



Cognitive Impairments in Substance Use Patients Treated with Methadone

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Abstract

Introduction: Substance abuse remains a critical global challenge with social, economic, and health impacts. Cognitive impairments are recognized as significant risk factors for relapse and poor treatment outcomes in individuals undergoing substance abuse treatment. This study investigated the prevalence of cognitive impairments and associated factors among patients receiving methadone maintenance therapy (MMT).

Methods: A cross-sectional analytical study was conducted among 370 patients receiving MMT at substance abuse treatment centers in Rasht in 2022. Participants were selected through a two-stage cluster sampling method after obtaining informed consent. Data were collected using demographic questionnaires, the Depression, Anxiety, and Stress Scale-21 (DASS-21), and the Montreal Cognitive Assessment (MoCA). Statistical analyses, including standard deviation, Spearman's correlation, and the Kruskal-Wallis test, were conducted using SPSS version 21 ($P=0.0001$).

Results: Cognitive impairments were observed in 11.1% of participants, with an average age of 49.58 ± 14.40 years. Male participants scored significantly higher on the verbal fluency ($P=0.004$) and delayed recall ($P=0.030$) subscales. Employed or retired patients demonstrated better cognitive performance compared to their unemployed counterparts ($P=0.0001$). Cognitive scores were inversely correlated with age ($P=0.0001$) and positively correlated with education level ($P=0.0001$). Longer primary substance use duration, higher methadone doses, and longer treatment durations were inversely associated with cognitive performance ($P=0.0001$). Stress, depression, and anxiety scores were inversely correlated with MoCA scores ($P=0.0001$).

Conclusion: Cognitive impairments were identified in 11.1% of participants. Longer durations of primary substance use, higher methadone maintenance doses, and extended treatment durations were significantly associated with poorer cognitive performance.

Keywords: Cognitive impairments, Methadone, Substance abuse

Citation: Abdollahi E, Iravani B, Novin MH, Amini Khodashahri F, Bayat Z. Cognitive impairments in substance use patients treated with methadone. Addict Health 2026;18:1693. doi:10.34172/ahj.1693

Received: May 10, 2025, **Revised:** November 4, 2025, **Accepted:** August 2, 2026, **ePublished:** August 5, 2026

Introduction

Substance Use Disorder (SUD) is a chronic and relapsing mental health condition characterized by compulsive substance use, impaired behavioral control, and the emergence of negative emotional states during periods of abstinence.¹ Classified under the ICD-10 as “mental and behavioral disorders due to psychoactive substance use,” SUD is associated with profound physical, psychological, social, and economic consequences.¹ A core feature of the disorder is a motivational shift from positive reinforcement (pleasure-seeking) to negative reinforcement (relief from withdrawal), largely driven by impulsivity and compulsion.²

One of the most critical and often overlooked complications of SUD is cognitive impairment, which involves disruptions in attention, memory, executive functions, decision-making, and behavioral regulation.³ These cognitive deficits are not only common among individuals with SUD but are also strongly associated with poor treatment outcomes and a higher risk of

relapse.⁴ According to the DSM-5, persistent substance use despite significant cognitive, behavioral, and physiological problems is a key diagnostic criterion for SUD.⁵ Neurocognitive models conceptualize addiction as a brain disorder characterized by structural and functional changes, particularly in the prefrontal cortex, limbic system, and striatal regions, which are essential for cognitive control and decision-making.⁶

Chronic opioid use, including methadone maintenance treatment (MMT), has been linked to reduced cortical thickness in the prefrontal cortex, insula, and ventral striatum—regions critically involved in executive functioning and emotional regulation.^{7, 8} Individuals undergoing MMT frequently exhibit impairments in attention, working memory, learning, and other executive functions.⁹ For example, poor performance on standardized neuropsychological tests such as the Wisconsin Card Sorting Test and the Wechsler Memory Scale has been repeatedly reported among methadone patients.^{10, 11}



