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Adherence, acceptability and tolerability of venlafaxine extended release at dose of 300 mg/day in patients with major depressive disorder

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ABSTRACT

Background. Adherence to antidepressants is essential for good outcomes when treating depressive disorders. The objective of the current study was to evaluate the adherence, acceptability and tolerability of venlafaxine XR at a dose of 300 mg/day, administered in one or two tablets, after a treatment period of 6 ± 2 months in patients with major depressive disorder (MDD).

Subjects and methods. Observational, cross-sectional study of routine clinical practice in 590 outpatients with MDD who attended at public or private centers all over country, of whom 361 and 229 received one (300 mg) or two tablets (150+150 mg o 225+75 mg) of venlafaxine XR, respectively. The study data were obtained from the interview with the patient, the clinical history and validated questionnaires.

Results. The Haynes-Sackett method and the Morisky-Green questionnaire revealed that adherence to treatment was similar in both groups. The patients who received the dose of venlafaxine XR in one tablet showed greater satisfaction with the treatment according to the TSQM-9 questionnaire. The MADRS scale revealed that in 23% of the patients the MDD had remitted, and only in 9% it remained severe, in 26% it was moderate and in 42% mild. The same result was obtained with the PHQ-9 questionnaire. In general, the patients showed good tolerability to high doses of venlafaxine XR with both dosing regimens, and the most common adverse effects were sexual dysfunction, sweating and constipation.

Conclusions. Adherence to treatment with venlafaxine XR 300 mg/day in one or two tablets was similar. Patients who received a single tablet showed greater satisfaction with the treatment. The safety profile of high dose venlafaxine was favorable and there were dropouts or clinically significant elevations that affected the dosing regimen.

Keywords. venlafaxine extended release; major depressive disorder; adherence; high dose; tolerability.

ADHERENCIA AL TRATAMIENTO, ACEPTABILIDAD Y TOLERABILIDAD DE VENLAFAXINA XR A DOSIS DE 300 MG/DÍA EN PACIENTES CON TRASTORNO DEPRESIVO MAYOR

RESUMEN

Introducción. La adherencia a los antidepresivos es fundamental para obtener buenos resultados en el tratamiento de la depresión. El objetivo del actual estudio fue evaluar la adherencia, aceptabilidad y tolerabilidad de venlafaxina XR a dosis de 300 mg/día, administrada en uno o dos comprimidos, tras un periodo de tratamiento de 6 ± 2 meses en pacientes con trastorno depresivo mayor (TDM).

Metodología. Estudio observacional, transversal, de práctica clínica habitual en el que participaron 590 pacientes con TDM que asistían a consultas de centros públicos o privados de toda España, de los cuales 361 y 229 recibieron uno (300 mg) o dos comprimidos (150+150 mg o 225+75 mg) de venlafaxina XR, respectivamente. Los datos del estudio se obtuvieron de la entrevista con el paciente, de la historia clínica y de cuestionarios validados.

Resultados. El método Haynes-Sackett y el cuestionario de Morisky-Green revelaron que la adherencia al tratamiento

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fue similar en ambos grupos. Los pacientes que recibieron la dosis de venlafaxina XR en un comprimido mostraron mayor satisfacción con el tratamiento según el cuestionario TSQM-9. La escala MADRS reveló que en el 23% de los pacientes el TDM había remitido, y solo en el 9% se mantenía grave, en el 26% era moderado y en el 42% leve. Igual resultado se obtuvo con el cuestionario PHQ-9. En general, los pacientes mostraron buena tolerabilidad a la venlafaxina XR a dosis altas con las dos pautas de administración, y los efectos adversos más comunes fueron la disfunción sexual, sudoración y estreñimiento.

Conclusiones. La adherencia al tratamiento con venlafaxina XR de 300 mg/día en uno o dos comprimidos fue similar. Los pacientes que recibieron un solo comprimido mostraron mayor satisfacción con el tratamiento. El perfil de seguridad de venlafaxina XR 300 mg fue favorable. No se produjeron abandonos, ni elevaciones clínicamente significativas de la presión arterial que condicionaran la pauta de uso.

