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Effectiveness of venlafaxine in the treatment of alcohol dependence with comorbid depression

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Introduction. There are no conclusive data on the effectiveness of antidepressant drugs in the treatment of comorbid cases of alcohol dependence and depression.

Objectives. To determine the effectiveness of venlafaxine on depression and on severity (need of treatment) of alcohol dependence and related problems.

Methods. Observational, open-label, multicenter, 24-week follow-up study.

Patients. 90 outpatients with diagnosis of alcohol dependence and associated major depression disorder (DSM-IV criteria). Outcomes measures: the Hamilton Rating Scale for Depression (HAM-D_{17}), European Addiction Severity Index (EuropASI) and Clinical Global Impression, severity and improvement subscales, (CGI-S and CGI-I). Evaluations were performed at baseline and at weeks 2, 4, 8 and 24.

Results. Mean age 44.94 ± 9.74 years; 73.3 % men. HAM-D_{17} mean scores significantly decreased from baseline (24.85 ± 5.94) to week 24 (5.97 ± 4.68) and at each of the follow-up visits vs previous visit ($p < 0.0005$). Significant decreases from baseline to week 24 were obtained in four areas of EuropASI: medical status (2.12 ± 2.45 to 1.07 ± 1.68), alcohol use (5.29 ± 2.24 to 3.04 ± 2.35), family/social relationships (3.68 ± 2.36 to 1.71 ± 2.06) and psychiatric status (5.61 ± 1.81 to 2.67 ± 2.03). Tolerance was excellent or good in 76.7 % of the patients.

Conclusions. Venlafaxine was demonstrated effective in the treatment of depressive alcoholic patients. Furthermore, it seems to be useful to decrease the severity of problems related with the alcohol use.

Key words:
Alcohol dependence. Depression. Treatment. Venlafaxine.

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Efectividad de venlafaxina en el tratamiento de la dependencia de alcohol con depresión comórbida

Introducción. Faltan datos concluyentes sobre la efectividad de los antidepresivos en el tratamiento de los casos comórbidos de dependencia de alcohol y depresión.

Objetivos. Determinar la efectividad de la venlafaxina sobre la depresión y sobre la gravedad (necesidad de tratamiento) de la dependencia de alcohol y problemas relacionados.

Métodos. Estudio observacional, abierto, multicéntrico de 24 semanas de seguimiento.

Pacientes. Noventa pacientes ambulatorios con diagnóstico de dependencia de alcohol y trastorno depresivo mayor (criterios DSM-IV). Medidas de resultados: escala de Hamilton de Depresión (HAM-D_{17}), Índice Europeo de Severidad de la Adicción (EuropASI) e Impresión Clínica Global (subescalas de gravedad y mejoría) (ICG-S e ICG-M). Evaluaciones basal y en las semanas 2, 4, 8 y 24.

Resultados. Edad media: 44,94 ± 9,74 años; 73,3 % varones. Disminución significativa de las puntuaciones en HAM-D17 desde la visita basal (24,85 ± 5,94) a la semana 24 (5,97 ± 4,68) y en cada una de las visitas de seguimiento frente a la visita previa ($p < 0,0005$). Reducciones significativas en el EuropASI desde la basal a la semana 24 en las áreas: situación médica (2,12 ± 2,45 a 1,07 ± 1,68), uso de alcohol (5,29 ± 2,24 a 3,04 ± 2,35), relaciones familiares/sociales (3,68 ± 2,36 a 1,71 ± 2,06) y estado psiquiátrico (5,61 ± 1,81 a 2,67 ± 2,03). La tolerancia fue excelente o buena en el 76,7 % de los casos.

Conclusiones. Venlafaxina demostró ser efectiva en el tratamiento de la depresión en pacientes dependientes de alcohol. Además parece ser útil para reducir la gravedad de los problemas relacionados con el uso de alcohol.

Palabras clave:
Dependencia de alcohol. Depresión. Tratamiento. Venlafaxina.

INTRODUCTION

The epidemiological studies on psychiatric comorbidity have manifested a frequent association between depression and alcohol dependence[1]. However, the reason for this elevated association is still unexplained, in spite of the important therapeutic implications[3]. Some authors advocate the existence of a causal relationship between both; either the alcohol dependent patients experience depression as a result of chronic use, because of the neurochemical changes produced or due to the psychosocial losses associated with alcohol use[3] or the excessive alcohol use responds to an attempt of the patient to self-medicate his/her primary depression[4]. Alternatively, other authors defend that depression and alcohol dependence are two different diseases with independent courses, but with common etiopathogenic factors.

