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Effectiveness of venlafaxine extended release and conventional antidepressants in elderly patients with depressive disorder

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Objectives. To determine and compare effectiveness, tolerability and safety of venlafaxine extended release (VXR) and other conventional antidepressants, mainly selective serotonin reuptake inhibitors (SSRIs), for the treatment of elderly patients diagnosed of depressive disorder in an out-patient psychiatry setting.

Methods. Multicenter, naturalistic, randomized, open-label study performed in elderly patients with depressive disorder (according to DSM-IV). Patients were randomized to 6 months of treatment with VXR or another conventional antidepressant (CA). Effectiveness was assessed using the Montgomery-Åsberg Depression Rating Scale (MADRS) and the Hamilton Anxiety Scale (HAM-A). Response was considered as a ≥ 50 % decrease and remission as a < 9 score in the MADRS.

Results. Sample of 120 patients older than 60 years; 68 received VXR and 52 CA (SSRI: 94.1 %). Most frequently used SSRI were citalopram (40.8 %), paroxetine (24.5 %) and sertraline (20.4 %). After 6 months of treatment, VXR achieved a higher response (75 %, VXR; 50 %, CA; p = 0.048) and remission (50 %, VXR; 28.9 %, CA; p = 0.048) and a higher decrease in the HAM-A score (–14.77, VXR; –10.84, CA). There were no significant differences in compliance rates (67.6, VXR; 71.1 %, CA) and adverse reactions (14.7 %, VXR; 13.46 %, CA) between both treatment groups. Blood pressure and heart rate remained within normal limits in both treatment groups.

Conclusions. In this study, venlafaxine extended release shows higher effectiveness than other conventional antidepressants, mainly SSRIs, in the treatment of depressive elderly patients in the out-patient psychiatry setting.

Key words:
Elderly. Venlafaxine extended release. SSRI. Depression. Remission.

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Efectividad de la venlafaxina retard y los antidepresivos convencionales en pacientes ancianos con trastorno depresivo

Objetivos. Determinar y comparar la efectividad, tolerabilidad y seguridad de venlafaxina retard (VR) y otros antidepresivos convencionales, principalmente inhibidores selectivos de la recaptación de serotonina (ISRS), en el tratamiento de pacientes ancianos con diagnóstico de trastorno depresivo en el ámbito de la psiquiatría ambulatoria.

Métodos. Estudio multicéntrico, naturalístico, abierto y aleatorizado en pacientes mayores con trastorno depresivo (criterios DSM-IV). Los pacientes recibieron aleatoriamente 6 meses de tratamiento con VR u otro antidepresivo convencional (AC). La efectividad fue evaluada mediante la escala de Montgomery-Åsberg para la depresión (MADRS) y la escala de Hamilton para la ansiedad (HAM-A). Se consideró respuesta como la reducción en la puntuación ≥ 50 % y remisión a una puntuación ≤ 9 en la MADRS.

Resultados. Muestra formada por 120 pacientes mayores de 60 años, 68 tratados con VR y 52 con AC (ISRS: 94,1 %). Los ISRS más utilizados fueron citalopram (40,8 %), paroxetina (24,5 %) y sertralina (20,4 %). Tras 6 meses de tratamiento, VR consiguió mayor respuesta (VR: 75 %; AC: 50 %; p = 0,048) y remisión (VR: 50 %; AC: 28,9 %; p = 0,048) y mayor decremento en puntuación HAM-A (VR: –14,77; AC: –10,84). No hubo diferencias significativas en las tasas de cumplimentación (VR: 67,6 %; AC: 71,1 %) y reacciones adversas (VR: 14,7 %; AC: 13,46 %) entre ambos tratamientos. La tensión arterial y frecuencia cardíaca se mantuvieron en límites normales en ambos grupos.

Conclusiones. Venlafaxina retard muestra en este estudio una superior efectividad al comparar con otros antidepresivos convencionales, principalmente ISRS, en el tratamiento de pacientes ancianos depresivos en el ámbito de la psiquiatría ambulatoria.

Palabras clave:
Ancianos. Velafaxina retard. ISRS. Depresión. Remisión.

