THE EFFICACY OF VENLAFAXINE ON DEPRESSIVE SYMPTOMS OF PATIENTS DIAGNOSED WITH BOTH ALCOHOL USE DISORDER AND MAJOR DEPRESSIVE DISORDER

Alkol Kullanım Bozukluğu ve Majör Depresif Bozukluk Tanısı Olan Hastalardaki Depresyon Belirtileri Üzerine Venlafaksinin Etkinliği

Ö. Ayhan Kalyoncu[1], Hasan Mırsal[1], Özkan Pektaş[1], Devran Tan[2], Mansur Beyazyürek[3]

ABSTRACT

Objective: The aim of our study was to determine the efficacy of venlafaxine on depressive symptoms of patients diagnosed with both alcohol use disorder and major depressive disorder.

Method: Patients with a diagnosis of both alcohol use disorder and MDD (Major Depressive Disorder) according to DSM-IV criteria, baseline Hamilton Depression Scale (HAM-D) scores of minimum 14 at first evaluation, abstinence from alcohol for at least 2 weeks and an age between 18 – 65 years were enrolled to the study. In the first week of the study, venlafaxine XR was administered at 75 mg/day. In the second week the dosage was increased to 150 mg/day which was the accepted treatment dosage. Hamilton Anxiety Scale (HAM-A), HAM-D, Clinical Glogal Impression Scale (CGI) and Symptom Check List (SCL-90-R) tests were applied to the patients. The patients were evaluated prior to study and on days -1, 8, 15, 22, 29, 43 and 57 of drug treatment.

Results: A total of 61 patients were screened for the study. As a result, 59 patients were included in the first visit and 4 of these patients discontinued the study. The reasons for discontinuation were: increase of depressive symptoms in two cases; one case manic shift; resumption of alcohol use in one case. HAM-D, HAM-A and SCL-90-R total scores decreased during the treatment period and this decrease was also statistically significant.

Conclusion: Our results suggest significant improvement in depression and anxiety symptoms during venlafaxine XR treatment in patients diagnosed with both alcohol use disorder and major depressive disorder.

Key words: Venlafaxine, depression, alcohol dependence, efficacy.

ÖZET

Amaç: Bu çalışmanın amacı alkol kullanım bozukluğu ve majör depresif bozukluk tanısı olan hastalardaki depresyon belirtileri üzerine venlafaksinin etkinliğini belirlemektir.

Yöntem: Çalışmaya; DSM IV tanı ölçütlerine göre hem alkol kullanım bozukluğu hem de majör depresif bozukluk tanısı alan, başlangıçta Hamilton Depresyon Ölçeği (HDÖ) puanı en az 14 olan, en az iki haftadan bu yana alkol almayan 18-65 yaşları arasındaki hastalar alınmıştır. Çalışmanın ilk haftasında hastalara 75 mg/gün venlafaksin verilmiştir. İkinci haftada doz çalışmanın tedavi dozu olan 150 mg/güne çıkılmıştır. Hastalara; Hamilton Anksiyete Ölçeği (HAÖ), HDÖ, Klinik Global Izlem (KGI) ölçeği, Belirti Tarama Listesi 90-R (BTL 90-) uygulanmıştır. Hastalar tedavi öncesi ve tedavinin 1., 8., 15., 22., 29., 43., 57. günlerinde değerlendirilmiştir.

Bulgular: Çalışmaya 61 hasta alınmıştır. İki hasta çalışma dışı kalmış ilk görüşmeye 59 hasta alınmış 4 hasta çalışmayı bırakmıştır. Çalışmayı bırakma nedenleri; iki olguda depresif belirtilerin artış göstermesi, bir olguda manik aşamaya geçiş ve bir olguda alkol kullanımıdır. Tedavi süreci içinde HDÖ, HAÖ ve BTL 90-R puanlarında istatiksel olarak da anlamlı azalma saptanmıştır.

Sonuç: Bulgularımız, hem alkol kullanım bozukluğu hem de majör depresif bozukluk tanısı olan hastalarda venlafaksin tedavisi ile depresyon ve anksiyete belirtilerinde belirgin iyileşme olduğuna işaret etmektedir.

Anahtar kelimeler: Venlafaksin, depresyon, alkol bağımlılığı, etkinlik.