Similarly, stimulant use, including amphetamines and cocaine, is also associated with disruptions in cognitive performance, particularly in memory consolidation and emotional processing due to alterations in the amygdala and dopaminergic systems.^{12,13} Long-term cocaine use, for instance, may lead to dopamine depletion and functional damage in the prefrontal cortex, cerebellum, and limbic corticostriatal circuits, thereby exacerbating impairments in learning, memory, and emotion regulation, which in turn increases vulnerability to relapse.¹⁴ Many studies have supported this hypothesis that substance abuse destroys the neural processes involved in memory, cognitive, and learning functions. For example, the use of cocaine and heroin can affect the stabilization and consolidation of memory by affecting the lateral amygdala area.¹⁵ Also, according to the study by Aram et al, cocaine use increases dopamine secretion, so that its long term use leads to the loss of dopamine reserves in the brain. In addition, by disrupting the functions of the prefrontal cortex, cerebellum, and various areas of the limbic corticostriatal circuit, it causes memory impairment, knowledge and emotions of the individual, which subsequently increase the temptation to consume in the individual.¹⁶

Recent findings by Redžepagić and Ladas have emphasized impairments in prospective memory, sustained attention, and response inhibition among methadone patients.¹⁷ However, the findings regarding the extent and reversibility of cognitive impairments in methadone-maintained individuals remain inconsistent. While several studies have demonstrated cognitive deficits among methadone patients,¹⁸ others have suggested that MMT may stabilize or partially improve cognitive performance. For example, Verdejo-García et al. (2019) reported that patients who experienced long-term MMT demonstrated relatively preserved working memory compared to heroin users.¹⁹ Rapeli et al. (2007) reported that patients undergoing MMT performed better on working memory and verbal learning tasks than active heroin users.²⁰ Arezoomandan et al. (2022) found that MMT may improve some inflammatory and cognitive parameters compared to untreated subjects.²¹ Nikraftar et al. (2021) reported that patients receiving MMT demonstrated relatively preserved visual memory and performed better than current opioid users and patients receiving buprenorphine on visual memory tasks, although healthy controls generally showed the best overall cognitive performance.²² These findings indicate that MMT may have differential effects across cognitive domains, highlighting the need for individualized treatment approaches. Moreover, most existing studies have been conducted in Western contexts, while limited evidence is available from Middle Eastern or Iranian populations. Therefore, despite general agreement that substance use can affect cognition, the specific pattern, severity, and modifiable factors of cognitive deficits among patients undergoing MMT remain unclear and context-dependent. Given these gaps and conflicting findings, the present study aimed to investigate the cognitive deficits among patients undergoing MMT attending treatment

centers in Rasht. Understanding the nature and extent of these impairments is essential for designing tailored cognitive rehabilitation and relapse prevention strategies within methadone maintenance programs.

Methods

Study design

This analytical cross-sectional study was conducted on patients undergoing Methadone Maintenance Treatment (MMT) at addiction treatment centers in Rasht, Iran, in 2022. Based on the previous studies, there is a 60% prevalence of cognitive deficits in this population.²³ The required sample size was calculated to be 370 participants using Cochran's formula with a confidence level of 95% ($\alpha=0.05$).

In this study, a two-stage cluster sampling method was employed. In the first stage, Rasht was divided into five regions, and a list of licensed MMT centers in each region was compiled. From each list, three centers (a total of 15 centers) were selected using simple random sampling via a random number table. In the second stage, a complete census was conducted: All eligible patients attending these 15 centers were invited to participate in the study. Participants were enrolled in the study after providing written informed consent, in accordance with ethical standards.

Inclusion Criteria

1. Patients currently undergoing MMT.
2. Willingness to participate and having the ability to provide informed consent.

Exclusion Criteria

1. Diagnosed severe psychiatric disorders (e.g., schizophrenia, bipolar disorder).
2. Diagnosed cognitive disorders (e.g., dementia, delirium).
3. Intellectual disability.
4. Current use of substances other than methadone during the MMT period.
5. Incomplete questionnaires.
6. Unwillingness to participate in the study.

The study protocol was reviewed and approved by the Ethics Committee of the Vice-Chancellor for Research, Guilan University of Medical Sciences (Ethical code: IR.GUMS.REC.1399.494). All information collected from participants was kept strictly confidential. Data were used solely for research purposes, reported in aggregate form, and no identifying personal information was disclosed.