INTRODUCTION

Depressive disorders make up the most frequent psychiatric disease in the elderly population[1-3]. Approximately 15 % of the elderly in general have depressive symptoms[2]. Depression is associated with deterioration in quality of life, greater morbidity, greater incapacity and greater risk of mortality[4,5]. In the year 1996, the WHO considered depression as the first cause of incapacity worldwide. The NIH Consensus Development Panel on Depression in Late-life also concluded that depression incapacitated and prevented normal functioning of the patients[6].

Depression of the elderly has differential characteristics regarding young adults, not only regarding its clinical manifestations but also regarding its pathogeny and pathophysiology. This fact, explained by the coexistence of chronic medical diseases, use of multiple drugs, presence or not of cognitive deterioration and a greater number of vital events in this age group, poses difficulties in the clinical management and therapeutic approach of the disease. The high suicide rate associated to advanced age is also characteristic, depression being the most frequently found psychiatric disease as background in suicide in old age[2,7].

As in the diagnosis and clinical setting, there are differential aspects in the treatment of depression in the elderly[8]. Here, the main objective of the treatment should be remission of the symptoms to improve quality of life, prolong maintenance in the community of the patient and delay institutionalization and dependence on third parties. Drug treatment of geriatric depression is hindered by the changes associated to old age regarding pharmacokinetic conditions such as absorption, distribution, metabolization and excretion of the drugs and pharmacokynamics as is the case of heterogeneity in the sensitivity of the target organ receptors that gives rise to variability in regards to the therapeutic and undesirable drug effects[9]. Deterioration of quality of life of the elderly patient is sometimes a direct consequence of some undesirable effects of the drug treatments used for depression. Thus, the Ray study[10] found a frequency of falls with hip fracture that was three times greater in the elderly who received treatment with tricyclic antidepressants than in those who did not receive medication. Other data to consider in the treatment of elderly depression is the presence of cognitive disorders (up to 15 %), either forming a part of the symptomatic group of depression or secondary to baseline dementia. Furthermore, up to 50 % of patients with dementia may be depressed[11-12].

Response rate to treatments in the elderly population is a relevant question in treatment of depression. Accelerating response to drugs and identifying possible non-responders as soon as possible is important. Compared with middle aged adults, the elderly take longer to respond to antidepressant treatments. Mean remission time of the symptoms is 12 weeks[13]. Furthermore, these patients have greater frequency of relapses during treatment. It must be remembered that geriatric age is the population group having less life time to invest in these processes with a high suicidal rate and important incapacity associated to the disease. Thus, one of the main problems established in the daily clinical activity is speeding up the clinical response and decreasing suicide risk[14]. Up to recently, the elderly were systematically excluded from drug trials and other similar studies. Thus, knowledge regarding treatment of depression in the elderly is insufficient[15,16].

Based on theoretical considerations and comparative studies of the different antidepressants, data have been obtained that suggest that dual action antidepressants such as venlafaxine, milnacipram and mirtazapine, that act on the two neurotransmission systems, serotoninergic and noradrenergic, could offer a greater therapeutic benefit than the classical antidepressants in the depressive pictures[14,17].

Effectiveness and safety of the new dual action antidepressants were proven with multiple studies on the general population, finding advantages regarding quickness of therapeutic action onset, greater proportion of responder patients, dose-response linear relationship and greater tolerability versus classical antidepressants. Furthermore, the more recently introduced antidepressants, on acting on multiple neurochemical systems, may reduce the need to combine antidepressant treatments[18]. This is why we could hypothesize that these third generation antidepressants would have therapeutic advantages versus classical antidepressants in the geriatric population as well. This study aims to compare treatment effectiveness with velafaxine extended release versus other conventional antidepressants in geriatric patients with depression diagnosis seen in the out-patient psychiatric setting.

METHODS

Design and patients

Multicenter, naturalistic, open label and randomized study done in the out-patient psychiatry setting with the main objectives of determining and comparing effectiveness, tolerability and safety of venlafaxine extended release (VXR) and other conventional antidepressants (CA), mainly selective serotonin reuptake inhibitors (SSRI) in the treatment of elderly patients with depressive disorder diagnosis. Fifteen specialists in psychiatry participated in it. The study was conducted according to the Good Clinical Practice (GCP) rules for clinical studies with human use drugs, the declaration of Helsinki and amendments and other guidelines in force. Informed consent from the patients was required for their enrolment in the study, always guaranteeing the confidentiality of the personal data.

