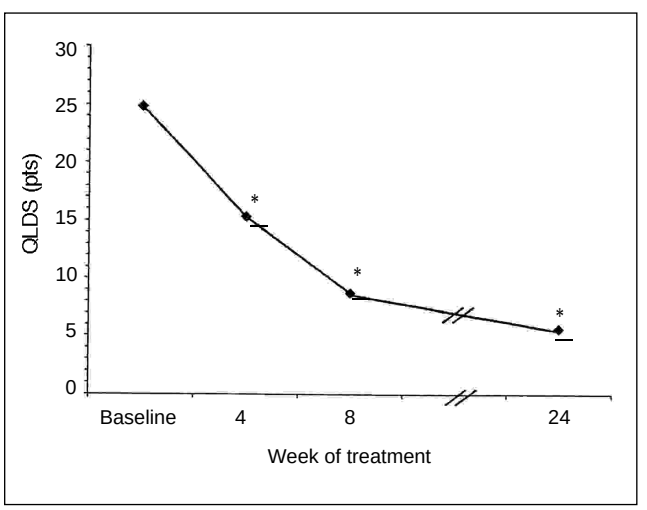

Figure 4. Evolution of the mean score on the QLDS during treatment with venlafaxine extended release, in all the patients. * $p < 0.0001$ in regards to previous visit. Analysis of variance for repeated series and Friedman test.

Treatment with venlafaxine extended release in week 24 did not cause clinically relevant changes in the endpoints analyzed in the physical examination, such as weight, body mass index, systolic and diastolic blood pressure (table 3) and heart rate, in comparison with the baseline data reported in table 1 (data not shown). In the final visit, 87 % of the patients received 75 mg/d of venlafaxine extended release.

A total of 12.7 % of the patients (550 patients) withdrew from treatment during the study; and treatment was discontinued in 1.3 % (54 patients) during the study. The causes of withdrawal or discontinuation were: 10.8 % due to loss to follow-up (467 patients); 0.1 % due to inefficacy (for patients), 1.1 % due to adverse events (46 patients), 0.2 % due to disease or another reason that justifies the withdrawal (seven patients), 0.6 % due to non-compliance with the treatment plan (25 patients) and finally 1.3 % due to other reasons (55 patients).

In the safety analysis, 191 patients (4.2%) presented some adverse event, whose intensity was considered «mild» in 38.9% of the cases, «moderate» in 50% and «severe» in 11.1%. A total of 3.5% of the events was not related with the treatment, in 8%, the relationship was considered "improbable," and in the rest «possible» or «probable». Temporary withdrawal of treatment was considered necessary in 53% of the cases. On the other hand, 25% of the adverse events required treatment, that was followed by «complete recovery» in 56% of the cases. The adverse events are summarized in table 4. Only 7 of the 321 adverse events reported were considered

TABLE 3. Evolution of systolic and diastolic blood pressure during the study

	Mean	*Standard dev.*
SBP inclusion	131.0	14.9
SBP visit 2	130.5	13.4
SBP visit 3	130.0	12.7
SBP visit 4	130.5	12.2
DBP inclusion	78.1	9.1
DBP visit 2	77.7	8.4
DBP visit 3	77.6	7.8
DBP visit 4	77.8	7.7

SBP: systolic blood pressure; DBP: diastolic blood pressure.

TABLE 4. Relationship of adverse events with an occurrence frequency > 0.1 % during treatment with venlafaxine extended release and their intensity. Values expressed as frequency and percentage

Adverse event	*Frecuency (%) (n = 4.557)*
Nausea and vomiting	52 (1.14)
Gastric discomfort	40 (0.88)
Tremor	30 (0.66)
Anxiety	20 (0.44)
Ansiedad	19 (0.42)
Diarrhea and/or constipation	16 (0.35)
Alteration of sexual desire	16 (0.35)
Headache	16 (0.35)
Mouth dryness	15 (0.33)
Drowsiness	12 (0.26)
Tachycardia	12 (0.26)
Asthenia	11 (0.24)
Insomnia	7 (0.15)
Sweating	5 (0.13)

serious (0.15%), and of these, only 1 corresponded to hypertensive heart disease. Nausea and/or vomiting were the most frequent adverse events recorded (52 cases: 1.14%). The remaining adverse events recorded presented a frequency inferior to 1.0%. In the final visit, week 24 of the treatment, tolerability to the drug was considered good or excellent in 98.7% of the patients while it was considered as fair or bad in the remaining 1.3% (data not shown).

DISCUSSION

Depression, more than other diseases, interferes with the patient's capacity to fulfill their needs and adapt to the setting, which is necessarily translated into a negative impact on the quality of life of the patient suffering it. Satisfactory treatment of depressive symptoms patently improves the subject's ability to reach and fulfill personal needs and thus leads to improvement of the QLRH. In this sense, treatment with antidepressive drugs has shown that improvement of the depressive symptoms is associated to an improvement in QLRH in both clinical trials as well as naturalistic studies[21-23].

