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Venlafaxine plus acceptance and commitment therapy enriched with compassion focus therapy in opioid-addicted patients undergoing methadone maintenance treatment: a clinical trial

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ABSTRACT

Introduction. The effect of venlafaxine and psychotherapy including acceptance and commitment therapy (ACT) enriched with compassion focus therapy (CFT) was evaluated on depression, anxiety, and stress in opioid-addicted patients undergoing methadone maintenance treatment (MMT).

Method. This study is a randomized clinical trial with a pre-test and post-test design. Sixty opioid-addicted patients undergoing MMT were selected by voluntary sampling, and they were divided into three groups including VNF, receiving venlafaxine (75 mg/day); ACF, receiving ACT enriched with CFT, and VACF, receiving a combination of venlafaxine and ACT enriched with CFT. The ACT enriched with CFT for participants was performed by a psychiatrist weekly. Patients were evaluated based on the anxiety-stress-depression questionnaire after 28 days of intervention.

Results. The findings showed that all three intervention methods effectively affected depression, anxiety, and stress. Regarding stress, the difference in means between the two groups of VACF and ACF, as well as between VNF and ACF, was significant (P<0.05). The combined treatment of ACT enriched with CFT and venlafaxine had a more substantial effect on the research variables, i.e., depression, anxiety, and stress, compared to other interventions (P<0.05).

Conclusion. The ACT enriched with CFT intervention and venlafaxine effectively reduces depression, anxiety, and stress in opioid-addicted patients undergoing MMT.

Keywords: ACT enriched with CFT, venlafaxine, methadone, depression, stress, anxiety, behavior

INTRODUCTION

The opioid-addiction treatment program with MMT has been dramatically developed in recent years to withdraw opioids, reduce high-risk behaviors, prevent drug relapse, and improve the mental and physical quality of opioid-addicted patients [1]. However, the mental disorders associated with substance abuse reduce the effectiveness of the interventions. Mental disorders and substance abuse disorders often occur, simultaneously [2], so patients undergoing MMT often suffer from depression, anxiety [3], and stress [4]. Therefore, it is necessary to consider complementary treatments for drug users in addition to MMT [5].

Venlafaxine is one of the medications that can be used to improve mental problems associated with addiction. Venlafaxine is a serotonin and norepinephrine reuptake inhibitor (SNRI) [6]. The individual characteristic of venlafaxine is its lack of effect

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on muscarinic, nicotinic, histaminergic, or adrenergic receptors. Therefore, venlafaxine is a favorite antidepressant for psychotherapy. Venlafaxine has gastrointestinal absorption with a half-life of 3.5 hours and a half-life of 9 hours for its metabolites [7]. Various studies established the effect of venlafaxine on depression [8], anxiety [9], and stress [10]. Although antidepressant medications such as venlafaxine are effective for depression, anxiety, and stress, their side effects, as well as recurrence and concern about the long-term consequences of their use, worry patients [10].

Hence, many interventionists consider psychological treatments along with antidepressants. These interventions greatly improve depression, anxiety, and stress [11]. The effectiveness of psychological treatments has been higher in the cases that underwent the combination of two complementary therapies [11]. So it seems that the variety of two interventions can reduce the existing deficiencies. In this regard, the ACT enriched with CFT is one of the interventions that has attracted the attention of many psychotherapists and has also had effective results in improving mental disorders [12,13].

In acceptance and commitment-based therapy, it is believed that getting rid of thoughts, feelings, and physical symptoms is the cause of aggravating psychological problems [14]. In this treatment of acceptance, trying to restore values, psychological flexibility, and achieving a prosperous life will be the primary goal [15]. The results of various studies indicate the effectiveness of treatment based on acceptance and commitment to depression, anxiety, and stress [16].

Gilbert (2014] believes that a person can achieve peace when he internalizes events, thoughts, external soothing behaviors, and images so that the mind reacts to the internal as it reacts to the external factors. Self-compassion can improve depression, anxiety, and stress due to its protective role against the symptoms of mental illnesses, and also improve acceptance and commitment-based therapy [17] because the goal of compassion therapy is to experience feelings and thoughts in a way that occurs naturally [18]. psychotherapy also brings issues such as being costly, lengthy, and complex [19], and this issue can create many obstacles at the beginning and continuation of the treatment. Therefore, therapists use a combination of medication and psychotherapy to reduce these problems. On the other hand, there are still many ambiguities and questions regarding the effectiveness of these methods, so the existing research has been conducted either in conflicting societies or with different techniques and tools and has had scattered results. Therefore, compared to combined therapy, the current study was conducted with ACT enriched with CFT and venlafaxine on depression, anxiety, and stress in addicts undergoing MMT.