Out-patients of both genders with age greater than 60 years and diagnosed of major depressive disorder, minor depressive disorder or dysthymia, according to DSM-IV criteria

(and annex), who could receive treatment with the antidepressant drugs accepted in the study according to clinical criteria, were included in the study. The accepted antidepressant drugs were venlafaxine extended release on the one hand and within the conventional antidepressants, non-dual drugs such as SSRI or trazonone. As they are presently not a standard practice of first choice in the elderly, heterocyclic antidepressants were also excluded. Considered within the study exclusion criteria were, among others, the following: known hypersensitivity to venlafaxine or to any conventional antidepressant, clinically significant heart, hepatic or renal disorders, myocardial infarction within 6 months prior to enrolment, pharmacologically uncontrolled high blood pressure, significant cerebrovascular disease, Alzheimer's disease or any other type of dementia, use of experiment drugs, antipsychotics, electroconvulsive therapy (ECT) or sumatriptan, in the 30 days prior to the study onset and administration of monoamine-oxidase inhibitors or Saint John's Wort in the 14 days prior to enrolment. Use of zolpidem, zopiclone and intermediate half life benzodiazepines (basically lorazepam), psychotherapy, if established previously and rhythm of session is uncharged and use of non-psychopharmacological substances with psychotropic effects was permitted as concomitant treatments if the patient received stable doses in the month prior to enrolment.

In the baseline visit, it was assured that the patient fulfilled the inclusion criteria and did not fulfill any of the exclusion ones. Patients were randomly assigned according to a pre-established randomization list to receive treatment with venlafaxine extended release or other convention antidepressants for 24 weeks. Given the naturalistic character of the study, both venlafaxine extended release and the other conventional antidepressants were administered by clinical criterion in the dose range authorized in the respective data sheets. Follow-up visits were conducted at 4, 12 and 24 weeks.

Assessment instruments

The Montgomery-Asberg Depression Rating Scale (MADRS)[19], Hamilton Anxiety Scale (HAM-A)[20] and the Clinical Global Impression Scale of Severity (CGI-S) and Improvement (CGI-I)[21] were used as principal instruments of measurement of intensity and course of depressive disorder, in agreement with the assertions of the physician and patient. Response rates, this considered as a reduction greater than or equal to 50 % in the MADRS scale score and remission determined by the percentage of patients with scores of ≤ 9 and ≤ 4 on the MADRS scale were considered principal criteria for the assessment and comparison of antidepressant effectiveness of venlafaxine extended release and the other conventional antidepressants administered. In addition, degree of treatment compliance was determined, recording all the reasons for withdrawal and drop-out. All the adverse effects reported during the study were recorded, determining their seriousness and relationship with the study treatments.

Statistical methods

Statistical analysis was conducted to assess and compare effectiveness, tolerability and safety of venlafaxine extended release and other conventional antidepressants. The quantitative variables were described as mean and standard deviations (SD) together with their 95 % confidence interval. Behavior of the quantitative variables was analyzed for each one of the independent variables categorized by the Student's *t* test (in comparisons of one variable with two categories). The qualitative variables were described by their frequency distribution. Association between qualitative variables was assessed with the χ^2 test or Fisher's exact test, when more than 25 % of those expected were less than 5. In the case of ordinal variables, the hypothesis of ordinal trend of proportions was contrasted. To study variation in time, differences of effect (scores of the scale) were calculated absolutely and relatively. The effect of multiple comparisons was corrected with the Bonferroni a posteriori test and the Dunnett test in relationship to the baseline situation. Confidence intervals were estimated at 95 % of the difference of means in absolute values and in relative increments, expressed in percentages. In every case, distribution of the variables in relationship to the theoretical models was verified and the hypothesis of homogeneity of variances contrasted. In all the contrasts of hypothesis, the null hypothesis was rejected with a type 1 error or error α less than 0.05. The computer program used for the analysis was SPSS for Windows, version 12.0.

