BMC Psychiatry

RESEARCH

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Executive function performance in high and low medication adherent patients with euthymic bipolar i disorder: a comparative study

Mona Rahimi Chahooei[1], Komeil Zahedi Tajrishi[1*], Ghazaleh Zargarinejad[1] and Amir Shabani[2]

Abstract

Introduction Medication nonadherence is a prevalent issue among patients with bipolar disorder, leading to substantial negative consequences. Despite documented cognitive deficits in this population, the relationship between executive dysfunction and medication nonadherence remains unclear. This study aims to investigate the association between executive functions and medication adherence in euthymic patients with bipolar I disorder.

Method In this cross-sectional, comparative study, we recruited 200 euthymic bipolar I disorder patients aged 18 to 55 years from the outpatient clinic of Iran Psychiatric Hospital in Tehran in 2024, using a convenience sampling method. The euthymic phase was confirmed using the Persian versions of the Young Mania Rating Scale and the Hamilton Rating Scale for Depression. Patients completed the Medication Adherence Rating Scale, along with a series of executive function tests including Go/No-Go, Wisconsin Card Sorting Test, and Iowa Gambling Task. Multivariate analysis of covariance was employed to analyze the results, controlling for demographic and clinical variables as covariates.

Results Of the participants, 54.5% had low medication adherence. Low adherent patients exhibited significantly poorer performance in Go/No-Go as indicated by higher commission errors ($F[1] = 7.63$, $p = 0.006$) as well as the Wisconsin Card Sorting Test, evidenced by a higher number of perseveration errors ($F[1] = 8.61$, $p = 0.004$) and fewer completed categories ($F[1] = 6.67$, $p = 0.011$), compared to high adherent patients. Notably, although differences in decision-making were observed between the two groups, these did not reach statistical significance ($p = 0.139$).

Conclusions This study establishes a correlation between low medication adherence and deficits in executive functions—specifically response inhibition and cognitive flexibility—in patients with bipolar I disorder. Furthermore, even after controlling for covariates, the differences in executive functions between medication adherence groups remained significant.

Keywords Bipolar disorder, Cognitive functions, Executive function, Medication adherence, Treatment compliance

*Correspondence:
Komeil Zahedi Tajrishi
zahedi.k@iums.ac.ir

[1]Department of Clinical Psychology, School of Behavioral Sciences and Mental Health (Tehran Institute of Psychiatric), Iran University of Medical Sciences, Tehran Hemat Highway next to Milad Tower, Tehran, Iran
[2]Mental Health Research Center, Psychosocial Health Research Institute, Iran University of Medical Sciences, Tehran, Iran

Introduction

Bipolar disorder (BD) is characterized by extreme mood swings, including manic, hypomanic, depressive, or euthymic states [1]. With a prevalence estimated between 0.3% and 1.2%, BD is associated with high hospitalization rates and symptom recurrence. Approximately 23% of individuals with BD relapse within a year. Frequent relapses are linked to several adverse outcomes, including increased suicidality, psychiatric comorbidities, disability, unemployment, and impaired functioning during follow-up [2–4].

Medication non-adherence, observed in 20–60% of patients, is a crucial factor contributing to relapse [5, 6]. Non-adherence, defined as the irregular use of prescribed medications, can result in disease recurrence and symptom exacerbation. It can occur both intentionally and unintentionally. Intentional non-adherence refers to the deliberate decision to deviate from prescribed medication regimens, including stopping, skipping, or adjusting dosages without consulting a healthcare provider. Conversely, unintentional non-adherence involves unplanned deviations, often attributed to factors beyond the patient's control, such as cognitive impairment (e.g., forgetting to take medication) [7, 8]. Both intentional and unintentional non-adherence can have a detrimental impact on quality of life, potentially leading to serious consequences, including an increased risk of suicide, more frequent relapses, and increased hospitalizations [9–11].

Numerous factors have been associated with low treatment adherence in BD, including male gender, residual symptoms, higher rates of adverse drug reactions, comorbidities, and depressive episodes [5, 6, 12–15].

Despite growing evidence of executive function deficits in BD, the relationship between these deficits and non-adherence remains inadequately explored [16–19]. Meta-analyses demonstrate that these deficits persist even during euthymic phases [18, 20–24]. This suggests that cognitive deficits in BD may represent trait-level impairments, independent of affective episodes.

