

Assessment of the Functioning Levels and Related Factors in Patients with Bipolar Disorder during Remission

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ABSTRACT

Introduction: The course of bipolar disorder (BD) is characterized by relapse and remission periods. Although the symptoms show a significant and sometimes almost complete improvement during remission, the patients' functioning levels may be lower compared to the premorbid period. This study aimed to compare the functional levels between patients with BD during remission period and healthy controls and to evaluate the factors related to the functional status of the patients.

Methods: In this cross-sectional study, functioning levels of the BD-I patients, who were in remission for three months or longer, were compared with those of the healthy controls. Young Mania Rating Scale and Hamilton Depression Rating Scale were used to determine remission status, and Bipolar Disorder Functioning Questionnaire (BDFQ) was used to determine the level of functioning.

Results: The study included 165 BD-I patients during remission and 63 healthy controls. The BDFQ scores of the patients including intellectual

functioning, sexual functioning, feeling of stigmatization, introversion, relationships with friends, participation in social activities, daily activities and hobbies, and taking initiative were found to be statistically significantly lower than those of the controls. When the functioning comparisons were carried out within the patients considering the drugs they were using, the functioning levels including domestic functioning and introversion domains were found to be significantly impaired in those who use at least one antipsychotic in addition to the mood stabilizers than in those who use only mood stabilizers.

Conclusion: In BD, the impairments within multiple functioning domains are observed even during remission periods. Besides targeting remission through pharmacological treatment, psychosocial interventions for functioning are also important in the treatment of these patients.

Keyword: Bipolar disorder, remission, functioning, disability

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INTRODUCTION

Bipolar disorder (BD) usually starts in young adulthood, with a course of illness comprising of mood symptoms that are mostly chronic, interspersed with remission periods. BD is one of the leading causes of disability (1). Impairments in occupation, marital adjustment and participation in social activities are observed in patients with BD (2). BD is a major public health problem because it is associated with functional impairment, caregiver difficulties, the use of health resources and increased mortality (3).

As a result of the biological and social treatment models developed in recent years, the assessment of quality of life and functioning has become the focus of attention in mental disorders. Assessment of functionality includes multiple domains such as familial, occupational, emotional, mental and sexual functioning. Although the symptoms show a significant and sometimes almost complete improvement during remission, the patients' functioning levels may still be lower compared to the premorbid period (4,5). It has been reported that patients with BD have cognitive impairments during both episodes and remission (6,7). Furthermore, significant improvement in functioning may not be achieved even in patients undergoing a customised treatment program (4). On the other

hand, stigmatisation, one of the consequences of loss of functioning, is an important problem in psychiatric disorders and especially in BD (8,9).

In this study, we aimed to compare the functioning of BD patients during remission with those of healthy controls and to evaluate the factors affecting functioning. Although there were studies investigating the level of functioning in BD, the scale used in this study, namely the BDFQ, was developed in Turkey. Previous studies using BDFQ are studies where the number of cases is relatively low or there is no control group. In addition, in previous studies, the functioning levels of patients have not been evaluated according to the drugs they used. Therefore, in our study, comparisons were carried out after the patients were grouped according their drug treatments as well as sociodemographic data, and the effect of drug dose and blood levels of the drugs on functioning were also evaluated.

METHODS

This study was a cross-sectional, comparative study. Written informed consent was obtained from the patients and healthy controls who

participated in the study, and the study was approved by the local ethics committee (Ethics committee decision number: 20172017-KAEK-189_2018.06.20_4).

Patients

Giving consent to participate in the study, 165 patients, who applied consecutively to the psychiatry outpatient clinic and were followed by the same clinic, were included in the study. The patients were diagnosed with BD-I according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (10) and were between 18-65 years of age, able to understand the guidelines of the study, mentally and physically competent to complete the scales without the support of another person and had been in a remission period for at least three months. Patients with a diagnosed psychiatric disorder other than BD, alcohol or substance use disorder, BD-II, and neurological or physical illness or disability, pregnant women and those who had received electroconvulsive therapy in the last six months were not included in the study.