RESULTS

The study sample is formed by a total of 120 patients over 60 years of age, 68 (56.7 %) patients of whom were treated with venlafaxine extended release while 52 (43.3 %) patients received other conventional antidepressants. The SSRIs constituted the most frequently used therapeutic group as conventional therapy, representing 94.1 % of all the conventional treatments administered. Twenty patients (40.8 %) received citalopram, 12 patients (24.5 %) paroxetine, 10 patients (20.4 %) sertraline, 6 patients (12.2 %) fluoxetine and 1 patient (2.0 %) fluvoxamine.

In the group of patients receiving venlafaxine extended release, mean age was 75 ± 7, range from 57 to 97 years. Women represented 69.1 % of the sample. Minor depressive disorder was the most frequently diagnosed category (47.0 % of the cases), followed by major depressive disorder (36.4 % of the cases) and dysthymia (16.7 % of the cases). In the case of other conventional antidepressants, women also predominated (73.1 %), mean age being 76 ± 7, range between 60 and 91 years. In this group 57.7 % of the cases were classified as minor depressive disorder, 23.1 % as dysthymia and 19.2 % as major depressive disorder.

A high percentage of patients had concomitant diseases (89.2 %) and received other medications (93.3 %), these pro-

portions being similar between both treatment groups. Differences were only observed when comparing the percentage of patients who received baseline benzodiazepine, significantly superior in the group who were then treated with venlafaxine extended release (p = 0.04) (table 1). Doses administered for each one of the antidepressants given in the study in the baseline and final visits are summarized in table 2.

In the venlafaxine extended release group, the patients had a mean score on the MADRS scale in the initial visit of 29.3 ± 8.0 points. These scores decreased to 20.3 ± 9.1, 14.24 ± 8.3 and 10.6 ± 7.2 (visits - baseline and weeks 4, 12 and 24 respectively). In the case of conventional antidepressants, the scores were 25.8 ± 5.9; 19.8 ± 7.2; 16.7 ± 8.2 and 13.5 ± 7.9 (visits - baseline and week 4, 12 and 24, respectively). No significant differences were observed between both groups, except in the baseline visit, in which the patients who received venlafaxine extended release had a significantly greater intensity of the clinical picture (p = 0.01). Decreased produced in the scores of the MADRS scale during the study were compared to see the effects of the treatment on the intensity of the depressive symptoms. Decrease in the score during the study was significantly greater in the venlafaxine extended release group than in the group of other conventional antidepressants (fig. 1A). The differences of means in the scores of each visit regarding baseline for both groups were: –2.38 (95 % CI: –4.61, –0.16) (p = 0.036), –5.04 (95 % CI: –7.98, –2.10) (p = 0.001) and –4.32 (95 % CI: –7.51, –1.14) (p = 0.008) (visits - week 2, 12 and 24, respectively).

In the case of the HAM-A scale, the mean score in the initial visit in the venlafaxine extended release group was 25.3 ± 8.6. This score decreased to 17.2 ± 8.7, 13.0 ± 8.9 and 9.9 ± 7.9 (visits - weeks 4, 12 and 24, respectively). In the case of conventional antidepressants, the scores were 24.0 ± 8.3; 18.7 ± 9.5; 15.6 ± 9.4 and 13.9 ± 10.2 (visits-baseline and week 4, 12 and 24, respectively). Significant differences were not observed between both groups. As is the case of the MADRS scale, the decreases produced in the scores of the HAM-A scale during the study were compared. Decrease of the score during the study was significantly greater in the

Table 1 Concomitant diseases and medication. Baseline visit

Variables analyzed	Study groups			
	Venlafaxine extended release		Conventional antidepressants	
	No. patients	%	No. patients	%
Concomitant diseases				
Central nervous system	14	20.6	7	13.5
Musculoskeletal system	38	55.9	27	51.9
Sense organs	21	30.9	18	34.6
Dermatological S.	3	4.4	3	5.8
Respiratory tract	11	16.2	4	7.7
Cardiovascular S.	27	39.7	31	59.6
Digestive tract	18	26.5	12	23.1
High blood pressure	12	17.6	15	28.8
Genitourinary tract	7	10.3	7	13.5
Others	15	22.1	12	23.1
Total patients	60	88.2	44	90.4
Concomitant medication				
Analg./antiinflammatory	25	36.8	20	38.5
Antiasthmatic	6	8.8	2	3.8
Anticoagulants	6	8.8	4	7.7
Antidiabetics	4	5.9	8	15.4
Antihipertensive	27	39.7	24	46.2
Benzodiazepines	39	57.4*	20	38.5
Lipid lower drugs	5	7.4	1	1.9
Others	26	38.2	28	53.9
Total patients	64	97.1	48	93.2

* Chi square test; p = 0.04. Venlafaxine extended release vs conventional antidepressants.