METHODS

This research is a semi-experimental study and a clinical trial with a pre-test and post-test plan. The statistical population consisted of all opioid addicts undergoing MMT, referred to addiction treatment clinics in Yazd, IRAN (2019). The sample size was determined based on existing and similar articles in this field. The maximum sample size is estimated at 20 people for each group, considering the confidence level of 95% and the power of 90% based on the average depression score in the mentioned study and the dropout rate of 20%. The output of stata14 software to estimate the desired sample size.

A voluntary sampling method was used to select the sample. First, by announcing a call, those interested in participating in the research were invited to attend a briefing session. At this stage, 117 people attended and answered the test questions (DASS21) after knowing the research objectives. People who scored higher than the average in the questionnaire dimensions and met other criteria were considered suitable for participating in the research. Finally, 60 people were selected, and after matching into three groups of 20, they were replaced. In this study, blindness was done only for the project statistics analyzer.

The researcher supervised the training process of the patients, and the participants were aware of the received intervention. The first group (ACF), ACT enriched with CFT for 28 days; The second group (VACF) received ACT enriched with CFT and venlafaxine (EFFEXOR® XR, 75 mg/day, 28 days), and the third group (VNF) received venlafaxine (EFFEXOR® XR, 75 mg/day, 28 days). A psychiatrist started venlafaxine before the start of psychotherapy.

Psychotherapy was conducted by a psychologist in 8 one-hour sessions. The criteria for entering the research include obtaining a higher than average score on the test (DASS21), willingness to participate in the study, not taking other medications that are similar and effective in the studied parameters, not participating in the research at the same time, as well as the criteria for leaving the sample from the study including unwillingness following participation in the research, non-adherence to the group's rules, the occurrence of unwanted reaction to the drug and the worsening of the patient's disorder was determined. Ethical considerations also included: the anonymity of questionnaires, informed and written consent, the confidentiality of information, non-receipt of medication and training course fees, and the right to withdraw at any research stage.

Research tool

Anxiety, stress, and depression questionnaire: To measure mental distress, Lavibond's anxiety, stress, and depression questionnaire (1995) (DASS-21) were used. The short form of this scale was prepared by Lavibond in 1995 and had 21 questions. Items are answered on a four-point Likert scale from zero (not at all) to three (very much), and a higher score indicates more severe symptoms. Seven items on this scale evaluate the three parameters of depression, anxiety, and stress. The reliability and validity of this scale for the Iranian sample have been reported as appropriate; The correlation of the depression subscale with the Beck depression test was 0.7, the correlation of the anxiety subscale with the Zanke self-assessment anxiety scale was 0.67, and the correlation of the stress subscale with the perceived stress scale was 0.49 [20].

The general framework of the treatment sessions based on ACT was prepared based on the therapeutic guidelines of Hayes et al. (1999), Tuohy (2007), and Gilbert (2014), in addition, four expert university professors confirmed its validity. A summary of ACT enriched with CFT sessions is presented in Table 1.

2 people in VNF, 4 people in VACF, and 5 people in ACF refused to continue the treatment. Finally, the collected data was analyzed using SPSS software version 26 and an error of 0.05. Mean and standard deviation were used to describe the data, and Paired-Samples T Test and covariance analysis were used to analyze the relationships between the variables.