Controls

Having no psychiatric, neurological, or chronic physical illnesses during their lifetime, 63 healthy controls were included in the study. The controls were similar to the patients in terms of age, sex and educational level and did not have any first-degree relatives diagnosed with BD, major depression or psychotic disorder.

Assessment Tools

Before being included in the study, the patients were re-evaluated by the researcher for the diagnosis via clinical examination. The Hamilton Depression Rating Scale (HDRS) (11) and the Young Mania Rating Scale (YMRS) (12) were used to determine whether the patients were in remission. Patients with a HDRS score of seven or less and a YMRS score of five or less were included in the study. The reliability and validity study of the Turkish version of HDRS and YMRS were conducted by Akdemir et al. (13) and Karadağ et al. (14), respectively.

The sociodemographic data form was a form that included the information obtained from the interview and patient records, such as age, sex, marital status, education level, work, monthly income, onset age and duration of the disorder, number of episodes and drug use. For evaluation of functioning, the patient and control groups completed the BDFQ. The BDFQ has been developed by the Scientific Section for Mood Disorders of the Psychiatric Association of Turkey. The scale consists of 52 questions and 11 sub-scales (emotional functioning, intellectual functioning, sexual functioning, sense of stigmatisation, introversion, domestic relations, relationships with friends, participation in community activities, daily activities and hobbies, taking initiative and using potential, and work (15). The 3-point Likert type scale does not have a cut-off score, and high scores indicate good functioning.

Statistical Method

Descriptive statistics were calculated for the data and the Kolmogorov-Smirnov test was applied to assess the distribution of normality. Sociodemographic data were compared with the Chi-square and Student's t-test. A one-way ANOVA test was used to compare the three independent groups when the data were normally distributed, and when there was a significant difference in ANOVA test, a post-hoc Tukey HSD test was applied to determine which two groups caused the difference. For variables without a normal distribution, the Mann-Whitney U test was used to compare the two independent groups. The Kruskal Wallis test was used for comparison of three independent groups when the data were not normally distributed, and pairwise comparisons of statistically significant values were made by the Mann-Whitney U test. For correlation analyses, Pearson and Spearman correlation tests were conducted to assess the data with normal and non-normal distributions, respectively.

A linear regression analysis was performed for significant relationships in the correlation analyses. The significance level was set at $p < 0.05$.

RESULTS

The study included 165 patients diagnosed with BD-I during remission and 63 healthy controls. The mean age of the patients was 38.07 ± 10.24 years (min-max: 18-64), and 60.6% ($n = 100$) of the patients were female. The mean age of the control group was 38.90 ± 12.96 years (min-max: 18-62), and 54% ($n = 34$) of them were female. There was no statistically significant difference between the patient group and the control group in terms of age, sex or duration of education ($p = 0.648$; $p = 0.363$; $p = 0.051$, respectively) (Table 1). YMRS and HDRS scores of the patients were below 5 and 7 respectively because all the patients were in remission, but both scores were statistically significantly higher when compared with the scores of the controls ($p < 0.001$) (Table 1). When the BDFQ scores of the patient and control groups were compared, functioning scores in the domains including intellectual functioning ($p = 0.03$), sexual functioning ($p < 0.001$), sense of stigmatisation ($p < 0.001$), introversion ($p < 0.001$), relationships with friends ($p < 0.001$), participation in community activities ($p < 0.001$), daily activities and hobbies ($p < 0.001$) and taking initiative and reaching full potential ($p < 0.001$) were significantly lower in the patient group (Table 1).