Table 2 Dosage. Baseline and final visit

Dose	Baseline	Week 24
Venlafaxine extended release	Mean: 100 mg/day Median: 75 mg/day Range: 775-300 mg/day	Mean: 121.5 mg/day Median: 131.5 mg/day Range: 75-300 mg/day
Fluoxetine	Mean: 18 mg/day Median: 20 mg/day Range: 20-30 mg/day	Mean: 17.5 mg/day Median: 20 mg/day Range: 10-20 mg/day
Paroxetine	Mean: 20 mg/day Median: 20 mg/day Range: 20-20 mg/day	Mean: 25.6 mg/day Median: 20 mg/day Range: 20-40 mg/day
Citalopram	Mean: 22 mg/day Median: 20 mg/day Range: 20-30 mg/day	Mean: 25.6 mg/day Median: 20 mg/day Range: 20-40 mg/day
Sertraline	Mean: 50 mg/day Median: 50 mg/day Range: 25-100 mg/day	Mean: 77.8 mg/day Median: 75 mg/day Range: 50-100 mg/day
Fluvoxamine	Mean: 150 mg/day	Mean: 150 mg/day

venlafaxine extended release group than in the group of other conventional antidepressants (fig. 1B). The differences of means in the scores of each visit regarding baseline for both groups were: –2.41 (95 % CI: –4.64, –0.19) (p = 0.034), –3.24 (95 % CI: –6.09, –0.39) (p = 0.027) and –3.93 (95 % CI: –7.19, –0.67) (p = 0.019) (visits - weeks 2, 12 and 24, respectively).

Treatment during 24 weeks with venlafaxine extended release was associated with greater response rates (≥ 50 % of the reduction in the total MADRS score) when compared with the conventional antidepressants. Response rates for venlafaxine extended release were 15.5 %, 59.6 % and 75 % (visits - weeks 4, 12 and 24, respectively) and 14.6 %, 26.2 % and 50 % for the conventional antidepressants (p = 0.048, visit - week 24). Remission rates, considering a score on MADRS ≤ 9, in each one of the follow-up visits were: 8.6 %, 36.5 % and 50 % for venlafaxine extended release and 12.5 %, 21.4 % and 28.9 % for the conventional antidepressant group (p = 0.048, week 24). Considering an even more restrictive remission criterion, MADRS ≤ 4, a greater number of patients treated with venlafaxine extended release remitted on visit 2 compared with the group of conventional antidepressants (5.2 % and 0 %, respectively), but without reaching statistical significance. No significant differences were observed for the other visits. The response and remission rates for venlafaxine extended release and the other conventional antidepressants are summarized in table 3.

Administration of venlafaxine extended release for 24 weeks was associated with greater improvement of the patient's condition, according to the assertions of the physician and patient (CGI-I scale). Thus, while 78.8 % of the patients treated with venlafaxine extended release and 78.5 % of those treated with other conventional antidepressants on the baseline visit were considered as moderate or markedly ill (CGI-S), in 80.9 % of the cases at the end of the study, the condition of the patients treated with venlafaxine extended release was considered by the physician as «much/very much better». This percentage was 68.4 % in the case of other conventional antidepressants (CGI-I; p = 0.19). According to the patient's opinion, 87.2 % of the patients from the venlafaxine extended release group and 62.2 % of those who received other antidepressants had a condition of «much/very much better» (CGI-I; p = 0.007).

