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Evaluation of Clinical Parameters of Patients with Bipolar Disorder According to Gender and Family History

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Abstract

Background: Family history is one of the most important known risk factors for the occurrence of bipolar disorder (BD). Identifying clustering factors in BD families may facilitate the identification of the hereditary sub-phenotypes of the disorder and might reveal the underlying genetic features. This retrospective study aimed to investigate the effect of family history and gender on the clinical features of the disease in a large BD sample followed in a specialized mood center in Turkey.

Methods: Research was carried out by reviewing the medical files of patients diagnosed with bipolar disorder who were followed up in the Raşit Tahsin Mood Clinic. Family histories and other demographic and clinical information of the patients were retrieved from the Mood Disorders Patient Registration Form (SKIP-TURK) completed for each patient. A patient's family history was considered positive if any diagnosis of mood disorders and/or psychotic disorders was present in their first and/or second-degree relatives.

Results: Family history was positive in 64.5% (n = 474) of 735 patients whose family history was recorded. Female patients made up 59.9% of the sample. Eighty point three percent (n = 590) of the patients were diagnosed with type 1 BD, 8.4% (n = 62) with type 2 BD, 11.3% (n = 83) with bipolar disorder not otherwise specified (BD-NOS). In the sample divided into 4 groups according to gender and family history, differences in the age at onset of the illness (F = 3.662, p = .012) were found to be statistically significant. In post hoc analysis, a significant difference was obtained between female patients without a positive family history and patients with a relevant family history. Regardless of family history status, the type of first episode in male patients tended to be hypomania/mania. Regarding treatment preferences, there was no significant difference between patients with and without a positive family history.

Conclusions: In the literature, some studies evaluating the familial burden only included first-degree relatives, while others considered first- and second-degree relatives, and some studies defined the family history including only relatives with mood disorders, while others would include any psychiatric disease. In the present study, family history of those diagnosed with mood disorders and/or psychotic disorders in their first- and/or second-degree relatives was considered positive. This study provides valuable information by evaluating the effect of family history and gender on the clinical features of the disease in a large BD sample in Turkey.

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INTRODUCTION

Bipolar disorder (BD) is a recurrent and chronic mood disorder characterized by episodes of mania, hypomania, and depression causing significant morbidity and mortality [1]. Lifetime prevalence is reported in the range of approximately 1–3% [2]. According to family, twin, and adoption studies, the phenotypic variation attributable to genetic effects in bipolar disorder ranges from 59% to 80%, and among polygenic diseases, BD shows a high level of heritability [3–5]. Close relatives of patients with BD have an approximately five-to-ten-times higher risk of BD and a ten-to-fifteen-times higher risk of major depression compared to close relatives of healthy individuals [5]. In addition, familial aggregation of BD has been demonstrated in controlled systematic studies [6-

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8]. However, it has been suggested that bipolar I disorder is more common among family members than bipolar II disorder [9].

In a study conducted with data from STEP-BD (*Systematic Treatment Enhancement Program for Bipolar Disorder*), the proportion of patients with BD where first-degree relatives were diagnosed with mania and/or depression was 68.6% (n = 1963) [10]. In a study by GAMIAN-Europe (Global Alliance of Mental Illness Advocacy Networks-Europe) carried out in 8 European countries, the proportion of patients with any psychiatric disorder in their family (including second-degree relatives) by country was between 31.7% and 76.2% [11]. In a multicenter study conducted in Turkey, any history of psychiatric disorder was found in first-degree relatives of 50.8% of patients with bipolar I disorder, the most commonly found psychiatric disorder being BD with 40.4% [12].

Some characteristic features in BD are associated with a family history of this disease. Firstly, the onset of the illness is earlier in BD patients with a positive family history [13]. The presence of a family history has been shown to be the strongest and most consistent risk factor for pediatric BD [13]. Another reported clinical feature is that episode frequency is significantly higher in individuals with BD in the same family [15]. Having family members with BD is one of the strongest and most consistent risk factors for an individual to develop BD [16]. In addition, a positive family history increases a person's risk to develop bipolar disorder and other psychiatric illnesses, especially major depressive disorder and schizophrenia [3]. In a study conducted in Turkish patients, it was found that postpartum episode frequency was more common in patients with FH [17]. The presence of a relevant family history is now a stronger predictor for determining the risk of BD than available genetic tests [18].