Instruments

Data were collected using various instruments to assess cognitive function:

Demographic Questionnaire: This instrument collected information on participants' age, gender, occupation, education level, and other relevant demographic details.

The Depression, Anxiety and Stress Scale-21 Items (DASS-21): It is a standardized self-report instrument

designed to assess the emotional states of depression, anxiety, and stress. The scale comprises 21 items, divided equally into three subscales—Depression, Anxiety, and Stress (seven items each). Responses are rated on a 4-point Likert scale ranging from 0 (“Did not apply to me at all”) to 3 (“Applied to me very much or most of the time”). To calculate the final scores, the sum of each subscale is multiplied by two, aligning the results with the original 42-item version. As such, each subscale score ranges from 0 to 42. The classification of depression, anxiety, and stress severity levels according to the DASS-21 scoring criteria is presented in Table 1.

The DASS-21 has demonstrated robust psychometric properties. The scale has a reported validity coefficient of 0.77, with Cronbach’s alpha coefficients of 0.89 for the Depression subscale, 0.84 for Anxiety, 0.82 for Stress, and 0.83 for the overall scale.²⁴

Montreal Cognitive Assessment (MOCA): The MOCA, developed by Nasreddin et al. in 2005,²⁵ is a brief screening tool for assessing cognitive impairment, including domains such as short-term memory, attention, working memory, and frontal-executive functions. Scores range from 0 to 30, with scores of 26 or lower indicating cognitive impairment.²⁶ The MOCA has demonstrated robust psychometric properties, with a Cronbach’s alpha of 0.85 and a reliability coefficient of 0.62.²⁷ Additionally, a study on patients with Parkinson disease in Isfahan reported a Cronbach’s alpha of 0.77, concurrent validity of 0.79, sensitivity of 0.85, and specificity of 0.90.²⁸

Statistical analysis

Statistical analysis was performed using SPSS version 21. Descriptive results of qualitative variables were reported by frequency (percent). The Shapiro-Wilks test, normality index, Q-Q plot, and P-P plot indicated that the normality of the total and subscales of the MoCA score was not assumed. Therefore, they were described as Median [Interquartile Range (IQR)] and compared between subgroups using the non-parametric Mann-Whitney U Test or Kruskal-Wallis test. The associations between the continuous variables and MoCA scores were explored using Spearman’s correlation. $P < 0.05$ was considered statistically significant.

Results

Three hundred and seventy patients treated with methadone, with an average age of 49.58 ± 14.40 years and average education of 9.37 ± 4.54 years, participated in this study. The majority of participants were male (79.2%) and married (67.8%). The majority of participants were

self-employed (59.5%) and lived in urban areas (83.0%). The findings of substance use patterns showed that 95.7% of participants used opium; 1.4% of patients also used Methamphetamine; 4.3% used heroin; 1.1% used cocaine; 2.7% used hashish; 1.9% used alcohol; and 3.8% used more than three drugs (Table 2).

Table 2. Demographic and Substance Use Characteristics of the Participants

Variable	Frequency (n)	Percentage (%)
Sex		
Male	293	79.2
Female	77	20.8
Marital status		
Single	60	16.2
Married	251	67.8
Divorced	45	12.2
Widowed	14	3.8
Education		
Illiterate	25	6.8
Elementary	64	17.3
Middle Schools	105	28.4
High school/diploma	108	29.2
Graduate studies	67	18.1
Occupational status		
Self-Employed	220	59.5
Employee/Retired	45	12.2
Unemployed	105	28.4
Place of Residence		
Urban	307	83.0
Rural	63	17.0
Substance Use		
Medical drugs		
Yes	97	26.2
No	273	73.8
Methamphetamine		
Yes	23	6.2
No	347	93.8
Heroin		
Yes	41	11.1
No	329	88.9
Cocaine		
Yes	8	2.2
No	362	97.8
Opium		
Yes	354	95.7
No	16	4.3
Cannabis		
Yes	19	5.1
No	351	94.9
Alcohol		
Yes	18	4.9
No	352	95.1

Table 1. DASS-21 Severity Levels for Depression, Anxiety, and Stress

Severity Level	Depression	Anxiety	Stress
Normal	0–9	0–7	0–14
Mild	10–13	8–9	15–18
Moderate	14–20	10–14	19–25
Severe	21–27	15–19	26–33
Extremely Severe	28+	20+	34+

With a cutoff score of 26 on the MoCA, 11.1% of participants were found to have cognitive impairment. It is worth noting that 44.9% of participants were unable to score on the visual-spatial/executive subscale, suggesting considerable difficulties in this area. On the other hand, 56.4% of participants achieved the naming subscale, and 66.1% achieved a perfect score in the abstraction section. Additionally, 85.1% of participants showed full accuracy in the orientation subscale, indicating a high level of awareness of time and place.

