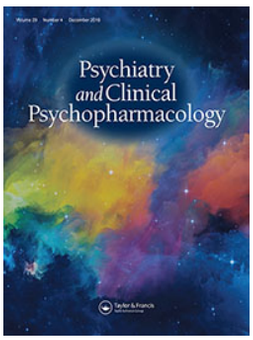

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Assessing the treatment adherence and clinical correlates of low adherence among bipolar disorder outpatients: a cross-sectional study

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ABSTRACT

OBJECTIVE: The aim of this study was to assess sociodemographic and clinical correlates of poor treatment adherence among outpatients with bipolar disorder (BD) in remission period.

METHODS: This was a cross-sectional study carried out in a University Hospital in Turkey, and 117 outpatients with BD according to DSM-IV-TR criteria were included. All participants were administered a sociodemographic form, the SCID-I, the Morisky 8-item Medication Adherence Questionnaire, the Hamilton Depression Scale, the Young Mania Rating Scale, Schedule for Assessing the three components of insight, and Global Assessment of Functioning Scale. Collected data were analysed via descriptive statistics and logistic regression was used to determine significant variables.

RESULTS: Patients with poor treatment adherence were low educated, were more likely to be not married, and had a greater prevalence of anxiety disorder comorbidity. The patients with poor adherence also showed more subsyndromal depressive symptoms but no significant differences were seen in terms of age, gender, living status, social support, or number of episodes between patients with good and poor adherence. Logistic regression analyses revealed that comorbid anxiety disorder, lower education level, and duration of depression period were the main predictors of poor adherence.

CONCLUSION: This outcome is consistent with previous studies, and assuring complete adherence in all bipolar patients is difficult, but increasing the number of adherent patients is possible and substantial for sufficient outcome. Improving subsyndromal symptoms and awareness of the patient about the features of the disorder may provide better adherence to treatment and greater functionality of the patient. Psychotherapeutic interventions and psychoeducation should be implemented along with the medical treatment to improve subsyndromal symptoms and to avoid treatment maladherence in advance. Further research is needed to assess the role of interventions in treatment adherence of patients with BD.

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Bipolar disorder; treatment adherence; comorbidity

Introduction

Bipolar disorder (BD), a common disorder with a prevalence of 1–3% in the population, can present with both depressive and manic episodes. It has a waxing and waning course characterized by recurrent episodes and followed by residual symptoms in some cases [1]. It is an important cause of disability in late adolescents and adults. Its clinical course differs in between the patients according to the type and severity of the symptoms [2]. Some researchers suggest that clinical features of the disease such as mixed episodes and rapid cycling pattern cause poor prognosis despite appropriate treatment [3,4]. Also, treatment adherence is important to determine the course of BD [5].

"Adherence" is defined as a person's behaviour corresponding with implemented recommendations from a health care provider by the World Health Organization [6]. Poor treatment adherence is widespread in BD in common with other chronic medical conditions [7–9]. Most studies report poor treatment adherence rates from 10% to 50% in BD depending on how poor adherence is measured [10–12]. Scott et al. reported that at least one-third of the patients stopped taking the medicines once or more times over the course of one year [13]. Poor treatment adherence in BD is associated with negative prognosis including increased rates of relapse, poor treatment response, rehospitalization, and poor community adjustment [14–17]. However, determiners of poor treatment adherence in BD still remain a challenging problem in the management [18]. Male gender, subsyndromal symptoms during remission, comorbidities especially substance use disorder, and side effects of medical treatment were associated with poor treatment adherence in previous studies [19–22].

Psychotherapeutic interventions, close follow-up, and psychoeducation might improve poor treatment adherence in patients with BD [23]. The primary aim

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of this study was to assess sociodemographic and clinical correlates of poor treatment adherence among outpatients with BD during remission period.

Methods

This was a cross-sectional study carried out in a University Hospital in Turkey. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and ethical approval for the study was given by the Ethical Commission of the Health Sciences University (IRB approval date and number: 27.06.2016-3107; Ankara, Turkey).