Palabras clave. venlafaxina XR; trastorno depresivo mayor; adherencia; dosis alta; tolerabilidad.

INTRODUCTION

Depression is a highly prevalent mental disorder in the world[1]. It is estimated that it affects 4.4% of the world´s population[2]. Depression is increasingly perceived as a chronic disease that substantially affects the quality of life, daily functioning and productivity of the people who suffer from it and those around them[3].

Depressive episodes can be classified as mild, moderate, or severe. At its worst, major depressive disorder (MDD) can lead to suicide[4].

Patients with MDD present high rates of inadequate treatment, lack of compliance, or lack of response due to insufficient prescribed dose[1]. In Spain and Latin American countries, the percentage of patients with MDD who maintain good adherence to treatment is around 70%, figures not very different from those shown by patients with schizophrenia or bipolar disorder[5]. Pharmacotherapy, especially SSRIs, remains the most common option for treating depression.

High-dose venlafaxine (≥ 300 mg/day) is a medication specially formulated for the treatment of MDD or for the prevention of recurrence of symptoms. It is an SNRI. It works by increasing the concentrations of the neurotransmitters serotonin and norepinephrine in the synaptic spaces of the central nervous system[6]. Venlafaxine has a rapid onset of action; and some studies have shown that it shows an antidepressant effect from the second week of treatment[7]. Rapid remission of depression is an important predictor of long-term remission of depressive symptoms[8].

The MDD treatment guidelines suggest that, once the drug is selected, it should be used up to the highest authorized dose before changing drugs or adding another. This recommendation is especially important for the specific case of venlafaxine. Its pharmacological profile has been shown to change from the 225 mg dose, at which point, the drug becomes be a norepinephrine reuptake inhibitor, in addition to serotonin[9]. This property places venlafaxine at high doses in the pharmacological group of dual-action antidepressants that may confer greater efficacy[10].

The administration of high-dose venlafaxine XR in patients who do not respond or are intolerant to treatment with first-line SSRIs, or in previous treatment with standard-dose venlafaxine, has shown efficacy at week 8[7], according to the Clinical Global Impression of Improvement Scale[7]. It has been observed that treatment with high doses of venlafaxine decreases the probability of MDD recurrence in 71.9% of patients[11] and that it exerts an additional effect in reducing physical symptoms associated with depression, such as headache, low back pain, muscle tenderness (for more than half of the muscles), fatigue or loss of energy in patients who have received treatment with doses up to 325 mg/day[8].

Venlafaxine XR or retard has a high tolerability index[12,13]. Only 4.7% of patients who received doses between 75 and 325 mg/day discontinued treatment due to mild adverse effects such as dizziness, nausea, anxiety, or sweating[7]. Another study describes a tolerability index of 11% in patients receiving standard doses of venlafaxine who discontinued treatment due to adverse effects such as dizziness, insomnia, decreased libido; and 13% in patients receiving high doses who discontinued treatment due to hypertension, constipation, anxiety, sweating or increased urination frequency[7]. Clinical practice guidelines recommend prescribing antidepressants at the appropriate dose in patients who require rapid effective remission of symptoms of severe major depression based on the duration of the episode and the evolution of symptoms[14]. There are studies that suggest that there is a dose-response relationship for venlafaxine[15]. Until recently, it was not easy to comply with this recommendation in the treatment of MDD with venlafaxine XR in Spain, probably because the commercialized presentations only reached the 225 mg dose, which made prescription difficult. Therefore, to achieve higher daily doses, it was necessary to use two tablets. For example, in the case of needing a dose of 300 mg, it was necessary to take two 150 mg tablets (or 225 mg + 75 mg), which could be a reason for low adherence

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to treatment[16] due to the fact that patient preferences and satisfaction play an important role in adherence to treatment and the greater number of daily doses is a factor that favors non-compliance[17].