Although some studies have examined the relationship between medication adherence and cognitive deficits in psychiatric disorders, research on bipolar disorder remains limited, with inconsistent findings. For example, some studies found a strong association between poor cognitive functions and low medication adherence in BD. Patients with low adherence performed worse on verbal learning, working memory, and executive function tasks than patients with high adherence and normal controls [25–28]. Conversely, several studies have shown that in individuals with BD and schizophrenia, cognitive impairment does not contribute to nonadherence [29, 30].

Our study attempts to address some shortcomings of previous studies on the relationship between executive functions and medication adherence. In particular, unlike previous studies [27, 31], we use a larger sample size, which improves the statistical power and generalizability of our results. To minimize potential bias due to different group sizes, we also ensured that participants were almost evenly distributed between the low and high adherence groups. In addition, most previous studies have examined both types of bipolar disorder [25–27, 29, 30, 32], which may be the reason for the inconsistent results. Only type 1 was included in our study and we focused exclusively on patients in the euthymic phase.

The selection of cognitive functions in this study was informed by existing literature. We focused on executive functions due to their significant impairment in individuals with bipolar disorder, particularly in the domains of response inhibition and cognitive flexibility [17–19, 24, 31–34]. Additionally, research has highlighted that individuals with bipolar disorder often experience difficulties in the decision-making process [35–37].

We hypothesized that executive dysfunctions would be associated with low medication adherence in euthymic BD-I patients. Additionally, we hypothesized that these associations would maintain their significance after controlling for demographic and clinical variables—including age, years of education, number of hospitalizations, number of manic or depressive episodes, duration of illness, and history of suicide attempts.

Method

Design

This cross-sectional, descriptive correlational study analyzed data from a separate structural equation modeling (SEM) study, which included 200 participants diagnosed with bipolar I disorder. These participants were from the outpatient clinic of Iran Psychiatric Hospital in Tehran, from December 2023 to June 2024, using convenience sampling.

Participants and procedures

Patients were included if they met the following criteria: (1) diagnosis of bipolar I disorder by a senior psychiatrist according to The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision (DSM-5-TR), (2) aged between 18 and 55 years, and (3) currently in remission as determined by the Persian versions of the Young Mania Rating Scale (YMRS) score below ≤ 17 [33] and the Hamilton Rating Scale for Depression (HRSD) score below ≤ 8 [34]. Exclusion criteria included substance abuse in the past 12 months and significant neurological or cognitive impairment that could impede participation in the study procedures.

Of the 623 patients initially eligible, 417 were excluded due to various reasons, including non-attendance, refusal to participate, or meeting exclusion criteria. A total of

206 patients completed the consent form and participated. Six participants withdrew during testing. Ultimately, data from 200 participants who fully completed the questionnaires were included in the analysis.

A senior psychiatrist referred euthymic bipolar I patients to the researchers. Participants provided written informed consent following a detailed explanation of the study, which was approved by the Ethics Committee of Iran University of Medical Sciences. To ensure that the patients were in the euthymic phase, the Young Mania Rating Scale and the Hamilton Rating Scale for Depression were administered by a clinical psychologist. Patients who were in remission for at least two weeks completed the Medication Adherence Rating Scale (MARS) and were evaluated with executive function tests by a clinical psychologist. This study used the computerized version of executive function tests, which lasted approximately 45 min for each participant.

Data collection

Clinical and demographic assessment

We collected age, gender, marital status, employment status, and years of education using a sociodemographic questionnaire. Clinical data, including the number of hospitalizations, frequency of episodes, illness duration, and history of suicide attempts, were obtained from medical records. We also used some of these variables as covariates in our analyses to control for their potential impact on executive function outcomes.

Persian version of young mania rating scale (YMRS)

This is an 11-item scale to assess the severity of manic symptoms [33]. The Scale's score ranges from 0 to 60 with values above 17 considered manic episode. The reliability of this scale is reported to be 0.66 to 0.92, and for the Iranian population, the Cronbach alpha coefficient is 0.72 [33, 35, 36].

Persian version of hamilton rating scale for depression (HRSD)

The Hamilton Depression Rating Scale is designed to indicate depressive symptoms and serve as a guide to assess recovery [37]. This scale includes 21 items to assess various symptoms of major depression, and the scoring is based on the first 17 items. The range of values for this scale is between 0 and 53. Values below 8 are indicative of the absence of depression. Test-retest reliability for the Iranian population on the Hamilton Depression Scale ranged from 0.81 to 0.96 [34, 38]. Reliability between reviewers was reported as 0.96 [34].

