Research Article

Pamukkale Medical Journal
doi:https://dx.doi.org/10.31362/patd.1537468

Relationship between duration of undiagnosed illness, clinical features and cognitive impairment in bipolar disorder

Bipolar bozuklukta tanısız geçen hastalık süresinin klinik özelikler ve bilişsel bozulmayla ilişkisi

Ekin Atay, Ömer Aydemir

Posted date:23.08.2024 Acceptance date:30.09.2024

Abstract

Purpose: It is believed that a delay in the diagnosis of bipolar disorder may adversely affect the clinical course and outcome. This study aimed to investigate the relationship between diagnostic delay and clinical variables, as well as neurocognitive and social cognitive disorders.

Materials and methods: Eighty-four patients with bipolar disorder in remission were included in the study. Participants were evaluated using a neuropsychological battery that assessed verbal memory and learning, visual memory and learning, verbal fluency, attention, processing speed, executive functions, working memory, and social cognition.

Results: The duration of undiagnosed illness was longer in patients with bipolar II disorder, those without psychotic features, those with at least one suicide attempt, those whose first episode was depressive, and those currently on antidepressants. A significant positive correlation was found between the duration of undiagnosed illness and scores on the Controlled Oral Word Association Test, total number of episodes, hypomanic episodes, depressive episodes, and their respective durations. Conversely, a significant negative correlation was found between the duration of undiagnosed illness and both the number and duration of manic episodes.

Conclusion: We found that a delay in diagnosis and treatment was associated with more recurrences in bipolar disorder, an increased number of depressive episodes, and at least one lifetime suicide attempt. However, the association between extended periods of untreated illness and poor clinical and functional outcomes did not align with cognitive impairment.

Keywords: Bipolar disorder, delayed diagnosis, neurocognitive disorders, social intelligence.

Atay E, Aydemir O. Relationship between duration of undiagnosed illness, clinical features and cognitive impairment in bipolar disorder. Pam Med J 2024;17:774-782.

Öz

Amaç: Bipolar bozuklukta tanıda gecikmenin klinik seyir ve sonlanım üzerine olumsuz etkileri olabileceği düşünülmektedir. Çalışmamızda tanıda gecikme ile klinik değişkenler ve nöro/sosyal bilişsel bozukluklar arasındaki ilişkinin araştırılması amaçlanmıştır.

Gereç ve yöntem: Bipolar bozukluk tanılı remisyonda 84 hasta çalışmaya alındı. Katılımcılar sözel bellek/öğrenme, görsel bellek/öğrenme, sözel akıcılık, dikkat, işlem hızı, yürütücü işlevler, çalışma belleği ve sosyal biliş alanlarında değerlendirme imkanı veren nöropsikolojik bir batarya ile değerlendirildi.

Bulgular: Tanısız geçen sürenin bipolar- II bozukluk tanılı hastalarda, yaşam boyu psikotik özellik göstermemiş hastalarda, yaşam boyu en az bir defa intihar girişiminde bulunmuş hastalarda, ilk epizodu depresif epizod olan hastalarda ve halihazırda tedavilerinde antidepresan bulunan hastalarda daha uzun olduğu bulundu. Tanısız geçen hastalık süresi ile Kontrollü Kelime Akıcılık Testi, toplam epizod sayısı, hipomanik epizod sayısı, depresif epizod sayısı, toplam epizod süresi, hipomanik epizod süresi ve depresif epizod süresi arasında anlamlı düzeyde pozitif yönde ilişki; manik epizod sayısı ve manik epizod süresi arasında ise anlamlı düzeyde negatif yönde ilişki saptanmıştır.

Sonuç: Tanıda ve tedavide gecikmenin bipolar bozuklukta daha sık nüksle, daha sık depresif epizodla ve yaşamı boyunca en az bir defa intihar girişiminde bulunmuş olmakla ilişkili olduğunu bulduk. Tanısız geçen sürenin uzunluğu ile klinik seyir ve işlevsellik açısından kötü sonlanım arasındaki ilişkiye bilişsel bozulma eşlik etmemektedir.

Anahtar kelimeler: Bipolar bozukluk, gecikmeli tanı, nörobilişsel bozukluklar, sosyal zeka.

Atay E, Aydemir Ö. Bipolar bozuklukta tanısız geçen hastalık süresinin klinik özelikler ve bilişsel bozulmayla ilişkisi. Pam Tıp Derg 2024;17:774-782.