The etiopathogenic hypotheses have special importance in regards to treatment implementation, antidepressive treatment being essential in the cases in which the problems with alcohol are secondary to depressive pathology. However, there are increasingly more data that suggest that antidepressive treatment is also effective in the cases of primary alcoholism[5]. This would be related, on the one hand, with faster recovery and consequent decrease in suicide risk and, on the other, with the role played by serotonin in depression and alcohol dependence[6].

Up to now, clinical trials have been performed with tricyclic antidepressants and with serotonin reuptake inhibitors for the treatment of alcohol dependence in patients with or without comorbid depression. The results of the studies performed with tricyclic antidepressants are contradictory[7,8], although it seems that these drugs have little effect on alcohol use reduction in manifestly depressed patients. On the contrary, there is some evidence on the effectiveness of the serotonin reuptake inhibitors to reduce alcohol use and improve depressive symptoms of this type of patients[5,9-11]. However, this fact has not been confirmed in other studies [12,13]. In the case of venlafaxine, three open studies with a reduced number of patients suggest that it could be effective and well-tolerated in the treatment of patients with substance abuse and comorbid depression or with associated attention deficit/hyperactivity disorder[14-16]. Upadhyaya et al., in a 12 week long open study in adult outpatients with attention deficit disorder and comorbid disorders due to substance use, found that venlafaxine is associated with a decrease in alcohol use frequency and amount and in the intensity of craving for alcohol[15]. Another study found that although venlafaxine did not affect the choice of using cocaine, it decreased its subjective effects in 10% to 20% of the cases[17].

Given the inconclusive results, it was decided to perform an exploratory study on the effectiveness of venlafaxine in the treatment of patients with associated alcohol use and depression disorder. The main objectives were to determine the antidepressive effectiveness and the seriousness of the alcohol dependence and related problems, understood as need for treatment, in dependent patients who had undergone alcoholic detoxification treatment. As secondary objectives, drug safety and tolerability and degree of treatment compliance were evaluated.

METHODS

This is an observational, open label, multicenter, 6 month follow-up study.

PATIENTS

The study was performed in adult patients diagnosed of alcohol use disorder who had undergone detoxification treatment and who had associated depression.

The study inclusion criteria were: fulfill the DSM-IV criteria for alcohol dependence and major depressive disorder (single episode, recurrent episode and depressive episode in the context of a bipolar disorder), obtain a score greater than 17 on the 17-item Hamilton rating scale for depression ($HAM\text{-}D_{17}$)[18,19] and be under detoxification treatment. Exclusion criteria were considered to be: pregnancy and breast-feeding, serious suicide ideation, history of myocardial infarction in previous 6 months, rhythm disorder and cardiac conduction and/or hypersensitivity to venlafaxine, as well as the administration of MAOIs in the two weeks prior to inclusion in the study or any other psychodrug in the previous 30 days.

The patients who fulfilled all the inclusion criteria and none of the exclusion criteria initiated treatment with venlafaxine with the initial dose at the investigator's criteria, it being possible to increase it until a maximum recommended dose of 375 mg/d. In addition to the baseline visit, follow-up visits were carried out at weeks 2, 4, 8 and 24 (final visit).

RESULTS MEASUREMENTS

As measures of main effectiveness, the 17-item $HAM\text{-}D_{17}$ (baseline visit and weeks 2, 4, 8 and 24), the European version of the Addiction Severity Index (EuropASI)[20,21] (baseline visit and week 24) and the Clinical Global Impression scale in its severity and improvement versions (CGI-S and CGI-I) according to the physician's and patient's opinion (baseline visit and weeks 2, 4, 8 and 24)[22] were used.

As secondary measures, therapeutic compliance degree and safety and tolerability to venlafaxne treatment were used. The latter was evaluated by determination of cardiovascular safety parameters (heart rate and blood pressure) and the recording of adverse reactions that occurred, assess-

ing their seriousness and the relationship with the study treatment (weeks 2, 4, 8 and 24). Furthermore, in the final visit (week 24), tolerability to venlafaxine treatment was determined according to the physician's and patient's opinion.

The EuropASI is a semistructured and standardized interview designed to evaluate the seriousness of the addiction, defining this as the need of treatment. Besides alcohol use and that of other drugs, it also evaluates other areas of the patient's life that can be influenced or influence his/her addiction problem. These areas are: medical status, occupation/support condition, family/social relationships, legal problems and mental status. From the clinical point of view, it provides useful information to describe the patients' needs at the onset of treatment, to assign the patients adequate therapeutic strategies and to evaluate therapeutic intervention results.

