

# Distinct Clinical Characteristics of Familial and Solitary Patients with Bipolar Disorder

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## ÖZET:

İki uçlu bozukluğu olan ailesel ve münferit hastaların farklı klinik özellikleri

**Amaç:** İki uçlu bozukluk da dahil majör ruhsal bozukluklar ailelerde kümelenmektedirler. Ailesel olmayan, tek vakalar da görülmektedir ve ailesel ve ailesel olmayan vakalar klinik özellikler bakımından farklılık gösterebilirler. Aileselliği dikkate alan çalışmaların büyük bölümü aynı aileden hastalarda hastalığın benzer olan ve olmayan özelliklerini incelemiştir. Farklı ailelerden olan ve ailesel özelliklerine göre hastalık özelliklerinin karşılaştırıldığı yeterince çalışma yoktur. Bu çalışmada ailesel olan ve olmayan tip I iki uçlu bozukluğu olan hastaların klinik özellikler açısından incelenmesi ve karşılaştırılması amaçlanmıştır.

**Yöntem:** Bu araştırma Bakırköy Prof. Dr. Mazhar Osman Ruh ve Sinir Hastalıkları Eğitim ve Araştırma Hastanesine bağlı Raşit Tahsin Duygudurum Merkezi'nde tedavi görmekte olan hastalarla yapıldı. İki uçlu bozukluğu olan 112 hastanın (69 kadın, 43 erkek, ortalama yaş: 41.54±11.19, dağılım aralığı: 22-75, ailesinde hastalık öyküsü olan 64, olmayan 48 hasta) tıbbi kayıtları incelendi ve veriler hastalardan ve birinci derece akrabalarından telefonla teyit edildi. Ailesinde hastalık öyküsü olmayan hastaların ailelerine sorularak ailede başka hastanın olmadığı doğrulandı.

**Bulgular:** Psikiyatrik ekhastalıklar, doğum sonrası depresyon oranları, nikotin bağımlılığı, karma hastalık dönemi geçirmiş hasta sayısı ve halen antipsikotik kullanan hasta sayısı aile öyküsü olan hasta grubunda istatistiksel olarak anlamlı derecede daha fazla oldukları saptandı. Hastalık başlangıç yaşı, hastalık dönemi sayıları ve hastaneye yatış sayıları açısından gruplar arasında fark saptanmadı.

**Sonuç:** Psikiyatrik ekhastalık, doğum sonrası depresyon, karma hastalık dönemleri ve sigara kullanma ailesinde hastalık öyküsü olan hastalarda daha fazla oranda buldukları tespit edilen klinik özelliklerdir ve iki uçluluk ile ilişkilidirler. Psikiyatrik ekhastalık ve postpartum dönem geçirmeye yatkınlık aile öyküsü olan hastalarda daha fazla görülmesi beklenebilir. Fakat klinik özelliklerin gruplarda farklılık gösterip göstermediğinin belirlenebilmesi için daha başka büyük örneklemli çalışmalar da gerekmektedir.

**Anahtar sözcükler:** Ailesel, ailesel olmayan, iki uçlu bozukluk

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## ABSTRACT:

Distinct clinical characteristics of familial and solitary patients with bipolar disorder

**Objective:** Major mental disorders including bipolar disorder aggregate in families. There are also non-familial, solitary cases and familial and non-familial cases may differ. Most of the studies regarding familiarity in bipolar disorder targeted similar and dissimilar characteristics of the disease within families. There is a lack of studies targeting between subject differences in patients from different families. The aim of this study is to assess and compare clinical characteristics of type I bipolar patients with and without a family history of bipolar disorders.

**Method:** This study was conducted on outpatients of Raşit Tahsin Mood Disorders Centre of Bakırköy Research and Training Hospital. The medical records of 112 participants (69 female, 43 male, mean age: 41.54±11.19, range: 22-75, 64 of which had family history and 48 without family history) with type I Bipolar Disorder were collected. Missing information was obtained by phone interviews from both patients and first degree relatives. Information of the patients without a family history of any psychiatric disorder was checked with a senior family member.

**Results:** Postpartum episode rates, comorbid psychiatric disorders, number of subjects ever had past mixed episodes, and nicotine dependency rates were found to be significantly higher in patients with family history. No significant difference was detected between groups in terms of age, gender, education, age at disease onset, number of episodes, and number of hospitalizations.

