ORIGINAL RESEARCH

The Role of Cognition and Opioid Substitution Therapy Adherence in Opioid-Dependent Patients

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ABSTRACT

Background: Opioid substitution therapy (OST) is a key intervention in the management of opioid dependence. However, treatment adherence remains a significant challenge, and cognitive impairment may play a critical role in influencing adherence patterns.

Aim: The study aimed to assess the relationship between cognitive function and adherence to opioid substitution therapy in patients diagnosed with opioid dependence syndrome.

Material and Methods: This prospective, observational study was conducted in the Department of Psychiatry at a tertiary care teaching hospital after obtaining Institutional Ethics Committee approval. Forty male patients aged 18–50 years, diagnosed with opioid dependence syndrome as per ICD-10 criteria, and undergoing maintenance therapy with buprenorphine or methadone for at least one month, were recruited. Cognitive function was assessed using the Mini-Mental State Examination (MMSE), Trail Making Tests A and B, Digit Span Test (forward and backward), and Stroop Test. Adherence to OST was evaluated through pill counts, clinical dosage records, and self-reports using the Medication Adherence Rating Scale (MARS).

Results: Demographic and clinical variables were comparable between adherent and non-adherent groups. Adherent patients had significantly higher MMSE scores (28.1 ± 1.2) compared to non-adherent patients (26.9 ± 1.4, $p = 0.01$). Neuropsychological testing showed better attention, working memory, and executive function among adherent patients. Adherence rates were slightly higher with buprenorphine (62.1%) than methadone (54.5%). Significant positive correlations were found between adherence and MMSE, Digit Span Forward, and Digit Span Backward, while negative correlations were observed with Trail Making Test scores and Stroop Test errors.

Conclusion: Cognitive functioning significantly influences adherence to opioid substitution therapy in patients with opioid dependence. Routine cognitive assessment and targeted cognitive interventions may improve adherence rates and overall treatment outcomes.

Keywords: Opioid dependence, Opioid substitution therapy, Cognitive function, Treatment adherence, Neuropsychological assessment

INTRODUCTION

Opioid dependence remains one of the most significant public health challenges worldwide. The global opioid crisis has led to widespread morbidity, mortality, and socio-economic burden. A critical component of managing opioid dependence has been the use of opioid substitution therapy (OST), which provides a safer, controlled alternative to illicit opioid use. Among the pharmacological agents employed, methadone and buprenorphine have emerged as the most studied and widely utilized options. Clinical trials and systematic reviews have consistently demonstrated the effectiveness of

buprenorphine maintenance therapy in reducing opioid use, promoting treatment retention, and lowering the risk of infectious disease transmission associated with injecting drug use.[1,2]

Buprenorphine, a partial opioid agonist with a ceiling effect on respiratory depression, offers a favorable safety profile compared to full agonists such as methadone. Its combination with naloxone has further improved safety by reducing the potential for misuse. OST not only mitigates withdrawal symptoms and cravings but also stabilizes individuals' lives, facilitating engagement with psychosocial support and harm reduction services. The World Health Organization collaborative studies have highlighted the importance of OST as a critical intervention in the prevention of HIV/AIDS among opioid-dependent individuals.[3,4]

Despite these benefits, opioid dependence treatment remains complex and multifactorial. Systematic reviews and economic evaluations have shown that both methadone and buprenorphine are cost-effective interventions, though buprenorphine may offer certain advantages in terms of patient acceptability and safety profile. Longitudinal studies, such as the Drug Abuse Treatment Outcome Studies (DATOS), have provided valuable insights into the long-term outcomes of drug treatment programs, including significant reductions in illicit drug use, criminal activity, and improvements in employment and social functioning.[5]

The prevention of HIV infection among injecting opioid users is a major public health goal. OST plays a pivotal role in this context by reducing risky behaviors, including needle sharing. In addition to preventing the spread of infectious diseases, OST contributes to improved overall quality of life, offering individuals the opportunity to reintegrate into society and reduce their dependence on healthcare and social welfare systems.[6]However, the use of long-term opioid substitution therapy is not without challenges. Clinical observations have reported evidence of specific cognitive deficits in patients undergoing prolonged OST, particularly those receiving high-dose or extended therapy. These deficits include impairments in memory, attention, and executive functioning, which may affect patients' daily activities and adherence to treatment regimens. A comprehensive meta-analysis further quantified these neuropsychological consequences, revealing that chronic opioid use, even under controlled therapeutic conditions, can lead to measurable cognitive decline.[7]The presence of neurocognitive impairment has critical implications for the management of opioid-dependent patients. Studies have demonstrated that patients with such impairments often experience difficulties in adhering to complex treatment protocols, including antiretroviral therapy in HIV-infected populations. Cognitive deficits may interfere with patients' ability to understand and follow medical instructions, attend regular clinic visits, and maintain consistent medication use.[8,9]

