Clinical trial

Acceptance and Commitment Therapy (ACT) Enriched with Compassion Focused Therapy (CFT) on Psychological Distress in Patients under Methadone Maintenance Treatment (MMT)

Running Title: ACT Enriched with CFT, Sertraline, and Venlafaxine on Psychological Distress

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Abstract

Introduction: Mental problems caused by opioid addiction or drug withdrawal can increase the risk of relapse in methadone maintenance treatment. The present study was conducted to compare the efficacy of acceptance and commitment therapy enriched with compassion-focused therapy on the effect of sertraline and venlafaxine on patients' psychological distress under methadone maintenance treatment.

Method: This study was a clinical trial with a pre-test and post-test design. Forty patients under methadone maintenance treatment were selected by voluntary sampling and randomly divided into two groups. The first group received acceptance and commitment therapy enriched with compassion-focused therapy and venlafaxine, and the second group received acceptance and commitment therapy enriched with compassion-focused therapy and sertraline for intervention days. The patients were evaluated based on the anxiety, stress, and depression questionnaire. The data were analyzed using the paired t-test and analysis of covariance at a significance level of 0.01.

Results: Both venlafaxine, and sertraline plus acceptance and commitment therapy enriched with compassion-focused therapy, were influential on psychological distress and its dimensions (depression, anxiety, and stress) (P<0.001). Sertraline had a more significant effect on psychological distress, and anxiety than venlafaxine (P<0.01). No significant difference was observed between them on depression and stress (p>0.05).

Conclusion: Sertraline is more effective than Venlafaxine in controlling psychological symptoms in methadone maintenance treatment.

Introduction

Drug abuse, as one of the most important global challenges, has had many destructive effects on the livelihood of families, the security of countries, and the responsibility, physical and mental health of consumers (1). This issue is worrying because in recent years, the number of consumers has increased, and the age of consumption has decreased (2).

Methadone, as a long-acting opioid, has wide use in the withdrawal of opioid addiction in the methadone maintenance treatment (MMT) method (3). However, the psychological problems associated with substance abuse can reduce the effectiveness of MMT (4). On the other hand, various studies show that substance abuse has a positive relationship with psychological distress (5-10).

Medications and psychotherapy alone or in combination are the methods used to reduce the mental distress of patients under MMT (11). The results of various studies show that interventions such as stress management (12), self-healing training (13), laughter therapy (14), and cognitive behavioral therapy (15) are effective in improving mental disorders associated with addiction.

In this regard, one of the treatments that have recently attracted the attention of researchers is acceptance and commitment therapy (ACT) enriched with compassion-focused therapy (CFT), which has been effective in treating problems related to psychological distress (16). ACT aims to help people accept challenging experiences as they are, identify their values, engage in activities consistent with their values, analyze barriers to engaging in valued activities, and develop strategies to overcome them (17). CFT helps individuals develop compassion for themselves and others (18). It refers to the theory and process underlying the use of the compassion model in psychotherapy (19). This therapy enables people to use their supportive inner voice to respond to self-criticism and shame with kindness (20).

The compassionate mind is an integral part of self-compassion. It uses physiological, psychological, cognitive, imaginative, and body-based practices, including mindfulness and concentration training, calming rhythmic breathing, memory exercises, and compassion-based imagery, to cultivate self-compassion (21). These practices activate the parasympathetic nervous system (22), increase levels of self-compassion and positive emotions, and reduce self-criticism, shame, and psychological distress (23, 24). The combination of these two therapeutic interventions better affects psychological problems. The results of various studies indicate the effectiveness of the ACT enriched with CFT on the dimensions of psychological distress (16, 25-27).

Combining medications and pharmacotherapy to improve the symptoms of psychological problems is one of the methods that therapists use to enhance the effectiveness of the therapy (28-30). Sertraline, a selective serotonin central reuptake inhibitor, is one of the drugs used in this regard (31). The results of various studies indicate the effect of sertraline on psychological distress (32-35). The other medication, venlafaxine is a reuptake inhibitor of serotonin and norepinephrine (36). Various studies indicate the effect of venlafaxine on psychological distress (37-40).

However, few studies have focused on substance abuse patients, so a study that compares the impact of these two treatment methods on the psychological distress of patients under MMT was not available. Therefore, to improve treatment decisions, differences in the effect sizes of these methods should be identified. The present study was conducted to compare the effectiveness of sertraline and venlafaxine in improving the efficacy of ACT enriched with CFT on the mental distress of patients under MMT.