**Conclusions:** Comorbidity, postpartum episodes, lifetime mixed episodes, and smoking were found to be higher in patients with family history and thus associated with bipolarity. Postpartum episodes and comorbidities can be expected to be more prevalent in patients with family history. However clinical characteristics should be further investigated in larger samples.

**Key words:** Familial, non-familial, bipolar disorder

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## Declaration of interest:

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## INTRODUCTION

Major mental disorders aggregate in families. The risk of developing bipolar disorder is 8.7% in first degree

relatives of bipolar probands and the same is 14.1% in unipolar depression (1). A variety of linkage findings emerged successfully (2,3) and there are some significant findings at genome-wide levels (4,5) in bipolar disorders.

However phenotypic heterogeneity is a major barrier to find out more consistent results and there is a lack of phenotypic traits to homogenize psychotic spectrum disorders. The concept endophenotype has been a prospect to detect traits to refine phenotypes and define subgroups. On the other hand better identifying variations of clinical variables in different subgroups may provide predictions of clinical traits to be candidates for endophenotype concept. Familial clustering of a symptom may indicate a shared genetic origin and puerperal mood disorders are instances shown to be largely familial traits (6-11).

A number of studies focusing on the differences between familial aggregated and solitary cases provided promising data. The course and severity of the disease is shown to correlate between affected relatives in schizophrenia (12,13). Findings regarding age of onset (14-16), course of disorder, premorbid functioning, and impairment during disorder (17) pointed out modest similarity within families. Some other studies found higher severity of negative symptoms (18-20), poorer outcome, and higher rates of hospitalizations (21) in familial patients. Lui and colleagues (22) compared familial and sporadic cases with magnetic resonance imaging and found that familial cases had more severe structural abnormalities than sporadic cases, particularly in the thalamus. Genetic studies have shown that to some extent schizophrenia and bipolar disorders overlap and share susceptibility loci (23,24,25). If there are differences between familial and non-familial cases in schizophrenia, then it is possible to expect differences between familial and non-familial forms of bipolar disorder.

Mood disorders are also studied in large samples with different methods. Fislagen and colleagues (26) examined 407 subjects from 86 families and investigated familial resemblance of number of episodes and episode frequency per year. They found that episode frequency is a highly familial trait. Schulze and colleagues (27) investigated 1246 individuals from 172 multiplex families and found that alcohol and substance abuse, psychosis, history of suicide attempts, and level of social functioning was familial, but clinical subtype, age at onset, and comorbid panic disorder did not show familial dispersion in the large sample. O'Mahony et al (28) found significant within-pair correlation for age at onset and degree of

psychosis in a sample with 160 families with mood disorders. In a recent study with a Turkish sample, patients with type I and II bipolar disorder and unipolar depression were grouped and compared according to family history (29). The patients with a family history were reported to have earlier age at onset in this study. Kassem and colleagues (5) studied 971 subjects from 507 families of patients with type I bipolar disorder and schizoaffective disorder and found that polarity at illness onset is a familial feature of bipolar disorders. In a large Danish cohort study, Steinhausen and colleagues (30) demonstrated that mental disorders including bipolar disorder aggregate in families with some differential patterns. Authors also reported that in families, mood disorders were strongly specified to probands' disorder, unlikely to schizophrenia.

Most of the studies regarding familiarity in bipolar disorder targeted similar and dissimilar characteristics of the disease within families. There is a lack of studies targeting subject differences among different families. Besides, most studies were done with heterogeneous samples including type I and II bipolar disorder, schizoaffective disorder and depressive disorders. Hence we aimed to compare familial and non-familial cases with type I bipolar disorder in terms of clinical variables to assess differences in clinical characteristics of the groups.

## METHODS and PATIENTS

This study was done with outpatients of Raşit Tahsin Mood Disorders Centre of Bakırköy Research and Training Hospital between November 2010 and January 2011. The current medical records of 112 participants (69 female, 43 male, mean age:  $41.54 \pm 11.19$ , range: 22-75) with type I Bipolar Disorder were collected. Investigations of medical records and interviews were done with guidance of a form including sociodemographic and clinical characteristics, psychiatric and medical history, and family history. All of the participants gave a written informed consent.