The entity of epidemiological and clinical differences between genders among patients with BD and the significance of these differences is a matter for debate. While population-based studies have characteristically found approximately equal rates of BD in males and females, several studies found differences regarding BD subtype, polarity, and frequency of mood episodes [16, 28]. Also, an increased risk of rapid cycling and mixed episodes in women has been reported [28]. There are some data suggesting that males might be over-represented in those diagnosed with a bipolar I disorder and females over-represented in those diagnosed with a bipolar II disorder [29]. There are also several psychiatric comorbid conditions that seem to be more frequent in bipolar women, including eating disorders and post-traumatic stress disorder [28]. On the other hand, alcohol use disorders seem to be more frequent in men with BD.

Identifying clustering factors in families with BD is expected to facilitate better identification of the hereditary sub-phenotypes of the disorder and reveal the underlying genetic features [7]. Complex mechanisms such as genetic heterogeneity and polygenicity and gene-environment interactions result in unpredictable disease-specific individual differences, some of which may be more prominent in one gender. In this retrospective study, it was aimed to compare the clinical parameters of bipolar disorder patients followed in a specialized mood center in Turkey according to family history and gender.

METHODS

Data Source and Study Population

This retrospective study was carried out as a review of the medical files of patients diagnosed with BD followed in the Raşit Tahsin Mood Disorders Center of Bakırköy Mazhar Osman Training and Research Hospital for Mental Health and Neurological Diseases. This center was established in 2003, and the treatment and follow-up of patients with BD referred from the general psychiatry outpatient clinics of Bakirköy Mazhar Osman Training and Research Hospital are ongoing. Patients' diagnoses were confirmed in this center after evaluation by at least two psychiatrists according to DSM-IV-TR diagnostic criteria. Since 2006, patient data have been recorded with a standardized medical form based on a nationwide mood disorders follow-up program named SKIP-TURK [19]. The SKIP-TURK form, which is similar to the "Clinical Monitoring Form" (CMF) used in the STEP-BD, was put into use to (i) assess the clinical characteristics of patients and (ii) to evaluate illness course of BD patients over clinical follow-up. In 2012, admission of new patients ended while previously registered patients continue to be followed up. At the time of the study, 1080 patients with BD are followed up regularly in this center.

Procedures

For this study, all patients with bipolar disorder whose exact family history was filled in SKIP-TURK form were selected. From the selected patients' SKIP-TURK form, we extracted demographic (gender, age, marital status, education year) and all the available clinical variables (age at onset of illness, duration of illness, age at initiation of treatment, type of the first episode, presence of suicide attempts, smoking status, and currently used long-term treatments). Any family history (FH) that included any diagnosis of mood disorders and/or psychotic disorders in the patient's first and/or second-degree relatives was considered positive. The study was conducted in accordance with the Declaration of Helsinki.

Statistical Analyses

For the analyses, SPSS (*Statistical Package for the Social Sciences*) version 20.0 was used. The sample distribution was examined by Kolmogorov-Smirnov test and histogram. All study data are reported using descriptive statistics (e.g. mean, standard deviation, frequency, percentage). A chi-square test was applied for qualitative independent

variables between the FH positive and FH negative groups, including the ratios of sex, working status, marital status, and current treatments. Also, the chi-square test was used between 4 groups according to gender and family history, including BD types, categorical age of onset, type of the first episode, presence of lithium monotherapy, presence of suicide attempt, and smoking. The independent samples t-test was applied for quantitative independent data with normal distribution between the FH positive and FH negative groups, including age and education years. One-way analysis of variance (ANOVA) test was applied quantitative independent data with normal distribution between 4 groups according to gender and family history, including age of onset, duration of illness, and duration from the first episode to preventive treatment. Tukey test was used to evaluate the difference between the groups in parameters for which ANOVA had found a significant relationship. Significance was defined as $p < 0.05$ with two-tailed tests.