The study compared the MoCA scores among various demographic subgroups (Table 2). No significant relationship was observed between gender and the total MoCA score ($P=0.077$). However, men outperformed women in the verbal fluency ($P=0.004$) and delayed recall ($P=0.030$) subscales. No other significant gender-based differences were identified across the remaining subscales. Unmarried individuals had the highest total MoCA scores, followed by divorced individuals, with married participants scoring lower and widowed individuals scoring the lowest ($P=0.001$). Patients who were employed or retired scored higher than those who were self-employed or unemployed ($P=0.001$). Additionally, participants in urban areas performed better than those in rural areas, indicating a possible impact of living environment on cognitive abilities ($P=0.001$). This trend was consistent across all subscales, except for the orientation subscale measuring awareness of time and place. As 95.7% of the study participants reporting previous opium use, we examined the substances consumed alongside opium to investigate this theory. According to

Table 2, there were no notable variations in the overall MoCA scores or its subtest scores among the different substances used by the participants ($P=0.921$).

As indicated in Table 3, the average duration of primary substance use among participants was 14.57 ± 9.73 years. The table also provides the correlation coefficients and significance levels for this analysis. A significance level of less than 0.05 indicates a significant inverse relationship between the duration of substance use and the total MoCA score, as well as scores across all subtests, with the exception of the orientation subtest. Notably, each additional year of substance use was associated with a decline in MoCA scores.

The average of methadone treatment duration for participants was 5.36 ± 2.72 years. The results show a significant correlation between the methadone treatment duration and the total MoCA scores ($P<0.001$), as well as scores on all subscales except for the orientation subscale related to time and place awareness. In particular, cognitive scores decreased with each additional year of methadone treatment (Table 4).

The median methadone dose among participants was 87.94 ± 34.28 mg. The analysis revealed no significant relationship between methadone dose and the overall MoCA score. However, there was a significant association in the abstraction subtest ($P=0.005$), indicating that abstraction scores increased with higher methadone doses. No significant correlations were found between methadone dose and any other subtests (Table 5).

In patients treated with methadone, the average score of stress, depression, and anxiety according to the DASS-21 was 6.05 ± 5.72 , 5.03 ± 4.96 , and 3.68 ± 3.0 , respectively. Table 6 shows the correlation between DASS-21 subscales and total and all subscales of the MoCA scores. There is a significant association between stress and cognitive assessment scores. Stress is positively correlated with total and all subscales of the MoCA score ($P<0.001$), except for the orientation subtest evaluating time and place awareness, indicating a negative correlation. Similarly, higher depression scores are significantly associated with higher total and all subscales of the MoCA score ($P<0.001$), except for the orientation subtest. This indicates that stress and depression can hinder cognitive function, with certain aspects of awareness being more affected under

Table 3. The Relationship Between the Duration of Primary Substance Use (the most frequently used substance) and MoCA Scores and Subtest Performance in Patients

Variable	Correlation coefficients	P-value
Total score	-0.366	0.0001
Visual-Spatial-Executive	-0.388	0.0001
Verbal	-0.313	0.0001
Attention-Focus-Memory	-0.321	0.0001
Naming	-0.293	0.0001
Abstraction	-0.173	0.001
Delayed Recall	-0.234	0.0001
Orientation	-0.051	0.327

Table 4. The relationship between the duration of treatment with methadone and the MOCA score and its subtests in patients.

Variable	Correlation coefficients	P-value
Total score	-0.317	0.0001
Visual-Spatial-Executive	-0.399	0.0001
Verbal	-0.271	0.0001
Attention-Focus-Memory	-0.278	0.0001
Naming	-0.264	0.0001
Abstraction	-0.161	0.002
Delayed Recall	-0.188	0.0001
Orientation	-0.007	0.896

Table 5. The relationship between methadone dosage and scores on the MOCA and its subtests.

