Venlafaxine extended release for the treatment of chronic pain. A series of 50 cases

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Venlafaxina retard como tratamiento del dolor crónico. Una serie de 50 casos

Summary

Introduction. *The objective of this study is to investigate analgesic effectiveness and safety of venlafaxine extended release in chronic pain of any etiology.*

Methods. *Six month, observational, open study, carried out in two pain units. Initially, a daily dose of 75 mg of venlafaxine extended release was administered, increasing it to 150 mg, following clinical criteria. Treatment response was measured using the Visual Analogue Scale (VAS), rest and mobilization, Hospital Anxiety and Depression Scale (HAD) and eastern Cooperative Oncology Group (ECOG) and an adverse event sheet to record adverse events occurring during the study.*

Results. *The study was carried out in a 50 patient sample with a mean age of 57.1 ± 1.8 years, with chronic pain. A total of 85-90 % of the patients was maintained with a daily dose of 75 mg of venlafaxine extended release. This produced a gradual reduction of the VAS scores at rest (significant reduction of 5.2 ± 1.1 to 2.7 ± 1.5 points;* ($p < 0.0005$) *and mobilization (significant reduction of 5.5 ± 0.8 to 3.1 ± 1.6 points;* $p < 0.0005$*). Pain relief increased progressively. Regarding physical activity measured by the ECOG scale, there was a reduction of the percentage of patients and increase of outpatients. Tolerability to venlafaxine was «excellent», «very good» or «good» for 72 % of the patients.*

Conclusions. *Extended release venlafaxine can be an effective and well-tolerated treatment in patients with chronic pain of any etiology, although it must be investigated in depth.*

Key words: *Venlafaxine extended release. Chronic pain. Outpatients. Analgesia.*

Resumen

Introducción. *El objetivo es investigar la efectividad analgésica y seguridad de la venlafaxina liberación sostenida (retard) en el dolor crónico de cualquier etiología.*

Métodos. *Estudio abierto, observacional, de 6 meses de duración, realizado en dos unidades del dolor. Se utilizó una dosis inicial de venlafaxina de liberación sostenida de 75 mg diarios, incrementándose a 150 mg a criterio clínico. El efecto antiálgico se determinó mediante la Escala visual analógica (EVA) de reposo y movilización y la Escala de actividad física del grupo Cooperativo del Este de la Oncología (ECOG), así como mediante la valoración de la eficacia y tolerabilidad por parte del médico y paciente. Adicionalmente se utilizó la Escala hospitalaria de depresión y ansiedad (HAD) y se registraron los acontecimientos adversos acaecidos durante el estudio.*

Resultados. *Muestra de 50 pacientes con una media de edad de 57,1 ± 10,8 años aquejados de dolor crónico. El 85-90 % de los pacientes se mantuvieron con dosis diarias de 75 mg de venlafaxina retard. Se produjo una reducción paulatina de las puntuaciones de la EVA de reposo (de 5,2 ± 1,1 a 2,7 ± 15 puntos;* $p < 0,0005$*) y movilización (de 5,5 ± 0,8 a 3,1 ± 1,6 puntos;* $p < 0,0005$*). Con respecto a la actividad física medida por la ECOG se produjo una reducción del porcentaje de pacientes y un aumento de los pacientes ambulatorios. La tolerabilidad a la venlafaxina fue considerada «excelente», «muy buena» o «buena» en el 72% de los pacientes.*

Conclusiones. *La venlafaxina de liberación sostenida puede ser un tratamiento efectivo y bien tolerado en pacientes con dolor crónico de cualquier etiología, aunque requiere ser investigado en profundidad.*

Palabras clave: *Venlafaxina de liberación sostenida. Dolor crónico. Pacientes ambulatorios. Analgesia.*

INTRODUCTION

Antidepressants have frequently been used as coadjuvants in the treatment of chronic pain syndromes. In effectiveness studies in patients with chronic pain[1-3], antidepressants seem to be effective, independently of any effect on the mood state, and they have been shown to be more effective at lower doses than those needed to treat depression. Their analgesic action is faster than the purely antidepressant effect, that usually appears at

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weeks or months of initiating treatment. Tricyclic antidepressants (TCA) have been studied most. It has been verified that these agents generally have a mild to moderate analgesic effect on chronic pain, above all that having a neuropathic character[1].