Subjects with a family history of mood and psychotic disorders were enrolled into group 1. Subjects without a family history were enrolled into group 2. The family history was limited to first and second degree relatives. Relatives were accepted to have the disease only if they

**Table 1: Sociodemographic and Clinical Characteristics (Continuous variables).**

|                            | All Subjects<br>(n=112) | Group 1<br>(n=64) | Group 2<br>(n=48) | p    |
|----------------------------|-------------------------|-------------------|-------------------|------|
| Age                        | 41.54±11.2              | 41.27±11.28       | 41.9±11.17        | 0.77 |
| Education <sup>¥</sup>     | 8.39±3.9                | 8.77±4.01         | 7.9±3.72          | 0.24 |
| Age at Disease Onset       | 21.6±7.69               | 22.25±8.49        | 20.73±6.47        | 0.3  |
| Total Number of Episodes   | 10.43±8.74              | 11.02±9.62        | 9.65±7.43         | 0.41 |
| Number of Hospitalizations | 3.35±4.69               | 2.97±4.41         | 3.85±5.04         | 0.33 |

\*t test; Group 1: Patients with family history; Group 2: Patients without family history; ¥: Years

were diagnosed by clinicians. Missing information was obtained by phone interviews from both patients and first degree relatives. The information of the patients without a family history of any psychiatric disorder was checked with a senior family member by phone interviews. The information regarding premenstrual dysphoria, lifetime suicide attempt, nicotine dependency was obtained from declaration of the patients. The information regarding mixed episode, rapid cycling, episodes with psychotic, melancholic or catatonic features, psychiatric comorbidities and postpartum depression were based on diagnoses given by clinicians.

The patients with neurological diseases, mental retardation, type II and III bipolar disorder, schizoaffective disorder, atypical forms of bipolar disorders, and unclear family history were excluded. 64 families had more than one member with bipolar disorder. 45 of the families had only the patients with bipolar disorder. 9 families had both members with bipolar disorder and unipolar depressive disorder. 8 families had members with schizophrenia as well as members with bipolar disorder. 2 families had members with anxiety disorders as well as members with bipolar disorder.

### Statistical Analyses

SPSS 17.0 for Windows was the software used. Patients were grouped as they have a family history of Bipolar Disorder (group 1) or without a family history of any psychiatric disorder (group 2). Groups were compared in terms of clinical characteristics. Continuous variables were compared with t test and categorical variables were compared with Chi-square test. And p values lower than 0.05 were accepted as statistically significant. Furthermore, for variables showing statistically significant

difference, odds ratios and %95 confidence intervals were obtained.

## RESULTS

Sociodemographic and clinical data are given in Table 1 and 2. There were no statistically significant difference between groups in terms of age, gender, and education. There was no significant difference between groups in terms of age at disease onset, total number of episodes, number of hospitalizations and history of episodes with psychotic, catatonic or melancholic characteristics.

Number of nicotine dependent individuals was significantly higher in patients with family history ( $p=0.029$ ,  $\chi^2$ : 4.78, RR: 2.35, %95 CI: 1.09-5.07) (Table 2). There were significantly higher numbers of patients "ever had mixed episodes" ( $p=0.014$ ,  $\chi^2$ : 6.05, RR: 3.63, %95 CI: 1.25-10.59) in patients with family history (Table 2).

Patients with comorbidities are given in table 3. 19 patients with family history had comorbid psychiatric disorders, while only 7 of the patients without family history had comorbidities. There was significant difference between groups in terms of comorbidities ( $p=0.003$ ,  $\chi^2$ : 8.95, RR: 4.01, %95 CI: 1.56-10.3).

Postpartum episode ( $p=0.006$ ,  $\chi^2$ : 7.49, RR: 5.88, %95 CI: 1.52-22.97) (Table 4) rates were significantly higher in patients with family history. Although there was a significant difference between groups in terms of premenstrual dysphoria ( $p=0.001$ ,  $\chi^2=10.97$ ) and number of subjects ever had electroconvulsive therapy ( $p<0.001$ ,  $\chi^2=12.51$ ), according to relative risks there was not statistically significant difference between groups (RR: 0.15, %95 CI: 0.05-0.49 and RR: 0.23; %95 CI: 0.1-0.53 respectively).