Treatment engagement has been shown to moderate the negative effects of neurocognitive impairment. Interventions that promote patient involvement and support can enhance adherence and improve health outcomes in this vulnerable population. The development of theory-based intervention models has provided a framework for understanding the relationship between cognitive functioning and health behaviors among drug users. These models emphasize the need for tailored treatment approaches that consider individual cognitive capacities and provide appropriate support to maximize treatment effectiveness.[10,11]

AIM AND OBJECTIVES

Aim

To evaluate the relationship between cognitive functioning and adherence to opioid substitution therapy (OST) in patients diagnosed with opioid dependence syndrome.

Objectives

1. **To assess the cognitive functioning** of patients with opioid dependence syndrome who are undergoing OST, utilizing standardized neuropsychological assessments.
2. **To evaluate adherence levels** to OST among these patients, employing both objective measures (such as pill counts and clinic dosage records) and subjective measures (like self-reported adherence scales).
3. **To analyze the correlation** between cognitive functioning scores and adherence levels to OST, determining if cognitive performance influences treatment adherence.
4. **To identify potential confounding factors** (e.g., demographic variables, duration of opioid use, type of OST medication) that

may affect the relationship between cognitive functioning and OST adherence.

MATERIALS AND METHODS

Study Design

This was a **prospective, observational study** aimed at evaluating the relationship between cognitive function and adherence to opioid substitution therapy (OST) in patients diagnosed with opioid dependence syndrome.

Study Population

A total of 40 male patients, aged between 18 to 50 years, diagnosed with opioid dependence syndrome as per the International Classification of Diseases, 10th Revision (ICD-10) criteria, were recruited. All participants were undergoing maintenance therapy with either buprenorphine or methadone for at least one month prior to inclusion.

Study Place

The study was conducted in the Department of Psychiatryin collaboration with Department of Community MedicineSaraswathi Institute of Medical Sciences, Hapur, Uttar Pradesh, India.

Study Duration

The study was carried out over a period of one year and six months, from June 2015 to December 2016 after receiving Institutional Ethics Committee approval, allowing sufficient time for recruitment, evaluation, and analysis.

Ethical Considerations

Prior to commencement, the study received approval from the Institutional Ethics Committee (IEC). Written informed consent was obtained from all participants before enrollment, ensuring adherence to ethical research standards.

Inclusion Criteria

- Male patients aged 18–50 years.
- Diagnosis of opioid dependence syndrome (ICD-10).
- Currently on stable OST (buprenorphine or methadone) for at least one month.
- Willingness to provide informed consent and participate in the study.

Exclusion Criteria

- Patients with co-occurring severe psychiatric disorders (e.g., schizophrenia, bipolar disorder).
- History of traumatic brain injury, neurodegenerative disorders, or intellectual disability.
- Current dependence on substances other than nicotine and caffeine.
- Severe medical illnesses that could interfere with cognitive testing.

Methodology

1. **Screening and Data Collection**:

Participants were screened for eligibility based on the inclusion and exclusion criteria.

Demographic and clinical data were collected, including age, duration of opioid use, type and dose of OST, and duration of therapy.

2. **Cognitive Assessment**:

Cognitive functioning was evaluated using a standardized neuropsychological battery:

- **Mini-Mental State Examination (MMSE)**: Assessed general cognitive status.
- **Trail Making Test (TMT) Parts A and B**: Evaluated attention and executive functioning.
- **Digit Span Test (Forward and Backward)**: Measured working memory.
- **Stroop Test**: Assessed cognitive flexibility and inhibitory control.

All assessments were administered in a quiet clinical setting by trained clinical psychologists to ensure consistency and accuracy.

3. **Adherence Evaluation**:

Adherence to OST was assessed through two methods:

- **Clinic Records**: Review of pill counts and dosage records maintained by the clinic.
- **Self-Report**: Participants completed the validated **Medication Adherence Rating Scale (MARS)** to report their medication-taking behavior.