A total of 46 patients (67.6 %) completed the study in the venlafaxine extended release group versus 37 patients (71.1 %) in the group of other antidepressants. The causes of drop-out/withdrawal were adverse events (1.47 % and

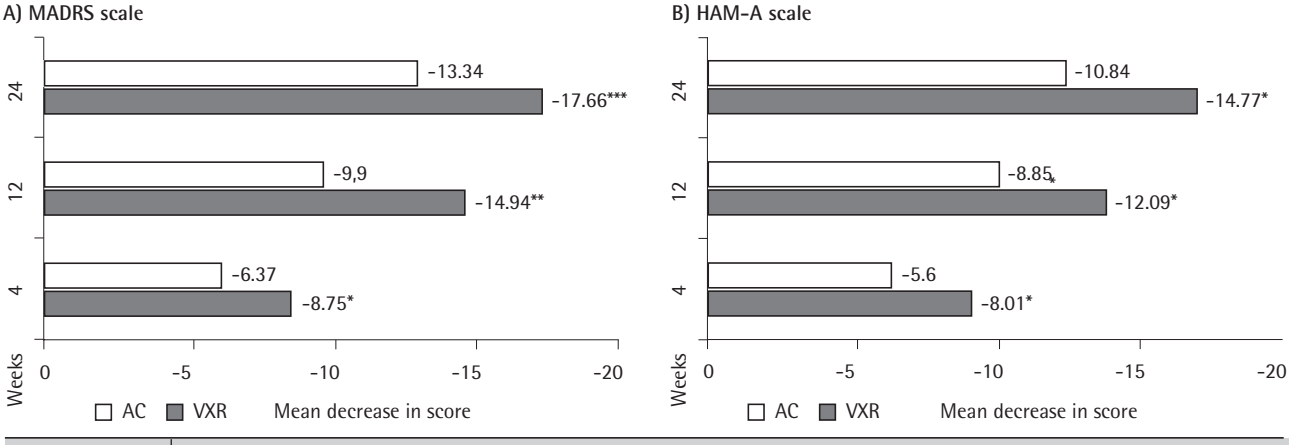

Figura 1 *Decrease mean scores on MADRS and HAM-A scales: baseline and final visits.* **A)** *Decrease in score versus baseline is significantly higher in the VXR group. Anova: *p = 0.036; ** p = 0.001; ***p = 0.008; VXR vs AC.* **B)** *Decrease in score versus baseline is significantly higher in the VXR group. Anova: *p < 0,05; VXR vs AC. VXR: venlafaxine extended release; AC: conventional antidepressants.*

Table 3 Response and remission rates (MADRS scale)

Variables analyzed	Study groups				p (chi square)
	Venlafaxine extended		Conventional antidepressants		
	No. patients	%	No. patients	%	
Response: decrease ≥ 50 % MADRS score					
Week 4	9	15.5%	7	14.6%	0.894
Week 12	31	59.6%	11	26.2%	0.001
Week 24	36	75.0%	19	50.5%	0.01
Remission: score of MADRAS ≤ 9					
Week 4	5	8.6%	6	12.5%	0.51
Week 12	19	36.5%	9	21.4%	0.11
Week 24	24	50.0%	11	28.9%	0.048
Remission: score of MADRAS ≤ 4					
Week 4	3	5.2%	0	0.0%	0.11
Week 12	4	7.7%	3	7.1%	0.92
Week 24	10	20.8%	8	21.1%	0.98

3.85 %), inefficacy (2.94 % and 0 %), loss to follow-up (23.53 % and 21,15 %) and other causes (4.41 % and 3.85 %) (venlafaxine extended release and other antidepressant groups, respectively). No significant differences were observed between both treatment groups for the variables analyzed. A total of 21 adverse events that affected 17 patients, 10 patients (14.7 %) treated with venlafaxine extended release and seven patients (13.46 %) with other conventional antidepressants were reported. No serious adverse events were reported related with the antidepressant treatments nor were there any cases of high blood pressure recorded. Adverse events reported during the study are shown in table 4. None of the treatments administered resulted in important modifications in the cardiovascular parameters evaluated during the study. Thus, the mean values of systolic and diastolic blood pressure and heart rate remained stable and within normal limits in both treatment groups (table 5).

DISCUSSION

Our study compares antidepressant drugs whose effectiveness, safety and tolerability are well established in adult depressive patients. Unfortunately, at present there are few predictors related with the patient that help to select a specific antidepressant drug for each specific patient. Thus, attention must generally be placed more towards the drug characteristics than to those of the patient. According to this, the greater complexity in the treatment of geriatric depression leads to questioning if the last generation antidepressants, due to their dual action mechanism, may supply additional benefits to those already found with the conventional treatment, fundamentally represented at present by the SSRI.