Participants

The outpatients aged 18 years or older with the diagnosis of bipolar-I disorder according to Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) who applied in December 2016 to the outpatient psychiatry clinic of the university ($n = 117$) were enrolled into the study [24]. 21 patients were not enrolled into the study because 7 of them were not in the remission period, 10 of them did not approve of attending the study, and 4 of them did not complete the scales. Subjects with scores of 13 points or less on the Hamilton Depression Rating Scale (HDRS), 12 points or less on the Young Mani Rating Scale (YMRS), and Clinical Global Impressions Scale (CGI) score <3 were accepted as "in remission" [25–27]. Written informed consents were obtained from all of the participants.

Measurements

Sociodemographic data form

Sociodemographic data form included semi-structured questions that address basic demographic information (e.g. age, education, and sex), some variables related to illness (e.g. having a social insurance and social support level), other treatment features (drug doses, age of onset, type and total number of attacks, and hospitalisations), and variables related to physical health (e.g. having a chronic medical disorder). Social support level of the bipolar patients was determined by a self-rated questionnaire, including three options and the options were adequate support, inadequate support, and no support.

The Structured Clinical Interview for DSM Disorders-I

The Structured Clinical Interview for DSM Disorders-I (SCID-I) is a semi-structured clinical interview for investigating the diagnosis of Axis-I mental disorders according to DSM-IV [24]. It was developed by First et al. and Turkish adaptation and reliability study was performed by Corapcioglu et al. [28,29].

The Morisky 8-item medication adherence questionnaire

The Morisky 8-item medication adherence questionnaire (MMAS-8), developed by Morisky et al., addresses how patients may fail to take medication as prescribed due to forgetfulness, carelessness, stopping the drug when they feel better or stopping treatment because they believe it makes them feel worse [30,31]. It is a self-rated questionnaire consisting of eight questions and the questionnaire's first seven elements include yes/no answers while the eighth element has five answers. When the answer indicates a negative adherence issue, a score of 1 is recorded.

Total score ranges from 0 (good adherence) to 8 (poor adherence). Score at a threshold of 2 on the MMAS-8 is supposed to be a valuable tool for identifying poor adherent patients [30–32]. Turkish adaptation and reliability study was performed by Hacıhasanoglu Asılar et al. [33]. Patients who scored 0–2 points at the MMAS-8 were taken in good adherent group and patients scored more than 3 points at the MMAS-8 were taken in poor adherent group. Also, blood mood stabilizer levels of the patients were tested on the same day with the measurement. Blood lithium level between 0.6 and 1.2 mEq/l and blood valproic acid level between 50 and 100 mg/ml were considered as adequate.

The Young Mania Rating Scale

The Young Mania Rating Scale (YMRS) was used to assess manic symptoms. YMRS was developed by Young et al. and Turkish adaptation and reliability study was performed by Karadag et al. [25–34]. YMRS consists of 11 items, scored between 0 and 4 points. Total sum of the scores of all items gives information about severity of mania. YMRS baseline scores can vary between different studies and YMRS score of 12 and higher were not included in this study.

Hamilton Depression Rating Scale

HDRS was used to assess depressive symptoms. HDRS was developed by Hamilton et al. and Turkish adaptation and reliability study was performed by Akdemir et al. [26,35]. HDRS consists of 17 items, scored between 0 and 4 points and the total sum of the scores of all items gives information about severity of the depression. Score of 0–7 is generally accepted to be within the normal range (or in clinical remission), while a score of 13 and higher indicates depression. HDRS score of 13 and higher were not got involved in this study.

The Clinical Global Impressions Scale

CGI scale, developed by Guy, was used to evaluate the severity of clinical status from 1 to 7; higher scores indicate severe psychopathology, while 1 point means

healthiness [27]. Patients with CGI score > 3 were not included in the study.