Ekin Atay, M.D. Department of Psychiatry, Kars Harakani State Hospital, Kars, Türkiye, e-mail: ekinatay@gmail.com (https://orcid.org/0000-0003-0430-5517) (Corresponding Author)

Ömer Aydemir, Prof. Department of Psychiatry, Faculty of Medicine, Manisa Celal Bayar University, Manisa, Türkiye, e-mail: soaydemir@gmail.com (https://orcid.org/0000-0003-3050-1263)

Introduction

Bipolar disorder (BD) is a recurrent, chronic illness that typically begins at a young age and significantly impairs an individual's social and occupational functioning [1]. The World Health Organization's World Mental Health Surveys have identified BD as the second leading cause of lost workdays [2]. Despite causing significant functional impairment, there is a considerable delay between the onset of BD and the start of appropriate treatment. Most patients diagnosed with BD receive their diagnosis approximately 6-10 years after first presenting with symptoms to a clinician [3].

One of the most significant factors contributing to the delay in diagnosis is that the first episode in BD is often a depressive episode, during which it is difficult to clearly distinguish between unipolar and bipolar disorders based on diagnostic criteria [4, 5]. Other reasons for the delayed diagnosis during psychiatric assessment include the inability to differentiate mood episodes with psychotic features from psychotic disorders and the misdiagnosis due to mild mood symptoms being mistaken for personality traits [6, 7].

The delay in diagnosis and treatment is not only a result of certain adverse clinical features but also believed to have negative impacts on functional and clinical outcomes [8, 9]. A delay in diagnosis and treatment has been associated with a diagnosis of bipolar II disorder, depressive onset, and a higher number of depressive episodes [10, 11]. Buoli et al. [10] found a relationship between the duration of untreated illness (DUI) and factors such as hospitalization in the past year, suicide attempts in the past year, absence of lifetime psychotic symptoms, and fewer manic episodes. Di Salvo et al. [11] identified early onset, long illness duration, a higher number of mood episodes, lifetime suicide attempts, and current medical comorbidity as clinical features associated with delay in treatment. Delay in diagnosis has also been linked to poor response to lithium [12] and cognitive impairment [13].

Although there are studies in the literature that associate the prolonged duration of untreated BD with adverse clinical outcomes, there is a limited number of studies investigating its relationship with cognitive impairment. Our study aims to explore the relationship between the delay in diagnosing BD and clinical variables as well as neuro/social cognitive impairments. We hypothesized that as the duration of undiagnosed illness lengthens, treatment would become more difficult, resulting in more frequent and prolonged episodes, which in turn would lead to a greater severity of cognitive impairment.

Materials and methods

The ethics committee approved the study, and all participants signed an informed consent form. The study sample included 84 patients diagnosed with BD in remission, who were consecutively chosen from volunteers meeting the inclusion and exclusion criteria. These patients were being followed at the psychiatry outpatient clinic of Manisa Celal Bayar University Hafsa Sultan Hospital between December 2020 and October 2022.

The inclusion criteria for the patients were as follows: meeting the diagnostic criteria for bipolar I disorder or bipolar II disorder according to the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5); being between the ages of 18-65, literacy in Turkish, and being in remission for the past 2 months (i.e., a Young Mania Rating Scale [YMRS] score <6 and a Hamilton Depression Rating Scale [HDRS] score<8).

The exclusion criteria were as follows: (i) having a prior diagnosis of schizophrenia spectrum, other psychotic disorders, or substance-induced disorders according to DSM-5 criteria; (ii) having intellectual disability or neurological diseases affecting the central nervous system; (iii) having been diagnosed with a substance or alcohol use disorder within the last 6 months; (iv) having hearing or vision impairments that interfere with the administration of cognitive tests and performance during testing; (v) having a history of electroconvulsive therapy or transcranial magnetic stimulation treatment within the last three months; and (vi) having been treated with benzodiazepines or psychostimulants within the last 6 months.

The Structured Clinical Interview for DSM-5 Disorders-Clinician Version (SCID-5/CV) was used to verify all current and past psychiatric diagnoses of the patients [14, 15]. The Vocabulary Subtest of the Wechsler Adult

Intelligence Scale-Revised (WAIS-R) was administered to assess premorbid intelligence [16]. The HDRS, Hamilton Anxiety Rating Scale (HARS), and YMRS were used to assess the current mood state [17-19].