Contradictory results are observed in a review of several studies[4] with selective serotonin reuptake selective inhibitors (SSRI) in chronic pain. These results suggest that mixed action antidepressants (serotonergic and noradrenergic) are the antidepressants of first choice to relieve pain. Venlafaxine is an antidepressant, whose action mechanism is based on serotonin and noradrenalin reuptake inhibition (SNRI)[5,6] without almost any affinity for cholinergic, histaminergic or adrenergic receptors[7,8].

Several studies have been carried out to assess if venlafaxine presents good tolerability and is effective in the treatment of chronic pain. In the studies revised, one on headache (open, retrospective study with 97 patients)[9], another on prophylaxis of migraine in tension-type headache in 112 patients[10] and the last in patients with fibromyalgia patients[11], venlafaxine was shown to be effective both in the treatment of pain as well as in the prevention of the appearance of headache, independently of its effects on depressive symptoms.

There are also a series of clinical cases that report pain relief with venlafaxine in patients with post-herpetic neuralgia[12,13], acute radicular back pain[14], reflex dystrophia[12], intercostal neuralgia[12], atypical facial pain 812), multiple sclerosis[12], post-infarction pain[12] and other pictures of neuopathic pain[15]. Furthermore, in a recent study that makes a randomized, double blind and cross over comparison of the efficacy of venlafaxine versus placebo in neuropathic pain after treatment of breast cancer, a mean relief of pain and a significantly lower maximum intensity of it is obtained with venlafaxine versus the placebo[16].

In these studies, in which many of the patients had pain refractory to other treatments, venlafaxine presented good effectiveness and tolerability, demonstrating that this antidepressant can be an option for chronic pain treatment[17].

This present study aims to also demonstrate the effectiveness of venlafaxine extended release in chronic pain patients treated in the pain units.

METHOD

Data is gathered on the patients who come consecutively to two Pain Units over six months and are treated with venlafaxine extended release at daily doses between 75 and 150 mg, which could be increased on the investigator's criterion. The inclusion criteria used were the following: adult patients of both genders, suffering from chronic pain of any etiology, with a previous score on the visual analogue scale (VAS) of pain intensity ≥ 50 mm and an intellectual and understanding level adequate to understand the handling of the protocol instructions. In regards to the exclusion criteria, the following were taken into consideration: acute pain, renal or hepatic dysfunction, known hypersensitivity to venlafaxine or lactose as well as a history of serious allergy or multiple adverse drug reactions, contraindications of venlafaxine, any mental disorder due to general medication, having suffered a myocardial infarction in the six months prior to the onset of the protocol, disorders in the cardiac rhythm or conduction, pregnant or nursing women or those having a positive Beta-HCG test, uncontrolled hypertension, use of any study drug, antipsychotic drug or electroconvulsive therapy or sumatriptan in the 30 days prior to the screening, MAO inhibitors or St John's Wort in the 14 days prior to screening, anxiolytic drugs or sedatives/hypnotics (except lorazepam or oxazepam) or any other psychotic substance or drug in the 7 days prior to the baseline visit.

In the baseline visit (visit 1), information was gathered on sociodemographic and anthropometric data, diseases and concomitant medication. In each follow-up visit (months 1-6: visits 2-7), data were recorded on effectiveness and tolerability of treatment with venlafaxine extended release.

The scales used for the evaluation of the antalgic effect exerted by venlafaxine extended release were: VAS scale at rest and on mobilization (to measure pain intensity) and the ECOG scale of physical activity (to measure the number of patients and their percentage with normal activity, restricted physical activity, walking with capacity to take care of themselves and limited activity, remaining in bed or chair 50 % of the time). In addition, the HAD scale (hospital anxiety and depression scale) was used to assess the anxious and depressive symptoms of patients with non-psychiatric medical problems as well as the effect exercised by the drug. In addition, in all the visits, the adverse effects occurring during the study were recorded while the global efficacy and tolerability of the treatment were recorded descriptively in the final visit, according to the physician's and patient's judgement.