Schedule for Assessing Insight Scale

The Schedule for Assessing Insight Scale (SAI) (a semi-structured scale consisting of eight items) was used to assess three components of insight. SAI is administered by a clinician and the components are adherence to treatment, awareness of illness, and correct identification of symptoms. Higher scores indicate higher levels of insight. The SAI was developed by David, and Turkish validity and reliability of the scale were confirmed by Arslan et al. [36,37].

Global Assessment of Functioning Scale

Finally, Global Assessment of Functioning Scale (GAF) was used to assess functional impairment [38]. GAF is a scale considering impairments in psychological, social, and occupational/school functioning to assign a clinical judgment of an individual's overall functioning level. The scale ranging from 0 (lower) to 100 (higher functioning) was developed by Endicott et al. and included in DSM-IV [24,38]. Score of 60 indicates moderate symptoms or moderate difficulty in social, occupational, or school functioning, while score of 50 and lower show serious impairment.

Statistical analysis

All of the data were presented as mean ± standard deviations (SD). Demographic and clinical psychiatric characteristics between good and poor adherent groups were analysed with chi-square test and independent samples *t*-test. Also, we applied logistic regression analysis to determine significant variables associated with poor adherence to medication at the final assessment. All the statistical calculations were performed using the Statistical Package for the Social Sciences (SPSS). All *p* values were calculated as two-sided, and *p* value less than .05 was considered significant.

Results

A total of 117 patients were included in the analysis. In terms of the sociodemographic characteristics of the patients, their mean age was 38.86 ± 11.30 years and females represented 59% ($n = 69$) of the sample. 56% ($n = 65$) of the respondents were married while 75% ($n = 88$) patients defined adequate social support level. The clinical characteristics of the patients revealed that 56% ($n = 65$) of the patients had a manic episode as the first episode and 57% ($n = 66$) of the patients had seasonal pattern episodes. Comorbid anxiety disorder was found 12% ($n = 14$), while mean HDRS and YMRS scores were 2.64 ± 3.57, and 5.08 ± 1.77 respectively.

16.2% of patients ($n = 19$) were classified as having poor medication adherence according to the MMAS-8 scale. A 2 × 2 contingency table demonstrating the relationship between treatment adherence and adequacy of the mood stabilizer level is shown in Table 1. Any significant differences were seen in terms of age, gender, living status, declared social support, or number of episodes between patients with good and poor adherence ($p > .05$). Patients with poor treatment adherence were low educated, were more likely to be not married, had a greater prevalence of anxiety disorder and mean duration of the depression period was longer in the poor adherent group ($p < .05$). Only 8% ($n = 8/98$) of the patients with good adherence had comorbid anxiety disorder, when compared with 32% ($n = 6/19$) of respondents in the poor adherence group and the difference was significant ($p < .05$ $X^2 = 8.284$). Mean duration of the depression periods were 15.34 ± 8.36 and 29.16 ± 7.98 days in good and poor adherent groups, respectively ($p < .05$, $F = 0.747$). Correlation between alcohol/substance use disorder comorbidity and poor treatment adherence in BD was not repeated in this study due to paucity of the comorbidity with alcohol/substance use disorder. HDRS scores were 2.17 ± 3.1 and 5.05 ± 4.80 in good and poor adherence groups, respectively ($p < .05$, $F = 14.652$). Also, the patients with poor adherence showed worse functioning than good adherent respondents, with total GAF scores of 79.3 (95% confidence interval 2.44–12.60), and 71.8 (95% confidence interval 1.12–13.18), respectively ($r = -0.383$, $p < .05$). Insight scores were higher in good adherence group but the difference was not significant ($p > .05$). Table 2 shows the differences of the main sociodemographic and clinical characteristics of two groups according to treatment adherence status.

Table 1. The relationship between treatment adherence and adequacy of the mood stabilizer levels.