Bağımlılık Dergisi 2007; 8: 59-65 **Journal of Dependence 2007; 8: 59-65**

[1] Doç. Dr. Balıklı Rum Hastanesi Vakfı, Anatolia Klinikleri
[2] Uzm. Dr. Şırnak Devlet Hastanesi
[3] Prof. Dr. Balıklı Rum Hastanesi Vakfı, Anatolia Klinikleri

Yazışma Adresi / Address reprint requests to: Doç. Dr. Ö. Ayhan Kalyoncu, Balıklı Rum Hastanesi Vakfı, Anatolia Klinikleri, Belgrad Kapı Yolu No:2 Zeytinburnu - İstanbul - TURKEY
Elektronik Posta Adresi / E-mail address: akalyon@superonline.com Telefon / Phone: +90 (212) 547 16 00

5 Şubat 2007'de alınmış, 4 Mayıs 2007'de kabul edilmiştir. / Received February 5, 2007; accepted for publication May 4, 2007.

INTRODUCTION

Epidemiological studies show that alcohol dependence is commonly associated with a variety of other psychiatric disorders, prominent among which are mood disorders, one of which is major depressive disorder (MDD) which is a common and severe mental illness with a 17 % lifetime prevalence (1,2). It has been reported that individuals with MDD are four times more likely to also be alcoholics and treatment seeking individuals appear to be at greater risk of having co-morbid depression and alcoholism when compared with individuals in the general population (3).

Because its cost to society in terms of lost productivity, health care demands, psychosocial disruption, increased risk of suicide and even mortality is enormous, many clinicians judge that pharmacological treatments for this comorbid condition may be appropriate (3,4). In some but not all cases, depressive symptoms resolve with abstinence from alcohol use(2). The persistence of symptoms after a period of abstinence suggests the presence of a comorbid depressive disorder that requires specific treatment. Additionally, that reductions in depressive symptoms have been associated with improved drinking outcomes suggest that treatment of depression can help to promote recovery from alcohol dependence (5).

There has been a dramatic increase in both alcohol dependence research and depression over the past few decades, with the ultimate goal of designing new treatments. However, fewer studies have looked specifically at treatment of individuals with comorbid alcoholism and depression, in spite of high rates of co-morbidity between these two disorders (3).

There are some controversial studies evaluating the effect of nefazodone –which is a norepinephrine and serotonin (5-HT) re-uptake blocker and 5-HT2 receptor antagonist- on mood and anxiety symptoms and drinking behavior in depressed alcoholics. Some studies demonstrated that the patients taking nefazodone had lower depressive symptom scores and a better antidepressant response rates than those receiving placebo (6). On the other hand, there are trials showing that nefazodone exerted no significant effect on depressive symptoms(5).

Medications with serotonergic activity in the central nervous system have been of particular interest in the treatment of depressed alcoholics, and several clinical trials have examined the use of selective serotonin re-uptake inhibitors (SSRIs) in alcohol dependent patients(2). It was predicted that depressed alcohol dependent patients would show the greatest reductions in alcohol use with an SSRI or other antidepressant. Supporting this idea, there are studies showing significant reductions with fluoxetine and sertraline compared to placebo in depression and alcohol, both on short and long term follow-up in patients with MDD and alcohol dependence (3,7,8). Similarly, Mason et al. (9) have demonstrated the efficacy of an antidepressant drug desipramine in reducing both depression and alcohol consumption in depressed alcoholics. Moreover, Pettinati et al. recently reported that drinking behaviour was reduced with sertraline compared to placebo in non-depressed patients while no change was observed in patients with either lifetime or current depression (10).

Venlafaxine is another antidepressant drug that inhibits serotonergic and noradrenergic re-uptake and, to our knowledge, there are only a very few controversial clinical trials that evaluate the antidepressant and anxiolytic efficacy of this drug in alcohol use disorder with comorbid MDD. One of these studies compared the antidepressant and anxiolytic effects of venlafaxine and mirtazapine – which is a noradrenergic and specific serotonergic drug – during the early alcohol withdrawal phase. In this study, it was shown that the addition of mirtazapine but not venlafaxine to a standard psychotherapy-oriented alcohol detoxification treatment improved symptoms of depression and anxiety (11). In addition, in a clinical trial that examined the effectiveness of venlafaxine in the treatment of alcohol dependence with comorbid depression, it was shown that Hamilton Depression Scale (HAM-D) scores significantly decreased from baseline with venlafaxine (12).

