

Depression and Suicidal Ideation among Patients Receiving Opioid Maintenance Treatments Considering Cognitive Flexibility

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Abstract

Objective: Cognitive flexibility is associated with psychiatric disorders. Drug addicts experience more psychiatric disorders. This research aimed to examine depression and suicidal ideation among those receiving opioid maintenance treatment (OMT), taking into account the mediating role of cognitive flexibility.

Method: This cross-sectional research was conducted on patients who were enrolled in the OMT program in Semnan in 2021 and abstained from opioid use for at least one year. 126 participants (115 males and 11 females) were randomly selected from among patients in three therapeutic groups (42 from each of the methadone, buprenorphine, and opium tincture groups). The main data collection tools were the Beck Scale for Suicide Ideation (BSSI), Cognitive Flexibility Inventory (CFI), and Beck Depression Scale (BDI-II). Data analysis was done through logistic regression models.

Results: Correlation analysis between depression scores, suicidal ideation, and cognitive flexibility showed a significant correlation between each of them. Adjusting for the type of treatment, the increase in cognitive flexibility was associated with a decreasing chance of depression (odds ratio [OR] = 0.87; 95% CI [0.82, 0.92]), and the use of buprenorphine (OR = 15.1) and opium tincture (OR = 9.3), compared to methadone, were associated with a depression increase. Yet, multivariate analysis did not show an independent and significant association between cognitive flexibility and the risk of suicide.

Conclusion: Based on the results, patients receiving maintenance treatments are in different conditions in terms of depression and suicide, and psychological flexibility is in correlation with depression and suicidal thinking and behavior in them. This suggests that these patients seem to benefit from cognitive training, at least in reducing their depression.

Key words: *Addiction; Executive Function; Depression; Opioid; Suicide*

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Currently, a very common treatment program for people with a history of opioid use disorder (OUD) is opioid maintenance treatment (OMT), also known as opioid substitution treatment. The opioid receptor full-agonist methadone is the most widely administered drug in OMT (1). The opioid receptor partial agonist buprenorphine and opium tincture (OT) are also used for detoxification and opioid replacement therapy which have gained increasing popularity (2, 3). Studies have shown that maintenance treatments are effective in reducing healthcare costs, hospital admission, opioid use, criminal activity, drug-related mortality, hepatitis, and HIV (4). They are effective in improving mental and physical well-being (5). Methadone is especially considered the treatment of choice for OUD in pregnant and breastfeeding women (6), with some recent evidence displaying an antidepressant effect for buprenorphine (7). However, despite the positive effects, OMT has negative side effects, including physical, psychological, and behavioral consequences. Although, it is recommended for treatment of opioid dependent mothers (6), children with prenatal and early opioid exposure show cognitive, behavioral and motor problems in the future (8-10). Also, several studies have shown that OMT may be associated with the deterioration of some cognitive and executive structures, especially for people who use this treatment for a long time (11, 12). For example, neuroimaging studies using functional magnetic resonance imaging (fMRI) have found deficiencies in brain functions of addicts during response inhibition (13). Impairments in cognitive flexibility and other executive functions result in many behavioral dysfunctions and relapse in Methadone Maintenance Treatment (MMT) patients and require particular consideration for medication and treatment programs (14, 15).

According to studies, drug addicts experience one or more psychiatric disorders, of which anxiety and depression are the most common comorbid disorders. Depressive symptoms are common in addicted patients receiving maintenance treatment (16). Depression can occur at the time of substance use or during and after withdrawal (17). In a study on drug users receiving maintenance treatment, a correlation was found to exist between lower brain gray matter volume, higher degrees in depression and anxiety, and lower degrees in executive function (18). Suicide is also a serious issue among opioid users and needs special attention (19, 20). Suicide attempts, suicidal ideation, and suicide death are more common in individuals with substance use than in the general population (21, 22). Individuals with a history of using heroin are 14 times more likely to die as a result of suicide than their counterparts in the general population (19). Although the initiation of therapeutic interventions is accompanied with a decrease in suicidal thinking and attempts, these indices are usually higher in patients receiving treatment or who have finished

treatment than in the general population (23, 24). The critical perspective of this issue is that the comorbidity of depression and drug use may increase the probability of suicide and other self-destructive behaviors (25). Recognizing the deep relationship between these variables will result in planning early interventions and minimizing the rate of suicide and other psychological problems (26, 27).