	Blood level adequate	Blood level inadequate	Total
MMAS-8 adherent	93	5	98
MMAS-8 non-adherent	4	15	19

Binary logistic regression analysis was used to identify a model to predict important variables related with poor treatment adherence. The results showed that variables like having a social security, anxiety disorder comorbidity, mean duration of depression episode, and lower education level were significant risk factors for treatment adherence (Table 2). Gender was added to those variables and binary logistic regression analysis was applied with five variables, and this model had a good fit under the Hosmer–Lemeshow goodness-of-fit test (Nagelkerke $R^2 = 0.601$, $\chi^2 = 2.652$, $p = .915$), and accuracy of the model was 83.8%. Logistic regression analyses revealed that comorbid anxiety disorder (Wald = 6.145, $p = .016$), lower education level (Wald = 4.989, $p = .026$), and mean duration of depression period (Wald = 17,009, $p = .000$) were the

Table 2 . Sociodemographic and clinical characteristics of the poor and good treatment adherence groups.

	Poor treatment group (*n*, %) (19, 16%)	Good treatment group (*n*, %) (98, 84%)	Significance (*p*)	Statistic
Age[a]	41.27 ± 10.49	38.39 ± 11.44	.432	$F = 0.621$
Gender[b]			.154	$X^2 = 2.029$
Female	14, 73%	55, 56%		
Male	5, 26%	43, 44%		
Marital status[b]			**.006***	**$X^2 = 7.619$**
Single/seperated	16, 84%	49, 50%		
Married	3, 16%	49, 50%		
Education level[b]			**.019***	**$X^2 = 7.969$**
Primary school or lower	9, 48%	26, 27%		
Middle school	5, 26%	12, 12%		
High school/ university	5, 26%	60, 61%		
Social security[b] presence	14, 82%	95, 97%	.454	$X^2 = 5.756$
Number of episodes[a]	10.05 ± 6.29	7.91 ± 7.20	.31	$F = 0.004$
Rapid cycling[b]	1, 1%	5, 4%	.977	
Seasonal pattern[b]	10, 53%	56, 57%	.681	
Mean duration of depression period	29.16 ± 7.98	15.34 ± 8.36	**.000***	**$F = 0.747$**
Comorbid anxiety disorder[b]	6, 32%	8, 8%	**.004***	**$X^2 = 8.284$**
YMRS[a]	1.01 ± 2.45	0.52 ± 0.90	.399	$F = 1.447$
HDRS[a]	5.05 ± 4.80	2.17 ± 3.10	**.001***	**$F = 14.652$**
Insight scores[a]	14.32 ± 3.33	15.66 ± 2.73	.492	

Note: Data; number of cases (percentage). # Mean ± S.D. Values in bold indicate statistical significance ($p < .05$).
[a]Independent sample *t*-test.
[b]Chi-square test for independence, $p < .05$*.

main predictors of poor adherence. The findings are depicted in Table 3.

Discussion

In terms of clinical variables, patients with poor treatment adherence showed a greater prevalence of comorbid anxiety disorder, longer duration of depression period, higher HDRS scores, and lower functionality. Poor treatment adherence was also related with lower education level and being single/ divorced among the sociodemographic variables (Table 2). But number of episodes, rapid cycling pattern, alcohol, and substance disorder comorbidity were not related with medication adherence. 16.2% of the patients ($n = 19$) were found to have poor medication adherence according to the MMAS-8 scale. Five patients with inadequate mood stabilizer level were not included in the poor adherence group and also four patients of the poor adherence group had adequate blood mood stabilizer level but they were not categorized in the good adherence group (Table 1). Because mood stabilizer level is affected by the weight of the patient, other drug interactions, blood collection time, laboratory conditions, etc., mood stabilizer level itself is not enough to determine the treatment adherence without the impact of other variables. Considering the sociodemographic and clinical characteristics of the patients, treatment adherence rate was similar with the previous studies which figured out the poor adherence rates from 10% to 50% in BD [17,39–41]. Female patients were higher and all patients were remitted in our study, which was a favourable effect on treatment adherence. Thirteen per cent of patients showed poor compliance in Lama et al.'s study consisting of 52.7% of female individuals [17].