The present study was undertaken to determine the efficacy, safety and tolerability of an eight week venlafaxin treatment on depression and anxiety symptoms in patients with alcohol use disorder – either hospitalized for a two week detoxification therapy and/or outpatients who use no alcohol– with comorbid major depressive disorder. All the patients included in the study had previously received inpatient detoxification treatment.

METHODS

Subjects

Subjects were recruited from patients of the Alcohol Treatment Center of the Anatolia Clinics in Balikli Greek Hospital between December 2003-June 2004 who met the inclusion and exclusion criteria and signed an ethics committee approved informed consent form after being informed in accordance with the Helsinki Declaration (Tokyo 2004) and International Conference on Harmonization (ICH) guideline for Good Clinical Practice (GCP) for this open, non-comparative, single center study. Inclusion criteria included a diagnosis of both alcohol use disorder and MDD according to DSM-IV criteria, baseline HAM-D scores of minimum 14 at first evaluation, a minimum of elementary school graduation (having five years of basic education), abstinence from alcohol for at

least 2 weeks (patients were included in the study following a recent detoxification inpatient treatment program or selected from the outpatient clinic) and an age between 18 – 65 years. Exclusion criteria included having another clinical psychiatric diagnosis such as bipolar disorder, other substance abuse disorder, psychotic disorder, primary anxiety disorder in accordance with DSM-IV criteria, having a MDD with psychotic signs and/or having a suicide risk, having a Clinical Institute Withdrawal Assessment for Alcohol (CIWA-Ar) total score exceeding 10 at the first evaluation, or to have suffered a relapse during the observation period. Relapse criteria were defined as follows: 1. Consumption of alcohol for 5 or more days over a period of one week; 2. Having consumed more than 5 standard drinks for men and 4 standard drinks for women at one time; 3. Having a blood alcohol level more than 100 mg/dl in the blood alcohol measure during a visit; 4. having a clinically based organic brain syndrome; 5. having a medical disorder related to alcohol use (alcoholic hepatitis, alcoholic cirrhosis, alcoholic dementia, Wernicke encephalopathy, Wernicke-Korsakoff psychosis etc.); 6. having a history of venlafaxine hypersensitivity or having a history of using venlafaxine for sufficient amount of time at adequate dose with/without benefit; 7. pregnancy, lactation, or having the potential of becoming pregnant and not using an approved method of birth control, or planning to become pregnant during the course of the study; 8. to have had an acute myocardial infarction within the previous 6 months, or having a history of or showing significant signs of cardiac, hematological, endocrinological, renal, hepatic or gastrointestinal disease; 9. a history of febrile convulsions during childhood, or epilepsy, head trauma, tumors etc.; 10. to have been diagnosed with a systemic neurological disease such as a mass inside the head; 11. having intellectual handicaps that would interfere with compliance to the study protocol 12; having significant abnormalities in pre-study physical examination, vital signs, electrocardiography (ECG), laboratory tests ; 13. to have participated in another drug study within the last 30 days.

Pre-study evaluations

Demographic characteristics of the patients were collected and a pre-study evaluation was performed a maximum 3 days before the onset of the study in order to assess compliance to the study criteria. The history of psychiatric disorders and psychotropic drug use of the patients were assessed and the diagnosis of major depression according to DSM-IV criteria was confirmed. Complete physical (including weight and height measurements) and neurological examinations were performed. Vital signs, such as heart and respiratory rate, and fever and blood pressure were recorded. The severity of withdrawal symptoms was defined using the CIWA-Ar scale. For this study, the authors prepared a Turkish translation of the CIWA-Ar, which was checked by blind back-translation and had good internal reliability with Cronbach's æ=0.80 (13). Laboratory tests were completed (whole blood including MCV, sodium, potassium, chloride, calcium, phosphorous, total protein, albumine, globuline, prothrombin time, AST, ALT, GGT, ALP, BUN, creatinine, uric acid, amilase). Complete urine tests, pregnancy tests and ECG examinations were performed. SCID-I was used for current alcohol dependence and other current diagnoses of psychiatric disorders. Hamilton Anxiety Scale (Total) (HAM-A), HAM-A psychic, HAM-A somatic, Hamilton Depression Scale (HAM-D), Clinical Glogal Impression Scale (CGI) and Symptom Check List-90-R (SCL-90-R) tests were applied.The Turkish clinical version of these scales and/or interviews have been demonstrated to be valid and reliable for the Turkish population (14, 15, 16, 17, 18, 19, 20, 21, 22). The vital signs were recorded before drug administration at the initial evaluation.