**Table 2: Subjects Characteristics (Categorical variables)**

|                                 | All Subjects<br>(n=112) | Group 1<br>(n=64) | Group 2<br>(n=48) | $\chi^2$ | RR<br>(%95 CI)       | p      |
|---------------------------------|-------------------------|-------------------|-------------------|----------|----------------------|--------|
| Gender (Female/Male)            | 69/43                   | 37/27             | 32/16             | 0.91     | 1.46<br>(0.67-3.18)  | 0.34   |
| Nicotine Dependency             | 53<br>(%47.3)           | 36<br>(%56.3)     | 17<br>(%35.4)     | 4.78     | 2.35<br>(1.09-5.07)  | 0.029  |
| Psychiatric Comorbidity         | 33<br>(%29.4)           | 26<br>(%40.6)     | 7<br>(%14.6)      | 8.95     | 4.01<br>(1.56-10.3)  | 0.003  |
| Rapid Cycling                   | 27<br>(%24.1)           | 19<br>(%29.7)     | 8<br>(%16.7)      | 2.54     | 2.11<br>(0.83-5.35)  | 0.111  |
| Mixed Episodes                  | 24<br>(%21.4)           | 19<br>(%29.7)     | 5<br>(%10.4)      | 6.05     | 3.63<br>(1.25-10.59) | 0.014  |
| Melancholic Episode             | 11<br>(%9.8)            | 7<br>(%10.9)      | 4<br>(%4.8)       | 0.21     | 1.35<br>(0.37-4.91)  | 0.647  |
| Catatonic Episode               | 8<br>(%7.1)             | 4<br>(%6.2)       | 4<br>(%8.3)       | 0.18     | 0.73<br>(0.17-3.14)  | 0.672  |
| Psychotic Episodes              | 82<br>(%73.2)           | 50<br>(%78.1)     | 32<br>(%66.7)     | 1.84     | 1.79<br>(0.77-4.15)  | 0.175  |
| Subjects ever had ECT treatment | 65<br>(%58)             | 28<br>(%43.8)     | 37<br>(%77.1)     | 12.51    | 0.23<br>(0.1-0.53)   | <0.001 |
| Suicide Attempt                 | 43<br>(%38.4)           | 29<br>(%45.3)     | 14<br>(%29.2)     | 3.02     | 0.49<br>(0.23-1.01)  | 0.082  |

Chi-Square test, RR: Relative Risk; CI: Confidence Interval; Group 1: Patients with Family History; Group 2: Patients without Family History; ECT: Electroconvulsive Therapy.

**Table 3: Distribution of Comorbidities**

|                                | All Subjects (n=112) | Group 1 (n=64) | Group 2 (n=48) |
|--------------------------------|----------------------|----------------|----------------|
| Patients without Comorbidity   | 86 (%76.8)           | 45 (%70.3)     | 41 (%85.4)     |
| Patients with Comorbidity      | 26 (%23.2)           | 19 (%29.7)     | 7 (%14.6)      |
| Anxiety Disorders              | 6                    | 5              | 1              |
| Obsessive Compulsive Disorder  | 6                    | 6              | 0              |
| Alcohol and Substance Abuse    | 8                    | 5              | 3              |
| Eating Disorders               | 2                    | 1              | 1              |
| Personality Disorders          | 3                    | 2              | 1              |
| Post Traumatic Stress Disorder | 1                    | 0              | 1              |

Group 1: Patients with Family History; Group 2: Patients without Family History

**Table 4: Premenstrual Dysphoria and Postpartum Depression Rates in Female Patients**

|                        | All Females<br>(n=69) | Group 1<br>(n=37) | Group 2<br>(n=32) | $\chi^2$ | R.R.<br>(%95 CI)     | p*    |
|------------------------|-----------------------|-------------------|-------------------|----------|----------------------|-------|
| Premenstrual Dysphoria | 44 (%63.8)            | 17 (%45.9)        | 27 (%84.4)        | 10.97    | 0.15<br>(0.05-0.49)  | 0.001 |
| Postpartum Depression  | 17 (%24.6)            | 14 (%37.8)        | 3 (%9.4)          | 7.49     | 5.88<br>(1.51-22.97) | 0.006 |

Chi-Square test; RR: Relative Risk; CI: Confidence Interval

## DISCUSSION

Postpartum episode frequency, number of patients with comorbid psychiatric disorders, number of subjects ever having past mixed episodes, and nicotine dependency rates were significantly higher in patients with family history. No significant difference was detected between groups in terms of age at disease onset, number of episodes, and number of hospitalizations.

Liability to postpartum episodes clusters in families (6-11) and postpartum episodes are suggested to be a familial form of bipolar disorder. Jones and Craddock (6) conducted a study with 313 births of 152 women with bipolar disorder. They found that women with family history of postpartum depression have greater tendency to postpartum episodes. Jones and Craddock (31) investigated family histories of 103 probands with bipolar disorder, 52 of which had postpartum episodes. They found that morbidity risk of mood disorders in first degree relatives of bipolar females was significantly higher than bipolar women with no episodes in the postpartum period. The authors commented that postpartum episodes identify a more familial subtype of bipolar disorder.