Methods

This research was a semi-experimental study and a clinical trial type with a pre-test and post-test design. The statistical population consisted of all opioid addicts under MMT referred to addiction treatment clinics in Yazd City, Iran in 2019. A voluntary sampling method was used to select the sample. The criteria for entering the research included: getting a higher than average score on the test (DASS21), willingness to participate in the study, not taking other medications with similar effectiveness, not participating in the research at the same time, and also the criteria for leaving the sample from the research is not wanting to continue participation in the research and non-adherence to the group rules, the occurrence of unwanted reaction to the drug and the worsening of the patient's disorder was determined. Forty people were selected based on the entry criteria and randomly replaced into two groups of 20 people. Randomization was done based on the RAND() function of Excel software. The ACV group received the combined treatment of ACT enriched with CFT and venlafaxine (Effexor®, 75 mg/day), and the ACS group received the combined therapy of ACT enriched with CFT and sertraline (Asentra®, 50 mg/day). Four people from the ACV group and three from the ACS group withdrew during the intervention. The training course was done only for the statistics consultant of the project, and the researcher who supervised the process of training the patients and the participants themselves were aware of the received intervention. For both groups, drug therapy was started by a psychiatrist about one month before the start of psychotherapy and continued until the end of the intervention. An expert psychotherapist also conducted psychotherapy in the field enriched with compassion in 8 one-hour sessions. 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 in both groups.

Research Tools

Anxiety, stress, and depression questionnaire

Lovibond's anxiety, stress, and depression questionnaire (DASS-21, 1995) was used to measure mental distress. Lovibond prepared the short form of this scale in 1995 with 21 questions. The questions 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. The three constructs of depression, anxiety, and stress are each evaluated by seven items on this scale. The reliability and validity of this scale have been reported for the Iranian sample; 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 (41).

The general framework of treatment sessions based on ACT was prepared based on the treatment guide of Hayes et al. (1999), Toohey (2007), and Gilbert (2014). Its validity was approved by four expert university professors (42-44). A summary of the ACT enriched with CFT sessions is presented in **Table 1**.

Table 1. Summary of ACT enriched with compassion sessions

Session	Content
First session	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, discussing what the members should do to reduce stress, anxiety, and depression and investigating its consequences, teaching breathing exercises and presenting assignments.
Second session	Examining assignments and 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 assignments.
Third 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), Cultivating and understanding that others also have defects and problems, cultivating a sense of human commonality against self-destructive feelings and shame, and presenting assignments.
Fourth 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 to visualize self-compassion, practicing self-compassion development and presenting assignments.
Fifth session	Examining assignments and receiving feedback from the previous session, getting to know the hidden features of language that confuse, expressing the fault, bus metaphor, practicing compassion skills (compassionate behavior, compassionate mental image, compassionate feeling), teaching empathy, and presenting assignments.
Sixth session	Examining assignments and receiving feedback from the previous session, introducing self types, chess metaphor, getting to know the conceptualized past and future, cultivating compassion towards others, teaching forgiveness, focusing self-pity toward others, and presenting assignments.
Seventh 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 the clients, teaching how to write compassionate letters, and preparing for the completion of the homework presentation sessions.
Eighth 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-exam.

Statical analysis

The collected data was analyzed using SPSS software version 26 and an error of 0.01. Mean and standard deviation was used to describe the data and covariance analysis were used to analyze the relationships between variables.

Results

According to the demographic findings, the average age in the ACV group was 38.18 years, and in the ACS group 32.05 years. Moreover, in the ACV group, 4 people (25.00%) were single and 12 people (75.00%) were married, and in the ACS group, 7 people (41.20%) were single, and 10 people (58.80%) were married. In terms of education, the ACV group had 12 people (75.00) with non-university education and 4 people (25.00) also with university education, and in the ACS group, 11 people (64.70%) had non-university education and 6 people (35.30%) also had a university education. The mean and standard deviation of the research variables are presented in **Table 2.**

Table 2. Comparing the mean and standard deviation of the scores of the research variables in the intervention stages.