Medication adherence rating scale (MARS)

Medication adherence was assessed using the Medication Adherence Rating Scale (MARS). This is a 10-item yes/no self-report questionnaire that assesses both intentional and unintentional medication nonadherence [39, 40]. Higher scores on the scale indicate a higher likelihood of medication adherence. The total score on the scale ranges from 0 to 10. Scores above 8 indicate high adherence, while scores below 7 indicate low adherence [41]. Some studies on the Iranian population preliminarily investigated the psychometric properties of the MARS and reported reliability coefficients ranging from 0.89 to 0.91 [42, 43]. The scale underwent translation and back-translation procedures, with linguistic accuracy verified by an English language expert. Ten nursing faculty members reviewed the scale and established its face and content validity [43, 44]. In our study, the MARS demonstrated acceptable internal consistency (Cronbach's $\alpha = 0.68$).

Neuropsychological assessment

The computer-based cognitive tests listed below were used in the assessment:

1. The Go/No-Go task [45], employed to assess response inhibition, presents two conditions: 'Go' stimuli requiring rapid responses and 'No-Go' stimuli requiring response inhibition. The main indicator of impulsivity in this task is the frequency of commission errors or false alarms in response to no-go stimuli. The task consists of forty randomized trials with green [Go] and red [No-Go] signals as naturalistic dominant stimuli. Each trial lasts 200 ms and there is an inter-stimulus interval of 1000 ms. When participants were given the "go" signal (green light), they were asked to respond, and when they were given the "no go" signal (red light), they were asked to stand down. For our study, we used the number of commission errors and the reaction time. Ghadiri et al.'s research states that this test's reliability is 0.87 in the Iranian population [46].
2. The Wisconsin Card Sorting Test [47] assesses cognitive flexibility and set-shifting ability in response to new stimuli or changing environmental demands. We used computer-based versions of 64 stimuli. The subjects are given a set of 4 reference cards, each differing from the other in terms of 3 categories: color, shape, or number. The subjects are asked to match the stimulus cards to the reference cards without further direction as to how they are to be matched. The computer provides simple feedback of "correct" or "incorrect" based on the predetermined criteria. In this study, we used scores related to the number of preservative errors and completed categories. Shahgholian et al. designed the computerized version of this test in 2011 for the Iranian population, and Cronbach's alpha coefficient was a reliability of 0.74 [48].

3. The Iowa Gambling Task [49] is a widely used neuropsychological test designed to assess decision-making under conditions of ambiguity and implicit rules governing gains and losses. This task requires participants to process feedback from previous decisions to implicitly learn to avoid disadvantageous options (A and B cards) and favor advantageous (C and D cards) alternatives. We recorded the number of choices for every card and then calculated the total Iowa gambling score for each one. The most common method for quantifying a preference for advantageous/disadvantageous decks is the net IGT score, originally employed by Bechara and colleagues. The total net score results from the subtraction of the disadvantageous deck choices from the advantageous deck choices during the entire test [(C + D) − (A + B)]. The threshold for impaired performance on the original IGT was a net score of less than 10, whereas a net score of 10 or greater indicated non-impaired performance [50, 51]. Ekhtiari et al. devised the Persian version of the task at the Institute for the Study of Cognitive Sciences, and it was shown to be reliable and valid after being applied to Iranian subjects [52, 53].

Statistical analysis

We conducted statistical analyses using SPSS version 26. We checked the assumptions for multivariate analysis of covariance (MANCOVA) before the main analysis. These assumptions included normality to make sure that the data distribution did not deviate significantly from normality (using skewness and kurtosis values), linearity to ensure that the relationships between variables followed a linear pattern (using Pearson correlation), independence of errors to find any autocorrelation (using the Durbin-Watson test), and multicollinearity to make sure that predictor variables were not highly correlated (using variance inflation factors (VIF) and tolerance values).

After confirming these assumptions, MANCOVA was used to compare neuropsychological test results (presented as means and standard deviations) between low and high adherent euthymic bipolar I patients. We used several demographic and clinical variables as covariates in our study to account for potential confounding effects. Variables included as covariates were age, years of education, number of mood episodes (manic and depressive), history of suicide attempts, hospitalizations, and duration of illness. To measure the effect size, the partial eta-squared was also calculated, with values of 0.01, 0.06, and 0.14 representing small, medium, and large effects, respectively.