TABLE 1. ACT enriched with CFT sessions

Content	Session
It was getting to know the group members and establishing a therapeutic relationship, determining the rules governing the therapy sessions, clarifying the therapeutic relationship, introducing the therapeutic intervention, discussing stress, anxiety, and depression and its causes, and discussing what the members do to reduce stress and anxiety. And depression, investigating its consequences, teaching breathing exercises, and presenting assignments.	first session
Receiving feedback from the previous session, the pit metaphor, introducing the three emotional regulation systems and how they interact with each other, getting to know negative and threatening emotions from the perspective of CFT, the nature of compassion, and presenting the assignment.	second session
Examining assignments and receiving feedback from the previous session, introducing control as an issue, discussing the inner world and its difference from the outer world, polygraph metaphor, and getting to know the characteristics of compassionate people (kindness, empathy, tolerance of distress, non-judgment), nurturing and understanding that others also have defects and problems. Cultivating a sense of human commonality against self-destructive feelings and shame and presenting homework.	third session
Examining assignments and receiving feedback from the previous session, introducing acceptance and willingness as an alternative to control, guest metaphor and expressing pure and impure feelings, practicing cultivating self-compassion (wisdom, strength, kindness, not judging yourself and responsibility), How visualize self-mushfiq, practice self-development, and present homework.	fourth session
We are examining assignments and receiving feedback from the previous session, learning the hidden features of language that confuse, expressing the fault, bus metaphor, practicing compassion skills (human behavior, compassionate mental image, compassionate feeling), and teaching empathy by presenting homework.	fifth session
We are examining assignments and feedback from the previous meeting, introducing self-types, chess metaphors, learning the past and the conceptualized future, cultivating compassion toward others, teaching forgiveness, focusing the self towards others, and presenting homework.	sixth session
Examining assignments and receiving feedback from the previous session, moving towards a valuable life with a self-accepting and observant self, identifying values and measuring the values of clients, teaching how to write compassionate letters, and preparing for the completion of homework presentation sessions.	seventh session
Examining assignments and receiving feedback from the previous session, commitment to action and values despite obstacles, seedling metaphor, evaluation of commitment to action, presentation of permanent assignment, completion of post-test.	eighth session

RESULTS

According to the demographic findings, the average age in the VNF group: was 41.8 years (std, 6.2), in VACF group, 38.2 (std, 3.8), and in the ACF group it was 43.3 (std, 5.9). The difference between the groups was not significant based on the chi-square test (P>0.05).

There is no statistically significant difference between the three groups in terms of demographic variables (chi-square test, P>0.05) (Table 2).

TABLE 2. Frequency distribution of marital and education status of test and control participants

	ACF		VACF		VNF		P value
	Relative frequency	Frequency	Relative frequency	Frequency	Relative frequency	Frequency	
Single	26.6	4	25.0	4	44.4	8	> 0.05
Married	73.4	11	75.0	12	55.6	10	
Total	100	15	100	16	100	18	
non-academic	73.3	11	75.0	12	77.8	14	> 0.05
academic	26.7	4	25.0	4	22.2	4	
Total	100	15	100	16	100	18	

TABLE 3. Comparison of the mean and standard deviation of the scores of the research variables in the intervention stages by group

Variable	Stage	ACF		VACF		VNF		Sig.
		Mean	STD	Mean	STD	Mean	STD	
Depression	pre-test	10.33	1.54	10.56	2.89	10.22	1.73	P=0.896 ANOVA
	post-test	7.13	1.45	5.43	1.45	6.44	1.82	
	p-value p.s.t test	0.001		0.001		0.001		
Anxiety	pre-test	7.80	2.42	7.25	1.06	7.11	1.84	P=0.544 ANOVA
	post-test	5.20	1.69	3.62	1.50	4.77	1.30	
	p-value p.s.t test	0.001		0.001		0.001		
Stress	pre-test	13.46	2.64	13.75	3.53	12.83	2.12	P=0.622 ANOVA
	post-test	9.00	1.36	7.12	.95	7.83	1.33	
	p-value p.s.t test	0.001		0.001		0.001		

TABLE 4. Presuppositions of covariance analysis test

Variable	group	Shapiro-Wilk		Levene's Test[2]		homogeneity of regression slopes		Box's Test[1]		
		Statistic.	Sig	F	Sig.	F	Sig.	Box's M	F	Sig.
Depression	VNF	0.955	0.507	0.149	0.293	1.337	0.184	8.314	0.626	0.822
	VACF	0.951	0.506							
	ACF	0.905	0.115							
Anxiety	VNF	0.948	0.395	0.041	0.849	1.590	0.215			
	VACF	0.893	0.062							
	ACF	0.900	0.094							
Stress	VNF	0.973	0.851	0.184	0.184	0.463	0.633			
	VACF	0.901	0.084							
	ACF	0.919	0.187							

[1]*Box's Test of Equality of Covariance Matrices*
[2]*Levene's Test of Equality of Error Variances*

TABLE 5. The results of covariance analysis with pre-test control

	Value	F	Hypothesis df	Error df	Sig.	Partial Eta Squared
Pillai's Trace	.440	3.952	6.000	84.000	.002	.220
Wilks' Lambda	.571	4.422[b]	6.000	82.000	.001	.244
Hotelling's Trace	.732	4.882	6.000	80.000	.000	.268
Roy's Largest Root	.705	9.863[c]	3.000	42.000	.000	.413

The comparison of the mean and standard deviation of the scores of the research variables in the intervention stages, by group, is presented in Table 3.

