# **Assessment of Cognitive Functions in Methadone Maintenance Patients**

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#### Abstract

**Original Article** 

**Background:** Methadone maintenance has received little scientific attention regarding neurocognitive effects. This study is aimed to assess the neuropsychological performance of methadone maintenance patients (MMP) compared to those healthy controls.

**Methods:** Thirty-five MMP and 35 healthy controls, matched for age, gender, education and employment status, examined on a battery of tests aimed at assessing verbal fluency, executive functions, verbal memory, and working memory, using controlled oral word association test (COWAT), trial making test (TMT) Part A and B, Rey auditory verbal learning test (RAVLT), and backward digit span.

**Findings:** MMP performed significantly poorly than controls in cognitive domains of verbal fluency, executive function, and verbal memory. MMP did not exhibit impairment in working memory, and TMT Part A compared to controls.

**Conclusion:** These results suggest that methadone consumption induces significant cognitive impairment that could compromise drug-treatment outcomes in MMP.

Keywords: Methadone maintenance, Opiates, Cognitive dysfunction

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# Introduction

An increasing body of evidence indicates that chronic use of opiates, such as heroin, is associated with widespread impairments in neuropsychological functions.1 Particularly, studies have shown individuals with current heroin abuse exhibited deficits in attention, working memory, episodic memory, and verbal fluency, and 7-14 days after admission to rapid treatment detoxification their performance reached the level of controls.<sup>2-4</sup> Other studies also have reported that opiate abstinent show better cognitive functions than during opiate abuse, indicating recovery of cognitive function.<sup>5</sup>

In opiate substitution treatment, the opioid-dependent patient receives long-acting mu opioid receptor agonists in order to prevent withdrawal symptoms and to reduce craving. The full mu opioid agonist methadone is the most commonly used drug for opiate addiction.<sup>6</sup> Methadone maintenance treatment (MMT) is probably the most accepted method of treatment in the field of drug abuse therapy.<sup>7</sup>

Although patients often show a reduction of illegal opioids and related problem behaviors, patients may experience adverse treatment effects, including cognitive disturbances. This is important, as having cognitive problems such as impaired attention leads poor treatment engagement and treatment prognosis in opioid dependent patients.8-11

The possible cognitive impairments associated with methadone use have not received as much attention as those related to heroin use.<sup>12,13</sup> So far, a few studies have investigated cognitive performance in methadone maintained patients (MMP) relative to controls.<sup>14</sup> Darke et al. found that MMP performed significantly worse than controls on measures of premorbid intelligence, psychomotor performance, information processing, attention, short-term and long-term memory, and problem-solving.<sup>15</sup>

In a larger sample size and using an extensive neuropsychological battery, Specka et al.<sup>16</sup> reported significantly poorer performance of MMP on tests of attention and visual orientation. Mintzer and Stitzer reported that MMP performed significantly worse than controls on tests of psychomotor speed, working memory, selective attention and decision-making measures.<sup>14</sup> Iran has the highest rate of opiate use in the world because of its proximity with Afghanistan. Also, Iran has the most number of MMP clinics for drug users in the Middle East region. Approximately, 700 centers offered MMP to drug-dependent people in 2007.<sup>17,18</sup> However, only one study assessed cognitive functions in an Iranian MMP group, using balloon analog risk task for analysis decision making. Their results showed that the degree of risk taking of opioid dependents was lower than controls after treatment with methadone.<sup>19</sup>

The present study designed to examine performances of a group of MMP in multiple cognitive functions relative to a control group without histories of drug abuse. Our assessment focused on different neuropsychological functions including: 1. The controlled oral word association test (COWAT) (executive function), 2. Trail making test A and B (speed of processing and mental flexibility), 3. Rey auditory verbal learning test (RAVLT) (verbal learning and memory), 4. Wechsler adult intelligence scale-revised (WAIS) backward digit span (working memory).

Since mood and anxiety disorders are common in MMP, we used Hamilton depression scale (HAM-D) and Hamilton anxiety scale (HAM-A) to statistically control for mood and anxiety.

# Methods

This cross-sectional study was conducted in Kerman, Iran, the center of Kerman province as the largest province of Iran. Participants consisted of 35 MMP recruited from outpatient methadone clinic of Shahid Beheshti Hospital, and 35 matched controls without histories of substance abuse recruited from the local community. Due to a higher prevalence of males than females during the sampling period, all the substance abusers, who volunteered for the study, were male. Both groups were matched with respect to age, years of education, and employment status.