Based on these assessments, patients were categorized as:

- **Adherent**: Took **80% or more** of the prescribed doses over the past month.
- **Non-Adherent**: Took **less than 80%** of the prescribed doses.

Outcome Measures

- **Primary Outcome**: Association between cognitive function scores and adherence levels to OST.
- **Secondary Outcomes**: Differences in cognitive test scores between adherent and non-adherent groups.

Statistical Analysis

- Data were analyzed using SPSS software version 15.0 (IBM Corp., Armonk, NY, USA).
- Continuous variables were presented as mean ± standard deviation (SD).
- Categorical variables were presented as frequencies and percentages.

- Independent t-tests and chi-square tests were employed to compare cognitive scores and adherence rates between groups.
- **Pearson's correlation coefficient** was used to examine the association between cognitive scores and adherence levels.

A **p-value of <0.05** was considered statistically significant.

RESULTS

Table 1: Demographic and Clinical Characteristics of the Study Population (n = 40)

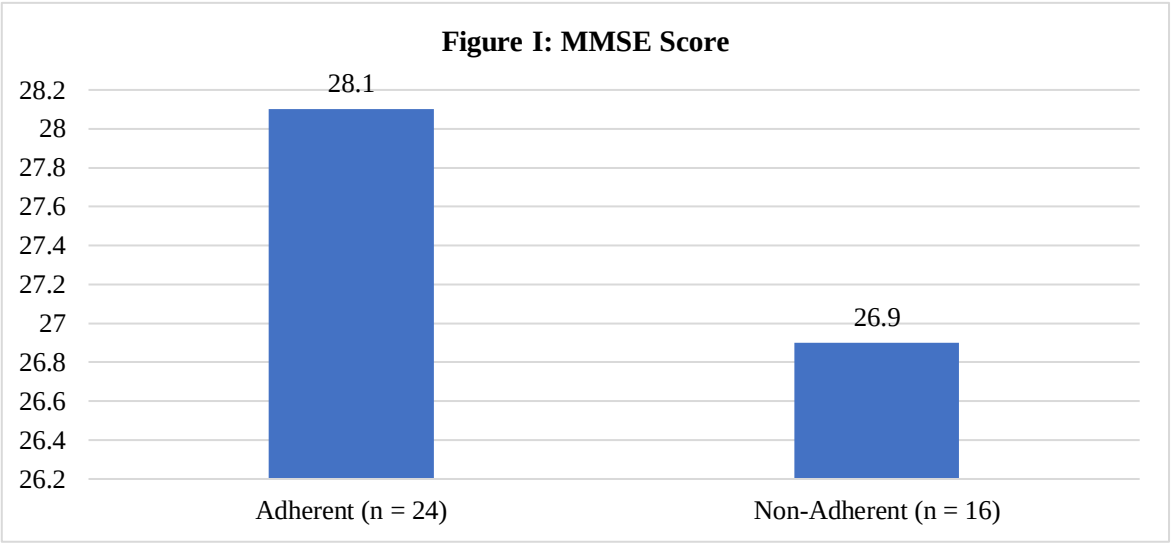
Variable	Adherent (n = 24)	Non-Adherent (n = 16)	p-value
Age (years, mean ± SD)	32.4 ± 6.1	33.2 ± 5.8	0.62
Duration of opioid use (years, mean ± SD)	7.1 ± 3.5	8.2 ± 4.0	0.32
Type of OST (Buprenorphine/Methadone)	18 / 6	11 / 5	0.79
Duration on OST (months, mean ± SD)	5.8 ± 1.9	4.9 ± 2.1	0.18

The demographic and clinical characteristics of the study population are summarized in Table 1. The mean age of the adherent group was 32.4 ± 6.1 years, compared to 33.2 ± 5.8 years in the non-adherent group; the difference was not statistically significant (p = 0.62). The duration of opioid use prior to starting opioid substitution therapy (OST) was also comparable between groups, with adherent patients reporting a mean of 7.1 ± 3.5 years and non-adherent patients reporting 8.2 ± 4.0 years (p = 0.32). The distribution of patients receiving buprenorphine or methadone showed no significant difference between the groups (p = 0.79), with a higher overall preference for buprenorphine (18 adherent vs. 11 non-adherent). Similarly, the duration on OST was slightly longer in the adherent group (5.8 ± 1.9 months) than in the non-adherent group (4.9 ± 2.1 months), but this difference did not reach statistical significance (p = 0.18). These findings indicate that demographic and treatment-related variables were largely comparable between the two groups.