The sociodemographic and clinical data form collected personal characteristics such as age, gender, marital status, education level, occupation, and place of residence, in addition to clinical features such as age of illness onset; polarity of the first episode; DUI ; total number, duration, and characteristics of episodes; number and duration of hospitalizations; subtype of BD; presence of episodes with psychotic features; history of suicide attempts; current treatment; duration of remission; history of comorbid psychiatric disorders; family history of psychiatric illness; and smoking status.

A neuropsychological battery, individually administered to all participants, provided an opportunity to assess verbal memory/learning, visual memory/learning, verbal fluency, attention, processing speed, executive functions, working memory, and social cognition.

The Rey Auditory Verbal Learning Test (RAVLT) was used to assess verbal learning and memory. Scores for the RAVLT included total scores for trials 1-5, delayed recall (Trial 7), and correct recall [20]. Visual learning and memory were assessed using immediate and delayed recall scores from the Visual Reproduction Subtest of the Wechsler Memory Scale [20]. To evaluate verbal fluency, the Controlled Oral Word Association Test (COWAT) was administered, utilizing the letters K, A, and S [20]. Processing speed and executive functions were assessed using the Stroop Test-Çapa Form (ST) [21] and the Trail Making Test (TMT) [22]. Working memory was evaluated with the Auditory Consonant Trigrams Test (ACT) [20, 23]. The Reading the Mind in the Eyes Test (RMET) [24] and the Hinting Test [25] were used to assess the visual and verbal aspects of the Theory of Mind (ToM) in the domain of social cognition.

Statistical analysis

Descriptive analyses of the total sample were performed. The Shapiro-Wilk test was used to assess the normality of the data. Due to the non-normal distribution of the DUI, the Mann-Whitney U test was used to compare groups defined by categorical variables such as gender, occupation, marital status, place of residence, smoking status, bipolar subtype, presence of psychotic features, history of suicide attempts, polarity of the first episode, presence of BD or major depressive disorder in first- or second-degree relatives, and the use of lithium, valproate, lamotrigine, and antidepressants.

Spearman correlation analysis was used to examine the relationship between cognitive performance and non-categorical numerical sociodemographic and clinical characteristics with the DUI. For analyzing the number of episodes, episode durations, illness duration, DUI, TMT, and ST results, which did not follow a normal distribution, log10 normalization was applied to transform them into a normal distribution [26]. Partial correlation analysis was conducted for the relationship between the number of episodes and hospitalizations, by controlling the illness duration. A p-value below 0.05 was deemed statistically significant for all analyses. Statistical analyses were performed using IBM SPSS Statistics 20.0.

Results

The total sample included 84 bipolar patients in remission: 41 women (48.8%) and 43 men (51.2%). The mean age of illness onset in the sample was 22.7±7.6 years, with a median DUI of 11.0 months and an interquartile range (IQR) of 2.0-33.0 months. Descriptive analyses, correlation analysis results, and DUI values by category for sociodemographic and clinical characteristics are shown in Tables 1 and 2.

The DUI showed significant differences based on BD subtype ($Z=2.56$, $p=0.010$), the presence or absence of lifetime psychotic features ($Z=2.08$, $p=0.038$), the presence or absence of lifetime suicide attempts ($Z=2.46$, $p=0.014$), the polarity of the first episode ($Z=5.5$, $p<0.001$), and whether antidepressants were included in the current treatment ($Z=2.33$, $p=0.020$).

The DUI was found to be longer in patients diagnosed with bipolar II disorder, in those who had not exhibited lifetime psychotic features, in those who had made at least one lifetime suicide attempt, in those with a depressive onset, and in those currently receiving antidepressant treatment.