In the common clinical practice, once the diagnosis is made, the question to answer is related to the choice of the specific antidepressive molecule. Converting this clinical question into an investigation, the study was designed in such a way that once the patient was diagnosed and it was established that he/she could be susceptible to antidepres-

Table 4 List of adverse events

Adverse events	Study groups			
	Venlafaxine extended release		Conventional antidepressants	
	No. cases	%	No. cases	%
Headache	1	1.47	0	0.00
Rash	1	1.47	0	0.00
Gastrointestinal	4	5.88	4	7.69
Sweating	1	1.47	0	0.00
Insomnia	1	1.47	0	0.00
Dizziness	0	0.00	2	3.85
Nervousness	0	0.00	1	1.92
Others	1	1.47	1	1.92
Somnolence	2	2.94	0	0.00
Tremor	1	1.47	0	0.00
Vertigo	1	1.47	0	0.00
Total cases	13	19.12	8	15.38
Total patients	10	14.71	7	13.46

Tabla 5 Cardiovascular parameters

Cardiovascular parameter	Study groups	No.	Mean	Standard deviation	95 % confidence interval for the mean 95 %		Minimum	Maximum
					Lower limit	Upper limit		
Week 4 V1 SBP (mmHg)	Venlafaxine extended release	68	143,51	17.794	139.21	147.82	95	210
	Conventional antidepressants	51	138.63	14.959	134.42	142.83	100	170
	Total	119	141.42	16.748	138.38	144.46	95	210
Week 4 V1 DBP (mmHg)	Venlafaxine extended release	68	80.01	10.899	77.38	82.65	50	110
	Conventional antidepressants	51	78.94	11.052	75.83	82.05	50	100
	Total	119	79.55	10.931	77.57	81.54	50	110
Week 4 V1 pulse (beats/min)	Venlafaxine extended release	68	79.62	9.330	77.36	81.88	63	110
	Conventional antidepressants	49	77.59	8.720	75.09	80.10	60	100
	Total	117	78.77	9.097	77.10	80.43	60	110
Week 24 V4 SBP (mmHg)	Venlafaxine extended release	47	137.89	13.181	134.02	141.76	100	175
	Conventional antidepressants	38	137.37	12.178	133.37	141.37	120	100
	Total	85	137.66	12.670	134.93	140.39	100	175
Week 24 V4 DBP (mmHg)	Venlafaxine extended release	47	77.55	0.308	74.82	80.29	60	100
	Conventional antidepressants	38	78.34	11.022	74.72	81.96	60	100
	Total	85	77.91	10.055	75.74	80.07	60	100
Week 24 V4 pulse (beats/min)	Venlafaxine extended release	44	75.57	6.645	73.55	77.59	60	92
	Conventional antidepressants	34	75.88	9.078	72.71	79.05	60	98
	Total	78	75.71	7.746	73.96	77.45	60	98

sive treatment with any of the drugs being studied in it, the patients were simply randomized either to venlafaxine extended release or to the so-called conventional treatment, basically made up by SSRIs, the investigators being free to use any molecule within this group. This type of naturalistic design aims to reproduce the clinical scenario of decision making in pharmacological choice as closely as possible. The naturalistic studies in Psychiatry complement the blind and controlled studies and supply essential information for application in «real life» that these are not successful in achieving[22].

In our study, the SSRI were almost exclusively the drugs used in the group of conventional antidepressants, representing 94.1 % of them. This reflects the present introduction of these drugs in the treatment. In comparison with this treatment that can be considered standard, venlafaxine extended release is associated in this study with significantly greater rates of remission and response. If we consider remission, 50 % is obtained for venlafaxine extended release and 28.9 % for the other conventional antidepressants, principally SSRI, data that are consistent with the results of three recent meta-analyses published in general population[23-25].