In our study, no significant correlation was found between duration of the disorder and BDFQ scores. There was a negative correlation between the number of manic episodes and daily activities and hobbies domain of functioning ($r = -0.204$; $p = 0.011$). Linear regression analysis showed that the effect of manic episodes on this domain of functioning was 3.8% ($F = 6.053$; $p = 0.015$). There was a negative correlation between the number of previous hypomanic episodes and the relationships with friends domain of functioning ($r = -0.312$; $p = 0.024$). There was a negative correlation between the total number of episodes and participation in community activities domain of functioning ($r = -0.203$; $p = 0.009$). It was found that the effect of the total number of episodes on deterioration of functioning in participation in community activities domain was 3.6% ($F = 6.053$; $p = 0.015$).

When the patients were divided into 3 groups according to the drugs they used, 41.2% ($n = 68$) of the patients were receiving mood stabilisers (MS) (lithium, valproic acid or lamotrigine), and their mean age was 38.84 ± 10.60 years. The proportion of the patients receiving at least one atypical antipsychotic (AP) in addition to MS (MS-AP) was 50.9% ($n = 84$), with a mean age of 37.68 ± 9.66 years, and the proportion of those were receiving only AP was 7.9% ($n = 13$), with a mean age of 36.62 ± 12.42 years (Table 2). When the functioning scores of the patients were compared according to the drugs they used, introversion ($p = 0.001$) and domestic relations ($p = 0.016$) domains of functioning were significantly different among the groups. When pairwise comparisons were carried out to determine which groups were responsible for this difference, introversion and domestic relations domains of functioning of those receiving MS-AP were found to be more significantly impaired than those receiving MS ($Z = -3.700$, $p < 0.001$; $Z = -2.750$, $p = 0.006$, respectively) (Table 3). The number of previous manic episodes was significantly higher in the MS-AP group compared to the AP group ($p = 0.014$), while the total number of episodes was significantly lower in the AP group compared to the MS and MS-AP groups ($p = 0.008$). The number of hospitalisations in the MS-AP group was significantly higher than in MS ($p = 0.013$) and AP groups ($p = 0.028$). The duration of use of the current treatment was significantly shorter in the AP group than in MS ($p = 0.005$) and MS-AP ($p = 0.008$) groups (Table 3).

Among the patients that were on MS treatment ($n = 68$), 25 (36.8%) were on lithium, 30 (44.1%) were on valproic acid, 12 (17.6%) were on both

Table 1. Comparisons of sociodemographic data and scale scores of patient and control groups

	Control (n=63) Mean±SD	Patient (n=165) Mean±SD	t	p*
Age	38.90±12.96	38.07±10.24	0.458	0.648
Monthly Income (TRY)	2773±1393	1698±1135 ^a	5.468	<0.001
Cigarettes smoked per day	16.75±8.47	22.91±15.09 ^b	2.031	0.045
YMRS	2.25±0.74	3.76±1.39 ^b	10.514	<0.001
HDRS	2.81±0.84	4.05±1.64 ^b	7.470	<0.001
Education span (years)	10.20±3.77	9.03±4.13	1.965	0.051
Gender % (Female-Male)	54-46	60.6-39.4	0.829	0.363
	Median (IR)	Median (IR)	Z	p**
Emotional functioning	8 (2)	7 (3)	0.347	0.729
Cognitive functioning	11 (3)	10 (3) ^a	2.936	0.003
Sexual functioning	11 (2)	8 (4) ^a	4.901	<0.001
Sense of stigmatization	11 (1)	8 (5) ^a	7.483	0.001
Introversion	7 (2)	6 (2) ^a	4.083	<0.001
Domestic relations	14 (4)	14 (6)	1.019	0.308
Relationships with friends	12 (3)	10 (3) ^a	5.004	<0.001
Participation in community activities	15 (4)	11 (6) ^a	5.797	<0.001
Daily activities and hobbies	15 (4)	12 (4) ^a	5.701	<0.001
Taking initiative and using the potential	8 (3)	5 (2) ^a	7.219	<0.001
Work	10 (5)	10 (4)	0.782	0.434

*Student's t test.