Variable	Experimental steps	ACV	ACS
Psychological Distress	Pre-test	31.56±6.12	46.94±5.72
	Post-test	16.18±1.93	22.70±4.46
	P value Paired-Samples T Test	0.001	0.001
Depression	Pre-test	10.56±2.89	14.17±3.10
	Post-test	5.43±1.45	6.58±2.21
	P value Paired-Samples T Test	0.001	0.001
Anxiety	Pre-test	7.25±1.06	13.88±3.01
	Post-test	3.62±1.50	6.52±1.84
	P value Paired-Samples T Test	0.001	0.001
Stress	Pre-test	13.75±3.53	18.88±3.38
	Post-test	7.12±3.06	9.58±0. 95
	P value Paired-Samples T Test	0.001	0.001

ACV: Acceptance and Commitment Therapy enriched with Compassion Focus Therapy plus Venlafaxine
ACS: Acceptance and Commitment Therapy enriched with Compassion Focus Therapy plus Sertraline
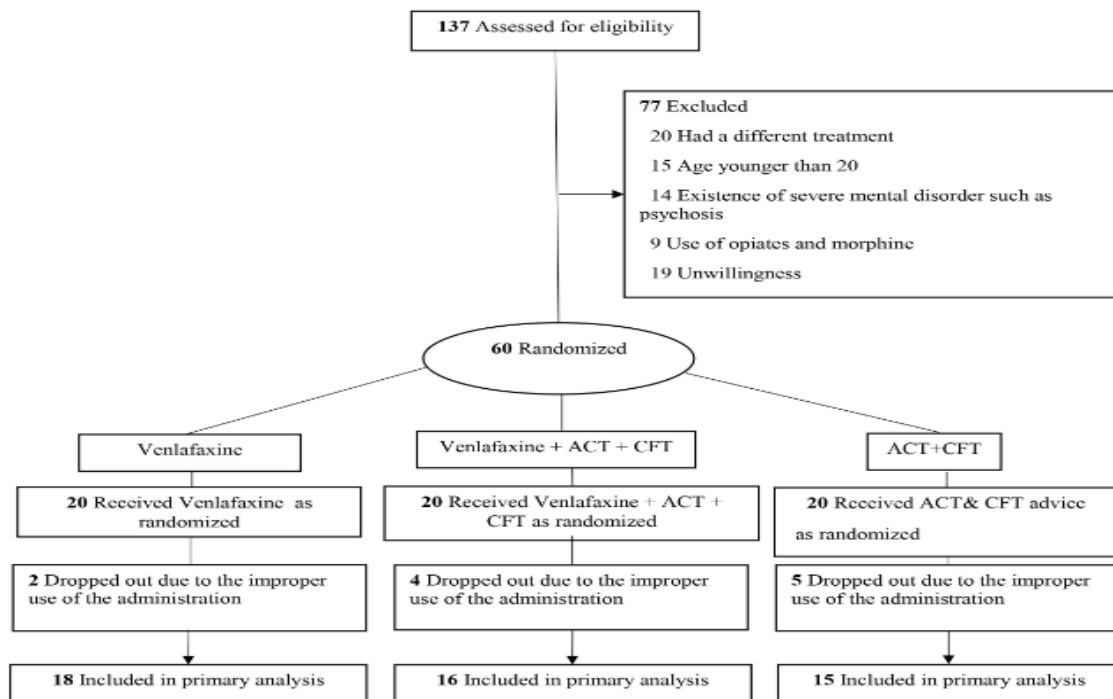
CONSORT DIAGRAM

Based on the findings of **Table 2** and the paired t-test, the effect of both ACV and ACS interventions on mental distress and its dimensions, i.e., depression, anxiety, and stress, was statistically significant and caused a decrease in its scores in the post-test stage (p<0.001). To investigate the main hypothesis of the research, the statistical method of covariance analysis was used, and the presumptions of analysis of covariance were tested **(Table 3).**

Table 3. Presumptions of analysis of covariance test for psychological distress variable

group	Shapiro-Wilk		homogeneity of regression slopes		Levene's Test	
	Statistic	Sig.	F	Sig.	F	Sig.
ACV	.878	.037	6.673	.015	7.361	.011
ACS	.932	.236				

The results showed that all the values of the Shapiro-Wilk test, Levene, and homogeneity of the regression slopes for the mental distress variable in the intervention groups are insignificant (**Table 3**, P>0.01), and the presumptions of the univariate covariance analysis test have been properly met. The results of the univariate analysis of covariance are presented in **Table 4.**

Table 4. The results of ANCOVA analysis on the average post-test scores of psychological distress with pre-test control.