Lack of adherence or compliance with antidepressant treatment affects response and therefore can lead to probable worsening or recurrence of symptoms, or chronicity of depression[16,18]. It is recommended to maintain the antidepressant treatment for at least one year, or for six months after having achieved the desired response[19]. However, some studies reveal that between 30% and 70% of patients abandon treatment in the first three months[16,18], some due to lack of response caused by a prescription with an inadequate dose.

The objective of the current study was to obtain information on adherence, acceptability, satisfaction and tolerability of the previously indicated treatment with venlafaxine XR 300 mg/day, after a period of use of 6 ± 2 months, comparing the dose taken in a single tablet versus two venlafaxine tablets.

METHODOLOGY

A post-authorization, observational, cross-sectional study of routine clinical practice was carried out with venlafaxine XR or retard of any brand available on the national market, used under the authorized conditions. The protocol, with AEMPS code: EXE-VEN-2020-01, was approved by the Drug Research Ethics Committee of the Getafe University Hospital, Madrid, before enrolling any patient in the study. All patients provided written informed consent, before inclusion in the study, which was carried out in accordance with the Declaration of Helsinki and the standards of Good Clinical Practice monitored by an independent organization. Participation was voluntary, without remuneration of any kind.

Participants

A total of 590 patients with MDD participated in the study, who were attended by 59 psychiatric specialists in public and private centers from all over Spain. The evaluation visits were between the months of May and December 2021.

The inclusion criteria were: being at least 18 years old, having a diagnosis of a depressive episode (F32), recurrent depressive disorder (F33) or dysthymia (F34) of any severity, according to the ICD-10 classification; having received treatment with venlafaxine XR or retard at a dose of 300 mg/day during the 6 ± 2 months prior to the study visit, being able to participate and respond adequately to the rating scales, and having given written consent to participate in the study. The exclusion criteria were: receiving simultaneous treatment with other psychotropic medications (other antidepressants, antipsychotics, corticosteroids), diagnosis of moderate or severe substance use disorder (DSM-5), any other condition that the investigator considered an impediment to participation in the study.

All study data were obtained from the patient interview, medical history, and validated questionnaires completed by the investigator or patient, as seen appropriate, during each patient's single visit with their physician.

Clinical Assessment

Physicians recorded anthropometric characteristics and evaluated vital signs, as well as medical history and concomitant medication.

The procedures and questionnaires completed by the physicians were: Haynes-Sackett method[20] to assess adherence to treatment, Montgomery-Asberg Depression Scale (MADRS)[21] and Clinical Global Impression of Improvement scale (CGI-I) to assess depression, in addition to recording adverse reactions and vital signs. The patients completed the Morisky-Green questionnaire[22], the treatment satisfaction questionnaire (Treatment Satisfaction Questionnaire for Medication, TSQM-9),[23] the impact of depression questionnaire (Patient Health Questionnaire, PHQ-9)[24] and the Clinical Global Impression of Improvement (CGI-I).

Statistical Analysis

A descriptive analysis of the categorical and quantitative variables was performed. Sociodemographic and clinical data are presented as mean and standard deviation, in addition to the 95% confidence interval of the means to assess the precision of the estimate. To compare the distribution of the mean of the parametric data, Student's *t* test was used. The summarized results of categorical variables are presented as absolute and relative frequencies. Adherence rate and treatment satisfaction were compared between the one- and two-tablet groups using the Chi-square test. The tolerability of the treatment was described. The significance level was set at 0.05 and all tests were two-tailed. For data analysis, the statistical package SPSS for Windows, version 20.0 (IBM software) was used.

RESULTS

The age of the patients ranged from 18 to 93 years (mean ± SD: 50.2 ± 13.3 years; 95% CI: 49.09, 51.25); 62.2% were women. The body mass index (BMI) was 25.38 ± 4.18

kg/m^2; 95% CI: 25.03; 25.73. A total of 58.8% (n=361) of the patients took one 300 mg venlafaxine XR tablet, and the rest took the same daily dose, but in two tablets.

Table 1 shows the anthropometric and clinical characteristics of the patients stratified according to the venlafaxine formulation in one or two tablets to complete the 300 mg/day dose. The characteristics of both groups were similar, with the exception of age (p=0.016).