Table 2: Mini-Mental State Examination (MMSE) Scores

Group	MMSE Score (mean ± SD)	p-value
Adherent (n = 24)	28.1 ± 1.2	
Non-Adherent (n = 16)	26.9 ± 1.4	0.01*

Figure I: MMSE Score



*Significant at p < 0.05

Table 2 figure I, presents the results of global cognitive function assessed using the Mini-Mental State Examination (MMSE). The adherent group scored significantly higher

with a mean MMSE score of 28.1 ± 1.2 compared to 26.9 ± 1.4 in the non-adherent group (p = 0.01). This statistically significant difference suggests that better overall cognitive status may be associated with improved adherence to OST.

Table 3: Performance on Neuropsychological Tests

Test	Adherent (n = 24) (mean ± SD)	Non-Adherent (n = 16) (mean ± SD)	p-value
Trail Making Test A (sec)	38.5 ± 7.2	45.2 ± 8.9	0.02*
Trail Making Test B (sec)	85.7 ± 12.3	94.5 ± 13.8	0.04*
Digit Span Forward	6.1 ± 0.8	5.5 ± 0.7	0.03*
Digit Span Backward	4.9 ± 0.6	4.2 ± 0.5	0.02*
Stroop Test Errors	3.1 ± 1.2	5.0 ± 1.7	0.01*

*Significant at $p < 0.05$

Performance on detailed neuropsychological tests is shown in Table 3. Adherent patients consistently performed better across all tests. For attention and executive functioning, the adherent group completed the Trail Making Test A in 38.5 ± 7.2 seconds compared to 45.2 ± 8.9 seconds by the non-adherent group (p = 0.02). The Trail Making Test B also showed a significant difference, with adherent patients taking 85.7 ± 12.3 seconds versus 94.5 ± 13.8 seconds for non-adherent patients (p = 0.04). Working memory scores, as measured by the Digit Span Test, were significantly higher in the adherent group for both forward (6.1 ± 0.8 vs. 5.5 ± 0.7, p = 0.03) and backward (4.9 ± 0.6 vs. 4.2 ± 0.5, p = 0.02) spans. The Stroop Test, which assesses cognitive flexibility and inhibitory control, revealed that adherent patients made fewer errors (3.1 ± 1.2) than non-adherent patients (5.0 ± 1.7), a difference that was statistically significant (p = 0.01). These findings strongly suggest that cognitive impairments are more prevalent among non-adherent individuals.

Table 4: OST Adherence Rates

OST Type	Adherent (n)	Non-Adherent (n)	Total (n)	Adherence Rate (%)
Buprenorphine	18	11	29	62.1
Methadone	6	5	11	54.5
Total	24	16	40	60.0

Table 4 shows the adherence rates by type of OST. Of the 40 patients, 29 were on buprenorphine and 11 were on methadone. Adherence rates were slightly higher in the buprenorphine group (62.1%) compared to the methadone group (54.5%), although no statistical comparison was made for this table. Overall, 60% of the study population met the adherence criteria. This pattern may suggest a marginally better adherence profile for buprenorphine-treated patients in this sample.

Table 5: Correlation Between Cognitive Scores and Adherence (Pearson's r)

Cognitive Test	Correlation Coefficient (r)	p-value
MMSE	0.41	0.01*
Trail Making Test A	-0.39	0.02*
Trail Making Test B	-0.35	0.03*
Digit Span Forward	0.33	0.04*
Digit Span Backward	0.36	0.03*
Stroop Test Errors	-0.42	0.01*

*Significant at $p < 0.05$

Table 5 provides the correlation analysis between cognitive performance and OST adherence. Positive correlations were observed between adherence and MMSE (r = 0.41, p = 0.01), Digit Span Forward (r = 0.33, p = 0.04), and Digit Span Backward (r = 0.36, p = 0.03), indicating that better global cognitive function and working memory were associated with improved adherence. Negative correlations were observed for Trail Making Test A (r = -0.39, p = 0.02) and B (r = -0.35, p = 0.03), indicating that slower completion times (poorer performance) were

linked to lower adherence. Similarly, a strong negative correlation was found for Stroop Test errors ($r = -0.42$, $p = 0.01$), suggesting that higher error rates were associated with poor adherence. All correlations were statistically significant and support the hypothesis that cognitive functioning is closely related to adherence behaviors in patients on OST.