The statistical methodology included the descriptive analysis of the variables included in the anamnesis and the clinical examination, calculating the statistics of the central tendency and dispersion of the quantitative variables and the absolute and relative frequencies of the qualitative variables, in the total sample available on each study visit. The sample by intention to treat included all the patients who entered the study. In order to include all the patients in the corresponding analyses, the last observation was carried forward (Last Observation Carried Forward [LOCF]) in those who did not have the corresponding measure available on visit 7. The sample by protocol was formed by the patients who completed the study, that is, who performed the 7 programmed visits. For the efficacy analysis in the sample by intention to treat, comparison of means in paired data (visit 1-visit 7) was used for quantitative measures, calculating the difference between visits and its 95 % confidence interval (95 % CI) and the Wilcoxon test (visit 1-visit 7) for the qualitative variables. In the sample by protocol, in the quantitative variables, the ANOVA test of repeated mea-

sures with an intra-subject factor with 7 levels (visits 1-7) was used, employing the Greenhouse-Geisser correction of the degree of freedom in the necessary cases. For the comparison between paired time points, the Bonferroni correction of the critical level was used. In the qualitative variables, the Friedman test was used. The statistical analysis was used with the SPSS version 10.0 program. Values of $p < 0.005$ were considered significant.

RESULT

An analysis was made of a total of 50 patients (50 % male) with chronic pain having different etiology and variable topography (table 1), between 3 and 96 months evolution (median of 8 months and mean of 17 ± 20 months), no significant differences being observed between genders in the duration of the picture (mean difference of 5.6 months; CI of -5.9 at 17 months; $p = 0.207$). Age ranged from 31 to 80 years (median 58 years) with a mean value of 57.1 ± 10.8 years. Except one, all the patients (98%) reported previous use of analgesics and all were receiving antalgic treatment on inclusion. A total of 28 cases (56%) presented concomitant diseases.

The patients initially received treatment with venlafaxine extended release at a dose of 75 mg/day in a single dose. Only between 10-15 % of the patients required a dose of 150 mg/day as they did not obtain clear improvement during the study. On visit 7, 88.1 % of the patients were still receiving a daily dose of 75 mg. Once treatment was established with venlafaxine extended release, the percentage of patients who needed rescue drug was less than 60 % at any time of the study. The percentage of patients who used rescue drug was reduced by 3, 4 and 5 times between each one of the consecutive visits, simultaneously increasing the number of patients who did not use it or did so only once between visits (table 2). In 31 patients, in whom a registry was available in all the study visits, the average usage was slowly reduced over time significantly ($p < 0.0005$). In regards to the way the rescue drug was managed, 3 patterns were basically found: when the intense episode pain crisis appeared; use during the day (without specifying period) and use in the afternoon.

The mean score on the VAS at rest was reduced during the study. The descriptive data in each visit are shown on table 3. In the analysis by intention to treat, the score was significantly reduced from 5.2 ± 1.1 points to 2.7 ± 1.5 points ($p < 0,0005$). The mean difference between the initial and final moment of the study was 2.5 points

TABLE 1. Etiology and topography of the pain

	N	%
Etiology		
Postsurgical	8	16
Postherpetic neuralgia	7	14
Tension-type headache	7	14
Arthrosis	7	14
Diabetic neuropathy	5	10
Oncological condition	3	6
Rheumatic disease	3	6
Phantom limb	2	4
Vasculopathy	2	4
Chronic pancreatitis	1	2
Talamic syndrome	1	2
Atypical facial neuropathy	1	2
Brucellosis with chronic back pain	1	1
Chronic back pain	1	1
Unknown origin neurpathic pain	1	1
Site		
Limbs	18	36
Spine	12	24
Thorax and/or abdomen	9	18
Head	9	18.
Hemibody	1	2
Generalized bone	1	2

TABLE 2. Use of recue drug during the study. Maximun number of times declared

No. of times	*0*		*1*		*2*		*3*		*4*		*5*	
No. visit	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%
Visit 2	21	42	7	14	8	16	10	20	2	4	2	4
Visit 3	18	42.9	10	23.8	7	16.7	5	11.9	2	4.8	0	0
Visit 4	20	50	12	30	2	5	4	10	2	5	0	0
Visit 5	22	64.7	9	26.5	1	2.9	1	2.9	1	2.9	0	0
Visit 6	23	62.2	11	29.7	2	5.4	0	0	1	2.7	0	0
Visit 7	23	63.9	8	22.2	4	11.1	1	2.8	0	0	0	0