12.9% (n=79) of the patients presented medical history of interest, in terms of the clinical history. On the date of inclusion in the study, the pathological situation had been resolved in 24 of them (30.4%), generally by surgical treatment. 56.9% of the patients received psychotherapeutic support and 44.2% took previous and concomitant medication. The most frequently used drugs were first-step analgesics, as well as anxiolytics, hypnotics, and sedatives, since most of the frequent concomitant pathologies were anxiety and insomnia.

Treatment adherence

The result of the Haynes-Sackett test showed an advantage in adherence to treatment with venlafaxine 300 mg/day in one tablet, but this difference was not statistically significant. 81% and 73.4% of the patients who received one and two tablets, respectively, stated that they had little or no difficulty in taking the medication (p=0.054).

The percentage of treatment adherence in both groups was similar (p=0.356) according to the Morisky-Green self-reported questionnaire. Table 2 shows that a significant percentage of patients sometimes forget or stop taking the medication when they feel that their symptoms are under control. Approximately half of the patients responded that they sometimes feel pressured to adhere to the treatment and, furthermore, that they have difficulty remembering to take all their medications.

Treatment satisfaction. TSQM-9 Questionnaire

This questionnaire has 9 items on a Likert scale from 1 to 7 and from 1 to 5 that evaluate three domains: efficacy (items 1 to 3), comfort (items 4 to 6) and global satisfaction (items 7 to 9) of the patient with the study drug. Most of the patients marked the highest scores on the Likert scale in all three domains. Figure 1 shows the average scores obtained in the TSQM-9 questionnaire discriminated between the two treatment groups. Scores

Table 1 Sociodemographic and clinical characteristics of the sample

	Treatment with venlafaxine XR 300 mg				p
	1 tablet (n= 361)		2 tablets (n= 229)		
Sex	n	%	n	%	
Males	139	62.3 %	84	37.7 %	
Females	222	60.5 %	145	39.5 %	0.664
	Mean	S.D.	Mean	S.D.	p
Age (years)	49.12	12.99	51.82	13.67	**0.016**
Height (cm)	167.99	8.52	167.80	8.96	0.806
Weight (kg)	72.21	13.0	70.58	12.94	0.147
BMI (kg/m2)	25.60	4.30	25.01	3.95	0.104
Cardiac Frequency (ppm)	78.04	11.80	76.89	11.77	0.257
Systolic blood pressure (mmHg)	126.22	15.20	125.98	14.61	0.851
Diastolic blood pressure (mmHg)	77.06	10.40	78.14	11.13	0.240

Anthropometric and clinical characteristics of the patients stratified according to the formulation of venlafaxine. in one or two tablets. to complete the 300 mg/day dose.

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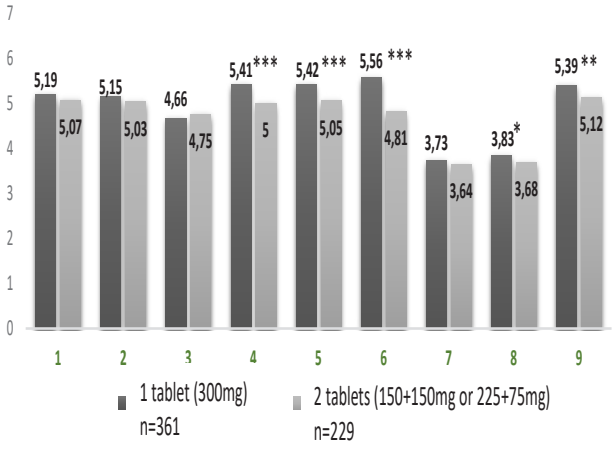
Table 2 Morisky-Green questionnaire. Adherence to treatment. Answer: "never/rarely"

