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Memory function in patients with opioid dependence treated with buprenorphine and methadone in comparison with healthy persons

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Methadone and buprenorphine are commonly used for drug abuse treatment but may impair cognitive function. This study assessed memory performance in patients receiving these treatments compared to healthy controls. A cross-sectional study was conducted on 93 buprenorphine- and 120 methadone-treated patients, compared with 120 healthy controls. The Wechsler Memory Scale was used, and scores were compared among the study groups using Kruskal–Wallis with Tukey's post-hoc test. Maintenance therapy duration was compared between case groups using an independent t-test or Mann–Whitney U test. Healthy controls were superior to both treatment groups in mental control. The methadone group surpassed controls in personal and general information ($P < 0.05$), while buprenorphine-treated patients scored lower in associate learning. Patients receiving methadone for > 2 years had a higher mean score of awareness of place and time than those on long-term buprenorphine ($P = 0.034$). Longer buprenorphine treatment correlated with improved total memory scores ($P = 0.03$). The mental test showed no significant adverse effect for either medication on most mental aspects, except for mental control, which was worse than the control group in both medications. In some aspects, treated patients even outperformed controls. Buprenorphine preserves memory function better than methadone over time.

Keywords Addiction, Methadone, Buprenorphine, Maintenance therapy, Memory function

Opioid abuse is a great harm to populations, estimated to involve about 40.5 million people around the world (in 2017), resulting in 109,500 deaths from opioid overdose[1]; a higher burden is observed in countries with a lower sociodemographic index[2]. About 15% of disability-adjusted life years (DALYs) and 28.5% of years lost to premature mortality worldwide are attributed to substance use disorders (SUDs), which are regarded as the primary cause of disability and early mortality worldwide[3]. Among the several damages substance abuse causes, including severe health complications, its negative impact on the brain is of great significance, as it impairs the social, cognitive, behavioral, and physiological functions of the individual, despite which individuals persist in using these drugs[4].

Methadone and buprenorphine are two examples of opioid agonist treatment (OAT) used to treat opioid dependence and mitigate its negative effects. OAT programs have prevented about half of the deaths, regardless of patient sex, age, geographic region, underlying diseases (human immunodeficiency virus [HIV] or hepatitis C), and whether the patients injected the drug or used other forms of administration[1,5]. Buprenorphine is a partial long-acting opioid agonist of the mu-opioid receptor (one of the four natural opioid receptors responsible for pain control), with a half-life varying from 3 h after intravenous injection to 28–37 h after sublingual administration. The extended half-life of this drug provides patients with sufficient stability for daily activities[6]. Methadone is another mu–receptor agonist with a longer half-life of 24 to 36 h compared to other opiates. It is prescribed as a single oral dose per day to prevent withdrawal symptoms during the day[7,8]. Methadone and buprenorphine have substantial differences in clinical application; patients on high-dose buprenorphine have higher retention rates (and drug-free urine tests) compared with low-dose methadone, and the partial mu-

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agonist activity of buprenorphine results in milder withdrawal syndrome, easing discontinuation. Conversely, patients with severe opioid dependence benefit more from methadone. The two drugs also have different effects when combined with other medications, such as benzodiazepines[9].

However, buprenorphine and methadone can also have adverse effects, including not only cardiac and liver disorders[10] but also cognitive disturbances. These impairments in attention, concentration, memory, learning, decision-making, emotion, and cognitive flexibility can lead to poor treatment engagement, compromise the OAT protocol[11,12], and result in sleep disturbances, depression, anxiety, and increased risk of suicide/self-harm[13]. Although research consistently shows that patients receiving buprenorphine maintenance treatment (BMT) or methadone maintenance treatment (MMT) exhibit lower cognitive performance compared with healthy controls[11], the results of comparing the mental defects between MMT and BMT are conflicting. Some studies suggest that BMT leads to better cognitive function, including improved verbal and working memory performance and delayed word recall, compared with MMT[14]. Others, however, report no significant differences between MMT and BMT, noting that treatment duration, alcohol abuse, and co-medications also play a role in these side effects[11]. Considering the controversial results and the lack of similar studies in Kurdistan province, Iran, the present study aimed to compare the memory performance of individuals with opioid dependence undergoing BMT or MMT with that of healthy controls.