Only 8% ($n = 8/98$) of the patients with good adherence had a comorbid anxiety disorder, when compared with 32% ($n = 6/19$) of the respondents in poor adherence group. Comorbidity with anxiety disorders was found to disrupt course of the disorder and cause functional disability in previous studies as in our study [40–43]. Longer depression period and higher HDRS scores were associated with poor treatment adherence according to this study. That result was also illustrated in many previous studies [21,44–46]. Longer duration of depression and more severe subsyndromal depressive symptoms may lower treatment adherence due to different reasons such as hopelessness about the future or helplessness cognition of the patient [42,44–47]. Several factors (including male gender, lower education level, young age, being not married, comorbid psychiatric disorders, especially alcohol and drug abuse) are demonstrated to be associated with poor treatment adherence in BD according to previous studies [39,47–49]. Poor adherence rate was not associated with age, gender, living status, and social support level between patients with good and poor adherence, in this study. Female gender, being married, and higher social support were associated with good adherence in some previous studies, but only being married was associated with good treatment adherence in our study [21,44–47]. Being married provides a regular life and supports social coping, which makes easier for patients to adhere to medical treatment. Having a social security was related with good treatment adherence and this was not surprising as social security is a key tool to access to health service in a developing country [50–53]. Lower education level (primary school or less) was 47% ($n = 9/19$) in poor adherent group while it was 26% ($n = 25/98$) in good adherent group, and higher maladherence rates in lower education level were shown in many previous studies

Table 3. Logistic regression analysis for variables associated with poor treatment adherence.

Variables	*B*	SE	Wald	Exp(*B*)	Exp(*B*) 95%CI		*p*
					Lower bound	Upper bound	
Gender	0.591	0.864	0.468	2.049	0.360	11.660	.494
Social security	−2.885	1.815	2.527	0.049	0.001	2.056	.112
Comorbid anxiety	2.288	0.923	6.145	10.937	1.569	76.325	**.016***
Education level			6.182				.103
Primary school or less	2.730	1.222	4.989	15.330	1.397	168.196	**.026***
Middle school	2.481	1.357	3.343	11.950	0.837	170.698	.067
High school/University	0.928	1.477	0.395	2.529	0.140	45.690	.530
Mean duration of depression	0.374	0.091	17.009	1.454	1.210	1.748	**.000***

Note: Values in bold indicate statistical significance ($p < .05$).
[a]Hosmer–Lemeshow test GFI: 0.915.
*$p < .05$.

[22,40,51]. Lower education is associated with worse socioeconomic conditions, which bring insufficient facilities for health access, and possibly lower awareness of the disorder [21,39,40]. Nevertheless supplying better facilities for health access, arranging psychoeducational programmes can improve treatment adherence [51,52].

Avoiding mood episodes is the primary aim according to treatment algorithms and that aim can usually be achieved with medical treatment. However, sustaining medical treatment and providing better functionality of the patient can be succeeded with advanced health access and implementation of psychotherapeutic interventions [40,50–52]. It was remarkable that subsyndromal depressive symptoms and anxiety disorder comorbidity were closely related with treatment adherence in this study. Subsyndromal symptoms or comorbidities during the remission period should be considered cautiously to try out supplementary treatment options during remission periods.

Our study has several limitations. First, a cross-sectional study cannot permit drawing causal associations between the factors studied and results should be confirmed in prospective follow-up studies. Second, patient's knowledge level or awareness of features of the disorder was not evaluated and education level of the individuals was compared between the two groups. Standard questionnaires targeting understanding of the disorder itself should be applied to support a direct relationship with the treatment adherence. Also, our study has some strengths as treatment adherence was measured using a valid self-report questionnaire rather than asking to patient directly. Second, treatment adherence was confirmed with drug blood levels during the evaluation.

Finally, assuring full adherence in bipolar patients may be unfeasible, but improving adherence can be achieved by overcoming possible causes of poor adherence. Severe subsyndromal depressive symptoms and anxiety disorder comorbidity were related with poor treatment adherence in our study, this consequence suggested that some clinical features during remission may trigger treatment maladherence. Psychotherapeutic interventions might be considered to improve treatment adherence and provide better functionality during remission periods.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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