RESULTS

Of the 1080 patients with BD followed up regularly, 735 individuals with an exact family history was filled in SKIP-TURK form were reached. Family history was positive in 64.5% (n = 474) of these 735 patients. Female patients made up 59.9% of the sample; the mean age was 49.2 ± 11.24 years, duration of education was 9.26 ± 4.4 years, age at onset was 23.86 ± 8.69 years, and the duration of illness was 26 ± 9.15 years. The distribution of the patients' sociodemographic data according to their family history is given in Table 1. Age, gender, marital status, working status, and duration of education were similar for the patient groups with and without a positive family history.

Of the patients in the study sample, 80.3% (n = 590) were diagnosed with type 1 BD, 8.4% (n = 62) with type 2 BD, and 11.3% (n = 83) with bipolar disorder not otherwise specified. Patients were divided into 4 groups according to their gender and family history. Age at onset differed statistically significantly between the 4 groups ($F = 3.662$, $p = .012$). In post hoc analysis, it was observed that there was a significant difference between women with and without a positive family history. Compared to female patients with a negative FH, the illness started on average 2.5 years earlier in female patients with a positive FH and 3.3 years earlier in male patients with a positive FH (Table 2). After dividing the patients into 3 groups according to previous admixture analysis to identify the model best fitting the observed distributions of age at onset of illness (≤ 18 years, 19-40 years, > 40 years), a difference between the groups was found ($x^2 = 16.195$, $p = .013$) [38-40]. Of the patients with positive FH, 39.9% of the women and 36.6% of the men had an age at onset of illness of 18 years or less, while 23.6% of the women and 22% of the men with negative FH had been in that group. Distribution of age at onset of the disease over the age of 40 was similar in 4 groups and ranged between 5.3% and 7.3%. Irrespective of FH, in female patients the type of the first episode was almost equally divided between depression and hypomania/mania, whereas in male patients, hypomania/mania was the more common type of the first episode; the difference was significant ($x^2 = 19.913$, $p < .001$). In both male and female patients, suicide attempt rates were higher in the presence of a positive FH than in patients with a negative FH, but the difference was not statistically significant. Distributions of all clinical parameters examined are presented in Table 2.

Table 1. Demographics characteristics of patients by family history

	Positive FH (n=474)	Negative FH (n=261)	x^2/t	p
Age (years) (mean± SD)	49±11.4	49.6±10.9	0.686	0.493
Gender n (%) - Female - Male	 285(60.1%) 189(39.9%)	 155(59.4%) 106(40.6%)	0.038	0.845
Marital Status n (%) - Married - Single - Divorced	 218(46%) 194(40.9%) 62(13.1%)	 130(49.8%) 87(33.3%) 44(16.9%)	4.723	0.094
Working Status n (%) - Working/Student - Not working - Disabled - Retired - Housewife	 186(39.2%) 47(9.9%) 53(11.2%) 34(7.2%) 154(32.5%)	 105(40.2%) 27(10.3%) 26(10%) 18(6.9%) 85(32.6%)	0.324	0.988
Education years (mean± SD)	9.26±4.45	9.24±4.35	0.071	0.94

x^2:Chi Square Test; t:Student's t-test; SD: Standard deviation; FH: Family History

Table 2. Clinical characteristics of patients by gender and family history

	Positive FH Female (n=285)	Positive FH Male (n=189)	Negative FH Female (n=155)	Negative FH Male (n=106)	x^2/F	p
Diagnosis **BD Type 1** **BD Type 2** **NOS BD**	 224 (78.6%) 29 (10.2%) 32 (11.2%)	 162 (85.7%) 12 (6.3%) 15 (7.9%)	 117 (75.5%) 17 (11%) 21 (13.5%)	 87 (82.1%) 4 (3.8%) 15 (14.2%)	10.54	0.104
Age at illness onset (years) (mean ± SD) [a,&]	23.49±8.68	22.73±8.13	26.03±9.55	23.93±8.09	3.662	**0.012**
Age at illness onset (years) [&] **≤18** **19-40** **>40**	 97 (39.9%) 133 (54.7%) 13 (5.3%)	 59 (36.6%) 93 (57.8%) 9 (5.6%)	 29 (23.6%) 85 (69.1%) 9 (7.3%)	 20 (22%) 65 (71.4%) 6 (6.6%)	16.195	**0.013**
Duration of illness (years) (mean ± SD)	25.9±9.51	27.06±9.69	25.81±9.56	24.71±9.1	1.191	0.313
Duration from first episode to preventive treatment (years)[#], (mean ± SD)	4.75±6.26	4.87±6.86	4.6±6.7	4.25±6.25	0,185	0.906
First episode [%] **Hypomania/mania** **Depression**	 114 (49.4%) 117 (50.6%)	 98 (60.1%) 65 (39.9%)	 53 (46.9%) 60 (53.1%)	 66 (73.3%) 24 (26.7%)	19.913	**<0.001**
Lithium monotherapy n (%) **Yes** **No**	 41 (14.4%) 244 (85.9%)	 15 (7.9%) 174 (92.1%)	 23 (14.8%) 132 (85.2%)	 16 (15.1%) 90 (84.9%)	5.5	0.139
Suicide attempt n (%)* **Yes** **No**	 49 (22.9%) 165 (77.1%)	 35 (26.3%) 98 (73.7%)	 17 (16.5%) 86 (83.5%)	 13 (17.6%) 61 (82.4%)	4.219	0.239
Smoking **Yes** **No**	 76 (26.7%) 209 (73.3%)	 68 (36%) 121 (64%)	 39 (25.2%) 116 (74.8%)	 33 (31.1%) 73 (68.9%)	6.463	0.091