	Total sample (n= 590) %	Treatment with venlafaxine XR 300mg 1 tablet (300 mg) (n= 361) %	2 tablets (150+150 mg o 225+75 mg) (n= 229) %
1. Do you ever forget to take medicines?	344 (58.3%)	224 (62.0%)	120 (52.4%)
2. People sometimes skip taking their medications for reasons other than forgetting. Over the past 2 weeks. were there any day you did not take your medication?	404 (68.5%)	257 (71.2%)	147 (64.2%)
3. Have you ever cut back or stopped taking your medicine without first talking to your doctor because you felt worse after taking it?	408 (69.2%)	261 (72.3%)	147 (64.2%)
4. When you travel or leave home. do you sometimes forget to take your medicine?	392 (66.4%)	250 (69.3%)	142 (62.0%)
5. Did you take all medication yesterday? (Yes)	549 (93.1%)	340 (94.2%)	209 (91.3%)
6. When you feel better. do you stop taking your medicine?	376 (63.7%)	238 (65.9%)	138 (60.3%)
7. Taking medication every day is a real inconvenience for some people. Do you ever feel pressured to stick to your treatment plan?	300 (50.8%)	193 (53.5%)	107 (46.7%)
8. How often do you have trouble remembering to take all your medication?	326 (55.3%)	206 (57.1%)	120 (52.4%)

Cuestionario autocumplimentado de Morisky-Green que muestra la adherencia al tratamiento con venlafaxina 300 mg/día en uno o dos comprimidos.

indicating satisfaction with treatment were found to be higher on all three comfort items (4 to 6) and on two of the three global satisfaction items in patients taking a single 300 mg tablet compared with those taking the same venlafaxine dose in two tablets.

Figure 1 Mean Score of the TSQM-9 Questionnaire Treatment Satisfaction



*p=0,033; **p=0,002; ***p<0,000 calculated with Student´s t test.

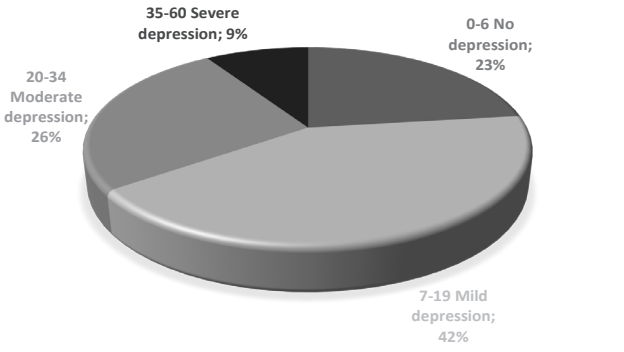
1. How satisfied or dissatisfied are you with the ability of the medication to prevent or treat your condition?
2. How satisfied or dissatisfied are you with the way the medication relieves your symptoms?
3. How satisfied or dissatisfied are you with the amount of time it takes the medication to start working?
4. How easy or difficult is it to use the medication in its current form?
5. How easy or difficult is it to plan when you will use the medication each time?
6. How convenient or inconvenient is it to take the medication as instructed??
7. Overall, how confident are you that taking this medication is a good thing for you?
8. How certain are you that the good things about your medication outweigh the bad things?
9. Taking all things into account, how satisfied or dissatisfied are you with this medication?

Results of the TSQM-9 Treatment Satisfaction Questionnaire for Medication obtained for 590 patients with major depressive disorder (MDD) who received treatment with venlafaxine XR 300 mg/day in one or two tablets. Items 1 to 3 evaluate efficacy, 4 to 6 comfort, and 7 to 9 global satisfaction with the treatment

Assessment of Depression

After 6 ± 2 months of treatment, according to the MADRS scale, MDD had completely remitted in 23% of the patients, only 9% of the patients had severe, 26% moderate and 42% mild depression. (Fig. 2).

Figure 2 | Madrs scale. Assessment of depression



Results of the MADRS scale (Montgomery-Asberg Depression Scale) obtained for 590 patients with major depressive disorder (MDD) after 6 Â± 2 months of treatment with venlafaxine XR 300 mg/day in one (300 mg) or two tablets (150+150mg or 225+75mg).

The Self-Completed Patient Health Questionnaire (PHQ-9) that assesses patients' impression of the severity of their depression over the past two weeks showed that most patients (71.7%) had minimal or mild depression (Fig. 3).

