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The efficacy of venlafaxine in the treatment of depression, withdrawal symptoms, and craving in individuals with methamphetamine dependence

Faezeh Tatari[a], Vahid Farnia[a], Fatemeh Lalehgni[a], Asieh Moradi[b], Farnaz Radmehr[c], Omran Davarinejad[c], Sara Hookari[c], Safora Salemi[a], Farzaneh Golmohammadi[c], and Mostafa Alikhani[c]

[a]Department of Psychiatry, Substance abuse Prevention Research Center, Health institute, Kermanshah University of Medical Sciences, Kermanshah, Iran; [b]Department of Psychology, Faculty of Social Sciences, Razi University, Kermanshah, Iran; [c]Clinical Research Development Center, Imam Khomeini and Mohammad Kermanshahi and Farabi Hospitals, Kermanshah University of Medical Sciences, Kermanshah, Iran

ABSTRACT

Background: Currently, there is no confirmed drug intervention in the treatment of methamphetamine (MA) dependence. In the present study, we tested the possible influence of venlafaxine in individuals with MA dependence.

Methods: A total of 52 male patients (mean age: 33.93 years) diagnosed with MA dependence referred to Farabi Hospital in Kermanshah, Iran, was randomly assigned either to enlafaxine or a placebo condition. At the baseline, as well as 4 to 8 weeks later, patients completed questionnaires on depression, withdrawal symptoms, and cravings.

Results: The mean scores of withdrawal symptoms (hyperarousal, anxiety, reversed vegetative), depression, and cravings (desire & intention, negative reinforcement, and control) during the study and in both groups had a descending trend. Unlike the effect of the studied groups, the effect of time on the repeated measure model was significant. The mean of inverse symptoms, desire, and control from the fourth week to the end of the study did not have a statistically significant difference.

Conclusion: The results showed that venlafaxine can be effective in reducing depression, withdrawal symptoms, and cravings in people who are dependent on MA, though these results were observed in parallel in the placebo group, and as such warrants further study.

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KEYWORDS
Withdrawal symptoms; depression; craving; methamphetamine dependence

Introduction

Methamphetamine (MA) is a substance derived from amphetamines with strong psychotropic components (Sulaiman et al., 2014). It enters the central nervous system (CNS) quickly, resulting in the rapid onset of euphoria, which further encourages drug use (Vearrier et al., 2012). MA is highly addictive (Shariat & Elahi, 2010). Considering the use and dependency, along with MA, amphetamine (A) has become one of the most prevalently used drugs globally (United Nations Office on Drugs and Crime Vienna, 2012).

Previous research has reported high levels of depressive symptoms among MA-dependent users (Baker et al., 2005). Recent national epidemiologic data indicate that 41.6% of the adults with amphetamine use disorders and 35.7% of those with cocaine use disorders have a lifetime history of depression (Conway et al., 2006). Depression is one of the most prominent psychiatric complaints of MA users, which must be considered in the treatment of MA users (Glasner-Edwards et al., 2007; Srisurapanont et al., 2003). After abstinence, some patient's symptoms resolve or diminish during the first few weeks (Zorick et al., 2010) but some remain which may extend beyond a year or more (Iudicello et al., 2010). If left untreated, depression can reduce adherence to drug treatment, increase the risk of relapse to stimulant use, and elevate the risk of suicide (Baker et al., 2005; Glasner-Edwards et al., 2009).

On the other hand, dependence on MA includes a group of behavioral and cognitive factors, which, along with the significant problems it creates for the person, cause recurrence and continuous use of the drug. Cessation of MA use causes withdrawal syndrome, which is an important factor in continuous use or recurrence after withdrawal. The onset of withdrawal symptoms caused by stopping the use of drugs can sometimes lead to irreversible risks and make it difficult to treat drug addicts (Gold et al., 1978).

The symptoms of MA withdrawal, which are related to physical symptoms, are primarily psychological and emotional. According to various studies, the first symptoms of MA withdrawal symptoms include fatigue, lethargy and excessive drowsiness, increased appetite, dry mouth, and in some people, it occurs with the experience of aggression (McGregor et al., 2005). Studies have also shown that many people using MA, after withdrawal, experience severe depression and anxiety (Hellem, 2016; Marshall & Werb, 2010; Zhang et al., 2015).

In addition to withdrawal symptoms, the issue of cravings in MA addicts is very important. The craving for consumption is generally multidimensional (behavioral, cognitive, emotional). It is also the core of consumption and has a complex relationship with persistence, dependence, and recurrence, which as

CONTACT Mostafa Alikhani Mostafaalikhani18@gmail.com Substance Abuse Prevention Research Center, Health Institute, Kermanshah University of Medical Sciences, Kermanshah 6719851115, Iran

a mental experience of a strong temptation or desire and urgency, strongly predicts a return to drug use (Breese et al., 2011).

Although MA dependence has been considered a health and social problem for many years, the studies on pharmacological treatments are in the early stages (Elkashef et al., 2008; Rose & Grant, 2008).