BD: Bipolar Disorder; NOS: Not otherwise specified; FH: Family History; x^2:Chi Square Test; F: One-way analysis of variance; SD: Standard deviation. **a** According to Tukey post-hoc analysis, significance was found between female patients with a negative FH and female patients with a positive FH (p=0.041) and between female patients with a negative FH and male patients with a positive FH (p=0.008); * In total, data of 524 patients were obtained; # In total, data of 573 patients were obtained; % In total, data of 597 patients were obtained; & In total, data of 618 patients were obtained.

Of the patients with a positive FH, 23.3% were followed up with a single mood stabilizer (MSD), this rate was 25.3% for patients with a negative FH similarly. A total of 94 patients were followed up with lithium monotherapy, and the rates of lithium monotherapy did not differ between the 4 groups (Table 2). More than one-third of the patients were followed up with any MSD and antipsychotic drug combinations. No difference was found between the groups with regard to the drugs used. The distribution of drugs used by patients is shown in Table 3.

Table 3. Distribution of current treatments of patients

Medication, n (%)	Positive FH (n=474)	Negative FH (n=261)	x^2	p
Drug-free	13 (2.7%)	5 (1.9%)	3.487	0.837
Li/VPA/CBZ/LAM	110 (23.3%)	66 (25.3%)		
≥2 MSD	37 (7.8%)	21 (8%)		
AP	20 (4.2%)	8 (3.1%)		
Li/VPA/CBZ/LAM + AP	181 (38.3%)	93 (35.6%)		
≥2 MSD + AP	71 (15%)	40 (15.3%)		
≥1MSD + AD	17 (3.6%)	15 (5.7%)		
≥1 MSD + AP+ AD	24 (5.1%)	13 (5%)		

x^2 :Chi Square Test; FH: Family History; Li: Lithium; MSD: Mood Stabilizer; VPA: Valproic Acid; CBZ: Carbamazepine; AP: Antipsychotic; AD: Antidepressant; LAM: Lamotrigine

DISCUSSION

This study investigated the effect of family history and gender on the clinical course of bipolar disorder in a sample with a relatively long-term follow-up. In this study, it was determined that BP started earlier in patients with a FH, and the type of first episode in male patients without a FH was more likely to be hypomania/mania. In addition, no differences in treatment preferences were found in patients with and without a FH during the long-term follow-up.

In this study, patients were considered FH positive if their first and/or second-degree relatives had a diagnosis of mood disorders and/or psychotic disorders. According to this definition, the positive FH ratio was 64.5% (n = 474). This rate was similar to those based on STEP-BD data reported by Antypa and Serretti (68.6%) and the GAMIAN-Europe study (64.8%), though it was higher than the rate in the study carried out in Turkey by Akkaya et al. (50.8%); however, the definitions of positive FH differ between the studies [10-12]. Some of the research that also evaluated the family burden included only first-degree relatives in the family history, while others also considered second-degree relatives. Furthermore, some studies only investigated mood disorders in the family history, while others included

all psychiatric diseases in the definitions of positive or negative FH.