This questionnaire asks an additional question: *"If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?"*

The patients responded:

- Not difficult at all: 181 (30.7%)

- Somewhat difficult: 284 (48.1%)

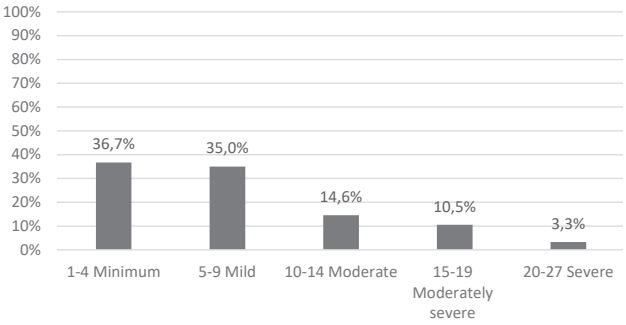
- Very difficult: 84 (14.2%)

- Extremely difficult: 20 (3.4%)

- No answer: 21 (3.6%)

Based on investigator assessment and after completing the Clinical Global Impression of Improvement (CGI-I) scale,

Figura 3 | PHQ-9 Questionnaire. Assessment of Depression



Assessment of depression during the last two weeks of treatment with venlafaxine XR 300 mg/day in one or two tablets, declared by the 590 study patients.

most patients (76.4%) were much better or moderately better (46.6% and 29.8%, respectively), compared to the initial moment of treatment. No difference was observed between the patients who took one or two tablets (Chi^2 p=0.107).

Tolerability

The adverse effects registered by the doctors were mainly of mild nature, none of them was a reason for discontinuation of treatment. The most frequent effects were sexual dysfunction, sweating and constipation (Table 3). Only 7.5% of patients who received venlafaxine showed mild hypertension, therefore it does not seem like blood pressure figures have increased due to the use of venlafaxine.

DISCUSSION

Guidelines on depression recommend that antidepressant treatment be maintained for at least one year before starting to gradually withdraw it or for 6 months after obtaining an adequate response[2,19]. Despite the proven efficacy of treatment, lack of compliance is associated with a risk of recurrence of depressive disorders and evolution towards chronicity[16,18,25]. In this study, an attempt was made to determine adherence to treatment in order to achieve active participation of the patient, assuming responsibility together with that of their prescribing physician. The most frequent reason for lack of adherence indicated by the patients was forgetfulness.

The estimation of adherence to treatment was really complex because it was based on the patient's verbal responses in the case of the Haynes-Sackett Method (H-

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Table 3 Registry of adverse effects in total sample

	Mild	Moderate	Severe	Total n (%)
Sexual dysfunction	218 (36.9%)	122 (20.7%)	29 (4.9%)	369 (62.5%)
Sweating	120 (20.3%)	37 (6.3%)	1 (0.2%)	158 (26.8%)
Constipation	103 (17.5%)	38 (6.4%)	3 (0.5%)	144 (24.4%)
Dry mouth	98 (16.6%)	30 (5.1%)	3 (0.5%)	131 (22.2%)
Nauseas	99 (16.8%)	18 (3.0%)	-	117 (19.8%)
Insomnia	76 (12.9%)	26 (4.4%)	-	102 (17.3%)
Headache	89 (5.1%)	11 (1.9%)	-	100 (17.0%)
Nervousness	66 (11.2%)	32 (5.4%)	-	98 (16.6%)
Fatigue	64 (10.8%)	15 (2.5%)	3 (0.5%)	82 (13.8%)
Dizziness	70 (11.9%)	8 (1.3%)	-	78 (13.2%)
Abdominal pain	54 (9.2%)	5 (0.8%)	1 (0.2%)	60 (10.2%)
Daze	48 (8.1%)	7 (1.2%)	-	55 (9.3%)
Hipertension	44 (7.5%)	-	-	44 (7.5 %)
Muscular pain	37 (6.3%)	3 (0.5%)	1 (0.2%)	41 (7.0%)
Drowsiness	26 (4.4%)	4 (0.7%)	-	30 (5.1%)
Diarrhea	28 (4.7%)	2 (0.4%)	-	30 (5.1%)
Migraine	15 (2.5%)	5 (0.8%)	1 (0.2%)	21 (3.5%)
Fainting	3 (0.5%)	2 (0.4%)	-	5 (0.9%)

Reported adverse effects from 590 patients with MDD after 6 ± 2 months of treatment with venlafaxine 300 mg/day in one (300 mg) or two tablets (150+150 or 225+75 mg).