Venlafaxine, a well-known antidepressant, has shown efficacy in the treatment of cocaine dependence in humans (McDowell et al., 2000). On the other hand, another study reported that venlafaxine was effective in the relapse of MA-induced Conditioned Place Preference (CPP) in rats (Althobaiti, 2019). Venlafaxine inhibits the neuronal uptake of HT-5 and norepinephrine (significantly less). The relative tendency of venlafaxine for HT-5 inhibition and norepinephrine uptake is dose-dependent and ascending. Venlafaxine at low doses is essentially an SNRI whose noradrenergic effects increase with dose elevation (Sadock et al., 2015).

Venlafaxine, however, is a novel antidepressant that has a unique pharmacological profile. Unlike other antidepressants, venlafaxine does not inhibit MonoAmine Oxidase (MAO) nor does it alter the activity of other receptors, such as adrenoceptors, histaminergic receptors, or muscarinic receptors (Richelson, 1996). Thus, it has fewer side effects when compared to other nonspecific antidepressants (Althobaiti, 2019).

This study was performed on MA addicts referring to Farabi Hospital in Kermanshah, where the researchers sought to answer the question of whether drug interaction with venlafaxine is effective enough to reduce depression, withdrawal symptoms, and cravings in male patients with MA dependence.

Methods

This research is a before-after clinical trial, double-blind with random allocation and control group study, along with a 2-month follow-up period and three stages of evaluation, which has been registered in the Iranian clinical trial site with the code IRCT20160717028967N8. The statistical population of the study included all patients with MA dependence who were referred to Farabi Hospital (Kermanshah University of Medical Sciences, Kermanshah, Iran) in 2018 for treatment; exclusive use of MA in them was confirmed by Thin-layer chromatography testing (TLC) or based on a Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) interview by a psychiatrist.

The required sample size according to the type of the study and taking into account the values reported for the effect of duloxetine, 0.6, against venlafaxine on the improvement of depression in depressed people equaled to 33 people in each group, which was obtained from the study of Cipriani et al. (2012), with the help of the following formula, $n = \frac{\left(z_{\frac{\alpha}{2}} + z_{1-\beta}\right)^2 \left(\sigma_1^2 + \sigma_2^2\right)}{\left(\mu_1 - \mu_2\right)^2}$ at the error level of 0.05 and the second type of error, 0.2 (80% power), as well as considering a 10% drop (6 people), where a total of 66 people were selected. After initiating the study, 11 people in the placebo group and 3 in the venlafaxine group were excluded from the study (Figure 1). The subjects were selected by the available method, during the project implementation period and from the members of the study community, according to the entry and exit criteria of the study.

The criteria for inclusion in the study for these people were male and exclusive users of MA and undergoing standard treatments to stop MA dependence. People with conditions, such as intellectual disability (intellectual developmental disorder), history of suicide attempt or suicidal ideation in the last 12 months, confirmation of psychotic symptoms over the last 6 months by one of the study physicians, receiving concomitant pharmacological and psychological interactions while receiving venlafaxine, having schizophrenia or bipolar disorder of any kind, recent use (within the last 2 weeks) of medications expected to interact with venlafaxine, medical prohibition on taking venlafaxine (e.g., severe hepatic impairment), and lack of willingness to participate in the study were excluded from the study according to the study exit criteria. Patients who reported adverse side effects due to the use of venlafaxine during the follow-up period of the study or those who did not complete the follow-up and the medication process in the study were also excluded from the study according to the exit criteria.

Regarding the methodology, after explaining the objectives of the study and obtaining informed and written consent, eligible volunteer patients entered the study. The participants, one by one, were divided into two equal groups of 33 people through random assignment. The first group consisted of patients receiving drug therapy with venlafaxine capsules, while the second group was composed of patients receiving placebo. To conceal the allocation and maintain the blindness in the study, venlafaxine and placebo were placed in similar capsules and in the same packages that were numbered. Out of 66 packages, 33 packages were numbered with code 1 and 33 packages with code 2. Inside the code 1 capsule was venlafaxine for the group being treated with venlafaxine, while there was a placebo inside the code 2 capsules for the group being treated with placebo. Inside each package with code 1, there were two blister packs, the first pack had 30 capsules of venlafaxine containing 37.5 mg of venlafaxine, for consumption in the first 4 weeks of the study, 1 capsule for each day, while the second pack had 30 capsules of venlafaxine containing 70 ml, for the second 4 weeks of the study, 1 capsule each day. In packages with code 2, there were two blister packs with the same number of capsules in them, each capsule containing 37.5 or 70 mg placebos. Thus, 66 drug packages were prepared, each belonging to one of the participants, where neither the experimenter nor the participant in the study knew in which group (the group treated with venlafaxine or the group treated with placebo) the patient was. These capsules were given to the patient without informing the patient and the experimenter, and the code for each drug was recorded in the patient's questionnaire. Venlafaxine was provided by Darou Pakhsh Pharmaceutical Company, Tehran, Iran, and the placebo were provided by the Faculty of Pharmacy of Kermanshah University of Medical Sciences, Kermanshah, Iran. Venlafaxine capsules (containing 37.5–70 mg of