TABLE 3. Scores of the VAS at rest and on mobilization during the study

	Mean	*Median*	*Standar dev.*	*Minimum*	*Maximum*
VAS at rest					
V1	5.2	5	1.1	1.5	7.3
V2	4.4	4.6	1.3	1	7
V3	3.3	3	1.4	1	7
V4	2.5	2.5	1.1	0	5
V5	2.4	2	1.1	0	5
V6	2.1	2	1	0	4
V7	2.2	2	1	0	4.8
VAS on mobilization					
V1	5.5	5.3	0.8	3.5	7
V2	4.6	5	1.3	1	7
V3	3.8	3.6	1.4	1	7
V4	3	3	1.2	0	5.1
V5	2.9	3	1.3	0	5.7
V6	2.6	2.6	1.2	0	5.1
V7	2.6	2.7	1.3	0	5.5

TABLE 4. ECOG during the study

Activity	*Normal*		*Restricted*		*Walking*		*Limited*	
Visit No.	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*
Visit 1	20	40	21	42	8	16	1	2
Visit 2	20	40	21	42	8	16	1	2.2
Visit 3	17	37	22	47.8	6	13	1	15.2
Visit 4	17	38.6	23	52.3	4	9.1	0	0
Visit 5	18	40.9	22	50	4	9.1	0	0
Visit 6	16	37.2	23	53.5	4	9.3	0	0
Visit 7	17	40.5	22	52.4	3	7.1	0	0

Intention to treat (n=50). Wilcoxon signed rank test: Z: –2.236; p : 0.025. Completers (n=42) Friedman test; Chi squared: 18,545; gl: 6; p : 0.005.

(95% CI: 2-3). In the sample by protocol, the score was slowly reduced during the study from 5.2 ± 1.1 points to 2.2 ± 1.0 points, finding significant decreases in pairs of consecutive visits between 1 and 4, establishing the score after visit 4. In the same way, the mean score of the VAS of mobilization was reduced during the study. The descriptive data of each visit are presented in table 3. In the analysis by intention to treat, the score was significantly reduced from 5.5 ± 0.8 points to 3.1 ± 1.6 points ($p < 0.0005$). The mean difference between the initial and final time of the study was 2.4 points (95% CI: 1.9-2.9). In the sample by protocol, the score was slowly reduced during the study from 5.5 ± 0.8 points to 2.6 ± 1.3 points, finding significant decreases between pairs of consecutive visits between visits 1 and 4, and establishing the score after visit 4.

In reference to ECOG, the percentage of outpatients with limited activity was reduced over time, and that of patients increased with greater activity, while the percentage of patients with normal activity remained stable during the study (table 4). Significant differences were found both in the sample by intention to treat ($p = 0.025$) as well as in the sample by protocol ($p = 0.005$). The number of patients and the percentage of those who modified relief of the pain are shown in table 5. The number of patients who did not experience any relief was reduced to 0 during the study, while those who experienced little relief also decreased. On the contrary, the percentage of patients who experienced sufficient, much or complete relief increased. Significant differences were found both in the sample by intention to treat ($p < 0.0005$) as well as the sample by protocol ($p < 0.0005$).

TABLE 5. Relief during the study

Relief	*No.*		*Little*		*Sufficient*		*Much*		*Complete*	
Visit no.	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*
Visit 2	24	48	20	40	4	8	2	4	0	0
Visit 3	5	10.9	17	37	17	37	7	15.2	0	0
Visit 4	2	4.5	5	11.4	24	54.5	12	27.3	1	2.3
Visit 5	2	4.5	5	11.4	22	50	14	31.8	1	2.3
Visit 6	0	0	5	11.6	23	53.5	13	30.2	2	4.7
Visit 7	0	0	6	14.3	21	50	13	31	2	4.8

Intention to treat (n = 50). Wilcoxon signed rank test: Z: –5.437; p<0.0005. Completers (n=42) Friedman test; Chi squared: 116,010; gl: 5; p<0.0005.