Results

Characteristics of the sample

The average age of the 200 study participants was 38.52 years (SD = 8.69), and their average educational background was 11 years (SD = 3.79). The majority of participants were male (60.5%, $n = 121$), unemployed (67.5%, $n = 135$), and single (59%, $n = 118$).

When comparing their demographic and clinical characteristics, there were significant differences between groups with high adherence ($n = 91$) and low adherence ($n = 109$) in terms of years of education, history of suicide attempts, and number of hospitalizations.

The high adherence group had more years of education (M = 12.04, SD = 3.2) than the group with low adherence (M = 10.85, SD = 4.15; $p = 0.026$). The percentage of people with a history of suicide attempts was significantly higher in the group with low adherence (39.4%) than in the group with high adherence (25.3%; $p = 0.034$). Similarly, the low adherence group reported a significantly higher number of hospitalizations (M = 4.16, SD = 3.57) than the high adherence group (M = 3.12, SD = 2.91; $p = 0.02$).

While both groups had similar average ages ($p = 0.56$), they differed in the frequency of depressive episodes. In the group with low adherence, more participants (47.7%) had experienced two or more depressive episodes than in the group with high adherence (26.4%; $p = 0.002$). However, the two groups did not differ significantly in the frequency of manic episodes ($p = 0.339$). In addition, the unemployment rate was higher in the low adherence group (75.2%) than in the high adherence group (58.2%; $p = 0.011$) (see Table 1).

Neurocognitive performance

Analysis of neurocognitive performance in high and low adherence groups revealed significant executive function differences, even when demographic and clinical variables were considered as covariates.

As shown in Table 2, in the response inhibition task (Go/No-Go task), commission errors were significantly higher in patients with low adherence (M = 5.30, SD = 5.41) than in the high adherence group (M = 3.01, SD = 4.31) (F [1] = 7.63, $p = 0.006$). This indicates a significant difference in response inhibition between groups.

Similarly, the Wisconsin Card Sorting Test for cognitive flexibility showed that patients with low adherence made a lot more perseverative errors (M = 12.51, SD = 6.80) than patients with high adherence (M = 9.15, SD = 7.22) (F [1] = 8.61, $p = 0.004$). Furthermore, low adherence patients completed significantly fewer categories (M = 2.00, SD = 1.70) than those with high adherence (M = 2.80, SD = 1.85) (F [1] = 6.67, $p = 0.011$).

Although there were differences in reaction time and decision-making results between groups, these differences were not statistically significant ($p = 0.494$

Table 1 Demographic and clinical profile by medication adherence level in euthymic bipolar I disorder patients

Characteristics	High Adherence ($n=91$)	Low Adherence ($n=109$)	*P* value
Demographic Variables			
Age (years), Mean ± SD	38.13 ± 8.76	38.84 ± 8.65	0.565[b]
Education (years), Mean ± SD	12.04 ± 3.20	10.85 ± 4.15	0.026*[b]
Sex (male), n (%)	55 (60.4)	66 (60.6)	0.987[a]
Marital status (single), n (%)	56 (61.5)	62 (56.9)	0.505[a]
Occupational status (unemployed), n (%)	53 (58.2)	82 (75.2)	0.011*[a]
Clinical Variables			
Depressive Episodes, n (%)			
– 1 episode	67 (73.6)	57 (52.3)	0.002*[a]
– 2 or more episodes	24 (26.4)	52 (47.7)	
Manic Episodes, n (%)			
– 1 episode	18 (19.8)	16 (14.7)	0.339[a]
– 2 or more episodes	73 (80.2)	93 (85.3)	
Suicide attempts (yes), n (%)	23 (25.3)	43 (39.4)	0.034*[a]
Illness duration (years), Mean ± SD	12.30 ± 8.62	14.47 ± 8.93	0.084[b]
Number of hospitalizations, Mean ± SD	3.12 ± 2.91	4.16 ± 3.57	0.020*[c]

*p-value < 0.05

[a] Chi-Square

[b] t-test

[c] Mann-Whitney U

Table 2 Executive functions in low and high adherence patients with bipolar I disorder

	Score							
	High Adherence		Low Adherence		MANCOVA			Partial Eta squared
Measure	Mean	SD	Mean	SD	F	df	p	
Response inhibition (GNGT)								
Commission errors	3.01	4.31	5.30	5.41	7.63	1	0.006**	0.038
Reaction time (ms)	418.73	118.36	436.01	123.52	0.47	1	0.494	0.002
Decision making (IGT)								
IGT score	-1.19	25.75	-9.08	22.56	2.20	1	0.139	0.011
Cognitive flexibility (WCST)								
Preservative errors	9.15	7.22	12.51	6.80	8.61	1	0.004**	0.043
number of categories completed	2.80	1.85	2	1.70	6.67	1	0.011*	0.034