**Mann-Whitney U.

^aSignificantly lower compared to control group, ^bSignificantly higher compared to control group, Mean±SD: Mean±standard deviation; IR: Interquartile range; HDRS: Hamilton Depression Rating Scale; YMRS: Young Mania Rating Scale; TRY: Turkish Lira

lithium and valproic acid, and only one was on lamotrigine. When these patients were divided into three groups according to the MS they used (i.e., lithium, valproic acid, and lithium and valproic acid combination), there were no significant differences in the functioning levels ($p > 0.05$). Lithium dose and serum levels of lithium and valproic acid did not show any significant relationships with the functioning levels ($p > 0.05$). The dose of valproic acid showed a positive correlation with functioning levels in relationships with friends and participation in community activities domains ($r = 0.260$, $p = 0.030$; $r = 0.257$, $p = 0.032$, respectively). There was a positive correlation between the lithium dose and the number of hospitalisations ($r = 0.306$, $p = 0.026$).

DISCUSSION

In this cross-sectional, case-control study, the functioning of patients with BD-I disorder during remission was assessed with BDFQ and compared with healthy controls. In addition, the patients were divided into three groups (MS, MS-AP and AP) according to the medications they used, and the functioning levels of these groups were compared.

Functioning may become significantly impaired in people with BD and other psychiatric disorders. Because the clinical course of BD consists of episodes and remission periods, assessing functioning in remission and comparing this with healthy controls is particularly important in terms of evaluating the effect of the disorder on functioning. In this study, it was found that several functioning domains of the patients in remission were significantly impaired as compared to the control group, and introversion and domestic relations domains of functioning of the patients receiving MS-AP were more significantly impaired than those receiving MS.

Comparison of the level of functioning between the patients with BD and healthy controls

In this study, patients' functioning in the domains including intellectual functioning, sexual functioning, sense of stigmatization, introversion, relationships with friends, participation in community activities, daily activities and hobbies and taking initiative has shown more deterioration as compared to the control group.

It is known that BD impairs social functioning and negatively affects almost every aspect of patients' lives (16). Despite clinical remission, the majority

Table 2. Sociodemographic data of patient groups according to the drugs they used

	Used drugs (n=165)		
	MS (41.2%; n=68)	MS+AP (50.9%; n=84)	MS+AP (7.9%; n=13)
Age (years) (Mean±SD)	38.84±10.60	37.68±9.66	36.62±12.42
Female	67.6%	53.6%	69.2%
Male	32.4%	46.4%	30.8%
Duration of disease (months) (Mean±SD)	144.18±97.58	147.71±99.39	100.62±65.27

Mean±SD: Mean±Standard Deviation; MS: Mood stabilizer; MS-AP: at least one antipsychotic in addition to the mood stabilizers; AP: Atypical antipsychotic

Table 3. Comparisons of functioning levels, duration of treatment, number of episodes and hospitalisations of patients according to the drugs used

	MS (41,2%; n=68)	MS+AP (50,9%; n=84)	AP (7,9%; n=13)	χ^2	p^*
BDFQ	Median (IR)	Median (IR)	Median (IR)		
Emotional functioning	8 (3)	7 (4)	7 (3)	1.168	0.558
Cognitive functioning	10 (3)	10 (5)	10 (5)	0.372	0.830
Sexual functioning	8 (4)	8 (6)	9 (3)	1.882	0.390
Sense of stigmatization	9 (5)	8 (4)	10 (3)	3.509	0.173
Introversion	7 (2)	6 (3) ^a	6 (3)	13.774	0.001
Domestic relations	15 (5)	13 (5) ^a	13 (6)	8.249	0.016
Relationships with friends	11 (4)	10 (3)	10 (4)	2.316	0.314
Participation in community activities	12 (6)	11 (5)	11 (6)	0.176	0.916
Daily activities and hobbies	12 (4)	12 (4)	14 (4)	1.631	0.442
Taking initiative and using the potential	5 (2)	4.5 (2)	4 (2)	2.041	0.360
Work	10 (4)	10 (3)	10 (3)	0.974	0.614
Clinical and treatment data				χ^2	p^*
Number of manic episodes	2 (2)	3 (3) ^b	1 (2)	6.304	0.043
Total number of episodes	4 (4)	4 (4)	2 (3) ^d	9.733	0.008
Number of hospitalizations	1 (2)	2 (2) ^c	1 (2)	8.914	0.012
Duration of use of current treatment (months)	36 (72)	36 (60)	12 (16) ^d	8.117	0.017