Table 1. Socio-demographic variables of the total sample and values of DUI/Spearman correlation according to these variables

Variables		Total Sample (n=84)	DUI, months, median (IQR)	Z	*p*
Gender, n (%)	Female	41 (48.8)	12.0 (1.75-48.0)	0.01	0.989
	Male	43 (51.2)	10.0 (2.0-23.0)		
Occupation, n (%)	Unemployed	30 (35.7)	10.5 (2.0-30.0)	0.07	0.948
	Other	54 (64.3)	11.5 (2.0-39.0)		
Marital Status, n (%)	Married	39 (46.4)	11.0 (2.0-48.0)	0.52	0.605
	Not married	45 (53.6)	10.0 (1.75-20.5)		
Place of residence, n (%)	Urban	77 (91.7)	11.0 (2.0-48.0)	0.45	0.650
	Rural	7 (8.3)	9.0 (2.0-22.0)		
Smoking status, n (%)	Present	51 (60.7)	12.0 (2.0-24.0)	0.40	0.693
	Absent	33 (39.3)	8.0 (1.5-54.0)		
Variables		**Total Sample (n=84)**	***Spearman rho, p***		***p***
Age, years, M±SD		40.5±12.1	0.07		0.525
Education, years, M±SD		11.2±4.1	0.14		0.189
Vocabulary Raw Score, M±SD		40.9±11.8	0.11		0.341

Note DUI=duration of untreated illness, M=mean, SD=standard deviation, n=number of sample, IQR=Inter Quantile Range

Table 2. Clinical variables of the total sample and values of DUI /Spearman correlation according to these variables

Variables		Total Sample (n=84)	DUI, months, median (IQR)	Z	*p*
Bipolar Subtype, n (%)	Bipolar I Disorder	66 (78.6)	8.0 (1.50-22.25)	2.56	**0.010**
	Bipolar II Disorder	18 (21.4)	16.0 (12.0-63.0)		
Psychotic Features, n (%)	Present	34 (40.5)	4.25 (1.0-14.0)	2.08	**0.038**
	Absent	50 (59.5)	12.0 (3.5-51.0)		
Suicide Attempt, n (%)	Present	23 (27.4)	12.0 (8.0-72.0)	2.46	**0.014**
	Absent	61 (72.6)	8.0 (1.25-22.5)		
First Episode Polarity, n (%)	Mania	34 (40.5)	1.5 (0.5-6.25)	5.5	**<0.001**
	Depression	49 (58.3)	14.0 (9.5-60.0)		
	Undetermined	1 (1.2)	-		
Bipolar Disorder in 1st or 2nd Degree Relatives, n (%)	Present	26 (31)	11.0 (2.0-60.0)	0.58	0.564
	Absent	58 (69)	11.0 (2.0-23.25)		
Major Depressive Disorder in 1st or 2nd Degree Relatives, n (%)	Present	36 (42.9)	11.5 (2.0-60.0)	0.77	0.444
	Absent	48 (57.1)	10.5 (1.63-23.5)		
Lithium (Current Treatment)	Present	40 (47.6)	10.5 (2.0-23.75)	0.14	0.889
	Absent	44 (52.4)	11.5 (1.63-45.0)		
Valproate (Current Treatment)	Present	42 (50.0)	8.5 (1.38-22.5)	1.42	0.157
	Absent	42 (50.0)	12.0 (3.5-60.0)		
Lamotrigine (Current Treatment)	Present	13 (15.5)	12.0 (5.0-78.0)	1.24	0.215
	Absent	71 (84.5)	11.0 (2.0-24.0)		
Antidepressants (Current Treatment)	Present	18 (21.4)	14.5 (11.25-120.0)	2.33	**0.020**
	Absent	66 (78.6)	8.0 (1.88-23.25)		

Table 2. Clinical variables of the total sample and values of DUI /Spearman correlation according to these variables (continued)

Variables	Total Sample (n=84)	*Spearman rho, p*	*p*
Age at Onset, years, M±SD	22.7±7.6	0.03	0.761
Duration of Illness, years, median (IQR)	16.6 (7.33-27.4)	0.07	0.537
Total Number of Episodes, median (IQR)	6.0 (4.0-9.0)	0.26	**0.017**
Manic Episodes, median (IQR)	2.0 (1.0-3.0)	-0.37	**0.001**
Hypomanic Episodes, median (IQR)	1.0 (0.0-2.0)	0.27	**0.014**
Depressive Episodes, median (IQR)	2.5 (1.0-5.0)	0.51	**<0.001**
Mixed Episodes, median (IQR)	0.0 (0.0-0.0)	-0.08	0.469
Total Episode Duration, months, median (IQR)	12.0 (7.12-16.75)	0.27	**0.014**
Mania Duration, months, median (IQR)	2.0 (0.81-6.0)	-0.38	**<0.001**
Hypomania Duration, months, median (IQR)	1.0 (0.0-2.0)	0.25	**0.022**
Depression Duration, months, median (IQR)	6.0 (3.0-11.0)	0.49	**<0.001**
Mixed Episode Duration, months, median (IQR)	0.0 (0.0-0.0)	-0.08	0.450
Total Number of Hospitalizations, median (IQR)	1.0 (1.0-3.0)	-0.21	0.052

Note DUI=duration of untreated illness, M=mean, SD=standard deviation, n=number of sample, IQR= Inter Quantile Range

Gender, employment status, marital status, residence in rural or urban areas, smoking habits, family history of mood disorders, and the use of lithium, valproate, or lamotrigine in current treatment did not exhibit significant differences in the DUI.