Inclusion criteria for all participants were age between 18 and 50 years and for MMP group were: Being involved in a formal MMT, being stabilized in their current methadone dose for at least 1-month and a minimum abstinence period of 48 hours from any drug except methadone.

Participants who had diagnosed with any other disorder from Axis 1 of the diagnostic and statistical manual of mental disorders-4<sup>th</sup> edition (DSM- IV) according to psychiatric interview were excluded from the study. Potential participants who had been previously diagnosed with neurological disorders, human immunodeficiency virus (HIV) infection, history of head trauma and epilepsy, magnetic resonance, acute alcohol abuse and medical problem were also excluded.

The interview and neuropsychological testing took approximately 90 minutes. Written informed consent was obtained from all participants. The study was approved by the Ethics Committee of Kerman University of Medical Sciences.

Cognitive performance was determined by a small battery of cognitive tests to probe different aspects cognition. All tests were administered manually using paper and pencil testing. The testing battery included:

1. COWAT: The verbal fluency test was administered using both letter and semantic categories. In the letter fluency subtest, subjects were asked to generate as many words as possible in a minute starting with the letter "F." The subjects then repeated this task with the letters "A" and "S." In the category fluency subtest, they were asked to generate as many names from the semantic category "animals" within 60 seconds. Mean word generation for both letter and category fluency was measured.<sup>20</sup>

2. Trial making test (TMT): TMT is a measure of visual conceptual and visual motor tracking skills, with a focus on the ability to shift and mental flexibility. TMT consists of two parts namely, Trails A and Trails B. Trails A consists of 25 consecutive numbered circles that the participant connects by drawing a line through each element in the series. Trails B is a more complex task in which a series of numbers (1-13) and letters (A-L) are presented on the page enclosed within circles. The participant is asked to connect numbers and letters (i.e., 1-A-2-B-3-C ... L-13) until the 25<sup>th</sup> circle is reached, as quickly as possible. The final score for both parts was the number of seconds required to complete the task.<sup>21</sup>

3. RAVLT: Evaluates short-term auditoryverbal memory. Participants are given a list of 15 unrelated words repeated over five different trials and are asked to repeat.<sup>22</sup>

4. Wechsler memory scale-revised (backward digit span subtest): This task examines working memory. Several series of digits of increasing

length were read to the participants, who were required to repeat each series. Each set length was tested twice. A backward condition was used. Participants earned one-point for each correctly repeated set.<sup>23</sup>

5. HAM-D: The HAM-D form lists 21 items, the scoring is based on the first 17. It generally takes 15-20 minutes to complete the interview and score the results. Eight items are scored on a five-point scale, ranging from 0 = not present to 4 = severe. Nine are scored from 0 to 2.<sup>24</sup>

6. HAM-A: The HAM-A is a rating scale developed to quantify the severity of anxiety symptomatology, often used in psychotropic drug evaluation. It consists of 14 items, each defined by a series of symptoms. Each item is rated on a five-point scale, ranging from 0 (not present) to 4 (severe).<sup>25</sup>

The data were analyzed using SPSS software (Version 17, SPSS Inc., Chicago, IL, USA). We carried out multivariate analyses of variance to test for group differences. Group (methadone and control) was used as fixed factor, while scores of RAVLT, COWA, backward digit span, TMT A, and TMT B were used as dependent variables. Anxiety and depression scores were used as covariates. A combination of independent t-test and chi-square were used to test demographic group differences.

#### Results

Table 1 shows demographic characteristics of the two groups. There were no significant differences in age, employment, or educational levels between the two groups.

Table 2 shows mean scores of the two groups on different cognitive tasks. Statistical comparisons on the basis of Wilkes criterion revealed overall significant effects of group,  $F_{(5,62)}$  = 15.2, P < 0.001. Effect of covariate was not significant, anxiety score  $F_{(5,62)} = 1.1$ , P = 0.300, depression score  $F_{(5,62)} = 0.9$ , P = 0.400. The main effect of group had a statistically significant effect on three out of five dependent measures, namely RAVLT (P = 0.009), COWAT (P < 0.001), TMT B (P = 0.002). The MMP group performed significantly worse than controls in verbal fluency (P = 0.001), verbal memory (P = 0.009), and psychomotor speed/conceptual flexibility TMT B (P = 0.002). There were no significant differences between the groups on TMT A, and backward digit span.