*Kruskal Wallis Test was conducted, IR: Interquartile range; BDFQ: Bipolar Disorder Functioning Questionnaire; MS: Mood stabilizer; MS-AP: At least one antipsychotic in addition to the mood stabilizers; AP: Atypical antipsychotic

^aSignificantly lower compared to the group using MS,

^bSignificantly higher compared to the group using AP,

^cSignificantly higher compared to the group using MS+AP,

^dSignificantly lower compared to the groups using MS and MS+AP

of patients may not return to premorbid levels of social functioning (17). Occupational functioning is also affected in the patients during remission (18). The most common factors associated with low functioning are subsyndromal conditions, particularly persistent depressive symptoms, anxiety disorders, alcohol abuse and other concomitant conditions. The results of studies are less pronounced for other clinical factors such as depressive episodes, psychotic symptoms, number of episodes, duration of the disorder or earlier age at onset (17).

In the study of Kaya et al., it was reported that the social functioning of BD patients in remission was more impaired than the control group (19). In a study conducted on 80 patients with BD during remission and 80 healthy controls, it was reported that patients showed worse functioning than controls in domains including intellectual and sexual functioning, sense of stigmatisation, introversion, domestic relations, relationships with friends and participation in community activities (20). It has been shown that emotion processing, which is an indicator of psychosocial functioning, deteriorates in patients with BD in remission as compared to healthy controls (21). In a study by Çam et al., it was reported that patients with BD had moderate functioning and that patients could not return to their premorbid functioning even if they recovered. However, Çam et al. did not include a control group and compare patients according to episodes (22). It has been reported that the functioning of elderly patients with BD in terms of autonomy, occupational functioning, cognitive function, financial issues and interpersonal relations were significantly impaired compared to control group (23). The findings of our study support the results of these studies.

Factors affecting the patients' levels of functioning

There are studies reporting that factors, such as duration of the disorder, age at onset and number of episodes have negative effects on functioning (17). In our study, no correlation was found between the duration of the disorder and levels of functioning. Frangou et al. reported that the duration of the disorder and severity of symptoms contributed to the occurrence of observed cognitive impairment and tended to affect

executive functions (24). It has been reported that an earlier age at onset of the disorder has a negative effect on functioning and that functioning is better in patients with late age at onset (25). In our study, although there was no statistically significant relationship between duration of the disorder and functioning scores, the numbers of episodes and hospitalisations affecting clinical course were found to be related to functioning. This can be explained by the cross-sectional structure of the study, the relatively small number of the cases included and the quality of the assessment scale used.

In this study, it was found that: the number of previous manic episodes had a negative correlation with daily functioning; the number of previous depressive episodes had a negative correlation with introversion and relationships with friends; and the number of previous hypomanic episodes had a negative correlation with relationship with friends. Previous studies have shown a relationship between the number of depressive episodes and poor functioning (26,27). Moreover, in a study evaluating functioning in patients with BD in remission, residual depression symptoms were reported to have a negative effect on psychosocial functioning (28). In our study, it was found that social functioning was impaired as the total number of episodes increased. It has been reported that the total duration of episodes predicts future recurrences and as a result is associated with a poor prognosis for the disorder (29,30). It has been suggested that recurrent episodes and prolonged duration of the disorder may cause permanent changes in the brain, which may explain the functional impairment in psychiatric patients (31). In this study, as the number of hospitalisations increased, domestic relations and daily functioning were found to be impaired. In a study of elderly patients with bipolar disorder, the number of previous hospitalisations was strongly associated with impairment in functioning (23).