A significant positive correlation was found between the DUI and the total number of episodes (p=0.26, p=0.017), number of hypomanic episodes (p=0.27, p=0.014), number of depressive episodes (p=0.51, p<0.001), total episode duration (p=0.27, p=0.014), duration of hypomanic episodes (p=0.25, p=0.022), and duration of depressive episodes (p=0.49, p<0.001). In contrast, a significant negative correlation was found between the DUI and the number of manic episodes (p=-0.37, p=0.001) and the duration of manic episodes (p=-0.38, p<0.001).

The correlation between cognitive tests and the DUI is shown in Table 3. No significant correlation was found between the DUI and variables such as age, education level, vocabulary test score, age of illness onset, illness duration, total number of hospitalizations, cognitive tests, or the number and duration of mixed episodes.

Table 4 presents the correlation between the DUI and various variables, after controlling for illness duration and normalizing variables such as the number of episodes, episode durations, illness duration, and the DUI.

When controlled for illness duration, the DUI showed a significant positive correlation with the COWAT (r=0.22, p=0.045), total number of episodes (r=0.27, p=0.013), number of hypomanic episodes (r=0.27, p=0.012), number of depressive episodes (r=0.48, p<0.001), total episode duration (r=0.28, p=0.011), duration of hypomanic episodes (r=0.25, p=0.024), and duration of depressive episodes (r=0.45, p<0.001). A significant negative correlation was found between the DUI and the number of manic episodes (r=-0.37, p=0.001) and the duration of manic episodes (r=-0.40, p<0.001).

Table 3. The correlation between cognitive tests and the DUI

Neuro/Social Cognitive Tests, M ± SD	Total Sample (n=84)	Spearman rho, *p*	*p*
Trail Making Test A Duration, s	46.2±25.7	0.09	0.382
Trail Making Test B Duration, s	154.9±102.6	0.00	0.997
Trail Making Test B-A Duration, s	108.8±83.9	-0.04	0.708
Stroop C Duration, s	99.7±36.5	-0.01	0.944
Stroop Interference, s	66.4±30.6	0.03	0.811
Rey 1-5 Recall Number	44.6±8.3	0.10	0.352
Rey 7 Recall Number	8.3±2.6	0.01	0.924
Rey Correct Recall	11.7±2.5	-0.11	0.306
Auditory Consonant Trigrams	47.6±8.5	0.11	0.335
COWAT	30.9±13.4	0.13	0.237
WMS-R VR immediate recall	29.1±8.2	0.07	0.544
WMS-R VR delayed recall	23.7±9.9	0.05	0.672
RMET	20.5±5.2	0.13	0.257
Hinting Test	15.3±3.3	0.20	0.068

Note DUI=duration of untreated illness, COWAT= Controlled Oral Word Association Test, RMET= Reading the Mind in the Eyes Test WMS-R VR= Wechsler Memory Scale—visual reproduction subtest, s= second, M=mean, SD=standard deviation, n=number of sample

Table 4. Correlation between dui and various variables, controlling for illness duration and normalized variables

Variables/Cognitive Tests	Partial Correlation (r)	*p*
Trail Making Test A Duration, s	0.04	0.683
Trail Making Test B Duration, s	-0.04	0.683
Trail Making Test B-A Duration, s	-0.08	0.455
Stroop C Duration, s	-0.06	0.595
Stroop Interference, s	-0.07	0.519
Rey 1-5 Recall Number	0.12	0.289
Rey 7 Recall Number	0.01	0.934
Rey Correct Recall	-0.09	0.382
Auditory Consonant Trigrams	0.19	0.083
COWAT	0.22	**0.045**
WMS-R VR immediate recall	0.08	0.432
WMS-R VR delayed recall	0.08	0.497
RMET	0.19	0.078
Hinting Test	0.21	0.057
Age of illness onset	0.01	0.933
Total number of episodes	0.27	**0.013**
Number of manic episodes	-0.37	**0.001**
Number of hypomanic episodes	0.27	**0.012**
Number of depressive episodes	0.48	**<0.001**
Number of mixed episodes	-0.15	0.177