Variable	Correlation coefficients	P-value
Total score	-0.073	0.159
Visual-Spatial-Executive	-0.079	0.131
Verbal	0.014	0.748
Attention-Focus-Memory	-0.115	0.072
Naming	-0.078	0.092
Abstraction	0.145	0.005
Delayed Recall	-0.066	0.209
Orientation	0.073	0.163

Table 6. The relationship between stress, depression, anxiety and the score of the MOCA and its subtests in patients.

Stress Depression Anxiety						
Variable	Correlation coefficients	P-value	Correlation coefficients	P-value	Correlation coefficients	P-value
Total score	0.340	0.0001	0.318	0.0001	-0.505	0.0001
Visual-Spatial-Executive	0.278	0.0001	0.290	0.0001	-0.425	0.0001
Verbal	0.316	0.0001	0.267	0.0001	-0.445	0.0001
Attention-Focus-Memory	0.342	0.0001	0.306	0.0001	-0.495	0.0001
Naming	0.320	0.0001	0.326	0.0001	-0.437	0.0001
Abstraction	0.150	0.004	0.114	0.028	-0.164	0.002
Delayed Recall	0.285	0.0001	0.274	0.0001	-0.325	0.0001
Orientation	-0.102	0.0001	-0.087	0.093	-0.117	0.024

increased stress. Additionally, there is a significant negative association between anxiety and all subscale and total MoCA scores ($P < 0.001$).

Discussion

In this study, we investigated the prevalence of cognitive impairments among patients receiving methadone maintenance treatment and exploring contributing factors. The findings demonstrated that the overall prevalence of cognitive impairments in the population undergoing maintenance treatment with methadone was 11.1%, which is consistent with the range observed in both the general population and among substance users.^{29, 30} In a recent systematic review study, Ricardo Pais et al. have reported a global prevalence of cognitive disorders over 50 years of age of 5.1 to 41%, with a median of 19%, varying by region. Specifically, the reported prevalence in Europe, North America, South America, Asia, Africa, and Australia was 5.1–41%, 7.1–28.3%, 24.3–37.5%, 6.5–37%, 18.4–33%, and 7.7–33%, respectively, with no statistically significant differences between regions.³⁰ The prevalence observed in this study appears to be consistent with global rates and falls within the reported range for the Asian population. Bruijnen C et al. reported an overall prevalence of cognitive impairment among substance users to be 33%, with a rate of 38% specifically in opioid users.³¹ However, our study revealed a lower prevalence of cognitive disorders among patients undergoing MMT compared to these figures. Furthermore, while previous research reported mild to moderate cognitive disorders in approximately 40% of individuals undergoing treatment for substance use disorders, the prevalence in this study was notably lower.³²

Additionally, the prevalence of cognitive impairments observed in our study was 11.1%, which is significantly lower than that reported in some prior studies, as it was 52.2% among Chinese MMT patients. This discrepancy may be attributed to variations in the cognitive assessment tools used and differences in the demographic characteristics of the study populations.³³

In the present study, 59.5% of participants were self-employed, and 28.4% were unemployed. An analysis of income sources revealed that the majority of participants relied on financial assistance and government support to meet their expenses. These findings are consistent with the findings of the study by Yang et al, which reported that

76% of patients were unemployed and dependent on family support and government aid. These results underscore the need for strategies to improve the social functioning of these patients, highlighting the critical importance of addressing both cognitive and mental health.³³