Drug administration, visits and concomitant drugs

Venlafaxin XR was applied - either as Efexor® 75 mg or as Efexor® 150 mg capsules - on full stomach 30-45 minutes after breakfast. In the first week of the study, venlafaxine XR was administered at 75 mg/day. In the second week the dosage was increased to 150 mg/day which was the accepted treatment dosage. In the event of no adequate treatment response by the 43rd day, dosage was increased to 225 mg/day. During the 8 week clinical observation, the patients were evaluated prior to study (Visit 1) and on days –1, 8, 15, 22, 29, 43 and 57 (Visits 2, 3, 4, 5, 6, 7 and 8) of drug treatment. Non-psychotropic drugs used to treat internal diseases or nonbenzodiazepine hypnotics (zopiclone etc.) were allowed to be used throughout the study. In case of anxiety, 1 mg single dose lorazepam not exceeding of 2 times a day could be used during the first two weeks of the study. The use of new medications, alcohol and other psychoactive substances was not allowed. In addition, for the course of the study, psychopharmocological medicines (antipsychotics, anticonvulsives, anxiolytics, other antidepressants, lithium, sumatriptan and sedative hypnotics), antihistaminics and beta blockers and electroconvulsive treatment were not applied.

Efficacy assessment

CIWA-Ar, Hamilton Anxiety Scale (HAM-A), Hamilton Depression Scale (HAM-D), Clinical Glogal Impression Scale (CGI) and Symptom Check List-90-R (SCL-90-R) tests were applied to the patients. At the initial evaluation before drug administration, the vital signs were recorded. CIWA-Ar was only performed once at the pre-study evaluation to determine the

severity of the patients' withdrawal symptoms. The other scores were obtained as follows: HAM-D (pre-study evaluation and on days 8, 15, 22, 29, 43, and 57; HAM-A (pre-study evaluation and on days 8, 15, 22, 29, 43, and 57) (total, psychic and somatic); CGI (pre-study evaluation and on days 15, 29, 43, and 57); SCL-90-R (pre-study evaluation and on days 15, 29, 43, and 57); blood alcohol level (pre-study evaluation and on days -1, 8, 15, 22, 29, 43, and 57). Primary efficacy variables as total HAM-D, HAM-A, SCL-90-R scores were obtained on day 57 or before. The secondary efficacy variable was CGI scores. The final efficacy score was determined by the data obtained at the final visit. Compared to patients' initial HAM-D scores if there was a 50 % or greater improvement in HAM-D score determined on day 43, this would be accepted as a clinical response. In such cases, the patient was followed without any further increase in the dose of venlafaxine.

Safety assessment

Full physical and neurological examinations of all participants were performed on pre-study evaluations and on day 57. Vital signs were taken on pre-study evaluation and on day -1, 8, 15, 22, 29, 43, 57. Body weight was measured on pre-study evaluation and on days 43 and 57. All laboratory tests other than the pregnancy test were performed on pre-study evaluation and on day 57. Serum pregnancy test was only performed in the pre-study evaluation. Side effects were followed on days 8, 15, 22, 29, 43 and 57.