Source	df	MS	F	Sig	Eta	Observed Power[b]
Pre-test	1	7.622	.621	.44	.020	.119
Group	1	80.722	6.574	.01	.180	.699
Error	30	12.278				

Based on the findings, after pre-test control, the post-test difference between ACV and ACS groups is statistically significant (**Table 4**, p<0.01). The average score of mental distress in the ACV group was 15.38 and in the ACS group was 24.24, so ACS compared to ACV had a more significant effect on the variable of mental distress **(Table 2)**. To compare the effect of ACV and ACS on the variable dimensions of psychological distress, i.e. depression, anxiety, and stress, the multivariate covariance analysis test was used. The presumptions of the multivariate covariance analysis test are presented in **Table 5**.

The results of **Table 5** show that all values of the Shapiro-Wilk, Box, Levene test (except for the stress variable) and the homogeneity of the regression slopes for depression, anxiety, and stress variables in both groups are insignificant (P>0.05). The results of the multivariate

covariance analysis test are presented in **Tables 6 and 7**.

Table 5. Presuppositions of covariance analysis test

Variable	group	Shapiro-Wilk		homogeneity of regression slopes		Levene's Test[2]		Box's Test[1]
		Statistic	Sig.	F	Sig.	F	Sig.	P>0.01
Depression	ACV	.506	.951	.189	.179	.587	.450	
	ACS	.179	.925					
Anxiety	ACV	.175	.924	.068	.645	2.594	.117	
	ACS	.062	.893					
Stress	ACV	.084	.901	.034	.848	18.494	.001	
	ACS	.483	.952					

[1].Box's Test of Equality of Covariance Matrices [2]. Levene's Test of Equality of Error Variance

Table 6. The results of covariance analysis with pre-test control conclusion

Effect		Value	F	Hypothesis df	Error df	Sig.	Partial Eta Squared	Observed Power
group	Pillai's Trace	.423	6.355[b]	3.000	26.000	.002	.423	.939
	Wilks' Lambda	.577	6.355[b]	3.000	26.000	.002	.423	.939
	Hotelling's Trace	.733	6.355[b]	3.000	26.000	.002	.423	.939
	Roy's Largest Root	.733	6.355[b]	3.000	26.000	.002	.423	.939

Table 7. The results of the analysis of covariance in MANCOVA text with pre-test control

Source	Variable	Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared	Observed Powerd
group	Depression	3.642	1	3.642	1.146	.294	.039	.179
	Anxiety	49.880	1	49.880	19.922	.000	.416	.991
	stress	1.049	1	1.049	.228	.636	.008	.075
Error	Depression	89.008	28	3.179				
	Anxiety	70.107	28	2.504				
	stress	128.556	28	4.591				

Tables 6 and **7** show that after removing the effect of the pre-test and according to the calculated F, there is a significant difference between the adjusted averages of the scores of the research variables according to the group membership "ACV and ACS" in the post-test stage only in the anxiety variable (P<0.001) Considering the averages obtained in **Table 2**, it can be concluded that ACS had a greater effect on anxiety compared to ACV. Also, the results showed that although ACS compared to ACV had a more significant impact on depression and stress

in substance abuse patients under MMT, this difference was not significant.

Discussion

The present study was conducted to compare the effectiveness of sertraline and venlafaxine on the efficacy of ACT enriched with CFT on the psychological distress of patients under MMT. The results showed that ACS compared to ACV had a more significant effect on the psychological distress variable (P<0.001). The results showed that the impact of both ACV and ACS interventions on mental distress and its dimensions, i.e., depression, anxiety, and stress, was statistically significant and caused a decrease in its scores in the post-test stage (P<0.01). The results showed that after removing the pre-test effect, ACS compared to ACV had a more significant impact on anxiety (p<0.001). Also, the results showed that although ACS compared to ACV had a more significant effect on depression and stress in opioid abuse patients under MMT; this difference was insignificant (p>0.01). This difference can be attributed to drug side effects. In the ACV group, more patients complained of drug side effects, which can be anxiety-inducing.

