Recurrence in Patients with Bipolar Disorder and its Risk Factors

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Objective: The aim of this study was to identify prognosis factors associated with recurrence in patients with bipolar disorder.
Method: This retrospective cohort study was conducted in Hamadan Province, the west of Iran. All patients (n = 400) with bipolar disorder who were hospitalized for the second time or more during April 2008 to September 2014 were included in this study. Ordinal logistic regression analysis was employed to determine the effective factors in each recurrence, and odds ratio (OR) and 95% confidence intervals (CI) were obtained.
Results: The mean (SD) age of the participants at the entrance to the study was 34.62 (11.68) years. There was an association between recurrence and type of bipolar disorder (P = 0.033). The OR of recurrence was 0.28 (95% CI: 0.09, 0.90) for bipolar disorder II; 0.35 (95% CI: 0.13, 0.92) for the patients with college education; 0.39 (95% CI: 0.25, 0.60) for employed patients; 0.55 (95% CI: 0.35, 0.87) for patients who received both drugs and electroconvulsive therapy, and 1.89 (95% CI: 1.23, 2.92) for patients who stopped using drugs. In addition, a non-significant association was found between recurrence and age, sex, marital status, place of residence, season, mood classification and family history of mood disorder.
Conclusion: Type of bipolar disorder and cessation of medication were the leading causes of an increase in the relapse of the disease. Furthermore, patients who received both drugs and electroconvulsive therapy had a fewer risk of recurrence.

Key words: *Bipolar Disorder; Ordinal Logistic Regression; Prognosis Factors; Recurrence*

Bipolar disorder is defined as a severe, chronic, disabling mental disorder with significant effects on the economy, the patient and the society (1, 2). According to the fourth edition of Diagnostic and Statistical Manual of Mental Disorders Text Revision (DSM-IV-TR), two major categories of bipolar disorder exist: Bipolar I disorder and bipolar II disorder (3). Bipolar disorders types I and II affect about 2% of the world's population (4). The lifetime prevalence of this illness was reported differently in different studies. The reported lifetime prevalence of bipolar disorder I is between 0 and 2.4%, and for the whole bipolar spectrum, in which bipolar disorder II and cyclothymia and hypomania are also included, it is between 2.6 and 7.8%. The annual incidence of bipolar illness is less than one percent (5).

Gaining knowledge about the course of bipolar disorder is of prime importance. Bipolar disorders have long episodes, and many patients experience recurrence during their lifetimes. Close to 60% of the patients experience a recurrence of bipolar disorder in the first two years, and about 75% experience a recurrence in over five years following the initial diagnosis (6,7). Salvatore et al (1) indicated that the risks of relapse and recurrence were very high in the first two years. World Health Organization reported that bipolar disorder is the sixth leading cause of life long disability among persons aged 15 to 44 years worldwide (8). In some studies, it was reported that non-adherence to treatment and family history of mood disorder are associated with an increased number of episodes and more hospitalizations (9-11). Studies have shown that a poor occupational status, alcohol dependence and male

gender were all factors that contributed to a poor prognosis (5).

Joy Albuquerque et al. (12) investigated the recurrence rates in Ontario physicians monitored for major depression and bipolar disorder. They made exploratory analysis on recurrence predictors including age, sex, psychiatric diagnosis, psychiatric comorbidity, medical comorbidity, number of past episodes, past hospitalizations, and family history of psychiatric disorder. They concluded that recurrence rates are high and markedly hastened by the presence of psychiatric comorbidity. in the world and especially in Iran; few studies have been done to find the possible relationships between prognostic factors and recurrence of bipolar disorders. Since preventing recurrence in the patients is important, the aim of this study was to identify the prognosis factors of recurrence among patients with bipolar disorder.

Materials and Method

This retrospective cohort study was conducted in Hamadan Province, the west of Iran, from April 2008 to September 2014. The population of this study was patients with bipolar disorder with more than one recurrence leading to hospitalization in Farshchian hospital, the only psychiatric hospital in Hamadan province. Data were extracted from hospital records using a checklist of items according to the context of the patients' records and clinical examination of psychiatrists.

The checklist included data on demographic variables such as age, sex, marital status, education, occupation, place of residence and ethnicity. Moreover, information on the disease such as type of treatment, season, mood classification, family history of mood disorder, and cessation of medication were assessed. Recurrence was the response variable.

Ordinal logistic regression analysis was performed to assess the effect of various risk factors on recurrence. Odds ratio (OR) was reported to address the association between recurrence and the associated predictors. All statistical analyses were performed at a significance level of 0.05 using Stata software, Version 11 (Stata Corp, College Station, TX, USA).

Results

All the patients with bipolar disorder (n = 400) who were hospitalized for the second time or more during April 2008 to September 2014 were included in this study.