Data analysis

The changes in HAM-D, HAM-A (psycic HAM-A, somatic HAM-A) and SCL-90-R (somatization, obsessive compulsive, personal susceptibility, depression, anxiety, phobic anxiety, paranoid thoughts, psychotism) scores throughout the treatment period were evaluated by Friedman test. In addition, CGI scores were analyzed by Wilcoxon Signed Ranks Test. Whenever a statistically significant difference was determined, all scores recorded in a visit were compared to the scores observed during treatment and the initial scores were compared to the scores after treatment by Wilcoxon rank sum test with Bonferronni correction.Bonferronni correction is a method that requires repetition of the statistical method according to the new significance level by dividing the existing significance level into a pair-wise comparison number. Because the pair-wise comparison number for HAM-D, psychic HAM-D, somatic HAM-D and HAM-A scores was 7 (For visits 1-3, 1-8, 3-4, 4-5, 5-6, 6-7 and 7-8), the significance level that was determined as 0.01 was altered to 01/7=0.0014 after Bonferronni correction. Likewise, because the double comparison number for SCL-90 (somatization, obsessive compulsive, personal susceptibility, depression, anguase, anxiety, phobic anxiety, paranoid thoughts, psychotism) scores was 5 (For visits 1-4, 1-8, 4-6, 6-7 and 7-8), the significance level was determined as 0.01/5=0.002 after Bonferronni correction. These significance levels are only valid for Wilcoxon rank sum tests that are used to make pairwise comparisons. All significance levels in the other evaluations were 0.05. The weight, temperature, pulse rate, systolic and diastolic blood pressure and respiration rate values were compared by Student's paired t test.

RESULTS

A total of 61 patients were screened for the study. One of the patients was not included because he had a CIWA-Ar total score exceeding 10 at the first evaluation and another patient was totally excluded from the study in the first visit because he refused to use the study drug. As a result, 59 patients were included in the first visit and 4 of these patients discontinued the study. The reasons for discontinuation were: relapse of depression in two cases (4th and 5th visit); one case manic shift (4th visit); resumption of alcohol use in one case (6th visit).

The demographic characteristics of the patients were presented in Table 1.

Table 1: The demographic characteristics of the patients

Gender	N	Mean age	Standard deviation	Minimum	Maximum
Female	9	40.38	4.66	33.50	49.28
Male	50	42.37	7.02	26.41	56.29
Total	**59**	**42.07**	**6.72**	**26.41**	**56.29**

All 59 patients enrolled were appropriate according to the inclusion criteria and did not show any of the exclusion criteria. No abnormal finding showing clinical significance were observed in either the physical or neurological examinations and laboratory tests that were performed, nor in vital signs such as heart and respiratory rate, fever and blood pressure. The CIWA-Ar mean score was 7.66 SD: 1.35 (minimum=3, maximum=9). The descriptive statistics concerning the CIWA-Ar total score, which is a scale to evaluate alcohol abstinence was presented in Table 2.

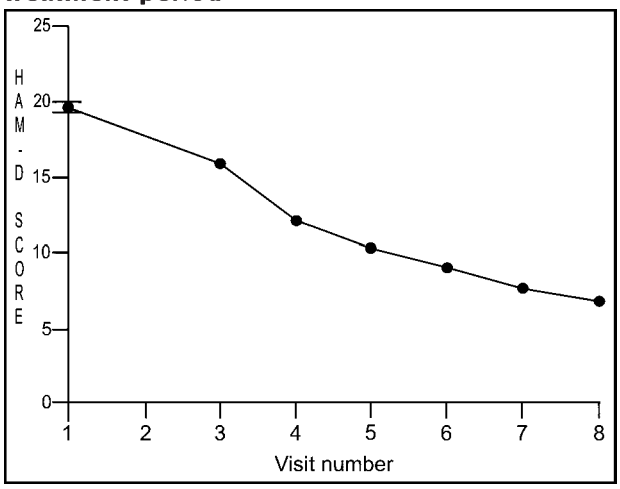
Table 2: The proportional distribution of CIWA-Ar total points

CIWA-Ar Total Points	N	%
3	1	1.69
4	1	1.69
5	2	3.39
6	5	8.47
7	14	23.73
8	17	28.81
9	19	32.20
Total	**59**	**100**

Efficacy results

As is clearly shown in Figure 1, HAM-D total scores decreased during the treatment period and this decrease was also statistically significant.