Regarding the elderly population, some clinical studies that have compared venlafaxine with other antidepressants have been published. One six week study with venlafaxine (75-150 mg/day), clomipramine (50-100 mg/day) and trazodone (150-300 mg/day) according to a double blind design[26] indicated that both venlafaxine and clomipramine caused greater decreases than trazodone on the MADRS and HAM-D_{17} scales. In another double blind study, that included 92 patients between 64 and 87 years of age, it was observed how venlafaxine (50-150 mg/d) reached a response rate of 60 % after six months of treatment versus 53 % achieved for dothiepin (50-150 mg/d) according to the MADRS scale [27]. A third 8 week long study, also double blind, included 300 patients over 65 years of age with major depression who were randomized to receive venlafaxine

(75-222 mg/day), fluoxetine (230-60 mg/day) or placebo[28]. A higher rate of response and remission rates at week 8 were obtained for the patients in the venlafaxine group than those of the two other groups, although without reaching significant differences. In weeks 3 and 4, the patients from the venlafaxine group obtained significantly lower scores on the HAM-D and MADRS compared with fluoxetine and placebo.

In addition, Allard et al. compared the effect of treatment with venlafaxine and citalopram for 6 months[29], obtaining a 93 % response rate (50 % reduction in the MADRS score) for both treatment groups, a percentage superior to that observed in our study (75 % in the venlafaxine extended release group). In the last of the studies reviewed and conducted in Spain[30], effectiveness of venlafaxine extended release (225-300 mg/d) and nortriptyline (50-100 mg/d) were compared according to a simple blind design in the treatment of elderly patients (mean age 71 years) with major depressive disorder. A total of 68 elderly out-patients and hospitalized subjects were included. Treatment duration was 6 months. Remission rates (HAM-D $\leq$ 7) were similar in both groups: 71 % and 70 % for VXR and SSRI respectively, also superior to those observed in our study.

Both treatment groups, venlafaxine extended release and other conventional antidepressants, showed similar profiles of safety in this study, with a 14.7 % percentage of adverse effects in the venlafaxine extended release group and 13.46 % one in the group of other antidepressants. The possibility of increased blood pressure due to venlafaxine[31] was not found in this study and this drug behaved in this regards similarly to the SSRIs. No significant differences were observed in the number of patients who completed the study, 67.6 % in the venlafaxine group and 71.1 % in the group of other antidepressants. The most frequent cause of drop-out/withdrawal was loss to follow-up, 23.53 % in the venlafaxine extended release group and 21.15 % in the group of other antidepressants. This percentage is greater than that observed in other studies with antidepressants and is largely explained by the naturalistic design of the study. Another possible explanation is that the visits were quite spaced in time (4, 12 and 24 weeks) on the contrary to the studies with a shorter period in which the visits were weekly.

Our study has limitations. The first and most important limitation is that inherent to the naturalistic and open label design, with absence of control group. Its naturalistic group is both an advantage and disadvantage since the possibility of introduction of biases in the assessment of the results cannot be excluded, although these may go in both senses a priori, as it is not a blind study for the treating physician. On the other hand, this design is that which approaches the real situation most closely when giving a response to the usual question referring to the choice of type of molecule to treat the depressed elderly subject in the out-patient consultation. However, it would be interesting to perform double blind controlled studies with venlafaxine extended release versus conventional antidepressants in this type of geriatric patients that would assure homogeneous comparative groups and permit the comparison with the results we have obtained. Another limitation is that the study was not specifically designed to compare effectiveness data of venlafaxine extended release and SSRI. Consequently, the sample size allowed for comparison between venlafaxine extended release with the combination of other conventional antidepressants, but not with the combination of the SSRIs or with each one of them individually. Up to now, all the comparative studies with SSRI have not provided noticeable differences between them. This would make it possible to group then under the circumstances of the present study. However, it is true that a comparison of venlafaxine with the combination of SSRIs and with each one of them individually could have shown interesting information.

The advantage obtained by venlafaxine extended release, over the whole of other conventional antidepressants, mainly SSRIs, may be attributed to its character of dual antidepressants. It remains to be compared if these results are replicable with other dual drugs, such as the monoamine reuptake inhibitors, that will be available in Spain in the future.

CONCLUSIONS

In this study, venlafaxine extended release has a superior effectiveness when compared with other conventional antidepressants, mainly SSRI, in the treatment of geriatric depressive patients in the out-patient psychiatry scope. It is associated with greater response and remission rates and with greater increases in the reduction of symptoms over 6 months of treatment. Tolerability and safety were similar for venlafaxine extended release and other conventional antidepressants administered, including the cardiovascular and blood pressure parameters. All this suggests that venlafaxine extended release is an effective and safe therapeutic option in the treatment of geriatric depression and could be considered as one of the drugs of first choice in this indication.

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