Statistical analysis

For the quantitative variables, previous hypothesis tests were used: Barlett's test for homogeneity of variances, Cochran's test for homogeneity of variances, Kolmogorov-Smirnov normal distribution goodness of fit test. In the intergroup comparisons, the Student-Fisher *t* test for independent data in those variables that fulfilled the normality and homocedasticity condition and the Mann-Whitney U Test for the non-parametric treatment of variables or when these maintained order between values. In the latter test, correction for ties was applied. For the intragroup comparisons, the Student-Fisher *t* test for paired data was used when the test application conditions were fulfilled, and if not, the Wilcoxon matched pairs signed range test, with correction for ties was used. In the qualitative variables, in the case of intergroup comparisons, the chi squared and Fisher's exact test (or Yates correction when the data characteristics required it) were used. When the expected frequency did not fulfill the test application conditions, regrouping of the contiguous columns was performed. In every case, a $p<0.05$ value was considered statistically significant. The analysis was performed with the SPSS 7.5 standardized statistical program in Windows versions.

RESULTS

A total of 90 patients were included. The mean age was 44.94 years (SD 9.74), 73.3% being men. Most of the patients (65.9%) had a single major depressive episode, while 34.1% were diagnosed of recurrent depressive disorder. A total of 78% of the patients took concomitant medications in the baseline visit, the most frequently used being clorazepate dipotassium and calcium carbamide (28.2% and 24.4%, respectively).

Venlafaxine was administered orally continuously for 24 weeks. The mean dose of venlafaxine prescribed in the baseline visit was 92.19 ± 34.34 mg/day (median of 75 mg/day). The venlafaxine dose increased in each one of the study visits ($p=0.005$). At the end of the 24 weeks of the study, the mean venlafaxine dose was 112.03 ± 46.02 mg/day (median of 75 mg/day).

The effectivity analysis was performed on a total of 81 patients, given that 9 patients were withdrawn from it due to protocol violation (2 cases) or dropped out before the third follow-up visit - week 8 (7 cases). Continued treatment with venlafaxine during 24 weeks was associated with a significant decrease ($p<0.0005$) of the score on the HAM-D_{17} scale in each one of the follow-up visits compared with the score on the previous visit. Thus, the mean score decreased from 24.85 ± 5.94 (median: 23; range: 28-40) on the baseline visit to 5.97 ± 4.68 (median: 5; range: 0-20) in week 24 (table 1). The mean scores on the HAM-D_{17} scale in the intermediate visits were: 17.06 in week 2, 11.11 in week 4 and 8.32 in week 8.

Equally, significant reductions were observed in the EuropASI scores in the following areas: medical status, with an initial score of 2.12 ± 2.45 and 1.07 ± 1.68 in the final visit ($p<0.001$); alcohol use, from 5.29 ± 2.24 in the baseline visit until 2.24 ± 2.35 in the final visit ($p=0.000$); family/social relationships, with scores of 3.68 ± 2.36 and 1.71 ± 2.06 (initial and final visits, respectively, $p=0.000$) and mental status, with an initial score of 5.61 ± 1.81 and final one of 2.67 ± 2.03 ($p= 0.000$). In the remaining areas of the EuropASI, although reductions were observed in the scores, they did not reach statistical significance (table 1). In regards to the picture severity according to the clinician's opinion, 95% of the patients were considered as moderately/noticeably/intensely depressed (CGI-S) in the baseline visit. This percentage decreased to 9.1% in the final visit ($p=0.000$). Treatment with venlafaxine was associated to the 24 weeks with

Table 1 Evolution of the mean scores of the Halmilton Rating Scales for Depression (HAM-D) and EuropASI, from the baseline visit to the end (week 24)

	Baseline visit	Week 24	p <
HAM-D_{17}	24.85 (5.94)	5.97 (5.97)	0.0005
EuropASI			
Medical status	2.12 (2.45)	1.07 (1.68)	0.001
Employment/supports	1.28 (2.06)	1.29 (1.87)	ns
Alcohol use	5.29 (2.24)	2.24 (2.35)	0.000
Drug use	0.23 (0.94)	0.13 (0.59)	ns
Family/social relationships	3.68 (2.36)	1.71 (2.06)	0.000
Legal problems	0.28 (1.01)	0.19 (0.74)	ns
Mental status	5.61 (1.81)	2.67 (2.03)	0.000

a significant improvement of the patient's condition (CGI-I), according to the physician's and patient's opinion (p=0.000). The scores obtained in the CGI-S and CGI-I scales are summarized in table 2.