The results obtained in the first research hypothesis are consistent with the results of other studies. Kamenov et al., Liu et al., and Xiang et al., have shown in their studies that the combination of medication and psychotherapy can bring more effective results to mental problems(28-30). In explaining the research findings, it can be said that drug abuse is associated with some intellectual, emotional, and behavioral symptoms such as guilt, the temptation

to use, self-blame and rumination, sadness and anger, and presence in places of consumption. Patients, in many cases, try to eliminate these symptoms. An effort that usually brings photo results. On the other hand, it is often difficult for these patients to participate in psychotherapy sessions. Patients may not have enough physical and mental strength due to depression, anxiety, and stress, and physical exhaustion due to substance abuse. Their vision is often low to participate in meetings. Reducing negative symptoms through medication can create more motivation and commitment for patients to participate in meetings. Sertraline can play this role by increasing the amount of serotonin by inhibiting its reabsorption. In their studies, GE et al., Lofgren et al., Kassis, Gilliam et al., and Rauch et al. showed that sertraline is effective in improving symptoms of psychological distress(31-35). Venlafaxine can also increase norepinephrine and dopamine, in addition to inhibiting the reuptake of serotonin(36). The results of various studies indicate the effect of venlafaxine on psychological distress(37-40). Therefore, the effects of sertraline and venlafaxine will be very similar. The small effect size of 14% also shows that ACS and ACV did not have much difference in psychological distress.

Therefore, venlafaxine and sertraline, by reducing the severity of mental distress symptoms, improved the motivation and ability of patients to participate in ACT sessions enriched with CFT and greater effectiveness. According to the results of various studies, the ACT enriched with compassion is effective in the dimensions of psychological distress (16, 25-27). In the sessions,

people were taught to experience their disturbing thoughts as just a thought and to become aware of the ineffectiveness of their efforts to eliminate these thoughts and feelings. Instead of responding to their thoughts and feelings, patients learned to do what is valuable to them in life and direct their efforts in line with their values. Also, self-compassion made patients learn skills to strengthen self-compassion and use it to reduce guilt, rumination, and self-blame.

In general, the drug reduced the severity of the initial symptoms and improved motivation and insight in the patients; Psychotherapy was able to reduce the patients' worries about the side effects of the drug and improve their skills in dealing with dysfunctional thoughts, feelings, and behaviors. It seems that especially in addicts under MMT who have great resistance to treatment or people for whom psychotherapy is more complicated, the drug can create a more appropriate context for improving therapeutic cooperation in clients and enhancing the effectiveness of psychotherapy.

Conclusion

The research findings indicated the effectiveness of ACS and ACV on mental distress in substance abuse patients under MMT. Sertraline is more effective than venlafaxine in controlling psychological symptoms in MMT.

Limitations

Some of the most critical limitations of the present study were non-compliance with some presuppositions of the covariance analysis test, a small number of sample members, the impossibility of holding face-to-face meetings due

to the spread and risk of covid-19, no follow-up period, and no control of intervening variables.

Suggestions

It is suggested to use ACS and ACV in addition to MMT to reduce the symptoms of mental distress in substance abuse patients. It is also recommended that other components related to addicts under MMT, such as the temptation to use, self-compassion, and psychological well-being, should also be investigated in future research.

Conflict of interests: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. The authors confirm that all methods were performed in accordance with the relevant guidelines and regulations.

 Ethical considerations: Before conducting the study, the code of ethics was obtained from the ethics committee of Shahid Sadoughi University of Medical Sciences (IR.SSU.MEDICINE.REC.1399.170). With the approval of the research by the Iranian Registry of clinical trials (IRCT), the code IRCT20191106045356N3, 21/04/2021 was obtained. All patients consciously signed the consent form. During the study, they were under

the supervision of a physician. In case of exacerbation of the disease, they were excluded from the study and treated appropriately.

All of the participants have explained that the research may not be of direct benefit to me. My participation is completely voluntary. My right to withdraw from the study at any time without any implications to me.

All of the authors give consent for the publication of identifiable details, which can include photographs, tables, and details within the text to be published in the above Journal and Article.

Authors' contribution: Conceptualization, Supervision, and Methodology: M.Z, M.S, G.D, and Z.M; Investigation: All of the authors; Writing – original draft: M.H; Review & editing: M.Z, M.S, G.D, and Z.M; Data collection: M.H and A.B; Data analysis: M.S; Funding Administration: M.Z.

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