Figure 1: HAM-D total scores during the treatment period

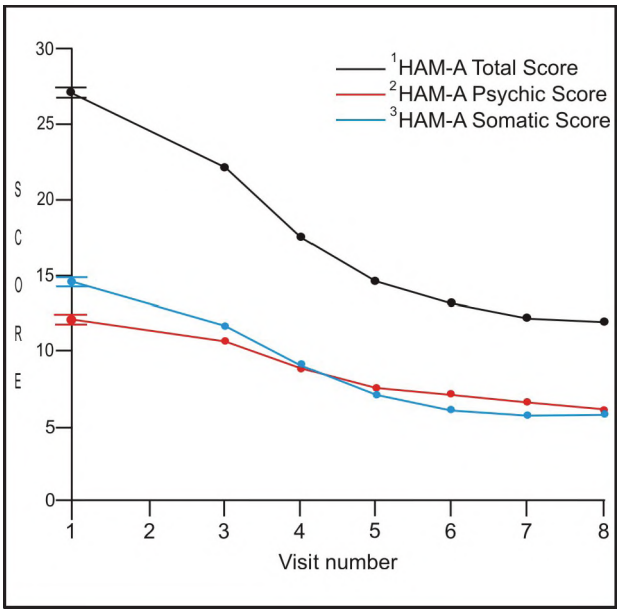


*(F = 271.90, P<0.0001)

Similarly, HAM-A total scores, psychic HAM-A, somatic HAM-A scores and SCL-90-R (somatization, obsessive compulsive, personal susceptibility, depression, anxiety, phobic anxiety, paranoid thoughts, psychotism) scores throughout the treatment period all decreased significantly as presented in Figures 2, 3.

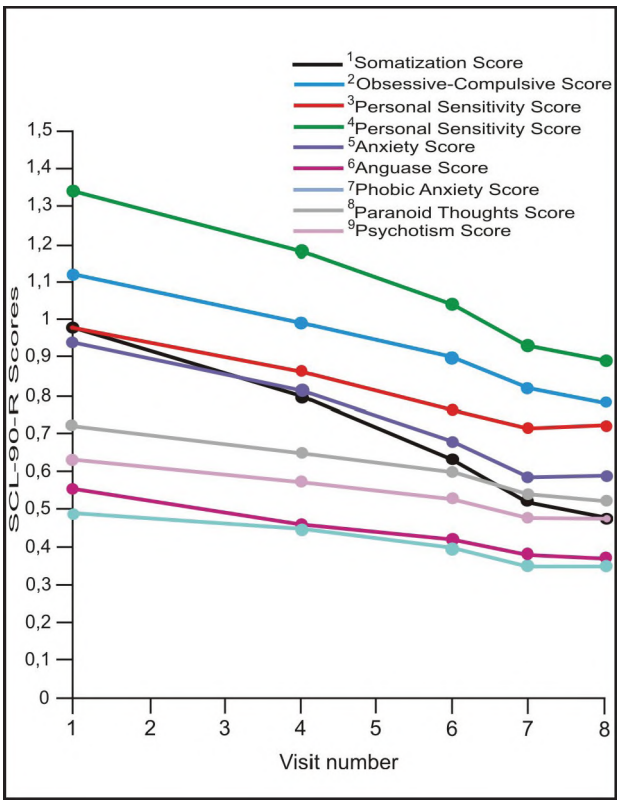
After the pair-wise comparisons with Bonferronni corrections made between the consecutive visits and between the 1st and 8th visits for HAM-D, HAM-A total, HAM-A psychic and HAM-A somatic scores, the differences between the 1st and 3rd visits, 1st and 8th visits and 3rd and 4th visits were determined to be significant. When the pair-wise comparisons with Bonferronni correction were made between the consecutive visits and between the 1st and 8th visits for SCL-90-R (somatization, obsessive compulsive, personal sensitization, depression, anxiety, anguase, phobic anxiety, paranoid thoughts and psychotism), no significant differences were found.

Figure 2: HAM-A total, psychic and somatic scores throughout the treatment period



[1](F=260.94, p<0.0001)
[2](F=262.20 P<0.0001)
[3](F=248.77, p<0.0001)

Figure 3: SCL-90-R scores throughout the treatment period



[1](F=71.56 p<0.0001)
[2](F=67.41, p<0.0001)
[3](F=56.67, p<0.0001)
[4](F=46.90, p<0.0001)
[5](F=69.08, p<0.0001)
[6](F=42.41, p<0.0001)
[7](F=21.88, p=0.0002)
[8](F=68.30, p<0.0001)
[9](F=28.58, p<0.0001)

The descriptive statistics that define the severity of the disease in different visits of the study as CGI were presented in Table 3. The difference was found to be statistically significant when all the visits of the study were evaluated.