DISCUSSION

The present study found no significant differences in demographic and clinical variables between adherent and non-adherent groups, with mean ages of 32.4 ± 6.1 years and 33.2 ± 5.8 years respectively ($p = 0.62$). Similarly, the duration of opioid use was comparable between groups (7.1 ± 3.5 vs. 8.2 ± 4.0 years, $p = 0.32$). These findings are consistent with the results of Soyka et al. (2008), who demonstrated that demographic factors such as age and duration of opioid use had limited predictive value for treatment adherence in a cohort of patients undergoing opioid maintenance therapy.[12] Their study emphasized that psychosocial and cognitive factors are stronger determinants of adherence than baseline demographics.

Our study observed significantly higher Mini-Mental State Examination (MMSE) scores among adherent patients (28.1 ± 1.2) compared to non-adherent patients (26.9 ± 1.4, $p = 0.01$), suggesting that global cognitive functioning is associated with better adherence. These results are in line with Darke et al. (2000), who reported that opioid-dependent patients often display mild to moderate cognitive impairments, which may interfere with medication-taking behaviors and clinic attendance.[13] Their findings suggest that cognitive dysfunction may be a barrier to consistent engagement in substitution therapy.

Performance on detailed neuropsychological tests in our study revealed that adherent patients had significantly better scores in attention, working memory, and executive functioning. For instance, Trail Making Test A scores were 38.5 ± 7.2 seconds in adherent patients versus 45.2 ± 8.9 seconds in non-adherent patients ($p = 0.02$), while Digit Span Forward scores were 6.1 ± 0.8 vs. 5.5 ± 0.7 ($p = 0.03$). Similar associations were documented by Verdejo-García et al. (2005), who found that opioid users with executive dysfunctions and working memory deficits were more likely to relapse or drop out from treatment programs.[14]Their study highlighted the relevance of neuropsychological assessments in predicting treatment outcomes.

In our cohort, the Stroop Test also showed a significant difference, with fewer errors in the adherent group (3.1 ± 1.2) compared to the non-adherent group (5.0 ± 1.7, $p = 0.01$). This finding reinforces the link between inhibitory control and treatment adherence. Ersche et al. (2006) similarly reported that stimulant-dependent individuals with poor inhibitory control had poorer adherence and worse clinical outcomes, supporting the role of cognitive flexibility in sustained recovery.[15]

The overall adherence rate in our study was 60%, with slightly better adherence for buprenorphine (62.1%) compared to methadone (54.5%). While our study did not statistically compare these rates, Mattick et al. (2003) in a systematic review showed that buprenorphine had a comparable, and sometimes more favorable, retention profile than methadone, depending on dosage and patient characteristics.[16] This may be partly due to the lower risk of sedation and overdose with buprenorphine, contributing to better acceptability.

Finally, our correlation analysis demonstrated significant associations between cognitive scores and adherence, with MMSE ($r = 0.41$, $p = 0.01$), Trail Making A ($r = -0.39$, $p = 0.02$), and Stroop errors ($r = -0.42$, $p = 0.01$). These findings are corroborated by the work of Verdejo-García and Pérez-García (2007), who emphasized that deficits in decision-making and executive function are reliable predictors of poor adherence and higher relapse risk in substance-dependent individuals.[17] Their research suggested that cognitive rehabilitation could be a potential adjunct to improve adherence in opioid-dependent populations.

LIMITATIONS OF THE STUDY

- **Sample Size**: The study included only 40 participants, which may limit the generalizability of the findings.
- **Gender Bias**: Only male patients were included, excluding potential gender-related differences in cognitive function and adherence.
- **Study Design**: As an observational study, causality between cognitive function and adherence cannot be established.
- **Self-Reported Data**: Reliance on self-reported adherence may introduce recall bias or social desirability bias.
- **Short Observation Period**: The study does not specify a long-term follow-up, limiting insights into adherence over extended periods.

CONCLUSION

This study demonstrated a significant association between cognitive functioning and adherence to opioid substitution therapy (OST) in patients with opioid dependence. Patients with better global cognition, attention, working memory, and executive functioning showed higher adherence rates. Buprenorphine was associated with slightly better adherence than methadone. These findings suggest that cognitive assessment and targeted interventions may enhance treatment adherence and outcomes in opioid-dependent individuals.

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