Materials and methods

In this cross-sectional study, individuals with opioid dependence undergoing BMT ($N=93$) or MMT ($N=120$) were included as the study population and compared with healthy controls. The cases were selected from individuals admitted to Ghods Hospital (Sanandaj, Iran) and other substance abuse treatment centers in Sanandaj city. Eligible participants were enrolled in the study using a census (non–randomized) method. The controls were selected among the companions and family members of patients hospitalized in non-psychiatric departments of Sanandaj hospitals, taking care of them, through a random sampling method ($N=120$) and were matched with the case group for age and educational level.

The inclusion criteria for all study groups, including both case and control groups, were as follows: participants aged 18–60 years, with a minimum literacy level (able to read and write in Persian) and a maximum educational attainment of a bachelor's degree. The control group should have been completely healthy with no history of addiction, physical or mental illness. The MMT group should have been under maintenance treatment with a fixed dose of 20–60 mg/day, and the BMT group with a constant dose of 2–8 mg/day; both started at least 2 months prior to the study. The cases with a positive urine test for morphine, tramadol, and methamphetamine (based on recent clinical records), intellectual disability (determined using the Wechsler IQ test in case of clinical doubt), thyroid function disorders (based on the medical records and the researcher's interview), history of major psychiatric disorders, such as depression, neurocognitive disorder, or psychotic disorders, use of antipsychotic drugs, benzodiazepines, lithium, Z drugs, memantine, donepezil, rivastigmine, or any type of illegal substance (according to the clinical records and the researcher's interview) were excluded from the study. The researcher selected the individuals based on the inclusion criteria and enrolled the eligible ones in the study after they received a complete explanation of the study objectives and read and signed the written informed consent. The study was conducted in compliance with the Helsinki Declaration at every stage, and the protocol was approved by Kurdistan University of Medical Sciences Research Ethics Committee with the number IR.MUK.REC.1399.127.

The participants were interviewed individually in a quiet and private room. During the interview, in addition to collecting demographic and clinical data, the researcher asked questions on the Wechsler Memory Scale (WMS) from all participants, blinded to their group allocation. The Persian version of the WMS-R (translated by Sadegh Nasiri and Seyyed Abbas Bagheri Yazdi under the supervision of Dr. Mohammad Naghi Brahni) was used, previously validated by a Cronbach's alpha of 0.65–0.85[15] and a reliability of 0.28–0.98[16]. The researcher was trained by a supervisor 1 week prior to conducting the interviews. Each interview session lasted about 15 min for administration and 10 min for scoring. The WMS includes seven subtests: general and personal information, awareness of time and place, mental control (to check working memory, attention, and concentration), logical memory (to check immediate recall and immediate verbal memory), numerical memory (to check attention, concentration, working memory, and short-term verbal memory), visual memory (to check short–term visual memory), and associate learning (to check immediate recall and immediate verbal memory). Each subtest has a specific scoring system, with the total score calculated as the sum of subtest scores and adjusted for age for calculation of the memory score, based on the suggested Table[17].

Data analysis was done using STATA software, version 14. Descriptive indices included number (frequency), mean, and standard deviation (SD), and analytic tests included the Chi-square test (for comparing categorical variables) and Kruskal–Wallis test (for comparing the scores among the three study groups), followed by Tukey's post-hoc test. The two case groups were categorized into two subgroups based on the treatment duration: 6 months to 2 years and more than 2 years. Treatment duration was compared within each group and between the groups receiving MMT and BMT. For these comparisons, the independent samples t-test was used when the scores had normal distribution and the Mann-Whitney U test when not normal. The results were compared between the case groups, the case and control group, and based on the treatment duration.

Results

The mean age of the case and control groups in this study was 41.42 ± 9.49 and 41.33 ± 9.66 years, respectively; 41.78 ± 8.60 years in the MMT and 41.08 ± 10.39 years in the BMT group without difference in mean age ($P=0.86$; Table 1) or educational level between the groups ($P=0.178$; Table 1).