Table 4. Correlation between dui and various variables, controlling for illness duration and normalized variables (continued)

Variables/Cognitive Tests	Partial Correlation (r)	*p*
Total Duration of Episodes	0.28	**0.011**
Mania Duration	-0.40	**<0.001**
Hypomania Duration	0.25	**0.024**
Depression Duration	0.45	**<0.001**
Mixed Episode Duration	-0.15	0.177
Total Number of Hospitalizations	-0.21	0.056

Note DUI=duration of untreated illness, COWAT= Controlled Oral Word Association Test, RMET= Reading the Mind in the Eyes Test WMS-R VR= Wechsler Memory Scale—visual reproduction subtest, n=number of sample

Discussion

In our study, we investigated the relationship between delays in diagnosing BD, clinical variables, and neuro/social cognitive impairments. Although the duration of undiagnosed illness was not found to be associated with cognitive impairment, it was observed that as the duration of undiagnosed illness increased, the total number and duration of episodes, particularly depressive episodes, also increased. These findings are consistent with the literature suggesting that patients who do not receive appropriate treatment in the early phase of the illness, experience more frequent recurrences over time [9, 11].

In line with the literature, our study found that delays in the diagnosis and appropriate treatment of BD were associated with not having experienced a psychotic episode, exhibiting a clinical presentation of bipolar II disorder, having the first mood episode as a depressive episode, being on antidepressant treatment, and having attempted suicide at least once in a lifetime [10, 11]. Consistent with the association between bipolar II disorder and DUI, our findings showed that the number of hypomanic episodes increased with longer undiagnosed periods, while the number of manic episodes decreased [10, 11].

When controlling for the duration of the illness, it was found that as the undiagnosed duration increased, the COWAT scores also increased. This finding contradicts our initial assumption and may not appropriately be considered as a positive effect of the delay in diagnosis. Instead, it could be due to certain clinical characteristics that lead to a longer undiagnosed period and are associated with a better cognitive profile [27, 28].

In our study, the mean duration of the undiagnosed illness was found to be 35.6±7.9 months, with a median of 11 months and an IQR of 2.0–33.0 months. This duration is significantly shorter than those reported in previous studies [3]. This difference may be attributed to the study sample, which consisted of patients who were being followed up at a university hospital located in a city center that includes a specialized mood disorders clinic.

To interpret the findings of this study, it is important to recognize its limitations. Firstly, the study was conducted at a single center, a specialized facility with a specific focus on BD, which limits the generalizability of the sample to the broader population. Additionally, the sample size was relatively small, and the cross-sectional design of the study allowed for the identification of associations only, rather than causal inferences. Another consequence of this being a cross-sectional study based on medical records and surveys is the potential for recall bias, particularly regarding the accuracy of information obtained about the early stages of the illness. Other than this, most longitudinal studies indicate that cognitive decline with age in people with bipolar disorder is similar to that of healthy individuals [29-31]. Cognitive functions diminish with age, regardless of contributing factors. Our study included participants aged 18 to 65, which may account for the variability in the severity of cognitive impairment observed. Moreover, participants were using various medications, which may have contributed to heterogeneity

in the assessment of cognitive functions. These patients were also fully recovered being followed up and treated in a specialized mood disorders clinic. This might have reduced the use of multiple medications or those that could impair cognitive functions during the disease while ensuring patients receive the best treatment through psychotherapeutic interventions when needed [32]. Therefore, symptom control and neurocognitive improvement were achieved in most patients. Finally, the study did not include certain sociodemographic characteristics, such as current income level, duration of employment, occupational changes, and changes in marital status, which could reflect functionality.

In conclusion, our study found that delays in diagnosis and treatment were associated with more frequent recurrences, a higher incidence of depressive episodes, and a history of at least one suicide attempt among patients diagnosed with BD. Our study has revealed that the association between extended periods of untreated illness and poor clinical and functional outcomes did not align with cognitive impairment. Future research should focus on identifying other factors that might mediate the relationship between poor outcomes and delays in treatment. To prevent the negative consequences of delayed treatment, clinicians are advised to be aware of the risk of missed diagnoses, especially in patients without a history of episodes with psychotic features or those presenting with depressive symptoms during their initial visit.