Table 3: CGI analysis throughout the treatment period

Treatment period	CGI – Severity of the disease					
	N	Mean	Median	Standard deviation	Minimum	Maximum
1st visit	59	4.31	4.00	0.53	3.00	6.00
4st visit	57	3.54	4.00	0.73	1.00	5.00
6st visit	55	3.11	3.00	0.96	1.00	5.00
7st visit	55	2.93	3.00	0.96	1.00	4.00
8st visit	55	2.75	3.00	1.11	1.00	4.00

*Z = -7.56, p<0.0001

When the 55 patients who completed the 8th visit on the 57th day were evaluated, it was found that there were 41 patients (74.75 %) showing a 50 % or more decrease when compared with the baseline values. The confidence limits for this value were determined as 63.06 – 86.06. The drug dose was not increased for these patients. On the other hand, the dose was increased only for 14 patients (25.54 %) who showed a more than 50 % decrease in the same visit when compared with the baseline values.

Safety results

No adverse events involving the study drug were observed throughout the study.

DISCUSSION

Experimental and clinical studies support the hypothesis that serotonergic and noradrenergic dysfunction may be of importance in the development of alcohol abuse and dependence. On this basis, pharmacological agents such as tricyclic antidepressants and selective serotonin re-uptake inhibitors have been used in the management of depressed and non-depressed alcoholics either to reduce craving and alcohol intake or for the treatment of depressive symptomatology.

Our results suggest significant improvement in depression and anxiety symptoms and CGI analysis during venlafaxine XR treatment in patients diagnosed with both alcohol use disorder and major depressive disorder. Recently, Venlafaxine have been demonstrated to be effective in the treatment of depressive alcoholic patients and to be useful to decrease the severity of problems related with the alcohol use. The significant improvement in mood and anxiety in depressed patients with alcohol dependence with venlafaxine as shown by HAM-D total scores, HAM-A total scores, psychic HAM-A, somatic HAM-A scores and SCL-90-R scores was consistent with the findings of Garcia-Portilla et al. In this study, it was clearly stated that venlafaxine had demonstrated itself to be effective in the treatment of depressive alcoholic patients and it was useful in decreasing the severity of problems related to the alcohol use (12).

On the other hand, Liappas et al. reported that addition of venlafaxine to a standard psychotherapy-oriented alcohol detoxification treatment was not effective in minimizing psychosocial discomfort. This effect was related to the reported dopamine reuptake inhibition by venlafaxine, especially at doses above 225 mg/day and it was noted that it may not act favorably during alcohol withdrawal (11). We have also shown that venlafaxin was well tolerated and none of the patients experienced adverse events throughout the study period.

However, there were some limitations in the present study. There was no control nor was placebo group, and the study was time limited. Side effect scales were not taken into consideration. However, there are no side effects reported during clinical sessions to cut off or reduce the dose of the medicine. Since side effect scale were not taken into consideration, this situation could not be interpreted clearly. On the other hand, there were found interesting results about alcohol dependents' venlafaxine tolerance.

In conclusion, the present study provides evidence that venlafaxin XR is effective, safe and well tolerated when used for depression and anxiety symptoms in patients with alcohol use disorder with comorbid major depressive disorder.

REFERENCES

1- Nellisery M, Feinn RS, Covault J,Gelernter J, Anton RF, Pettinati H, Moak D, Mueller T, Kranzler HR.Alleles of a functional serotonin transporter promoter polymorphism are associated with major depression in alcoholics. Alcohol Clin Exp Res 2003; 27: 1402-1408.

2- Brown ES, Bobadilla L, Nejtek VA, Perantie D, Dhilon A, Frol A. Open-label nefazodone in patients with a major depressive episode and alcohol dependence. Progress in Neuro-Psychopharmacology and Biological Psychiatry 2003; 27: 681-685.

3- Moak D, Anton RF, Latham PK,Voronin KE,Waid RL, Durazo-Arvizu R. Sertraline and cognitive behavioral therapy for depressed alcoholics: results of a placebo-controlled trial. J Clin Psychopharmacology 2003; 23: 553-562.

4- Clark DB, Wood DS, Cornelius JR, Bukstein OG, Martin CS. Clinical practices in the pharmacological treatment of comorbid psychopathology in adolescents with alcohol use disorders. J Subst Abuse Treat 2003; 25: 293-295.