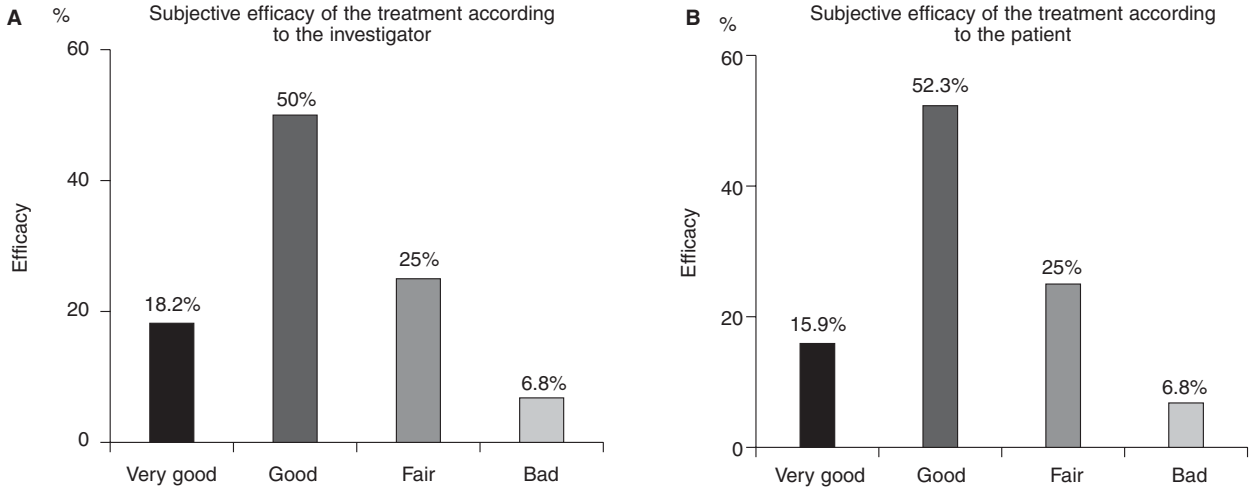
The mean score on the HAD of depression also decreased during the study (data not shown). In the analysis by intention to treat, the score decreased significantly from 9.2 ± 4.6 points to 7.3 ± 3.8 points ($p < 0.0005$); both scores are considered «probable case» of depression. The mean difference between the initial and final time of the study was 1.9 points (95% CI: 1.1-2.7). In the sample by protocol, the score decreased slowly during the study from 9 ± 4.6 (probably case) points to 6.9 ± 3.1 («normal» points, finding significant decreases until visit 5 and establishing the score after that visit. A similar effect was observed on analyzing the mean score on the HAD of anxiety, which decreased during the study. In the analysis by intention to treat, the score decreased significantly from 10.2 ± 4.2 points to 8 ± 3.6 points ($p < 0.00059$), both scores are considered «probable case» of anxiety. The mean difference between the initial and final time of the study was 2.1 points (95% CI: 1.2-3). In the sample by protocol, the score decreased slowly during the study from 9.9 ± 3.9 points to 7.4 ± 2.8 points, both scores are considered «probable case» of anxiety, finding significant decreases until visit 4, the score becoming stabilized after that visit.

In the opinion of the investigator, efficacy of the treatment was «very good» or «good» in 68% of the patients, while it was «fair» in 25% and «bad» in 7%; furthermore, in the opinion of the patients, efficacy of the treatment was «very good» or «good» in 68% of the patients, while it was «fair» in 25% and «bad» in 7% (figs. 1 A and B).

During the study, there were eight dropouts (16% of the sample) due to the following causes: seven due to adverse events and one patient due to lack of efficacy. A total of 24 patients (48%) reported 42 adverse events that gave rise to 131 episodes during the study. The most frequent adverse events were (percentage on the total of the adverse events); constipation in eight patients (19%), somnolence in six patients (14.3%), restlessness in four patients (9.5%) and nausea in four patients (9.5%). Only one of the episodes reported as a restlessness picture fulfilled the serious requirements while only 7% of the 131 episodes were considered to be possibly related with the study drug. No episode of arterial hypertension was observed.

According to the assessment of the investigator, treatment tolerance was «excellent» in 13% of the patients and «very good» or «good» in 59% of the patients while it was «fair» in 17% and «bad» in 11%. In the opinion of the patients, treatment tolerance was «excellent» in 13% of the patients and «very good» or «good in 59% of the patients, while it was «fair» in 19% and «bad» in 9% (figs. 2 A and B).