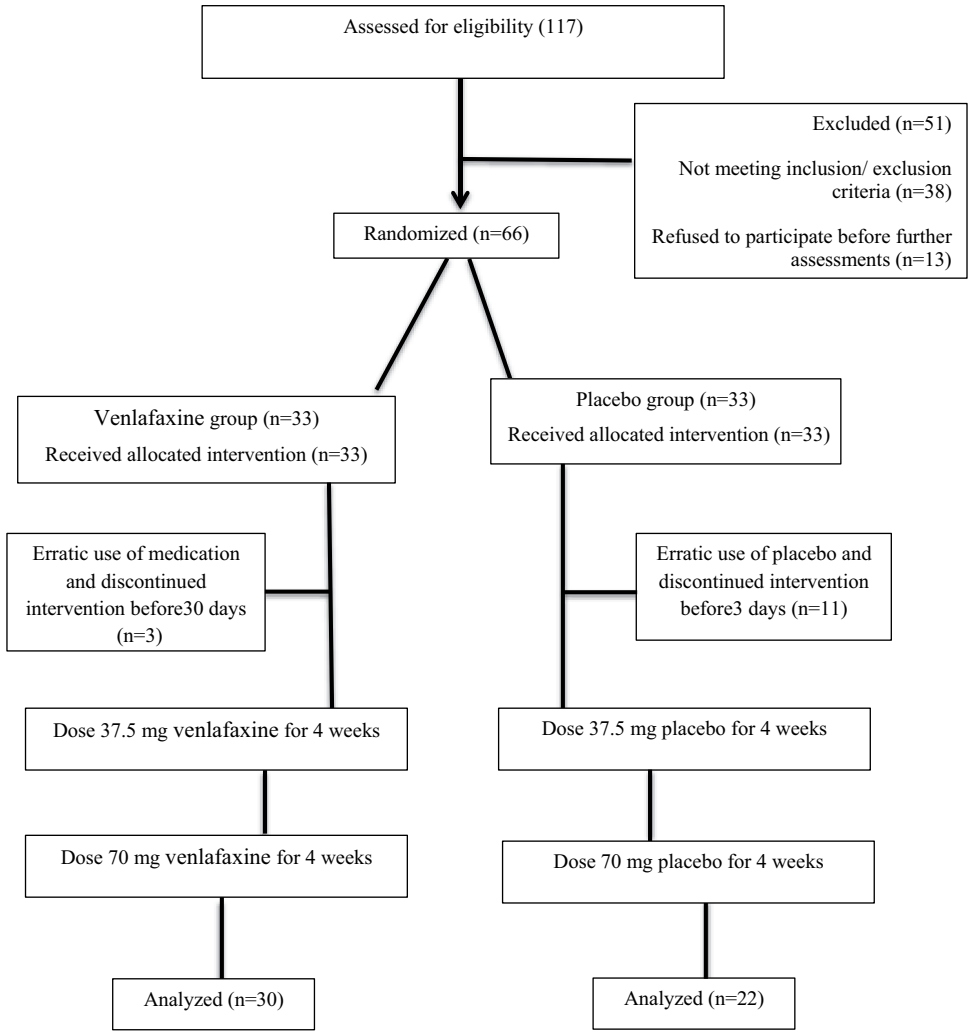

Figure 1. CONSORT diagram showing the flow of participants through each stage.

venlafaxine) and placebo capsules (containing lactose powder, 5% gelatin solution, and microcrystalline cellulose (MCC)) were similar in shape, size, color, and odor. Adverse side effects were checked and recorded by an experienced physician at each visit, and in case of any adverse side effects, use of the drug was discontinued and the person was excluded from the study. All patients participating in the study were evaluated for depression, withdrawal symptoms, and cravings in three stages over 8 weeks (at baseline, as well as 4 to 8 weeks later).

Desire for Drug Questionnaire (DDQ)

The DDQ is a 14-item questionnaire developed by Franken et al. (2002). This questionnaire has three subscales of desire and intention to use drugs, negative reinforcement, and perceived control over drug use. Its scoring method is based on a 7-point Likert scale (completely disagree to agree) (completely disagree answers receive a score of one and completely agree answers receive a score of seven). Franken et al. (2002) reported the total validity of this questionnaire by Cronbach's induction method of 0.85 and for its subscales by 0.77, 0.80, and 0.75, respectively. In Iran, in a study done by Mohammadi (2010), the total Cronbach's alpha value was 0.82, and its subscales were 0.70, 0.82, and 0.70, respectively (Mohammadi, 2010).

Amphetamine Withdrawal Symptoms Questionnaire Version 2 (AWQ-V2)

This questionnaire was designed by Srisurapanont et al. (1993). This questionnaire has 10 questions with Likert rating. Principal component analysis, eigenvalue-one test and a varimax rotation performed to elicit the factors of AWQ-V2 yielded a three-factor model of AWQ-V2: namely hyperarousal, reversed vegetative and anxiety factors. The reliability of this questionnaire has been reported 0.77 through Cronbach's alpha and 0.79 through retest. The validity of the questionnaire, through factor analysis, has also been reported appropriately (Srisurapanont et al., 1993).