Although mood, cognitive, and psychological deficits have been identified in patients receiving OMT, it is not clear whether the differences are due to treatments or the history of opioid use. As depression and suicidal ideation can predict relapse vulnerability in addicts, examining the relationship of depression and mood swings with cognitive functions in patients receiving OMT may provide insight into understanding the neurological foundations and strategies for setting up common mechanisms. Also, since comorbid psychiatric disorders in patients undergoing addiction maintenance treatments lead to high costs and poor prognosis and treatment outcomes (prolongation of treatment period), timely diagnosis and prompt treatment of comorbid disorders in these patients leads to longer-lasting abstinence and greater health. Accordingly, this study aimed to examine depression and suicidal ideation among patients receiving maintenance treatments, taking into account the mediating role of cognitive flexibility.

Materials and Methods

This study was an analytical cross-sectional study. The required sample size was determined to be 126 based on $\alpha = 0.05$, $1 - \beta = 0.80$, and effect size = 0.5. Participants were recruited randomly from 4 outpatient maintenance treatment clinics in Semnan, Iran ($n = 42$ methadone, $n = 42$ buprenorphine, and $n = 42$ opium tincture). They already met the DSM-5 (28) criteria for substance use disorder and abstained for at least one year. Other inclusion criteria were minimum literacy, no other diagnosed psychiatric disorders (such as depression and schizophrenia), and adherence to the treatment program for at least one year without discontinuation of treatment. Individuals were asked to complete an anonymous self-administered paper survey assessing their sociodemographic information, substance use patterns, psychological and cognitive functioning. An informed consent document was also administered. The main data collection tools were the Beck Scale for Suicide Ideation (BSSI), Cognitive Flexibility Inventory (CFI), and Beck Depression Scale (BDI-II). Logistic regression models were used for analysis.

Data collection tools

Cognitive Flexibility Inventory (CFI)

Dennis and Vander Wal introduced the CFI (29). It is a brief self-report scale consisting of 20 items developed to assess the aspects of cognitive flexibility needed to challenge dysfunctional thoughts and change them with beneficial ones. The inventory has three subscales which evaluate the capacity to see different elective alternatives

for life events and human behavior, the propensity to see troublesome circumstances as controllable, and the capacity to produce multiple alternative solutions to difficult circumstances. It is used to assess the average progress of a person in flexible thinking in clinical and non-clinical settings. The inventory has established reliability and validity in studies on different groups (30). Shareh *et al.* (31) found the Cronbach's alpha of 0.90 and test-retest coefficient of 0.71 for the Persian version of CFI.

Beck Scale for Suicide Ideation (BSSI)

The BSSI can be considered as one of the most empirically supported measures and widely used self-report instruments by clinicians and researchers for the assessment of self-destructive thinking and ideation (32). This questionnaire contains 19 items and it was developed to identify and measure the presence and severity of attitudes, behaviors, and planning for suicide during the past week. The overall score for BSSI ranges from 0 to 38, with a higher score indicating increased suicide ideation and beliefs. The validity and reliability of the BSSI have been established (33-35) and it has been shown to be appropriate for both inpatient and outpatient settings and can also be used in other settings such as forensic psychiatry. It has been translated into various languages, including Persian, with desirable psychometric properties (The Cronbach's alpha coefficients > 0.8) (32).

Beck Depression Scale (BDI-II)

The BDI-II is a brief 21-item self-report inventory. It is designed for measuring the severity of depression in youths and adults. It has been utilized by researchers and clinicians in research and clinical settings on both youths and adults. The inventory was first developed in 1961 by Beck *et al.*; it was then revised in 1996 to be more consistent with the DSM-5 criteria for depression (36). It has been translated into Persian, and its psychometric properties have been proved (37).