In our study, it was proposed to assess the effect of venlafaxine extended release on the depressive symptoms and its correlation with improvement of the QLRH of these patients treated in Primary Health Care. The results observed show how pharmacological intervention with venlafaxine extended release for 24 weeks achieved a drastic and significant reduction in the depressive symptoms measured by the HAM-D17 scale (mean reduction of 36.4 % at 4 weeks, 59.6 % at 8 weeks and 74.0 % at 24 weeks). This means considerable improvement of the QLRH of these patients at the end of the study. It must be considered that the baseline scores observed in our study on the QLDS scale was close to the extreme values of the instrument (median of 26 points for a possible maximum negative value of 34 points). The effect achieved by venlafaxine extended release was independent of the dose or of the presence of concomitant diseases. Elevated effectiveness in the reduction of the anxious symptoms of the depression was also observed, 95 % of the patients obtaining «mild» or «absent» anxiety after six months of treatment.

The results of this observational study are consistent with those observed in the comparative clinical trials of venlafaxine extended release with placebo and with immediate release (IR) venlafaxine, fluoxetine or paroxetine, in which doses similar to those used in this study or even greater ones were used with a follow-up between 8 and 12 weeks. Thus, in the Cummingham et al. study[24], the response rates sustained with venlafaxine extended release and immediate release were significantly higher than with the placebo ($p < 0.05$). Rudolph et al.[25] obtained remission rates of 37, 22 and 18 % for venlafaxine extended release, fluoxetine and placebo respectively. In the Thase et al. study[26], 35% remission rates of venlafaxine extended release are observed versus 19 % for the placebo and Poirier and Boyer[27] show remission rates of 42.3 and 20.0 in patients with resistant depression for venlafaxine and paroxetine respectively.

It should be stated that a statistically significant reduction was observed in our study in the depressive symptoms at 24 weeks of treatment, which meant that a high percentage of patients presented a response (86.2 %) after the treatment in week 24 of the study, or remission (73.8 %) of the depressive symptoms. Thus, 87.3 % of the physicians were satisfied with this pharmacological intervention. This remission rate is superior to that observed in the clinical trials previously mentioned both with venlafaxine extended release as well as with flouoxetine or paroxetine[24-27]. The response percentage (↓ > 50 % in the HAM-D_{17} scale score) observed at 8 weeks in our study (70.8 %) is similar to that documented for venlafaxine extended release (73.7 %) in a meta-analysis of 44 randomized clinical trials (4,033 patients) in which venlafaxine extended release, SSRI (fluoxetine, paroxetine, sertraline or citalopram) and tricyclic antidepressives (imipramine, desipramine, nortriptyline and amitriptyline) were compared at 8 weeks of treatment, the SSRI and the tricyclic antidepressants showing a significantly inferior response (61.1 and 57.9 %, respectively)[28].

In another meta-analysis of 8 clinical trials with 2,045 patients[29], it was observed that the remission rate of depressive symptoms (HAM-$D_{17} \leq 7$) seen at 8 weeks for venlafaxine extended release (45 %) was similar to that observed in our study at this same follow-up time (47.8 %), significantly superior to that observed for SSRI (35 %) or placebo (25 %).

Safety is demonstrated by the few patients who have presented adverse effects, only 4.2 % of them, this percentage being inferior to that reported in the revised studies[20,25-29]. In these studies, the most frequent adverse effects observed with treatment with venlafaxine exten-

ded release were: headache, gastrointestinal discomfort, sleep disorders, tiredness or agitation and dry mouth, while in our study, the following were recorded by order of frequency: nausea and vomiting, gastric disorders, vertigo, dizziness and instability. It should also be stated that one hypertensive crisis episode appeared in a sample of 4,557 patients in whom the safety analysis was performed, which reinforces the safety of the molecule.

One of the limitations presented in this study is that it was designed as an open, non-comparative study, performed in an observational way according to the usual medical practice, which does not make it possible to establish clearly which was the beneficial effect that can be exclusively attributable to the study drug or to compare it with another pharmacological intervention. However, the results observed in this study are coherent with those reached in comparative clinical trials with this same drug and even in long term follow-up open studies[3-7]. Furthermore, the performance of a naturistic study that reflects «real life» conditions of the use of drugs presents an added value to this study, as it makes it possible to draw conclusions on the behavior of venlafaxine extended release under the usual medical practice conditions, conditions far from those of clinical trials with rigid criteria for patient selection, with elevated internal validity but limited generability[28,29].

Finally, another important point in this study is that it has been developed in Primary Health Care, which reinforces this group in its role of being the first step in the treatment of depression in our setting, especially when drugs, such as venlafaxine extended release, that are easy to handle and have a simple posology, are available. In this study, there has been a reduced loss of patients evaluable for effectiveness, only 9%, which shows the adequate control of the patients with depressive symptoms by PHC physicians.

In conclusion, venlafaxine extended release effectively and safely reduces depressive symptoms of patients with depression treated in Primary Health Care, with the depression intensity normally treated by these clinicians, which means an improvement in the quality of life related with the health of these patients.

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