Abbreviations: GNGT = Go No Go Task, IGT = Iowa Gambling Task, WCST = Wisconsin Card Sorting Test

[a] 0.01 = small size effect, 0.06 = moderate size effect, 0.14 = large size effect

*$p < 0.05$

**$p < 0.01$

and $p = 0.139$, respectively). Notably, both groups had impaired decision-making abilities, as shown by their Iowa Gambling Task (IGT) scores (mean IGT total < 10).

Effect sizes

We found small to medium effect sizes for some measures of executive function. Cognitive flexibility showed the largest effect size, with partial eta-squared values of 0.043 for preservative errors and 0.034 for the number of categories completed. Response inhibition also showed a small effect size (partial eta squared = 0.038) (see Table 2).

It is worth pointing out that because human behavior is influenced by a variety of factors and human populations vary widely, small to medium effect sizes can be important and are often found in the social and behavioral sciences. In line with this, a meta-analysis study showed that traditional benchmarks for interpreting effect sizes, such as those proposed by Cohen, might not be appropriate for all fields. In social and behavioral studies, the general effect sizes are typically smaller than in other areas [54].

Furthermore, sometimes small effects accumulate into larger ones over time or across many individuals. A study found that an effect size r of 0.05 (which is similar to our partial eta squared values) indicates an effect that is very small for explaining single events but potentially consequential in the not-very-long run [55]. This perspective helps us consider our results, which were statistically significant and had small to medium effect sizes when

examining medication adherence and executive functions in individuals with bipolar disorder.

Discussion

This study aimed to compare the executive functions between low and high medication adherence groups among 200 patients with bipolar I disorder who were in remission. We hypothesized that patients with lower adherence would perform significantly worse on all executive function tasks compared to the adherent group. Our findings revealed significant differences in executive functions between low and high adherence groups especially in response inhibition and cognitive flexibility tasks.

Consistent with previous studies [25, 26] response inhibition was significantly impaired in patients with low adherence compared to patients with high adherence. Specifically, in the Go/No-Go task, patients with low adherence made more commission errors, suggesting they had difficulty controlling inappropriate responses. Executive functions are cognitive processes that lead to goal-directed behavior and are necessary for managing daily living activities [28]. Inhibitory control is essential for regulating behavior and making informed decisions, influencing behaviors like avoiding impulsive comments or maintaining a diet. This ability aids individuals in overcoming doubts about not taking the medication [56]. In short, individuals with greater response inhibition are likely to be better able to consider long-term consequences, manage their medication regimen more effectively, and avoid behaviors that interfere with treatment adherence when they have doubts about taking medication. However, as our study is cross-sectional, we cannot determine whether irregular medication use impairs inhibitory control or if poor response inhibition leads to nonadherence.

Furthermore, our findings indicate that non-adherent BD-I patients performed worse on the WCST compared to adherent patients, aligning with previous studies [28, 57]. This was reflected in a higher rate of perseveration errors and fewer completed categories. Non-adherence to prescribed treatment may result from difficulties in adapting to new instructions and routines. These difficulties in adaptation may be due to a lack of cognitive flexibility and a change in behavior in response to changing demands.

Although the low adherence group had lower average IGT score (M = -9.08, SD = 22.56) than the high adherence group (M = -1.19, SD = 25.75), this difference was not statistically significant (F [1] = 2.20, $p = 0.139$). As scores below ten on the task indicate deficits in decision-making [50, 51], both groups demonstrated impairments, as evidenced by their mean score in the IGT (Table 2). These findings are consistent with previous studies that demonstrated decision-making deficits in BD populations [58, 59]. Poor decision-making was observed across all patients, suggesting cognitive impairment in this domain regardless of medication adherence. Bipolar disorder itself, as a major psychiatric condition, may have a greater impact on cognitive function than medication adherence. The lack of significant difference in decision-making performance between adherence groups indicates that this cognitive ability may not be a key determinant of medication adherence.