S)[20] and on the Morisky-Green (M-G)[22] self-completed questionnaire. When comparing adherence to treatment for 6 ± 2 months between the two groups of patients applying the H-S method, the patients responded that taking the drug in either of the two presentations implied little or no difficulty. M-G's questionnaire revealed that almost all had taken the venlafaxine dose the day before the visit; however, a significant percentage of patients in both groups acknowledged that they sometimes forget or stop taking their medications or feel pressured to comply with a treatment plan. Given the impossibility of making a direct determination, indirect methods serve as a reference to assess adherence, knowing that they are susceptible to overestimating it. In one study, the M-G method showed a sensitivity between 72% and 84% and a specificity of 74.1% in the detection of poor compliance[25,26].

According to definitions based on psychosocial theories, satisfaction with treatment emphasizes the importance of the patient's attitude towards their treatment[18] and is related to adherence[27], so it is necessary to know the patient's preferences. If the possibility exists, the patient must be able to choose. According to Badía, *"a more satisfied patient takes the medication correctly for the prescribed time, which achieves the desired therapeutic result"*[27]. In the current study, 81% of the patients who took the 300 mg dose of venlafaxine in one tablet showed good adherence and higher treatment satisfaction than the patients who took the same dose in two tablets, probably because they considered it easier and more practical, according to their answers to the TSQM- 9, and stated that they were convinced that the advantages of the drug outweighed the disadvantages. These figures of good adherence are clearly higher than those estimated for the Hispanic population with MDD (69.8%)[5].

Although it was not an objective of this study, efficacy of venlafaxine treatment was observed. The MADRS scale score was low in most of the patients, as was the patients' impression of the severity of depression assessed using the PHQ-9 questionnaire. The CGI-I scale showed that 76.4% of the patients were much better (46.6%) or moderately better (29.8%), respectively, than before starting treatment.

In this study, the 300 mg/day dose of venlafaxine XR showed good tolerability, a low rate of adverse effects, and a very low potential for cardiotoxicity reflected in the fact that the number of people with hypertension was similar to that of the normal population and consistent with some

results previously published[8]. Even other adverse effects such as nausea showed a lower rate than that published in another study in which venlafaxine was used in doses of up to 225 mg/day as active control[28]. Side effects were generally derived from its serotonergic action, mild and self-limited at the beginning of treatment, as described by some authors[29,30]. The rate of sexual dysfunction present in the patients in this study was somewhat higher than that reported by Thase et al[7]. According to Solmi et al[16] different studies have shown that sexual dysfunction is not associated with treatment interruption. Regarding blood pressure, in the current study, with the use of venlafaxine XR 300 mg, there was no alarm signal in the incidence of hypertension, although causality could not be specified. In fact, no patient discontinued treatment, as has happened in other studies with a range of drop-off rates from 4.7%[8], 11%[31] to 13%[7].

CONCLUSIONS

Venlafaxine XR 300 mg/day is effective and well tolerated, showing a high remission rate of depressive symptoms in depressed outpatients. Patient satisfaction is significantly higher with a single tablet daily dose compared to two tablets.

Conflict of interests: IGR has collaborated with Jansen, Lundbeck, Pfizer, Exeltis and Lilly giving talks and participating in clinical studies. PLMF, has participated in publications promoted by Exeltis and Servier. PSG has received financial compensation for continued medical training from Janssen, Lundbeck, Rovi, Casen-Recordati and Angelini. FMC and CSG declare that they have no conflicts of interest.

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