Variable		Group			*P* value
		Healthy controls (N = 120)	Methadone group (N = 120)	Buprenorphine group (N = 93)	
Age					
Mean ± SD range		41.33 ± 9.66 (20–60)	41.78 ± 8.60 (22–60)	41.08 ± 10.39 (22–60)	0.86*
Educational level, n (%)	Diploma and below	95 (79.2)	99 (82.5)	67 (72)	0.178**
	Academic	25 (20.8)	21 (17.5)	26 (28)	

Table 1. Distribution of educational level and mean age in the studied groups. SD, standard deviation; N, number. *Independent sample one-way ANOVA. **Chi-square test.

Variable	Group			*P* value*
	Healthy controls (N = 120)	Methadone group (N = 120)	Buprenorphine group (N = 93)	
	Mean ± SD			
	Range			
Personal and general information	5.45 ± 0.65 (4–6)	5.66 ± 0.68 (2–6)	5.51 ± 0.70 (3–6)	0.008
Awareness of place and time	4.87 ± 0.34 (4–5)	4.88 ± 0.39 (3–6)	4.75 ± 0.48 (3–5)	0.039
Mental control	6.83 ± 1.73 (4–9)	6.13 ± 1.58 (2–9)	5.89 ± 1.67 (2–9)	< 0.001
Logical memory	7.98 ± 2.37 (3_16)	8.61 ± 3.11 (2–16.5)	8.06 ± 3.80 (1_19)	0.16
Numerical memory	9.47 ± 2.06 (6–15)	9.41 ± 1.83 (5–15)	9.22 ± 2.30 (4–15)	0.40
Visual memory	10.95 ± 2.45 (3–16)	10.22 ± 2.69 (4–14)	10.48 ± 2.47 (4–15)	0.08
Associate Learning	15.21 ± 3.35 (6_22.5)	14.27 ± 3.46 (7–20)	14.04 ± 3.24 (5.5–21)	0.02
Total memory	104.93 ± 14.96 (63_143)	102.86 ± 13.33 (70_143)	100.81 ± 14.54 (66_143)	0.68

Table 2. Comparing the mean of the Wechsler's memory subtest scores among the three study groups. SD, standard deviation; N, number. *Kruskal–Wallis test.

There was no statistically significant difference in the mean scores of total memory, visual memory, logical memory, and numerical memory among the three study groups ($P > 0.05$, Table 2), while there was a significant difference in mean subtest scores of personal and general information, time and place awareness, mental control, and associate learning among the three study groups ($P < 0.05$).

The post-hoc comparison by Tukey's test showed a significant difference in personal and general information between MMT and healthy controls ($P = 0.04$), while the two case groups were not different in this regard; also, the BMT group was not different from the control group. For the mental control subtest, the healthy group had a higher mean than each of the case groups ($P = 0.03$ for MMT vs. control and $P < 0.001$ for BMT vs. control). In the associate learning subtest, the healthy group had a higher mean score than the BMT group ($P = 0.03$), while the difference between the control and MMT was not significant.

Separating the results based on the treatment duration showed significant differences between the two case groups with treatment duration of > 2 years in awareness of place and time (higher mean score in the MMT group, compared with BMT; $P = 0.034$), while other scores were not different ($P > 0.05$; Table 3). Comparing the mean scores between the treatment durations in each group showed a significantly higher score in total memory of the BMT group with a longer duration of administration (> 2 years; $P = 0.010$), while other scores were not different ($P > 0.05$; Table 3).

Discussion

The current study's findings demonstrated minor differences between the individuals with opioid dependence under BMT or MMT (limited to better awareness of place and time in patients under MMT for > 2 years, compared with those under BMT with a similar duration, and better total memory scores in patients under BMT for more than 2 years). However, both treatment groups' mental health was shown to be compromised compared with healthy controls. Associate learning was also worse in the BMT, compared with the healthy group, while the third subtest (personal and general information) was better in the MMT group than the control group. The latter finding, along with no observed difference between the treatment groups and the healthy control in total memory scores and other mental functions, such as logical memory, numerical memory, and visual memory, shows that neither of these medications significantly impairs memory, except for mental control and associate learning (only in BMT).