Recent genetic studies conducted by the Psychiatric Genomic Consortium (PGC) detected more pleiotropic effects than expected in some psychiatric disorders [20]. Pleiotropy is defined as the expression of a genetic variant in more than one phenotype. A study conducted by Lee et al. found a genetic correlation of common variants between BD and schizophrenia of close to 0.6–0.7 and demonstrated a significant overlap [21]. However, there are studies showing familial coaggregation and common cognitive and neuro-structural endophenotypes between schizophrenia and BD [22–24]. In our study, we preferred to use mood disorders and/or psychotic disorders in defining a positive family history, considering that the pleiotropic effects detected in current genetic studies were greater than expected.

Besides the genetic effect on the susceptibility to bipolar disorder, some environmental factors and early negative life experiences such as childhood abuse and neglect are also known to increase the risk of disease development and worsen the course of the disease [25–28]. In the light of the various genetic and environmental factors involved in the etiology of BD and schizophrenia, a new research paradigm has emerged based on gene × environment (G × E) interactions to fill in for a missing link in the development of these diseases [28]. This approach suggests that the effects of some candidate genes will only be relevant in the presence of certain environmental factors. Following this paradigm, in this study positive FH was kept broader, as we included mood disorders and/or psychotic disorders in second-degree relatives in the definition of positive FH.

The female/male ratio in the study sample was approximately 1.5. In most 12-month and lifetime prevalence studies conducted, BD appears at similar rates both in males and females [28]. In a recent meta-analysis of 38 studies from 26 countries, the female/male ratio was 1.25 (95% CI 0.91–2.0) [30]. In the multicenter HOME (Health Outcomes of Manic Episodes) study involving 584 patients with type 1 BD in Turkey, the ratio of female to male was similar [31]. In some studies type 2 BD and a rapid cyclic course were found to be more common in females [28]. Although female patients are higher than male patients in the study sample, the rate of type 1 bipolar disorder (80.3%) is higher than expected. A large cross-sectional survey of 11 countries found the lifetime prevalence of bipolar spectrum disorders was 2.4%, with a prevalence of 0.6% for type 1 BD and 0.4% for type 2 BD [2]. The types of BD and the gender distribution in the study sample fit the distribution of all patients registered in the database of Raşit Tahsin Mood Clinic. The inequality of these gender rates and excessive rate of type 1 BD may be due to the specific conditions of this center rather than reflecting the proportion in society. Gender distribution (F/M) was found to be similar in both positive and negative FH groups at a level of 1.5. In the study by Antypa and Serretti, this rate was 1.6 in patients with positive FH and 1.3 in patients with negative FH, but the difference was not statistically significant [10]. The results of our and Antypa & Serretti's study can be interpreted as meaning that the genetic burden of psychiatric diseases in the family does not affect gender distribution in bipolar cases. However, in BD, complex mechanisms such as genetic heterogeneity and polygenicity and gene-environment interactions result in unpredictable disease-specific individual differences, some of which may be more prominent in one gender. For example, recently comorbid autoimmune and inflammatory diseases, which are considered to be the result of common genetic pathways were found to be more common in female bipolar cases than in males [32]. In epigenetic and genomic imprinting studies conducted in the early period that showed the effect of the parent's gender in the transmission, BD was more frequently transmitted by the mother than by the father [33]. When transmitted by the father, children showed a more severe disease form and an earlier age at onset according to the data available [34-35]. However, genomic imprinting in BD has only been demonstrated by statistical genetics, while no molecular biological evidence supporting this possibility has been found to date.

The age at illness onset may play an important role in the phenotypic distinction required for the identification of genes in complex genetic diseases. Therefore, the age at onset of BD has recently been proposed as a tool for clinical classification [36]. In the study sample, the average age at illness onset was 23.86 years. In studies conducted in Turkey, the average age at illness onset in BD varied between 23.8 and 27.7 years, which is consistent with the findings of this study [37]. Studies have shown the age at illness onset in BD to be similar for both sexes [38]. In this study, the analysis carried out according to gender and family history revealed that the disease started on average 2.5 years earlier in female patients with positive FH compared to female patients with negative FH and 3.3 years earlier in positive male patients. In male bipolar patients with negative FH, the mean age at illness onset was not different from other groups'. Although this finding shows that the difference was due to female patients with negative FH, it partially overlaps with the finding that the age at onset of the disease is lower in cases with familial BD.