The results show that all values of Shapirowilk, Box, Levin, and homogeneity of regression slopes for depression, anxiety, and stress variables in both groups are insignificant (P<0.05) (Table 4).

After controlling the effect of the pre-test, there is a significant difference between the average of the research variables in the post-test stage (p<0.001). And in the post-test, there is a significant difference between the intervention groups in at least one of the variables of depression, anxiety, and stress (Table 5).

TABLE 6. Tests of Between-Subjects Effects

Variable	Source	SS	df	MS	F	Sig	Eta	Observed Power
Depression	Group	19.653	2	9.82	3.94	0.027	0.16	0.68
	Error	107.195	43	2.49				
Anxiety	Group	21.700	2	10.85	5.08	0.010	0.19	0.79
	Error	91.793	43	2.14				
Stress	Group	26.562	2	13.28	8.31	0.001	0.28	0.95
	Error	68.703	43	1.60				

TABLE 7. Bonferroni post hoc test results to compare intervention groups in research variables

Variable	ACF & VACF		VNF & ACF		VNF & VACF	
	Mean difference	Sig.	Mean difference	Sig.	Mean difference	Sig.
Depression	1.55	0.029	1.000	0.46	1.09	0.159
Anxiety	1.67	0.009	0/648	0.66	1.01	0.157
Stress	1.85	0.001	0.035	1.19	0.66	0.423

The effect size coefficient shows that 24% of the difference between the two groups is related to the experimental intervention. To find out the differences between single variables, a single-variable covariance analysis was performed in the Mankwa text. There was a significant difference in depression, anxiety, and stress variables in at least two treatment groups of venlafaxine, ACT enriched with CFT, and combined treatment of venlafaxine and ACT enriched with CFT (P<0.05) (Table 6).

The results of Bonferroni's post hoc test to compare the intervention groups in the research variables are presented in Table 7. Regarding the variables of depression and anxiety, the difference in means was significant only between the two groups of ACT enriched with CFT and venlafaxine and ACT enriched with CFT (P<0.05). Also, regarding the stress variable, the difference in means between the two groups of ACT enriched with CFT and venlafaxine and ACT enriched with CFT, as well as between venlafaxine and ACT enriched with CFT, was significant (P<0.05). Thus, in the case of each research variable, i.e. depression, anxiety, and stress, the combination of ACT enriched with CFT and venlafaxine had a greater effect on the dependent variables.

DISCUSSION

The present study was conducted with ACT enriched with CFT and venlafaxine on depression,

anxiety, and stress in opioid addicts undergoing MMT. The results showed that all three interventions effectively improve depression, anxiety, and stress scores. In this regard, other studies also showed that a combination of medication and psychotherapy has a more significant effect on mental disorders.

Venlafaxine, as an efficient antidepressant, inhibits the reabsorption of serotonin and norepinephrine to a large extent and reduces depression, anxiety, and stress. It also lacks anticholinergic, anti-histaminergic, and anti-alpha-adrenergic effects. This drug has a relatively low protein binding ability and shows limited inhibition of the liver-enzyme system. Therefore, the clinical implications of venlafaxine include strong efficacy, favorable side effect profile, and relatively low potential for drug interactions, and these conditions reduce drug resistance. Venlafaxine can produce immediate therapeutic effects and be a quick booster for patients [8].

This profile makes it easier for patients under MMT to participate in psychotherapy sessions. Patients under MMT may try to eliminate the negative cognitive, physiological, and emotional symptoms caused by depression, anxiety, and stress from the experience and remove these negative symptoms, which in the end is an attempt that leads to the aggravation of these symptoms. ACT taught patients undergoing MMT to accept negative cognitive, physiological, and emotional symptoms. Instead of trying to eliminate and eliminate them, they should rebuild their life values and try to achieve them. Some studies also showed that acceptance and commitment therapy is effective on depression, anxiety, and stress. Self-compassion is the ability to turn understanding, acceptance, and love inward. Since many patients under MMT may be unable to express self-compassion, blame their mistakes and failures that may occur in the addiction treatment process, and abandon treatment due to guilt or experience depression, anxiety, and stress. Therefore, enriching the ACT with self-compassion can improve the effects of self-blame in trainees by developing skills to strengthen self-compassion.

CONCLUSION

The research findings indicated greater effectiveness of combined psychotherapy and drug therapy on depression, anxiety, and stress in opioid addicts undergoing MMT. In this way, the simultaneous use of psychotherapy and venlafaxine can further reduce the scores of depression, anxiety, and stress in patients undergoing MMT.

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