Variable	Group	Treatment duration (Mean ± SD)		*P* value*
		6 months to 2 years	More than 2 years	
Personal and public information	Methadone	5.46 ± 0.92	5.76 ± 0.48	0.061
	Buprenorphine	5.45 ± 0.74	5.55 ± 0.67	0.511
	P value	0.952*	0.057**	
Awareness of place and time	Methadone	4.83 ± 0.49	4.91 ± 0.32	0.342
	Buprenorphine	4.76 ± 0.48	4.75 ± 0.48	0.838
	P value	0.533*	0.034**	
Mental control	Methadone	5.95 ± 1.83	6.22 ± 1.44	0.389
	Buprenorphine	5.60 ± 1.65	6.14 ± 1.67	0.122
	P value	0.355*	0.779*	
Logical memory	Methadone	8.23 ± 3.31	8.81 ± 3.00	0.336
	Buprenorphine	7.23 ± 3.69	8.74 ± 3.79	0.057
	P value	0.201*	0.914*	
Numerical memory	Methadone	9.46 ± 1.73	9.38 ± 1.89	0.813
	Buprenorphine	8.89 ± 2.13	9.49 ± 2.42	0.216
	P value	0.186*	0.784**	
Visual memory	Methadone	9.95 ± 2.58	10.35 ± 2.75	0.439
	Buprenorphine	10.62 ± 2.59	10.37 ± 2.40	0.636
	P value	0.244*	0.969*	
Associate Learning	Methadone	14.70 ± 3.11	14.05 ± 3.63	0.332
	Buprenorphine	13.60 ± 3.37	14.41 ± 3.12	0.237
	P value	0.127*	0.568*	
Total memory score	Methadone	99.56 ± 12.53	104.57 ± 13.49	0.051
	Buprenorphine	96.55 ± 13.76	104.31 ± 14.35	0.010
	P value	0.300*	0.918*	

Table 3. Comparing the mean Wechsler's memory subtest scores between the case groups by treatment duration. SD, standard deviation; N, number. *Independent sample t-test. **Mann–Whitney U test.

Total memory is the most important variable in this assessment tool. The results showed no difference between the groups, indicating no adverse effect of any of the medications on total memory. Some studies have referred to the negative effect of both MMT and BMT on memory[11–13]. A randomized clinical trial investigating cognitive performance in patients under BMT and MMP patients showed weaker memory performance in the two treatment groups compared with healthy controls; however, after 8–10 weeks of stable substitution treatment, there was a significant improvement in concentration and executive functions[18], which is inconsistent with the results of the present study. These studies have either used different tools for evaluating the individual's cognitive function/memory, evaluated only one of the maintenance treatments, or compared them with another medication used for OAT and are therefore not directly comparable to the present study. To justify the impaired memory by BMT or MMT, they have referred to the detrimental effects of drug use on the brain areas, such as the frontal cortex and hippocampus, which are involved in memory and learning. This is one of the main hypotheses accepted. These effects are mainly driven by stress, oxidative stress, and inflammation, which increase the rate of apoptosis and prevent neurogenesis. Therefore, concomitant antioxidants have been suggested to reduce this adverse effect in BMT and MMT[19]. The two-phase studies by Rapeli and colleagues also confirmed that impaired immediate recall was maintained after 3 years of treatment with BMT and MMT[11,20], while we only observed worse associate learning in the BMT group compared with healthy controls.

Of note, the worse mental control (working memory, attention, and concentration) documented in the treatment groups compared with the control group is similar to the results of other studies. Rapeli and colleagues evaluated verbal and working memory using WMS-version III to compare MMT and BMT. The results showed impaired function in both groups compared with controls[20], which is consistent with the results of the present study. However, the study comparing MMT with healthy controls showed no impairment in working memory[12], which is not consistent with the present study's results. The mechanism for this effect is related to its antagonistic action on the kappa opioid receptor, influencing prefrontal dopamine tone, which is important for working memory[11]. Another mechanism involves the extensive activity of the neuronal network, including the bilateral frontal and parietal cortex, especially in the right hemisphere, which is crucial for effective working memory performance. Since both methadone and buprenorphine reduce blood supply to the brain, especially in the frontal cortex and the right hemisphere, the supply of essential neurotransmitters, especially catecholamines, needed for working memory is disturbed, resulting in performance loss[20]. A few years later, Rapeli and colleagues reported that this impairment in working and verbal memory improved over time, during 6–12 months and > 12 months in the BMT group[11]. Nonetheless, we did not observe any effect on the treatment duration on this subtest. The only effect we observed for the treatment duration was improvement in the total memory in the BMT group, as demonstrated by higher mean scores in the group with treatment duration exceeding 2 years. Another study