5- Hernandez-Avila CA, Modesto-Lowe V, Feinn R, Kranzler HR. Nefazodone treatment of comorbid

alcohol dependence and major depression. Alcohol Clin Exp Res 2004; 28: 433-440.

6- Roy-Byrne P, Pages KP, Russo JE, Jaffe C, Blume AW, Kingsley E, Cowley DS, Ries RK. A double blind placebo-controlled trial of nefazodone in the treatment of major depression in alcohol dependent patients 2000 ; J Clin Psychopharmacology 2000; 20: 129-136.

7- Cornelius JR, Salloum IM, Ehler JG, Jarret PJ, Cornelius MD, Perel JM, Thase ME, Black A. Fluoxetine in depressed alcoholics: a double blind, placebo controlled trial. Arch Gen Psychiatry 1997; 54: 700-705.

8- Cornelius JR, Clark DB, Bukstein OG, Kelly TM, Salloum IM, Wood DS. Fluoxetine in adolescents with comorbid major depression and an alcohol use disorder: a 3-year follow-up study. Addict Behav 2005; 30: 807-814.

9- Mason BJ, Kocsis JH, Ritvo EC, Cutler RB. A double blind, placebo controlled trial of desipramine for primary alcohol dependence stratified on the presence or absence of major depression. JAMA 1996; 275: 761-767.

10- Pettinati HM, Volcipelli JR, Luck G, Kranzler HR, Rukstalis MR, Cnaan A. Double blind clinical trial of sertraline treatment for alcohol dependence. J Clin Psychopharmacology 2001; 21:143-153.

11- Liappas J, Paparrigopoulos T, Tzavellas E, Rabavilas A. Mirtazapine and venlafaxine in the management of collateral psychopathology during alcohol detoxification. Progress in Neuro-Psychopharmacology and Biological Psychiatry 2005; 29: 55-60.

12- Garcia Portilla MP, Bascaran MP, Saiz PA, Mateos M, Gonzales-Quiros M, Perez P, Avila JJ, Torres MA, Bombin M, Caso C, Marin R, Prieto R, Bobes J. Effectiveness of venlafaxine in the treatment of alcohol dependence with comorbid depression. Actas Esp Psiquiatr 2005 ; 33: 41-45. (Spanish)

13- Sullivan JT, Sykora K, Schneiderman J, Naranjo CA, Sellers EM. Assesment of alcohol withdrawal: The revised clinical institude withdrawal instrument for Alcohol Scale (CIWA-Ar). Br J Addic 84:1353-1357.

14- First MB, Spitzer RL, Gibbon M, Williams JBW. Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I), Clinical Version. Washington, DC: APA: 1997.

15- Çorapçioğlu A, Aydemir Ö, Yildiz M, Esen A, Köroğlu E. "Structured Clinical Interview for Axis I Disorders", Clinical Version. Ankara. Hekimler Yayın Birliği, 1999 (Turkish).

16- Hamilton M. The assesment of anxiety states by rating. Br J Med Psychol 1959; 32: 50-55.

17- Yazıcı MK, Demir B, Tanrıverdi N, Karaağaoğlu E, Yolaç P. Hamilton Anxiety Rating Scale: interrater reliability and validity study. Turk Psikiyatri Derg 1998; 9:114-117. (Turkish).

18- Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960; 23; 56-62.

19- Akdemir A, Örsel SD, Dağ İ, Türkçapar H, İşcan N, Özbay H. Clinical use and the reliability and validity of the Turkish version of the Hamilton Depression Rating Scale. The Journal of Psychiatry Psychology Psychopharmacology 1996; 4:251-259. (Turkish).

20- Guy W. ECDEU Assessment Manual for Psychopharmacology - Revised (DHEW Publ No ADM 76-338). Rockville, MD, U.S. Department of Health, Education, and Welfare, Public Health Service, Alcohol, Drug Abuse, and Mental Health Administration, NIMH Psychopharmacology Research Branch, Division of Extramural Research Programs, 1976: 218-222.

21- Derogatis LR. SCL-90-R. Administration, Scoring and Procedure Manuel-I for the Revised Version. Baltimore, MD: John Hopkins Univ., School of Medicine, Clinical Psychometrics Unit, 1977.

22- Dağ İ. The reliability and validity of SCL-90-R for university students. Turk Psikiyatri Derg 1991; 2:5-12. (Turkish).