Beck Depression Inventory, second edition (BDI-II)

The Beck Depression Inventory was developed by Beck in 1978 to measure the severity of depression. This questionnaire was revised in 1996 by Beck, Steer, and Brown. The inventory includes 21 questions from different signs of depression, each question gets a score between 0 and 3. The total score of the questionnaire is between 0 and 63. The results of the study

reported the internal stability of this instrument from 0.73 to 0.92 with a mean of 0.86 and the alpha coefficient for the patient group of 0.86 and a non-patient group of 0.81 (Beck et al., 2000). The Persian version of this questionnaire, which was administered to 354 subjects, reported a Cronbach's alpha coefficient of 0.91 (Dobson & Mohammadkhani, 2007).

Statistical analysis

Due to the executive nature of the research, the trend of changes in the means was evaluated by multivariate analysis of variance with repeated measures (GLMRM: General linear model repeated measure) over time (at the baseline and 4 to 8 weeks later), for the studied groups and the dependent variables (depression rate, withdrawal symptoms, and MA craving). Follow-up analyses were performed using Bonferroni simultaneous comparisons to adjust the significance level in multiple and simultaneous comparisons. Line graphs were also used to show the trend of changes in the mean of the mentioned concepts graphically during the follow-up period of the study. All analyses were carried out using SPSS20 statistical software at a significant level of 5%.

Results

Thirty patients in the intervention group treated with venlafaxine and 22 patients in the control group treated with placebo completed three study evaluation phases (at the baseline, and 4 to 8 weeks later) which lasted 2 months. In both groups, the majority of the participants were 20–35 years old, single, and unemployed. The first age of drug use in the control group for the majority of the participants was in the age group of less than 18 and the Venlafaxine group was between 19 and 25 years old and the average dose of the drug, the first dose of MA, and the average dose of MA in both groups, for the majority of participants was less than 1 g. In both groups, a history of recurrent drug use was reported. Subsequently, the result of the comparison of age, marital status, level of education, occupation, economic status, history of mental illness in the patient, type of mental illness in the patient, history of physical illness, the first age of drug use, average dose of the drug, first age of amphetamine consumption, the first dose of MA, average dose of MA consumption, number of recurrences, family history of addiction and family history of psychiatric illness, among the two groups, using Chi–square test with an error level of 5%, showed that the distribution of these characteristics in these two groups is completely homogeneous (Table 1).

During the follow-up period and in the Venlafaxine group, the number of people with slight and severe depression decreased and the number of people with mild and moderate depression increased. However, in the control group, during the study, the number of people with mild and slight depression increased slightly and the number of people with severe depression decreased (Table 2).

The mean score of depression during the follow-up period separately in placebo group 19.09 (8 weeks later), 20.64 (4 weeks later), 32.32 (at baseline) and in venlafaxine group 13.70 (8 weeks later), 17.73 (4 weeks later) and 27.03 (at

Table 1. A descriptive and statistical overview of sociodemographic variables separately by treatment condition.

Variable	Levels	Studied groups n (%) placebo	Studied groups n (%) venlafaxine	Total	df	χ^2 (p-value)
Age (years)	20-35	15(44.1)	19(55.9)	34(100.00)	1	0.132
	35<	7(38.9)	11(61.4)	18(100.00)		(0.475)
Marital	Single	15(45.5)	18(54.5)	33(100.00)	1	0.336
	Married	7(36.8)	12(63.2)	19(100.00)		(379)
Educational level	<High school	10(31.3)	22(68.8)	32(61.5)	1	4.168
	>high school	12(60.00)	8(40.00)	20(100.00)		(0.055)
Occupation	Employed	8(40.00)	12(60.00)	20(100.00)	1	0.071
	unemployed	(14(43.8)	18(56.3)	32(100.00)		(0.51)
Income	Low	11(37.9)	18(62.1)	29(100.00)	1	0.515
	Middle	11(47.8)	12(52.5)	23(100.00)		(0.332)
	High	—	—	—		
The first age of substance use	<18	14(56.00)	11(44.00)	25(100.00)	2	3.774
	19-25	5(27.8)	13(72.2)	18(100.00)		(0.152)
	>25	3(33.3)	6.(66.7)	9(100.00)		
The average dose of the substance	<1	12(48.00)	13(52.00)	25(100.00)	2	1.85
	1-2	10(40.00)	15(60.00)	25(100.00)		(0.396)
	>2	—	—	—		
The first age of MA use	<25	15(58.3)	10(41.7)	24(100.00)	1	2.38
	>25	7(35.00)	13(65.00)	20(100.00)		(0.107)
The first dose of MA	<1	20(46.5)	23(53.5)	43(100.00)	2	2.03
	1-2	2(25.00)	6(75.00)	8(100.00)		(0.362)
	>2	0(0.00)	1(3.3)	1(1.9)		
The average dose of the MA	<1	17(48.6)	18(51.4)	35(100.00)	2	2.097
	1-2	5(31.3)	11(68.8)	16(100.00)		(0.350)
	>2	0(0.00)	1(3.3)	1(1.9)		
The number of times the history of relapse	Yes	19(47.5)	21(52.5)	40(100.00)	1	1.91
	No	3(25.00)	9(75.00)	12(100.00)		(0.147)
Family history of addiction	Yes	10(47.6)	11(52.4)	21(100.00)	1	0.41
	No	12(38.7)	19(61.3)	31(59.6)		(0.362)
History of psychiatric illness in the family	Yes	4(40.00)	6(60.00)	10(100.00)	1	0.286
	No	18(42.9)	24(57.1)	42(100.00)		(0.538)
Total		22(100.00)	30(100.00)	52(100.00)		