found that after 8–10 weeks of consistent BMT and MMP replacement treatment, concentration and executive functions improved[18], indicating a significant effect for treatment duration, although the parameters studied differed from those in the present study. Contrasting results are observed in the literature regarding the effect of treatment duration on cognitive function and the effective duration[14,21], highlighting the necessity of further studies in this regard. Additionally, the dose of treatments received can influence the outcome; although some rejected the dose-dependent effect on immediate recall performance[22]. Therefore, more studies are required to consider the effect of treatment duration and dose on cognitive and memory impairment in patients undergoing MMT or BMT.

Regarding the other subtests, our study showed no difference in visual memory between the groups, indicating no adverse effect of either medication. In another study in Tehran in 2021, the researchers compared the three groups we investigated, as well as current opioid users. They evaluated the participant's symptoms, neuropsychology, memory, and executive functioning. The results of the comparisons, based on WMS, showed that healthy subjects performed best, current users performed worst, and MMT performed better than BMT in visual memory but worse than the healthy subjects[23]. These findings are consistent with our results, as we did not find any significant difference between BMT and MMT in visual memory. The results of other studies are also inconsistent with our study regarding the impaired visual memory induced by MMT[12] and BMT[18,24]. This difference could be related to the different versions of the scale used or the difference in the participant's demographic and clinical characteristics.

Others have demonstrated decreased verbal working memory, sustained attention, and cognitive speed and flexibility for BMT, which persisted even after controlling for intellectual function and other confounders[24]. However, the treatment group they compared was those on naltrexone, and they did not include MMT in their study. Furthermore, the tools they used differed from those in the present study, resulting in different reported parameters. The impaired verbal memory induced by MMT can be related to the inhibitory effects of opioids on the release of acetylcholine, which plays an important role in learning and strengthening memory. Another explanation for this result is the dysfunction of the temporal lobe caused by methadone consumption, which plays an essential role in verbal memory[25].

As mentioned in other studies, opioid users had the worst mean values compared to all treatment groups. This indicates that whatever adverse effect the methadone or buprenorphine may have on mental health, they do not reach the severe complications opioids themselves have on cognitive function[23]. Therefore, we believe that the adverse effects of maintenance treatments are as minor as negligible. Further studies are required to determine the long-term effects of maintenance treatments on users with opioid dependence.

The present study had some limitations. Firstly, the patients in the treatment groups were neither enrolled in the study by a random method nor assigned to the groups by randomization. This was because of the limited eligible patients, especially opioid abusers with normal mental health before OAT. Secondly, we performed a cross-sectional study and did not follow the patients to observe the long-term effects of treatment on study variables; also, we could not establish a causal relationship between the variables, considering the study design. Last but not least, we could not compare the results with the patients' status before OAT and did not have a control group of current opioid users. Therefore, the effect of confounders should be considered when interpreting the results of the present study. The results are not generalizable to the whole population.

Conclusion

Both MMT and BMT were associated with impaired mental control in individuals with opioid use disorder, with BMT also affecting associate learning negatively. Long-term BMT was associated with better total memory over time, whereas long-term MMT improved awareness of place and time. These results can be helpful for designing more effective rehabilitation programs for individuals with opioid abuse. Considering the varied results in the literature and the limitations of the present study, further studies are required to outline different aspects of the effect of MMT and BMT on mental health and the possible mechanisms underlying this effect.

Data availability

The data supporting this study's findings are available through reasonable request from the corresponding author.

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Author contributions

SM, SK, and NSA contributed to the study design. Data collection, material preparation and interview were performed by SM. Statistical analysis was carried out by KHR. The first draft of the manuscript was written by SM and SK. All authors commented on the previous version of the manuscript. The final version and editing of the manuscript were conducted by SM and SK. All authors read and approved the final manuscript.

Declarations

Competing interests

The authors declare no competing interests.

Additional information

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