A total of 107 uses of concomitant medication was recorded by 49 patients (98%). Of these, 19 patients recorded the use of 1 concomitant drug and 16 patients



Figures 1 A and B. Subjective efficacy of the treatment according to the investigator and patient.

recorded the use of 2 concomitant drugs. Tramadol was among the concomitant drugs used most (44 times).

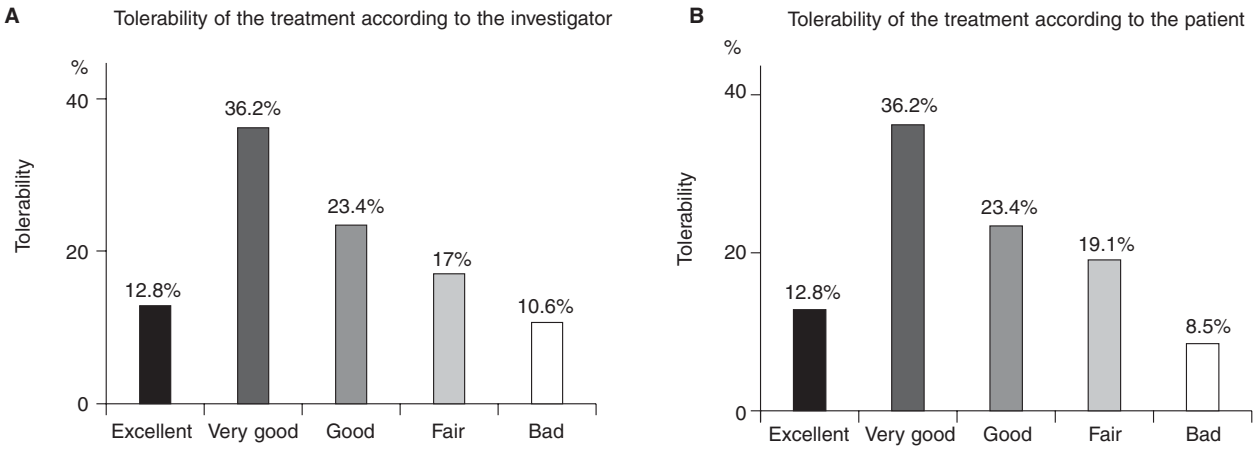
DISCUSSION

The clinical usefulness of venlafaxine extended release, a dual action antidepressant, in the management of patients with chronic pain of any etiology, can be inferred from the data obtained.

Until now, the clinicians who were devoted to seeing these so complicated patients had to recur to tricyclic antidepressants, but now the therapeutic armamentarium has increased, because there is an antidepressant that acts on the level of the 5-HT and NA receptors, without interacting with other receptors, which makes it possible to explain its better adverse effect profile[7-8]. The patients included in this study have also been polymedicated, which increases the risk of drug interactions. Venlafaxine extended release with its low rate of binding to plasma proteins of 27 % and its mild inhibition of cytochrome P450 has a minimum risk of interactions, so that it is profiled as a very useful antidepressant in this type of patients.

In this study, slow reductions are obtained on the specific pain scales, coinciding with the progressive increase in its relief. These results are not influenced by a progressive increase of the venlafaxine dose (maintained doses of 75 mg/day were basically used) or by an increase in the rescue drug, which, on the contrary, was reduced during the study.

No firm conclusions can be drawn in regards to the baseline state of anxiety and depression of the patient and thus on the effect of the drug on these disorders, given that the scale used, the HAD, is not a specific scale for depression but rather a scale used to assess the tendency in the initial screening of the patients diagnosed of medical diseases other than the depression itself. Although this was not the objective of this study and in spite of the limitations of this scale, a decrease was obser-



Figures 2A and 2B. Subjective tolerability of the treatment according to the investigator and patient.

ved in the scores of both anxiety as well as depression after its administration to these patients. However, the efficacy of venlafaxine in depressive disorders with or without anxiety has already been sufficiently demonstrated[18-21].

Chronic patients, who mostly (98%) took other drugs concomitantly, have been treated in the study so that it is complicated to distinguish if the adverse events reported during this study are due to venlafaxine extended release or to the other concomitant drugs.

The principal limitation of the study is that it lacks a control group, although it adequately reflects the medical practice in real health care conditions. Double blind, controlled studies will be able to supply more information on the effect of the drug in this type of patients.

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