Significant levels at $P < 0.05$.

Table 2. A descriptive overview of depression, withdrawal symptoms, cravings separately by assessment time (baseline 4 week, week 8) and group (placebo vs. venlafaxine).

		Assessment times					
		Baseline		Week 4		Week 8	
		Placebo (n=22) M (SD)	venlafaxine (n=30) M (SD)	Placebo (n=22) M (SD)	venlafaxine (n=30) M (SD)	Placebo (n=22) M (SD)	venlafaxine (n=30) M (SD)
BDI-II		32.32(14.02)	27.03(12.87)	20.64(14.37)	17.73(12.23)	19.09(14.37)	13.70(9.21)
AWQ-V2	hyperarousal	6.68(2.99)	5.60(2.78)	4.64(2.85)	3.60(2.14)	3.82(3.08)	2.83(2.04)
	anxiety	6.95(3.00)	5.30(3.12)	4.64(3.72)	3.93(2.98)	3.73(3.68)	3.30(2.51)
	reversed vegetative	7.32(2.69)	6.13(2.42)	5.95(2.61)	5.50(2.24)	5.45(2.69)	5.17(2.18)
	total AWQ-V2	23.64(8.50)	19.30(7.51)	17.00 (9.35)	14.33(6.47)	17.00(9.15)	14.33(6.37)
DDQ	desire & intention	2.74(1.61)	2.47(1.13)	1.95(1.17)	2.48(1.33)	2.03(1.05)	2.15(1.24)
	negative reinforcement	2.93(1.89)	2.94(1.49)	2.38(1.79)	2.63(1.29)	2.53(1.65)	2.34(1.18)
	control	2.25(1.67)	2.47(1.57)	2.07(1.53)	2.45(1.26)	1.25(1.28)	2.18(1.16)
	total DDQ	2.72(1.54)	2.60(1.04)	2.09(1.26)	2.52(1.22)	2.17(1.11)	2.21(1.13)

Abbreviations: n, number of subjects; M, mean; SD, standard deviation; BDI-II, Beck Depression Inventory-II; AWQ-V2, Amphetamine Withdrawal Questionnaire Version 2; DDQ, Desire for Drug Questionnaire.

baseline), showed that the mean of this concept in both groups of venlafaxine and placebo has a decreasing trend during the study (Table 2).

The mean score of MA withdrawal symptoms and its three sub-components, hyperarousal, anxiety, and reversed vegetative, in the three stages of the study evaluation and the studied groups, as shown in the table . Regarding the mean scores of hyperarousal components 2.83 (8 weeks later) and 3.6 (4 weeks later) and 5.6 (At baseline), anxiety 3.30 (8 weeks later) and 3.93: (four weeks later) and 5.30 (At baseline), reversed vegetative 5.17 (8 weeks later) and 5.50 (4 weeks later) and 6.13 (At baseline) as well as the total score of MA withdrawal symptoms 14.33: (eight weeks later) and 14.33 (4 weeks later) and 19.30 (At baseline), in the venlafaxine group and also their mean in the placebo group, hyperarousal 3.82 (end of the study) and 4.64: (end of the fourth week) and 6.68 (At baseline), anxiety 3.73 (8 weeks later) and 4.64 (4 weeks later) and 6.95: (At baseline), reversed vegetative 5.45 (8 weeks later) and 5.95 (4 weeks later) and 7.32 (At baseline) as well as the total score of MA withdrawal symptoms 17 (8 weeks later) and 17 (4 weeks later) and 23.64 (At baseline), during the follow-up period in the study, a decreasing trend was observed in the average value of each component during the evaluations (Table 2).

The mean score of MA craving symptoms and its three sub-components, desire, and intention, negative reinforcement, and control, by groups, is shown in Table 2. Regarding the mean score of MA craving symptoms as well as desire components, negative reinforcement, control in the venlafaxine group, and also the mean control component in the placebo group during the study follow-up period, a slightly decreasing trend was observed in the mean value of each component during the evaluations. Also, in the placebo group, for the mean components of desire, negative reinforcement, and the total score of MA craving symptoms, during the follow-up period of the study, a clear decrease and then a slight increase in the mean value of these scores can be seen (Table 2).