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Variables	MMT group	Control group	Р
Age (years)	35.43	35.66	NS
Married (%)	80.00	80.00	NS
Employment (% Employed)	80.00	85.70	NS
Years of education	11.88	12.57	NS
Mean depression score	9.74	1.86	< 0.001
Mean anxiety score	13.49	6.37	0.001
Duration in MMT (months)	55.74	-	-
Methadone dose (mg)	15.14	-	-

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MMT: Methadone maintenance treatment; NS: Not significant

Table 2. Task measures for methadone maintenance patients (MMP) and control groups

Cognitive measures	Methadone users	Controls	P
	Mean ± SD	Mean ± SD	
RAVLT	$52.1 \pm 7.1$	$56.4 \pm 3.3$	0.009
COWA	$20.8 \pm 5.1$	$28.4\pm2.6$	0.001
TMT A	$31.8 \pm 10.1$	$30.4 \pm 11.2$	0.707
TMT B	$98.4 \pm 42.3$	$66.9 \pm 19.1$	0.002
Backward digit span	$6.0 \pm 1.8$	$5.7 \pm 1.1$	0.607

RAVLT: Rey auditory verbal learning test; COWA: Controlled oral word association test; TMT: Trial making test; SD: Standard deviation

Correlational analyses were carried out on methadone dosage and measure of each cognitive task. The results showed no significant association between methadone dosage and these measures (all P > 0.050).

#### Discussion

The present study aimed to examine the performance of a group of MMP on different cognitive functions including verbal fluency, mental flexibility, verbal memory, and working memory.

MMP group exhibited poorer performance in all cognitive, with the exception of speed of processing and working memory. Also, the MMP group had significantly higher scores of anxiety and depression, but scores were not significantly related to cognitive performance when these variables were taken into account. There was no significant correlation between methadone dose and cognitive performance among the MMP group.

In our study, MMP group obtained lower scores on a test of verbal fluency (COWAT) than controls. Similarly, Darke et al.,<sup>15</sup> Davis et al.<sup>26</sup> and Ornstein et al.<sup>27</sup> reported that MMP performed poorly on verbal fluency test. Our finding indicates that MMP group has deficits in executive functions, particularly in planning, monitoring, judgment, and decision-making which are important for retrieval of words from memory.<sup>28</sup> Moreover, deficits in verbal fluency in MMP shows impaired function of frontal lobe since this test has been used as an index of frontal lobe function, and studies have shown impaired verbal fluency is associated with frontal lobe damage.<sup>29</sup> Supporting evidence comes from studies showing methadone-treatment reduces cerebral blood flow especially in frontal cortices.<sup>30</sup>

The results of the present study showed that performance of MMP was significantly poorer on TMT B which is congruent with Verdejo-Garcia et al.,13 Mintzer and Stitzer,14 and Specka et al.16 results. This finding indicates impaired mental flexibility and executive functions in MMP. Moreover, impaired in TMT B not in TMT A shows a decreased ability to shift between sets, which is critical component of mental flexibility. This result indicates that methadone might influence executive functioning, possibly through its impact on different monoaminergic systems converging in the frontal lobes.<sup>31</sup>

Consistent with other studies,14,15,26,32 our results showed that methadone-treated patients have impaired verbal memory. According to animal studies,33 one explanation for this finding is the inhibitory effects of opioids on acetylcholine release. Since, acetylcholine is an important neurotransmitter for learning and memory consolidation, decreased the level of acetylcholine results in memory deficits. Also impaired verbal memory in MMP might indicate disturbance of temporal lobe which is involved in verbal memory skills.<sup>34</sup>

The current study showed that MMP performed similarly to controls on test of working memory (backward digit span) and psychomotor speed (TMT A). Our results were in contrast with the impaired working memory and TMT A reported by Darke et al.,<sup>15</sup> Specka et al.<sup>16</sup> and other studies. There are a number of possible explanations for this difference, such as using different measures, sample size, demographic, and clinical characteristics (e.g. dependency on more than one substance) of the groups.