The relationship between executive functions and medication adherence remained significant even after controlling for demographic and clinical factors. This significant finding indicates that the relationship between executive functions and medication adherence is not simply a result of other clinical or demographic factors. However, several covariates showed noteworthy relationships with executive functions, consistent with previous findings [27, 30, 60–62]. Longer illness duration was associated with poorer performance in response inhibition and cognitive flexibility, suggesting that the cumulative effects of the disorder may eventually lead to cognitive decline. Our findings indicated that patients with higher levels of education perform more accurately on tasks involving response inhibition and cognitive flexibility. This protective effect of education could be attributed to cognitive reserve, which plays an important role in the ability to readjust cognitive performance in the event of pathology and in protecting cognitive status [63].

It is important to acknowledge the potential reciprocal relationship between low adherence and impaired executive functions. Low executive functions can make it difficult to adhere to a medication schedule, which in turn impacts medication adherence. On the other hand, sporadic medication use can be a factor in persistent cognitive decline. A longitudinal study is needed to better understand possible causal relationships between variables.

Moreover, further research is needed to determine the effectiveness of other factors such as cognitive reserve and various cognitive functions, to determine their specific contribution to treatment adherence.

To our knowledge, this is the first study in Iran examining the association between medication adherence and executive dysfunction in BD-I patients. Despite the methodological strengths of our study, which include a larger sample size compared to previous studies, control for bipolar type, inclusion of euthymic patients, selection of executive functions consistently identified as impaired in BD, and data collection from a psychiatric referral hospital providing services to a diverse patient population from various cultural and regional backgrounds, several limitations should be acknowledged. First, the reliance on self-reported measures for assessing medication

adherence may introduce bias. Future studies should consider combining patient-reported questionnaires with objective measures such as the medication possession ratio (MPR) and the proportion of days covered (PDC) to provide a more comprehensive assessment of adherence. Second, our focus was exclusively on executive functions; future research should extend this scope to include other domains of cognitive functions to obtain a more holistic understanding of the cognitive profiles associated with medication adherence in individuals with bipolar disorder. Third, the cross-sectional design of our study precludes the determination of causal relationships between executive functions and medication adherence, highlighting the need for longitudinal studies to identify the nature of this association. Fourth, we neither controlled for medication effects on cognitive functions nor drug side effects on medication adherence. Side effects, including weight gain or sedation, may affect patients' adherence to pharmacological treatment regimens and affect the association between executive functions and medication adherence. Further studies should include comprehensive assessments of drug classifications, doses, and side effects to better understand their effects on cognitive performance and treatment adherence. Finally, our study defined euthymia based on two weeks of remission using YMRS and HRSD, whereas other studies use longer periods (e.g., eight weeks). This methodological difference should be considered when comparing our results with other studies.

Conclusion

This study found associations between executive dysfunction—particularly response inhibition and cognitive flexibility—and medication adherence in people with bipolar I disorder (BD-I). The findings also suggest the potential value of incorporating executive function assessments into clinical practice to identify patients at risk of nonadherence. Moreover, cognitive tests such as the Wisconsin Card Sorting Test and the Go/No-Go task, could be incorporated into routine assessments by mental health professionals in clinical settings. Behavioral strategies and cognitive rehabilitation therapies—such as structured routines, mobile apps, and psychoeducational programs focusing on adaptive techniques—may help enhance cognitive flexibility, inhibitory control, and medication adherence.

Abbreviations

BD	Bipolar disorder
BD-I	Bipolar I disorder
DSM-5-TR	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision
EFs	Executive functions
GNGT	Go/No-Go Task
HRSD	Hamilton Rating Scale for Depression
IGT	Iowa Gambling Task
MANCOVA	Multivariate analysis of covariance
MARS	Medication Adherence Rating Scale
MPR	Medication possession ratio
PDC	Proportion of days covered
WCST	Wisconsin Card Sorting Test
YMRS	Young Mania Rating Scale

Acknowledgements
We would like to express our warm appreciation to the Iran Psychiatric Hospital and the study participants for their valuable contributions.

Author contributions
K.Z., Gh.Zn, and A.Sh contributed to the study design and supervised the procedures. M.R. collected the data, performed the statistical analysis, and drafted the initial manuscript. K.Z., Gh.Zn, and A.Sh reviewed and revised the manuscript. All authors read and approved the final version of the manuscript.

Funding
The authors received no specific funding for this work.

Data availability
The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
The study was approved by the ethics committee of Iran University of Medical Sciences (NO. IR.IUMS.REC.1402.718) and conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from all participants.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Clinical trial number
Not applicable.

Received: 23 November 2024 / Accepted: 27 February 2025
Published online: 13 March 2025

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