The postpartum episodes occur in 20 to 30% of pregnancies of women with bipolar disorder (32). Family studies regarding postpartum episodes show familial aggregation of psychiatric disorders with morbidity risks for first degree relatives in range from 10 to 50% (33,34,35). Higher prevalence of mood disorders in relatives of subjects with postpartum episodes suggests a major overlap in familial factors predisposing to postpartum episodes (6).

Number of patients with history of postpartum episodes was associated with familial aggregation of mood disorders in our study; but this finding is not in line with the researches regarding within family clustering. The groups of this study consisted of patients from different families and no other family members were enrolled. Instead, our aim was to find out if there is any association between bipolarity (familiality) and postpartum episodes. We found a higher postpartum episode rate among patients with family history of bipolar disorder and this finding indicates a relationship between postpartum episodes and familial features of genetic underpinnings of the disorder.

According to Schulze et al study (27) comorbid alcohol and substance abuse was found to be familial but panic disorders was not. On the contrary, risk for panic disorder in familial bipolar disorder was found to be higher in some studies (36,37). On the other hand, it is possible to comment that alcohol and substance abuse may cluster in families due to shared environment and learned patterns of behavior. Interestingly, MacKinnon and colleagues (37) reported that relatives of the patients with panic attacks were less likely to have substance abuse diagnosis than the relatives of probands without panic attacks. Although we found a greater prevalence of general comorbidity including anxiety disorders as well as alcohol and substance abuse; small sample size does not let us to further investigate subgroups. The higher comorbidity rates in patients with family history may be an indicator of increased genetic interference.

Having lifetime mixed episodes and rapid cycling may indicate more severe disease and necessitates reconsidering treatment options. Although we found a higher rate of mixed episodes in familial patients, age at disease onset, rapid cycling, psychotic episodes and other clinical features did not show significant difference between groups. We found a higher prevalence of history of ECT treatment in patients without family history. This finding may be an indicator of more severe disease in this group. On the other hand this finding may also indicate that this group of patients may be less responsive to mood stabilizers and episodes become more severe depending on this. Follow up studies are needed to prove this finding and to probe the reasons of higher ECT needs in treatments. Age of onset was found to be significantly earlier in patients with family history in two studies (25,39), however both of these studies have small sample sizes (n=150 and n=130 respectively) and a study with a large sample size (n=1246) (27) reported no significant difference between groups in terms of age at disease onset. Age at disease onset did not differ between the groups in this study. We also found higher rates of nicotine dependency in patients with family history. Smoking is assumed to be a measure of disease severity as well as caffeine consumption and alcohol and substance abuse (40). Psychosis (41,42) and suicide attempts (43,44) are also found to be related to smoking in patients with bipolar disorder. However, many factors may have

influences on nicotine consumption and this is a small sample to obtain generalizable results in terms of smoking. Studies with larger sample sizes are needed to determine differences in clinical features between familial and non-familial patients.

The concept “familiality” is problematic to classify in several ways and should be delineated more circumstantially. The sample of this retrospective study consists of outpatients of a specialized centre for bipolar disorders and thus results cannot be generalized. All families of the patients assigned to group 1 included patients with bipolar disorder; but 8 families also had members with schizophrenia and 2 families also had members with anxiety disorders. Enrolling pure bipolar families may have increased homogeneity. Obtaining missing data and family history with phone interviews are other limitations of this study. It would be better to obtain these data in interviews in person. It may be a better way to enroll all family members and scan syndromal and subsyndromal cases together to optimize reliability. Another limitation was that some information (i.e. premenstrual dysphoria, lifetime history of suicide attempts) was obtained from patients by self reports. On

the other hand, if there are multiple patients in a family, attitude towards patients and illness may change and affect the course of the disorder. Than control for attitudes towards the disorder, support from families, caregiver burden, and interpersonal interactions must be taken into account in future studies. Studies focusing on inheritance models should be done in much more bigger samples in order to reduce probability of type one and two errors.

To conclude, in general, this study modestly suggests that patients with family history might be expected to be influenced by more aspects of the disorder. In particular, postpartum episodes and psychiatric comorbidity are largely familial aspects. Studies have been focusing on familial characteristics of familial aggregated samples in bipolar disorder. Although we aimed to distinguish differential clinical features of familial and non-familial patients, small sample size did not let us to explore differences between groups in terms of other clinical characteristics. The familial and non-familial forms of the disorder should be investigated in larger samples in order to detect specific clinical features of subgroups in bipolar disorder.

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