Symptoms of depression, as measured with the BDI-II, symptoms of Withdrawal as measured with the AWQ-V2 and craving, as measured with the DDQ decreased over time. But the effect of the group and the interaction of time and group showed that BDI-II, AWQ-V2, and DDQ scores did not decrease significantly in the venlafaxine and placebo condition (Figures 2–4).

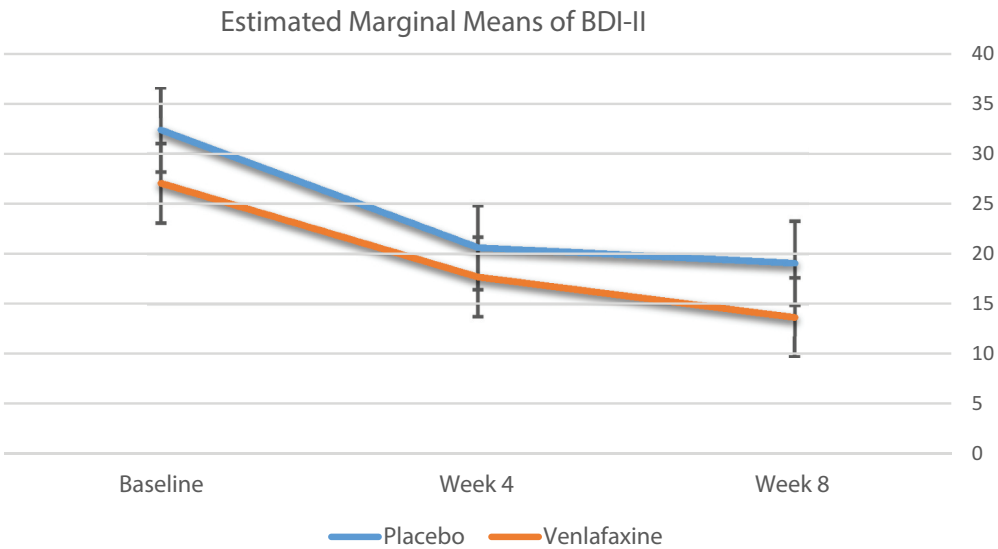

Figure 2. Symptoms of depression over time and within and between groups (placebo vs. venlafaxine) points are means. A lower score reflects fewer symptoms of depression.

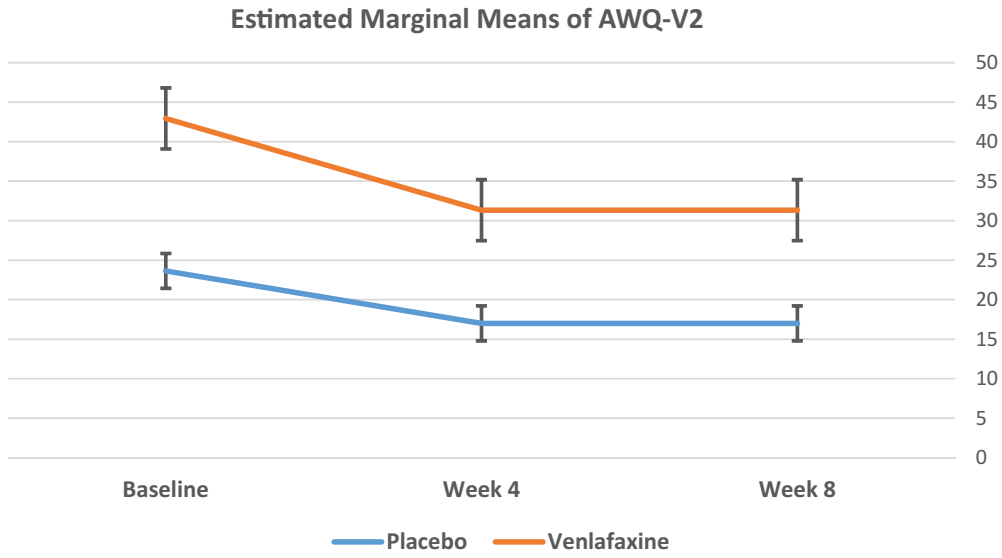

Figure 3. Symptoms of withdrawal over time and within and between groups (placebo vs. venlafaxine) Points are means. A lower score reflects fewer symptoms of withdrawal.