Conflict of interest: No conflict of interest was declared by the authors.

References

1. Grande I, Berk M, Birmaher B, Vieta E. Bipolar disorder. Lancet (London, England) 2016;387:1561-1572. https://doi.org/10.1016/S0140-6736(15)00241-X
2. Alonso J, Petukhova M, Vilagut G, et al. Days out of role due to common physical and mental conditions: results from the WHO World Mental Health surveys. Mol Psychiatry 2011;16:1234-1246. https://doi.org/10.1038/mp.2010.101
3. Dagani J, Signorini G, Nielssen O, et al. Meta-analysis of the Interval between the Onset and Management of Bipolar Disorder. Can J Psychiatry 2017;62:247-258. https://doi.org/10.1177/0706743716656607
4. Serafini G, Gonda X, Aguglia A, et al. Bipolar subtypes and their clinical correlates in a sample of 391 bipolar individuals. Psychiatry Res 2019;281:112528. https://doi.org/10.1016/j.psychres.2019.112528
5. O'Donovan C, Alda M. Depression preceding diagnosis of bipolar disorder. Front Psychiatry 2020;11:500. https://doi.org/10.3389/fpsyt.2020.00500
6. Altamura AC, Buoli M, Caldiroli A, et al. Misdiagnosis, duration of untreated illness (DUI) and outcome in bipolar patients with psychotic symptoms: a naturalistic study. J Affect Disord 2015;182:70-75. https://doi.org/10.1016/j.jad.2015.04.024
7. Faedda GL, Marangoni C, Serra G, et al. Precursors of bipolar disorders: a systematic literature review of prospective studies. J Clin Psychiatry 2015;76:614-624. https://doi.org/10.4088/JCP.13r08900
8. Altamura AC, Dell'Osso B, Berlin HA, Buoli M, Bassetti R, Mundo E. Duration of untreated illness and suicide in bipolar disorder: a naturalistic study. Eur Arch Psychiatry Clin Neurosci 2010;260:385-391. https://doi.org/10.1007/s00406-009-0085-2
9. Hong W, Zhang C, Xing MJ, et al. Contribution of long duration of undiagnosed bipolar disorder to high frequency of relapse: a naturalistic study in China. Compr Psychiatry 2016;70:77-81. https://doi.org/10.1016/j.comppsych.2016.06.013
10. Buoli M, Cesana BM, Fagiolini A, et al. Which factors delay treatment in bipolar disorder? A nationwide study focussed on duration of untreated illness. Early Interv Psychiatry 2021;15:1136-1145. https://doi.org/10.1111/eip.13051
11. Di Salvo G, Porceddu G, Albert U, Maina G, Rosso G. Correlates of long duration of untreated illness (DUI) in patients with bipolar disorder: results of an observational study. Ann Gen Psychiatry 2023;22:12. https://doi.org/10.1186/s12991-023-00442-5
12. Fico G, Anmella G, Gomez Ramiro M, et al. Duration of untreated illness and bipolar disorder: time for a new definition? Results from a cross-sectional study. J Affect Disord 2021;294:513-520. https://doi.org/10.1016/j.jad.2021.07.062
13. Galimberti C, Bosi MF, Volontè M, Giordano F, Dell'Osso B, Viganò CA. Duration of untreated illness and depression severity are associated with cognitive impairment in mood disorders. Int J Psychiatry Clin Pract 2020;24:227-235. https://doi.org/10.1080/13651501.2020.1757116
14. Elbir M, Alp Topbaş Ö, Bayad S, et al. Adaptation and reliability of the structured clinical interview for DSM-5-disorders - clinician version (SCID-5/CV) to the Turkish language. Turk Psikiyatri Derg 2019;30:51-56.
15. First MB. Structured Clinical Interview for the DSM (SCID). The Encyclopedia of Clin Psychology 2015:1-6. https://doi.org/10.1002/9781118625392.WBECP351