Data analysis

To analyze the data, descriptive and inferential statistical tests, including mean, SD, interquartile range (IQR), frequency, Kruskal-Wallis tests, Spearman's Rank Correlation Coefficients, and Logistic Regression

analyses were used. The Kruskal-Wallis test is a nonparametric method. The Spearman's Rank Correlation Coefficient was utilized to evaluate the severity of the association between each pair of depression, suicidal ideation, and cognitive flexibility scores. Simple and multiple logistic regression models, including a full model with all explanatory variables of interest and a reduced model made by backward likelihood ratio (LR test approach), were made to examine the relationship between cognitive flexibility and degrees of depression by adjusting maintenance treatment reporting odds ratios (ORs). The data were analyzed using SPSS version 16.0 (SPSS Inc., Chicago, Ill., USA). The level of significance was detected at a P value of 0.05.

Results

The sample consisted of 126 patients, including 115 male and 11 female drug users, receiving OMT with one of the three methods of methadone, buprenorphine, and opium tincture. The youngest patient was 18 years old, and the oldest was 77 years old; the mean ± SD age of all subjects was 45.2 ± 13.4 years. Patients had a history of drug use between 1 to 65 years, and the mean years of drug use was 12.7 ± 9.2. Among the participants, 102 (81.0%) lived in the city, and the rest lived in the suburbs (18) or in a village (6). Of these, 106 (84.1%) had a spouse, and the rest lived alone due to divorce, separation, death, etc. In terms of education, 75 participants had at least a high school diploma (59.5%). 87 patients (69.0%) had a job at the time of the study, and the rest were unemployed due to studentship, retirement, dismissal, unemployment, etc. 80 of them had a rental home (63.5%), and the rest owned a home. The main drug used by 109 of them (86.5%) was opium and shireh (opium juice). 15 patients (11.9%) also had a history of referring to a psychiatrist, and 13 patients (10.3%) used psychiatric drugs. Table 1 shows the personal and demographic characteristics of the participants in more detail. The results of three subgroups show that they did not vary statistically in terms of age and education.

Table 1. Personal and Demographic Characteristics of the Patients Who Were Enrolled in the OMT (Opioid Maintenance Treatments) Program in Iran (Semnan) in 2021

characteristics	Number	Percent	Characteristics	Number	Percent		
Age (years)	Less than 40	12	9.5	Place of birth	City of Semnan	67	53.2
	40 to 50	47	37.3		Inside the province	16	12.7
	50 and more	67	53.2		Outside the province	43	34.1
Gender	Man	115	91.3	Address	In the city	102	81.0
	Female	11	8.7		Suburbs	18	14.3
Number of family members	1	8	6.3	Housing situation	Village	6	4.8
	2	15	11.9		Land lord	80	63.5
	3	33	26.2		Rent	41	32.5

	4	49	38.9		Family home	4	3.2
	5 and more	21	16.7		Homeless	1	0.8
	Methadone	42	33.3		No income	14	11.1
Type of treatment	Buprenorphine	42	33.3		Less than 1 million	13	10.3
	Opium tincture	42	33.3	Monthly income	1 to 3 million	72	57.1
Participate in counseling	Yes	58	46.0		3 to 5 million	24	19.0
	No	68	54.0		5 million and more	3	2.4
	Single	12	9.5		Opium and Shireh	109	86.5
marital status	Married	106	84.1	Type of drug	Heroin	8	6.3
	Divorce	2	1.6		Meth	3	2.4
	Live apart	3	2.4		Over the Counter drug	1	0.8
	Death of wife	3	2.4		Other	5	4.0
	Illiterate	17	13.5		Eat	25	19.8
education	High school	34	27.0	How to use	Smoke	100	79.4
	High school diploma	59	46.8		Sniff	1	0.8
	University	16	12.7		5 years and less	32	25.4
	Freelance	64	50.8	Duration of use	6 to 10 years	33	26.2
	Private employee	9	7.1		10 to 15 years	24	19.0
	Government employee	6	4.8		15 years and more	37	29.4
Job	University student	1	0.8	Refer to psychiatrist	Yes	15	11.9
	Housewife	8	6.3		No	111	88.1
	Unemployed	12	9.5	Psychiatric drugs	Yes	13	10.3
	Retired	26	20.6		No	113	89.7