Comparison of functioning levels of patients according to the drugs they used

It was found that MS-AP users exhibited more impairment in the functioning domains of domestic relations and introversion than MS

users. The effect of drugs on functionality in BD is twofold. Drugs improve functioning by treating the disorder and create negative effects on functioning due to cognitive and other side effects (32). It has been shown that pharmacological treatment, especially using second-generation antipsychotic drugs, has an adverse effect on cognitive functions in patients with BD (33). It has been reported that lithium treatment increases the quality of life by preventing recurrence of episodes of the disorder (34). It has been reported that second generation antipsychotic drugs used in patients with BD in remission have negative effects on psychosocial functioning (28). In the study of Tıǧlı Filizer et al., patients were divided into three groups according to the drugs they used (i.e., MS, MS-AP, or 3 or more drugs), and when comparisons were carried out among the three groups, functioning levels of the MS group were better than those using 3 or more drugs (20). In another study, it was reported that there were no significant relationships between treatment types and the functioning levels of patients (25). Since AP treatment is often added as a combination therapy in more treatment-resistant patients that cannot be controlled by MS, it may be conceivable that patients with a poor clinical course already use MS-AP. For these reasons, more comprehensive research is needed to explain whether this result is a side effect of AP or a severe condition with a poor clinical course.

In our study, when the relationship between daily doses and blood levels of lithium and valproic acid and functioning levels of the patients were examined, we found a weak positive relationship between relationships with friends and social domains of functioning and daily doses of valproic acid. In another study, the effect of valproic acid on functioning was found to be similar to lithium (35). It is known that patients with standard serum lithium levels have better psychosocial functioning than patients with low serum lithium levels. This effect is partly due to the prevention of episodes (34). In our study, the reason we did not find any relationships between serum drug levels and levels of functioning may be due to the small number of cases. We found that those who have more hospitalisations use lithium at higher daily doses. This indicates that physicians prefer a higher dose of lithium for a protective effect in patients with more episodes.

Limitations of the study

The most important limitations of the study are its cross-sectional design, use of a self-assessment scale and relatively small number of cases. Furthermore, the fact that the cumulative disorder duration was not calculated by subtracting the remission periods from the total duration of the disorder of the patients is another limitation. The data collected in this study is insufficient to assess the effects of many variables on functioning. When the patients were grouped according to the drugs they used, the fact that the number of cases in the AP group was low may have decreased the power of statistical comparisons. The treatment used may have confounding effects on functioning. To compare the patient and control groups in terms of functioning, although we tried to match the factors that may affect functioning, it is not always possible to provide a similarity between groups in situations such as inability to work due to impact of the disorder and being married. Inability to work may occur as a natural consequence of episodes and impaired functioning due to the disorder. Long-term follow-up studies are needed to assess the relationship between clinical features and functioning. However, there are strengths of the study. The strengths are the inclusion of a control group, the higher number of patients in the study than in similar studies, the rigorous selection of cases, the inclusion of a homogeneous group of patients and the reduction of confounding factors as much as possible.

As a result, even in remission periods in BD, we conclude that there is a deterioration in many domains of functioning. The number of previous episodes, the number of hospitalisations and the duration of remission periods are among the factors that affect functioning during remission.

We also conclude that increasing the duration of remissions by reducing the number of episodes with adequate and proper treatment in BD will eventually positively affect functioning. Furthermore, targeting remission through pharmacological treatment and psychosocial interventions for functioning are also important in the treatment of patients with BD.

Ethics Committee Approval: The study was approved by the local ethics committee (Ethics committee decision number: 2017-KAEK-189_2018.06.20_4).

Informed Consent: Written informed consent was obtained from the patients and healthy controls.

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