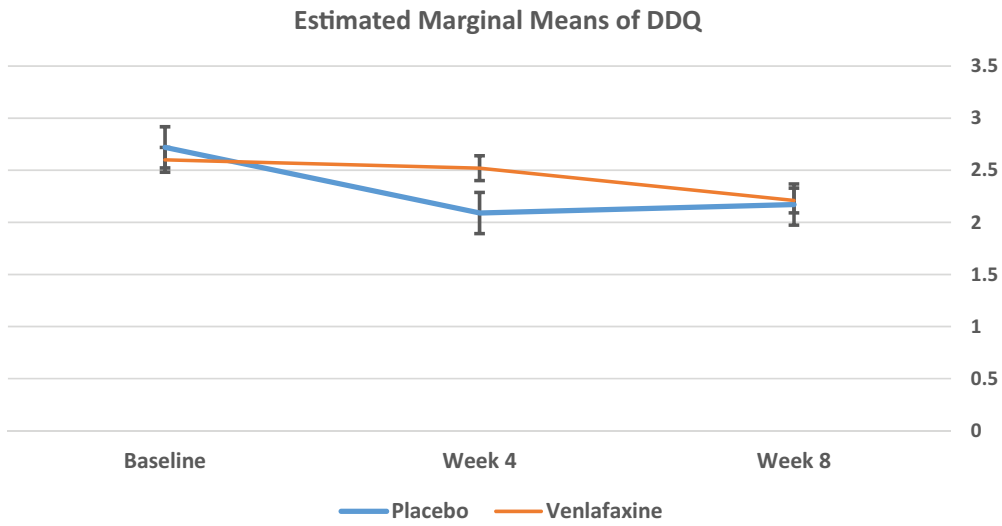

Figure 4. Craving over time and within and between groups (placebo vs. venlafaxine) Points are means. A lower score reflects less craving.

The results of examining the normality of the distribution of scores of depression symptoms; withdrawal symptoms of MA (hyperarousal, anxiety, reversed vegetative) and the score of MA craving symptoms (desire and intention, negative reinforcement, and control) in the three stages of the study evaluation and by study groups, and using Kolmogorov–Smirnov one-sample test showed that according to the significant levels of tests (not significant), the assumption of the normal distribution of scores of all these concepts in all the three stages is accepted between the two groups. To examine the trend of changes in the mean scores of MA withdrawal symptoms and its sub-component in detail, depression and cravings for MA and its sub-components during the study period and at the three study points. At the baseline and 4 and 8 weeks later, in the two studied groups, using repeated-measures analysis of variance method, the values of the dependent variables have been modelled based on their relationships with the periods in which they are measured as well as the studied groups.

Mean scores of depression, arousal, anxiety, reverse symptoms, total AWQ-II score, desire, negative reinforcement, control, and total DDQ score have decreased significantly over time. However, the effect of group, as well as the interaction of time and group, was not significant for any of the mentioned components over time. No statistically significant differences were observed between the two groups with using repeated-measures analysis of variance method.

For the interaction of time and group as well as the effect of time, the amount of effect size was reported to be small for all the studied concepts. But for the effect of time, the amount of effect of each of the components of depression, arousal, anxiety, inverse symptoms, the total score of AWQ-II was large and for the control component was small and for the concepts of desire, negative reinforcement, and the total score of DDQ was reported to average so that the average value of all of the mentioned components during the study time and in both

Table 3. Descriptive and inferential statistical indices of depression, withdrawal symptoms, and craving scores.

		Inferential statistics			
		Time	Group	Time x Group interaction	
BDI-II	Beck	F (2,118) = 26.91, p = 0.000; Partial.eta^2:0.350	F (1,59) = 2.67, p = 0.108; partial eta^2:0.051	F (2,118) = 0.272, p = 0.661; partial. eta^2: 0.005	Greenhouse-Geisser ε: 0.636
AWQ-V2	hyperarousal	F (2,118) = 33.59, p = 0.000; Partial.eta^2:0.402	F (1,59) = 2.78, p = 0.102; partial eta^2:0.053	F (2,118) = 0.009, p = 0.967; partial. eta^2:0.000	Greenhouse-Geisser ε:0.696
	anxiety	F (2,118) = 16.85, p = 0.000; Partial.eta^2: 0.252	F (1,59) = 1.74, p = 0.193; partial eta^2:0.034	F (2,118) = 0.968, p = 0.355; partial. eta^2: 0.019	Greenhouse-Geisser ε:0.684
	reversed vegetative	F (2,118) = 14.60, p = 0.000; Partial.eta^2: 0.226	F (1,59) = 1.11, p = 0.297; partial eta^2:0.022	F (2,118) = 1.57, p = 0.213; partial. eta^2: 0.030	Greenhouse-Geisser ε:0.885
	total AWQ-V2	F (2,118) = 25.37, p = 0.000; Partial.eta^2: 0.337	F (1,59) = 2.91, p = 0.094; partial eta^2:0.055	F (2,118) = 0.525, p = 0.472; partial. eta^2: 0.010	Greenhouse-Geisser ε:0.500
DDQ	desire & intention	F (2,118) = 6.24 p = 0.006; Partial.eta^2:0.111	F (1,59) = 0.167, p = 0.685; Partial eta^2:0.003	F (2,118) = 3.44, p = 0.052; partial. eta^2: 0.044	Greenhouse-Geisser ε: 0.789
	negative reinforcement	F (2,118) = 5.11 p = 0.019; Partial.eta^2: 0.093	F (1,59) = 0.004 p = 0.948; partial eta^2:0.000	F (2,118) = 0.89, p = 0.376; partial. eta^2: 0.017	Greenhouse-Geisser ε: 0.652
	control	F (2,118) = 1.55 p = 0.221; Partial.eta^2: 0.030	F (1,59) = 0.539, p = 0.466; Partial eta^2: 0.011	F (2,118) = 0.241, p = 0.716; partial. eta^2: 0.005	Greenhouse-Geisser ε:0.734
	total DDQ	F (2,118) = 7.66 p = 0.002; partial eta^2:0.133	F (1,59) = 0.143, p = 0.71; partial eta^2: 0.003	F (2,118) = 2.49, p = 0.101; partial eta^2: 0.048	Greenho use-Geisser ε: 0.783

Significant levels at P < 0.05.

groups faced a decreasing trend. The results of multiple and simultaneous Bonferroni comparisons showed that the amount of this decrease in the initial period of the study was more than in the second period of the study and the amount of these differences was significant at the baseline until the end of the fourth week and also from the beginning to the end of the study (all P s < 0.05). However, the mean inverse symptoms, desire, and control from the fourth week to the end of the study did not have a statistically significant difference (Table 3).