16. Torrent C, Martínez Arán A, Amann B, et al. Cognitive impairment in schizoaffective disorder: a comparison with non-psychotic bipolar and healthy subjects. Acta Psychiatr Scand 2007;116:453-460. https://doi.org/10.1111/J.1600-0447.2007.01072.X
17. Akdemir A, Türkçapar MH, Orsel SD, Demirergi N, Dag I, Ozbay MH. Reliability and validity of the Turkish version of the Hamilton Depression Rating Scale. Compr Psychiatry 2001;42:161-165. https://doi.org/10.1053/comp.2001.19756
18. Karadag F, Oral ET, Yalcın FA, Erten E. Young Mani Derecelendirme Ölçeğinin Türkiye'de geçerlilik ve güvenilirliği. Türk Psikiyatri Dergisi 2001;13:107-114.
19. Yazici MK, Demir B, Tanriverdi N, Karaağaoğlu E, Yolaç P. Hamilton Anksiyete Değerlendirme Ölçeği, değerlendiriciler arası güvenirlik ve geçerlik çalışması. Türk Psikiyatri Dergisi 1998;9:114-117.
20. Strauss E, Sherman E, Spreen O. A Compendium of Neuropsychological Tests, Third Edition 2006.
21. Emek Savaş DD, Yerlikaya D, Yener GG, Tanör ÖÖ. Validity, reliability and normative data of the Stroop test Çapa version. Turk Psikiyatri Derg 2020;31:9-21. https://doi.org/10.5080/U23549
22. Reitan RM. Validity of the trail making test as an indicator of organic brain damage. Perceptual and Motor Skills 1958;8:271–276. https://doi.org/10.2466/pms.1958.8.3.271
23. Anil AE, Kivircik BB, Batur S, et al. The Turkish version of the Auditory Consonant Trigram Test as a measure of working memory: a normative study. Clin Neuropsychol 2003;17:159-169. https://doi.org/10.1076/CLIN.17.2.159.16510
24. Yildirim EA, Kasar M, Güdük M, Ateş E, Kucukparlak I, Ozalmete EO. Investigation of the reliability of the "reading the mind in the eyes test" in a Turkish population. Turk Psikiyatri Derg 2011;22:177-186.
25. Bora E, Eryavuz A, Kayahan B, Sungu G, Veznedaroglu B. Social functioning, theory of mind and neurocognition in outpatients with schizophrenia; mental state decoding may be a better predictor of social functioning than mental state reasoning. Psychiatry Res 2006;145:95-103. https://doi.org/10.1016/j.psychres.2005.11.003
26. Feng C, Wang H, Lu N, et al. Log-transformation and its implications for data analysis. Shanghai Arch Psychiatry 2014;26:105-109. https://doi.org/10.3969/j.issn.1002-0829.2014.02.009
27. Bora E. Neurocognitive features in clinical subgroups of bipolar disorder: a meta-analysis. J Affect Disord 20187;229:125-134. https://doi.org/10.1016/j.jad.2017.12.057
28. Keramatian K, Torres IJ, Yatham LN. Neurocognitive functioning in bipolar disorder: What we know and what we don't. Dialogues Clin Neurosci 2022;23:29-38. https://doi.org/10.1080/19585969.2022.2042164
29. Delaloye C, Moy G, de Bilbao F, et al. Longitudinal analysis of cognitive performances and structural brain changes in late-life bipolar disorder. Int J Geriatr Psychiatry 2011;26:1309-1318. https://doi.org/10.1002/gps.2683
30. Gildengers AG, Chisholm D, Butters MA, et al. Two-year course of cognitive function and instrumental activities of daily living in older adults with bipolar disorder: evidence for neuroprogression? Psychol Med 2013;43:801-811. https://doi.org/10.1017/S0033291712001614
31. Samamé C, Cattaneo BL, Richaud MC, Strejilevich S, Aprahamian I. The long-term course of cognition in bipolar disorder: a systematic review and meta-analysis of patient-control differences in test-score changes. Psychol Med 2022;52:217-228. https://doi.org/10.1017/S0033291721004517
32. Mather M. Aging and cognition. Wiley Interdiscip Rev Cogn Sci 2010;1:346-362. https://doi.org/10.1002/wcs.64

Ethics committee approval: Permission was obtained from the Health Sciences Ethics Committee of Manisa Celal Bayar University Faculty of Medicine for the study (permission date: 30/12/2020, and permission number: 20.478.486).

Authors' contributions to the article

E.A., and O.A. designed the study. E.A. conducted data collection. E.A. and O.A. performed statistical analysis. Discussion section of the article written by E.A. and O.A. All authors discussed the entire study and approved the final version.