In a study conducted by Grigoroiu-Serbanescu et al. with type 1 BD patients, the onset age of female bipolar patients with a positive FH was found to be significantly lower than in female bipolar patients with a negative FH and in males with a positive FH [39]. A recent meta-analysis showed only a trend towards an earlier onset of the disease in bipolar cases with a family history of mood disorder (meta-regression coefficient: – .07, p = .06), and a 10% increase in the proportion of patients with mood disorders in their family reduced the average age at onset by about 1 year [38]. In this meta-analysis, the age at illness onset was not different according to gender and illness subtypes, and it was stressed that the onset age varied considerably by country, a situation requiring more research.

However, in the analysis of several studies conducted

especially on the onset age of type 1 bipolar disorder, 3 different onset age periods have been identified and it has been suggested that these onset periods can categorize bipolar cases more clearly [40–45]. In the study conducted with the largest sample to date, including cases with type 1 BD from Europe and America, the average age at onset for the early period was 19 ± 2.7 years in Europe and 14.5 ± 4.9 years in America, for intermediate-onset 27.2 ± 6.3 years in Europe and 26.5 ± 7.6 years in America, and for late-onset 41.8 ± 10.7 years in Europe and 39.5 ± 12.5 years in America [42]. Other studies examining onset-age periods determining 3 periods found early, middle, and late-onset age periods that differed by 1–3 years [40,41,44]. Only the study conducted by Lin et al. found a different late-onset age of 34.7 ± 6.6 years [43].

In our study, in the light of the values determined in previous research, the age at illness onset was divided into 3 categories, ≤ 18 years, 19–40 years, and > 40 years for comparison. An onset age of 18 and below was determined in 39.9% of bipolar women and 36.6% of men with a positive family history. This rate was lower in cases with a negative FH, being 23.6% in bipolar females and 22% in male patients. An onset between the ages of 19–40 was more common in bipolar cases with a negative FH. An onset age of over 40 years was similar for both groups with 5.3% and 7.3%, respectively. In a study conducted by Kesebir et al. in Turkey, the age at illness onset was found to be 40 and over in 13.4% of cases [46]. In a study conducted by Hamshere et al., this rate was found to be 11%, thus also higher than in the present study [45]. Due to the limitations of our study, that applied a retrospective design and was not a field study, the proportion of patients with a disease onset after 40 ages may not reflect the rate in the general population. The onset age varies widely; thus, this study may not have found any difference in the mean age at illness onset between the male bipolar cases with negative FH and all the bipolar cases with a positive FH. However, considering all the study findings regarding onset age, it can be said that familial burden plays a greater role in early-onset BD cases than in late-onset cases, which is consistent with the literature [13].

It is known that patients with bipolar disorder are diagnosed late and therefore have delayed access to long-term treatment. In the literature, the average period for patients to access long-term treatment is reported to be 9.6 years [47]. In the present study, this period was determined to be 4.5 years. One of the main reasons for this difference might be that the sample consisted of patients being followed up in a specialized mood center. In addition, our study calculated the time interval between the start of long-term treatment and the first episode, while previous studies used prodromal symptoms as a basis for calculating the onset, which may explain the difference in delay. Early-onset, the presence of less severe disease periods, female gender, dominant course of depression, and type 2 BD are factors associated with delayed access to long-term treatment [47]. Our study, too, found no correlation between family history and delayed long-term treatment [48]. This finding, which other researchers had also considered to be surprising, was explained with a more frequent depressive onset that may be found in patients with a positive FH [49]. In the literature, there is no study evaluating the relationship between time spent without long-term treatment and FH according to gender. In this study, no difference by gender was found between periods before long-term treatment and FH; while FH-negative women started treatment later than FH-negative men, this difference was not statistically significant. The length of the period without long-term treatment that may be accompanied by female gender may have been reflected in FH-negative patient group.