It should be mentioned that some studies have suggested that other factors indirectly related to opioid abuse, such as concurrent alcohol abuse, may be related to cognitive impairments in MMP.<sup>35,36</sup> However, none of the patients in our study uses any other drug, indicating that methadone consumption by itself may be associated with cognitive deficits.

In agreement with previous studies, our results showed higher rates of depression and anxiety in MMP, consistent with the notion that co-morbid psychological problem is common in substance-using individuals.<sup>37</sup>

Generally, there are possible explanations for the findings of cognitive impairment in MMP group. First, the direct effect of methadone may cause cognitive dysfunction, as studies have shown that opiates cross the blood-brain barrier (BBB). Moreover, neurocytotoxic effect of opiates on central nervous system has been reported in animal studies.<sup>38</sup> Second, it is possible that cognitive deficits of opiate abusers might be results of the direct toxic effects of concomitant substance abuse.<sup>15,39</sup> Third, according to Darke et al.,<sup>15</sup> indirect effects of opiates, such as lifestyle, poor nutrition, infections, or exposure to violence, might associated with their cognitive impairment.

One clinical implication of our results is that cognitive deficits observed in MMP, are possible to affect the daily functioning and their involvement in treatment. Importantly, recent

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studies have found that cognitive function influence the drug-abuse rehabilitation outcomes. Particularly, impaired executive function and verbal memory found in our study might result in difficulty in understanding complex instructions, and inhibiting inappropriate automatic behaviors in MMPs. Executive dysfunction could also have negative effects on their social relationships.<sup>13</sup> Finally, the finding that MMP have difficulties in acquiring verbal information might interfere with their social and occupational functioning. Altogether, cognitive deficits may be one of the important factors contributing to failure of patients to maintain in program.<sup>15</sup>

Several limitations of this study should be considered, including the limited sample size, some demographic differences between the MMP and controls, possible selection bias among controls. The deficits may be due to the acute effects of other drugs used in MMP group, although given our exclusion criteria; we believe it is unlikely to account for the deficits observed in MMP group. Finally, the performance deficits in MMP group may be related to differences between the groups on various factors (e.g., personality, brain dysfunction, and environment) that were not examined in the present study.

# Conclusion

In summary, the current study indicates that in addition to the high rates of psychiatric morbidity, MMP also show impaired cognitive functions particularly in domains of executive functions and verbal learning, shown with poor performance in TMT B and COWAT, and RAVLT.

# **Conflict of Interests**

The Authors have no conflict of interest.

#### Acknowledgements

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# اختلالات شناختی در بیماران تحت درمان نگهدارنده متادون

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چکیدہ

مقاله پژوهشی

**مقدمه:** تاکنون چندان به اثرات عصبشناختی درمان نگهدارنده متادون در مطالعات پرداخته نشده است. این مطالعه با هدف ارزیابی عملکرد عصب روانشناختی بیماران تحت درمان نگهدارنده متادون، در مقایسه با افراد گروه شاهد انجام گرفت.

**روشها:** ۳۵ بیمار تحت درمان نگهدارنده متادون و ۳۵ فرد سالم که از نظر سن، جنس، تحصیلات و وضعیت شغلی با همدیگر همسان شده بودند، با استفاده از یک مجموعه تست که حیطههای شناختی مختلفی را بررسی میکرد، مورد ارزیابی قرار گرفتند. حیطههای شناختی و آزمونهای مورد استفاده شامل روانی کلام (Controlled oral word association test یا COWAT یا Trial making test part A and B)، عملکرد اجرایی (Backward digit span)، حافظه در جریان (RAVLT)، حافظه کلامی (Backward digit span) بود.

**یافتهها:** بیماران تحت درمان نگهدارنده متادون از نظر روانی کلام، عملکرد اجرایی و حافظه کلامی به طور معنیداری عملکرد ضعیفتری را نشان دادند. این بیماران در حافظه کارکردی و سرعت پردازش مشابه گروه شاهد بودند.

**نتیجهگیری:** نتایج مطالعه حاضر نشان داد که مصرف متادون منجر به نواقص شناختی عمدهای میگردد که میتواند نتایج درمان را در بیماران تحت درمان نگهدارنده متادون با مشکل مواجه نماید.

**واژگان کلیدی:** درمان نگهدارنده متادون، اوپیوئید، اختلال شناختی

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