Discussion

Due to the high prevalence of MA use and the severe side effects this drug causes, treatment methods are of particular importance. So far, many drugs have been used to alleviate the problems of MA users. Unfortunately, most treatments for MA dependence have not been promising in clinical trials. Further, there is no approved treatment for this disorder. As a result, it is important to evaluate a drug with high efficacy, few side effects, and with the possibility of less dependence.

In a double-blind randomized controlled trial, the effect of venlafaxine was examined in the treatment of depression, withdrawal symptoms, and craving for MA in men with MA dependence.

Three hypotheses were formulated with each elaborated further. The results of the first hypothesis revealed that the changes in the mean score of depression at the baseline in both venlafaxine and placebo groups had an almost diminishing trend. However, these results were not significantly different in the two groups nor was the interaction between time and group significant.

Regarding the reduction of depression, relapse, and craving in the two groups, it can be noted that in parallel with the venlafaxine group, the mean of these variables also decreased in the placebo group, which can be considered the effect of induction in the control group.

The results of McDowell et al. (2000) research indicated that venlafaxine may be a safe, well-tolerated, rapidly acting, and effective treatment for patients with a dual diagnosis of depression and cocaine dependence.

We cannot stated with any certainty based on the evidence available from this study, why the results vary from those of other studies.

Perhaps one of the reasons for the discrepancy between these results and the findings of the previous study is the difference in venlafaxine dose, type of drug, methodology, and the sample size. McDowell et al. (2000) conducted a study on a very small sample of 13 patients who were diagnosed with cocaine dependence and comorbid major depression disorder.

The results of the second hypothesis indicated that there was no significant difference between the mean scores of withdrawal symptoms and their components (hyperarousal, anxiety, reversed vegetative) in venlafaxine and placebo groups. This finding of the study is consistent with the results of a study by Kelly et al. (2014) who examined the effectiveness of venlafaxine on 103 patients using marijuana; they found that this drug did not affect withdrawal symptoms.

Considering the third hypothesis of the study, the results showed that the number of changes in the mean scores of craving symptoms (desire, control, and negative reinforcement) was not significantly different between the two groups.

Regarding studies not in line with the present study findings, the results of a study on the effectiveness of venlafaxine showed that the majority of patients reported reductions in cocaine use during the abstinence period. All subjects reported a greater than 75% reduction in cocaine use compared to the baseline (McDowell et al., 2000). In another study conducted on a rat model, the results revealed that venlafaxine could be a good treatment option for MA relapse (Althobaiti, 2019).

The exact mechanism of action of venlafaxine is unknown, but appears to be associated with the potentiation of neurotransmitter activity in the CNS. Venlafaxine and its active metabolite, O-desmethylvenlafaxine (ODV), inhibit the reuptake of both serotonin and norepinephrine with a potency greater for the 5-HT than for the NE reuptake process (Bymaster et al., 2001).

Since MA causes serious damage to a person's health and there is no specific treatment for these adverse effects, the need for a more detailed and extensive study of effective treatments is obvious.

In the present study, only pharmacotherapy was used, so it is suggested that in future research new generations of psychological therapies, including commitment and acceptance therapy, be used and the results of pharmacotherapy and psychotherapy be compared. Also, in this study only the group of MA users and men were studied, and in future studies, opioid users and women can be examined as well. Research limitations here included the use of self-report tools that may have affected the answers to questions and led to bias. Also, the present sample only included the patients with MA dependence who were referred to Farabi Hospital in Kermanshah, so caution should be taken in generalizing the findings to patients from other psychiatric hospitals, clinics and other geographical areas.

Conclusion

Based on the results of this study, no significant difference was found between the mean scores of depression, withdrawal symptoms plus its components (hyperarousal, anxiety, reversed vegetative), and cravings (desire and intention, control, and negative reinforcement) in male patients with MA dependence, in the group treated with venlafaxine and the group taking placebo.

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ORCID

Faezeh Tatari http://orcid.org/0000-0002-4195-499X
Vahid Farnia http://orcid.org/0000-0003-0666-453X
Farnaz Radmehr http://orcid.org/0000-0003-0804-4393
Omran Davarinejad http://orcid.org/0000-0002-4267-7867
Safora Salemi http://orcid.org/0000-0002-4988-2521
Mostafa Alikhani http://orcid.org/0000-0001-6848-3027

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