The compliance of venlafaxne treatment was considered as «good» in 82.9 % of the patients at the end of the study. Global tolerability to treatment with venlafaxine was considered as «good» or «excellent» in 76.7% of the cases, according to the assertions of the physician and patient. In all, 18 patients (20 %) dropped out of the study. The causes of drop-out were: loss to follow-up in 9 cases (50 %); due to adverse reactions (increase of sweating and gastrointestinal disorder) in 3 cases (16.6 %) and voluntary drop-out in six cases (33.3 %). A total of 92 adverse reactions were reported during the study that affected 33 patients (36.7 %), their intensity being considered as «mild» or «moderate» in 83.2 % of the cases. Of these, the causal relationship with the drug was «probable» in 32.9% of the cases and «possible» in 60.0%. The most frequently observed adverse reactions were nausea (8 episodes reported), followed by epigastralgia, headache and decreased libido (reported in 7 occasions each one) and dizziness and somnolence (reported each one on 5 occasions). Ten percent of the patients (n=9) reported adverse reactions having serious intensity. Of these, 3 cases (mouth dryness, increased sweating and vomiting) were considered as probably related with the administration of venlafaxine. The percentage of patients with adverse reactions decreased in the follow-up visits, it not being necessary to take any therapeutic attitude in 61.4 % of the cases, while it was necessary to reduce the drug dose in 12.3 % and withdraw the medication in 8.8 %. The mean values of heart rate and systolic and diastolic blood pressure did not suffer significant changes during the study and no cases of arterial hypertension were reported.

Table 2 Evolution, in percentage of patients, of the assessment of severity (CGI-S) and improvement (CGI-I) of the clinical picture, from the clinician's and patient's point of view

	Clinician assessment		Patient assessment	
	Baseline	Week 24	Baseline	Week 24
CGI-S*				
Not ill	0 %	71.1 %	0 %	72.3 %
Borderline/mild	5 %	19.8 %	6.2 %	17.1 %
Moderate/intense	95 %	9.1 %	93.4 %	10.6 %
	Week 2	Week 24	Week 2	Week 24
CGI-I*				
Much improved	4.9 %	72.4 %	4.9 %	69.7 %
Quite improved	44.9 %	21.4 %	33.3 %	19.8 %
Minimally improved	27.9 %	2.6 %	28.4 %	5.3 %
No changes	20.2 %	2.6 %	29.6 %	0 %
Minimally worse	2.5 %	0 %	2.5 %	0 %
Quite worse	0 %	1.3 %	1.2 %	1.3 %
Much worse	0 %	0 %	0 %	0 %

* $p < 0.000$.

DISCUSSION

Although the antidepressive efficacy of venlafaxine in depressive disorders has already been stated in other studies[23-28], we understand that this is the first study in which antidepressive efficacy is observed in patients who have a baseline disease of problems due to alcohol use-abuse. Continued treatment with venlafaxine for 24 weeks was significantly associated with an improvement of the depressive symptoms and the addiction severity, with a reduction in the need for treatment for the problems related with alcohol and with a global improvement, perceived both by the clinicians and by the patients themselves. The improvement in the EuropASI scores during treatment with venlafaxine may be due to several factors, among which improvement of the depressive symptoms with the consequent improvement of social, family and occupational relationships, the fact that abstinence times are increased, the anxiolytic effect of venlafaxine and its anticraving capacity and capacity to decrease impulsiveness, stand out.

On the other hand, venlafaxine was well-tolerated by the patients. The type of adverse events agrees with those reported in previous studies in depressed patients[29]. If we deal with the adverse reactions of this study, the most frequent were nausea, epigastralgia, headaches, decreased libido, dizziness and somnolence. Ten percent of the patients reported adverse reactions having serious intensity and of these, only 3 cases (mouth dryness, increased sweating and vomiting) were considered to be probably related with administration of venlafaxine. The percentage of patients with adverse reactions was decreased in the follow-up visits. However, the percentage of patients with adverse events is slightly greater to that reported by other studies. This could be due to several factors, among them the use of the immediate release formulation, presenting comorbid disease and taking other medications that could be the causes of some of these events. The mean values of systolic and diastolic blood pressure did not suffer significant changes during the study, no cases of arterial hypertension being reported.

CONCLUSIONS

The results of this open label, observational study suggest that venlafaxine could be effective in the treatment of depression in alcohol dependent patients. Furthermore, it has been observed that treatment with venlafaxine may contri-

bute to improvement of alcohol dependence related problems detected by the EuropASI. However, these promising results need to be replicated with studies on larger, placebo controlled series.

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