Regarding the relationship between gender and cognitive disorders, no significant association was found between gender and the total cognitive score, although this difference was significant in the verbal and delayed recall subgroups. In the study by J. Allan et al, no significant relationship was reported between gender and cognitive impairment in the treated population.³² In the study of Overton et al, in the general population and people over 60 years of age, there was no difference between genders in the occurrence of mild cognitive impairments.³⁴ One possible explanation, as suggested by Levine et al, is that although women have greater cognitive reserves than men, the rate of decline in women's cognitive abilities is higher, which may neutralize gender differences in older ages.³⁵ In the present study, there was an inverse relationship between age and cognitive scores, indicating a decline in cognitive performance with increasing age. In contrast, a positive correlation was found between education level and cognitive function; greater years of education were associated with higher total scores and improved performance across all subtests. However, a study involving patients treated for addictive disorders reported no significant correlation between age and cognitive deficits, but only a weak correlation between education level and cognitive impairments.³² In the population of substance users, there was a significant inverse relationship between age and cognitive abilities in alcohol and cannabis users, but in the case of opioid users, although the relationship was inverse, it was not significant.³¹ The average age of the participants in our study was 50 years, but the average age of drug users in the study of Bruijnen C et al. was 40 years. This age difference may account for the higher prevalence of cognitive impairment observed among older participants.³⁴ Our study found that prior substance use did not significantly affect cognitive scores; however, both the duration of opioid use and the duration of methadone treatment were negatively correlated with cognitive performance.

Consistent with the findings of Bruijnen C et al. among substance users, no significant relationship was observed between the years of use, the severity of dependence, and

cognitive impairment scores,³¹ in the systematic review of Sophie Pask et al, as in the cross-group of elderly people treated with opioids, it was also reported that most studies showed that the use of opioids for pain relief in this group did not have much effect on cognitive deficits, and some studies that prescribed high doses of opioids (120-190 mg) have seen mixed effects of recovery and cognitive deficits. These studies reported deficits in attention, time and place awareness, language, memory, and psychomotor performance.³⁶

In the systematic review of Grace Y. Wang et al, most studies have shown that MMT is accompanied by cognitive deficits that involve a wide range of cognitive substructures.³⁶ Furthermore, an RCT conducted by James S.H. Wong et al. showed that treatment with agonists such as methadone and opium tincture improved cognitive function for up to 4 weeks; however, no further improvement was observed between 4 and 12 weeks, after which a plateau was reached.³⁷ Moreover, a study by Redžepagić and Ladas (2023) emphasized impairments in prospective memory, sustained attention, and response inhibition in individuals undergoing MMT, which underscores the importance of tailored cognitive interventions in this population.¹⁷ Supporting this, Yang et al. (2024) reported a high prevalence of depression and anxiety among MMT patients, with significant associations between these psychological conditions and cognitive impairments, highlighting the need for integrated psychological and cognitive interventions.³³ Additionally, Barahmand et al. (2016) observed that the duration and dosage of methadone significantly influenced executive functions such as decision-making and working memory, suggesting the importance of individualized treatment planning to mitigate cognitive side effects.¹⁸

Finally, the prevalence of depression and anxiety in patients undergoing treatment at specialized centers is high, with reported rates of approximately 49% and 21%, respectively.^{38, 39} Studies have demonstrated that patients with co-occurring depression, anxiety, and cognitive disorders exhibit greater cognitive deficits than those without these disorders, and they experience a faster progression toward dementia.⁴⁰ These findings are consistent with the findings of the present study, so that in patients with higher anxiety and depression scores, cognitive assessment scores were lower.

Conclusion

In this study, the prevalence of cognitive impairment among patients receiving methadone maintenance treatment was comparable to that of the general population and lower than the rates reported in other treated cohorts. The observed associations between age and duration of methadone use with cognitive deficits underscore the importance of monitoring these variables and providing follow-up throughout the maintenance treatment period. Additionally, the potential impact of co-occurring psychiatric disorders, such as anxiety, on cognitive functioning warrants further investigation and clinical

attention. The duration of initial opioid use may also serve as an early indicator of greater cognitive vulnerability at the start of treatment. Future studies with larger sample sizes and prospective designs are recommended to confirm and expand upon these findings.

Acknowledgments

The authors would also like to acknowledge the contribution of all subjects who participated in this research.

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Competing Interests

The authors declared no conflict of interest.

Ethical Approval

The Ethical code (ID IR.GUMS.REC.1399.494) was obtained from the Ethics Committee of the Research Vice-Chancellor at Guilan University of Medical Sciences. Patient information and names were kept confidential. Research results were published in aggregate form, and individual findings were presented without disclosing names or personal characteristics when necessary.

Funding

This study was self-funded by the authors and received no external financial support from any funding organization.

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