The mean and SD of scores of depression, suicidal ideation, and cognitive flexibility can be seen in Table 2, and the frequency distribution of participants in terms of depression and suicidal ideation can be seen in Table 3. As can be seen in Table 2, the mean and SD of the cognitive flexibility score in all participants was 91.4 ± 15.5 , and no significant difference could be reported between these scores in the three maintenance treatment groups ($P = 0.386$). Although the score of depression did not show a significant difference between the three groups, the difference between the three groups was significant in terms of the score of suicidal ideation ($P =$

0.004). According to Table 2, the highest score of suicidal ideation belonged to patients treated with opium tincture. The results of the post hoc test showed that the difference between the opium tincture and buprenorphine groups was statistically significant ($P = 0.003$). Table 3 shows that the number of cases at a higher risk of suicide was only one in the buprenorphine group, while in each of the other two groups, there were three high-risk individuals and one suicide attempter. According to Table 3, it can be seen that out of the total participants, 47 (37.3%) did not have depression, and the rest showed some degree of depression.

Table 2. Mean, Standard Deviation, Median, and Inter-Quarter Range of Depression Scores, Suicidal Ideation, and Cognitive Flexibility by Maintenance Treatment Groups

Characteristics	group	Mean	Standard deviation	Median	Inter-quarter range	P †
Depression	Methadone	13.6	9.9	12.5	12	0.127
	Buprenorphine	14.8	5.1	16	2	
	Opium tincture	16.4	10.2	15	13	
	Total	14.9	8.7	15	9	
Suicidal Ideations	Methadone	2.3	5.9	0	0	0.004
	Buprenorphine	0.5	2.5	0	0	
	Opium tincture	2.3	5.0	0	2	
	Total	1.7	4.7	0	0	
Cognitive Flexibility	Methadone	89.2	17.3	90	25	0.386

Buprenorphine	93.6	11.1	92	5
Opium tincture	91.4	17.3	95	24
Total	91.4	15.5	92	17

† Nonparametric Kruskal-Wallis test

Table 3. Frequency Distribution of Maintenance Treatment Groups in Terms of Depression and Suicidal Ideation

Condition	Methadone		Buprenorphine		Opium tincture		Total		
	Number	Percent	Number	Percent	Number	Percent	Number	Percent	
Depression	No depression	22	52.4	8	19.0	17	40.5	47	37.3
	Mild	11	26.2	28	66.7	13	31.0	52	41.3
	Moderate	5	11.9	6	14.3	6	14.3	17	13.5
	Severe	4	9.5	0	0.0	6	14.3	10	7.9
Suicidal Ideation	Down	38	90.5	41	97.6	38	90.5	117	92.9
	High risk	3	7.1	1	2.4	3	7.1	7	5.6
	Suicide	1	2.4	0	0.0	1	2.4	2	1.6

Correlation analysis between depression scores, suicidal ideation, and cognitive flexibility showed a significant correlation between each of the above three factors. The estimation of Spearman correlation coefficients and the P-value was $r = 0.479$ and $P < 0.001$ for depression and suicidal ideation scores, $r = -0.606$ and $P < 0.001$ for depression and cognitive flexibility scores, and $r = -0.427$ and $P < 0.001$ for suicidal ideation and cognitive flexibility. These show that there is a direct correlation between depression and suicidal ideation, suggesting

that increasing cognitive flexibility was associated with decreasing depression and suicidal ideation in participants. The results of simple logistic regression analysis to examine the relationship between cognitive flexibility and degrees of depression and the relationship between cognitive flexibility and a high risk of suicide or its attempt, according to maintenance therapy and other underlying and explanatory variables, are shown in Table 4.