Bipolar disorder often starts with a depressive episode [50]. A gender-specific analysis stated that the disease begins with mania in male patients and a depressive episode in female patients [51]. In addition, in male patients, the hypomania/mania period occurs earlier than in female patients and is more frequently accompanied by antisocial behavior [51]. In this study, while the type of first episode, regardless of FH, was close to equally distributed between depression and hypomania/mania in female patients, hypomania/mania was significantly more common as the type of first episode in male patients. Our findings suggest that family history has no effect on the type of first episode in either male or female patients. In the literature, it is reported that bipolar disorder should be treated carefully in bipolar patients where the first episode is depression and that a manic episode with psychotic features is frequently observed in the first episode especially in patients with FH [52]. However, there are no studies in the literature evaluating the effect of disease history in the family on the first episode type according to gender. As the relatively small sample of our study provides limited information about this relationship, it can be said that larger sample studies are needed.

At least one suicide attempt during their illness was reported by 21.4% of our patient group. In the literature, the rate of suicide attempts in BD patients is given in a wide range of 20–60%, which may be due to sample selection and methodological differences. It is known that patients with bipolar disorder having suicide attempts in their family attempt suicide more frequently [53]. However, it has also been shown that bipolar disorder patients with mood disorders in their family attempt suicide more commonly [54]. This information also seems to be compatible with the observation that patients with a FH of bipolar disorder are younger at the onset of their illness and shows a greater frequency of depressive episodes [55]. In our study, suicide attempts were more common in patients with a positive FH, but no statistical significance was found between gender and family history. In the literature, there is no study comparing the effect of FH on suicide by gender in patients with bipolar disorder.

BD patients are known to smoke more than the general public. The relationship between BD and smoking is dual. Studies show that patients often start smoking in the pre-illness period. Based on this, it has been stated that

smoking has a risk of triggering mood episodes in sensitive individuals [56]. Case about mania and depressive episodes after smoking cessation indicate that smoking has a regulatory effect on mood [57]. This information shows that the relationship between smoking and BD is a complex relationship with neurobiological origins. Data obtained from the STEP-BD study show that smoking is associated with more episodes of mania and depression, rapid cycling, comorbid psychiatric diseases, and substance use in patients with bipolar disorder [58]. The relationship between the presence of FH and smoking in STEP-BD has not been evaluated, and in subsequent studies, it has been shown that smoking does not increase in patients with a FH [59]. Similarly, in our sample, no relationship was found between smoking and FH in both genders. Studies with larger samples are needed to reveal the relationship between FH and smoking in BD.

Currently available treatments for patients have been divided into 8 categories: 1 mood stabilizer (MSD), 2 or more MSDs, a single antipsychotic (AP), an MSD and an AP, 2 or more MSDs and an AP, MSD and antidepressant (AD), MSD + AP + AD, and drug-free monitoring (Table 3). The distribution of these drug categories according to family history was similar. In the sample, 94 patients used lithium only. The distribution of these 94 patients according to FH and gender was not statistically different, but the rate of lithium monotherapy was lower in male bipolar patients with a positive FH compared to the other groups (Table 2). Although no scale evaluating the lithium response was used in our study, it can be roughly said that patients in maintenance treatment with lithium monotherapy responded better to lithium, considering the average disease duration of these patients. It has been reported that patients with a positive FH have a better response to lithium, though other publications do not support this assertion [60-61]. The more consistent finding here is that there is a better response to lithium in late-onset BD [61]. In our study, the wider diagnostic range of reasons included in the definition of FH may account for the inability to identify a relationship between FH and lithium monotherapy. Also, considering that the late-onset form was similarly distributed in the groups in our study, it should be appropriate to evaluate the lithium response according to FH and gender in future research. In a study conducted by Sportiche et al., more than 60% of the patients who responded well or partially to lithium were female, but no sub-analysis by gender were performed [60].

There are several limitations of this study to consider when interpreting these findings. Firstly, FH was determined only by anamnesis of patients with BD, not by directly interviewing with family members. It is essential to remark here that the aim of this study was not to provide a heritability or familial aggregation assessment, but only to compare patients that reported FH compared to those that did not report FH. The limitation of getting FH data through the patient is that patients may have unawareness with regard to psychiatric illnesses of their family members. Secondly, as this study was carried out in a sample of patients followed up regularly in a specialized mood center, it may be limited in reflecting the general patient population. However, our research provides valuable information by using a relatively large sample evaluating family history of illness and the effect of gender on the clinical characteristics of Turkish BD patients. Future multi-center studies may provide stronger results regarding the importance of family history in BD patients.

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Conflicts of Interest: None

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