Table 4. Results of Simple Logistic Regression Analysis to Investigate the Relationship between Cognitive Flexibility with Degrees of Depression and Suicide Attempt by Maintenance Treatment

Group Therapy	OR (Depression)	95%CI		P	OR (Suicide)	95% CI		P
		Lower limit	Upper limit			Lower limit	Upper limit	
Methadone	0.899	0.841	0.961	0.002	0.914	0.800	1,044	0.184
Buprenorphine	0.796	0.694	0.913	0.001				
Opium tincture	0.860	0.783	0.946	0.002	1.03	0.980	1,092	0.222
Total	0.877	0.834	0.922	< 0.001	1.009	0.959	1,061	0.738

OR: odds ratio, CI: confidence interval

According to Table 4, increasing cognitive flexibility in general and in each of the three maintenance therapy groups is associated with a reduced chance of developing depression. However, the results do not show a correlation between cognitive flexibility and a high risk of suicide or its attempt. The results of multiple logistic regression analysis to investigate the relationship between cognitive flexibility and degrees of depression by adapting the type of maintenance therapy and other contextual and explanatory variables are shown in Table 5. As seen within the last reduced model, the increase in

cognitive flexibility (OR = 0.87) is associated with a decreasing chance of depression. On the other hand, the use of buprenorphine (OR = 151) and opium tincture (OR = 9.3), compared to methadone, and not attending counseling sessions (OR = 5.4) are associated with an increase in depression.

Table 5. Results of Multiple Logistic Regression Analysis to Investigate the Relationship between Cognitive Flexibility and Degrees of Depression by Adjusting for Maintenance Treatment and Other Underlying and Explanatory Variables

Explanatory Variables	OR Full) (model	95% CI		P	OR (Reduced model †)	95% CI		P	
		Lower limit	Upper limit			Lower limit	Upper limit		
Cognitive Flexibility	0.86	0.81	0.92	< 0.001	0.87	0.82	0.92	< 0.001	
Maintenance treatment	Methadone	1			1				
	Buprenorphine	17.3	3.1	97.0	0.001	15.1	3.3	68.5	< 0.001
	Opium tincture	7.7	1.1	53.6	0.040	9.3	2.1	41.1	0.003
Age (year)	1.0	0.9	1.1	0.886					
Use duration (year)	1.0	0.9	1.1	0.724					
Gender	Man	1							
	Female	1.1	0.0	34.7	0.932				
Number of Family Members	1.2	0.7	2.0	0.545					
Counseling sessions	Yes	1			1				
	No	3.9	1.0	15.7	0.057	5.4	1.7	17.8	0.005
Living with wife/husband	No	1							
	Yes	0.7	0.1	4.7	0.766				
Education	High school	1							
	Diploma and above	1.0	0.2	4.2	0.956				
Landlord	No	1							
	Yes	0.6	0.2	2.4	0.514				
Monthly Income	No income	1							
	Less than 1 million	0.3	0.0	6.8	0.491				
	1 to 3 million	0.5	0.0	10.9	0.647				
	3 million and more	0.7	0.0	18.4	0.833				
Main used drug	Opium and Shireh	1							
	Other drugs	1.3	0.2	7.6	0.741				
Refer to psychiatrist	Yes	1							
	No	0.2	0.0	2.6	0.199				

OR: odds ratio, CI: confidence interval, †Reduced by backward LR test approach

Discussion

The present study examined and compared depression and suicidal ideation between patients receiving maintenance treatments (methadone, buprenorphine, and opium tincture) and tried to find the relationship between these factors regarding the cognitive flexibility of addicts.

According to many previous studies, depression is an important prognostic factor of relapse vulnerability in opiate addicts, and depressive symptoms are common in OUD and OMTs (16, 38-40). According to Table 3, 62.7% of the participants in the study showed some degree of depression. In previous studies, this figure has been reported from 20% to 60%. However, this study found no differential outcome regarding depressive symptoms in the three kinds of maintenance treatment.

This is in line with previous research, showing that methadone and buprenorphine alleviate the symptoms of depression in patients to the same extent (41). Depression is a situation defined by lack of flexibility in various areas of behavior and function. People with depression consider the world unchanging and constant; they find the environment stable, boring, empty, and useless (42). Studies have shown the correlation between cognitive flexibility and depression in healthy people (43, 44).

The present study showed that the rate of suicidal ideation was lower among patients treated with buprenorphine maintenance compared to other drugs. This difference was even statistically significant between the opium tincture and the buprenorphine groups of treatment, which is consistent with the findings of

previous research demonstrating buprenorphine's anti-suicidal and mood-stabilizing capabilities (1, 45-48). This finding highlights buprenorphine as a treatment for depression, as well as its anti-suicidal effects. Drug users face many problems and negative phenomena, one of which is suicide. Substance abuse has long been considered a risk factor for suicidal behaviors, with about half of suicides occurring by drug addicts (19). A study in the United Kingdom found that about one-third of patients had suicidal ideation before entering treatment programs (49). Studies have shown that suicidal thoughts and behaviors are more prevalent in addicted women and patients who consume higher amounts of drugs (50). On the other hand, studies emphasize the strong association of anxiety and depression with suicidal behaviors and thoughts (51).

This study suggests that psychological flexibility is in correlation with depression and suicidal thinking and behavior in people receiving maintenance treatment. Many previous studies have demonstrated this relationship in various situations (52-55). Adjusting for the type of treatment, increasing cognitive flexibility level was associated with a decreasing chance of depression; while receiving buprenorphine and opium tincture, compared to methadone, was associated with increased risk of depression. However, the results of the multivariate analysis did not show an independent and significant association between cognitive flexibility and the risk of suicide. Based on the results, addicted patients seem to benefit from cognitive training. Furthermore, based on some studies, methadone/buprenorphine dependency and long-term use of it cause cognitive deficiencies in users. For instance, in a study, patients receiving methadone treatment were compared with patients who abstained from heroin in terms of visual-spatial attention and cognitive flexibility; the results showed that methadone users had lower performance than patients who abstained from heroin in terms of processing speed, visual-spatial attention, cognitive flexibility, active memory, and deductive reasoning (56). In addition to affecting other aspects of life, it can also reduce commitment to treatment in these patients. Impairment in executive functions, such as response inhibition and impulsivity, correlates positively with the risk of relapse in patients receiving maintenance treatment. In the long term, these cognitive disorders reduce the individual, family, and social efficiency of the user (15).

Limitation

This study has some strengths and limitations. Using validated international scales to measure psychological conditions of participants should be mentioned as a strength. However, some limitations should be acknowledged. First, a causal relationship cannot be established because of the cross-sectional design of the study. Second, all participants were recruited from treatment centers of one city, which limits the

generalizability of the findings. The small sample size and use of self-report questionnaires should be taken into account as limitations of the study. There is a correlation between three factors, but the lack of a significant correlation between cognitive flexibility and suicidal ideation requires further investigation. Usually, many clients of addiction treatment centers are multidrug abusers; therefore, it is not easy to determine the exact amount and mechanism of action of various factors. In addition, the question of whether treating addiction and comorbid disorders can be fully done by adjusting cognitive flexibility is still awaiting further investigation.

Conclusion

In summary, this study focused on the comparison of depression, suicidal ideation, and cognitive flexibility in addicted patients receiving maintenance treatments. In addition to the importance of paying attention to the type of drug treatment, cognitive flexibility is in correlation with depression and suicidal thinking and behavior in these patients. These results highlight the importance of cognitive training in improving cognitive and executive functions, resulting in decreasing negative dimensions of addiction and improving treatment outcomes.

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Conflict of Interest

None.

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