Table1. Characteristics of the Patients with Bipolar Disorder

Variables	Number	Percent
Sex		
Male	288	72.0
Female	112	28.0
Marital status		
Married	189	47.3
Single	161	40.3
Divorced/ Widowed	50	12.5
Education		
Illiterate	39	10.1
Without College education	304	79.0
College education	42	10.9
Occupation		
Employed	207	51.8
Unemployed	193	48.3
Region		
Urban	272	68.3
Rural	126	31.7
Ethnicity		
Persian	176	44.0
Other [†]	224	56.0
DSM-IV-TR classification		
Bipolar I disorder	389	97.3
Bipolar II disorder	11	2.8
Season		
Spring	89	22.3
Summer	115	28.8
Autumn	106	26.5
Winter	90	22.5
Type of treatments		
Drug	268	67
Drug and ECT [‡]	116	29
Drug and Psychosocial	16	4
Mood classification		
Manic episode	256	69.9
Depressed episode	96	26.2
Mixed episode	14	3.8
Family history of mood		
No	280	70
Yes	120	30
Cessation of medication		
No	244	61
Yes	156	39
Number of recurrence		
2	150	37.5
3	126	31.5
4	76	19.0
5	27	6.8
6	14	3.5
7	7	1.8

[†] Turkish, Lurish or Kurdish.
[‡] Electroconvulsive therapy.
[§] Family history with mood disorder included of Bipolar or Unipolar disorder

Table2. The Odds Ratio (OR) of Different Variable on Reccunce of Patients with Bipolar Disorder

Variables	OR (95% CI)	P value
Age (yr.)	1.01(0.99, 1.04)	0.138
Sex		
Male	1.00	
Female	0.71(0.44, 1.13)	0.150
Marital status		
Married	1.00	
Single	0.96(0.54, 1.70)	0.890
Divorced/ Widowed	1.00(0.50, 1.88)	0.945
Education		
Illiterate	1.00	
Without College education	0.79(0.37, 1.67)	0.545
College education	0.35(0.13, 0.92)	0.035
Occupation		
Unemployed	1.00	
Employed	0.39(0.25, 0.60)	0.001
Region		
Urban	1.00	
Rural	0.73(0.46, 1.16)	0.195
Ethnicity		
Persian	1.00	
Other [†]	0.56(0.37, 0.87)	0.009
DSM-IV-TR classification		
Bipolar I disorder	1.00	
Bipolar II disorder	0.28(0.09, 0.91)	0.033
Season		
Spring	1.00	
Summer	1.09(0.62, 1.92)	0.755
Autumn	1.13(0.63, 2.04)	0.670
Winter	0.69(0.37, 1.29)	0.253
Type of treatments		
Drug	1.00	
Drug and ECT [‡]	0.55(0.35, 0.87)	0.011
Drug and Psychosocial	2.82(0.97, 8.17)	0.056
Mood classification		
Manic episode	1.00	
Depressed episode	1.20(0.75, 1.91)	0.437
Mixed episode	1.25(0.45, 3.51)	0.659
Family history of mood		
No	1.00	
Yes	1.42(0.91, 2.20)	0.116
Cessation of medication		
No	1.00	
Yes	1.89(1.23, 2.92)	0.004

[†]Turkish, Lurish or Kurdish
[‡] Electroconvulsive therapy
[§] Family History with Mood Disorder including Bipolar or Unipolar Disorder

The mean (SD) age of the participants at the time they entered into the study was 34.62(11.68) years. The number of male patients was 288 (72%) and the number of females was 112 (28%); the number of patients who lived in urban and rural areas was 272 (68%) and 126 (31%), respectively. The minimum and maximum recurrence observed during the study period was 2 and 7, respectively. The characteristics of patients are given in Table 1.

The results of proportional ordinal logistic regression analysis are presented in Table 2. An increase in relapse rate was observed with an increase in age. A non-significant association was detected between recurrence and the group with no college education compared to illiterate patients. However, a significant association was detected between the group with college education and recurrence (P = 0.035). Moreover, a strong association was found between occupation and recurrence, and the OR of recurrence in employed patients was 0.39 (95% CI: 0.25, 0.60) compared to the unemployed. The recurrence in non-Persian (Kurdish, Turkic and Lurish) patients was significant compared to the Persian (P = 0.009).

There was a significant association between bipolar II disorder and recurrence compared to bipolar I disorder (P = 0.033).

The cessation of medication was a strong risk factor in recurrence of the disease. The OR of recurrence in patients who ceased the use of drugs was 1.89 (95% CI: 1.23, 2.92) compared to those who used drugs. Compared to patients with manic episode, the patients with depressed or mixed episode were at higher risk of recurrence. However, these associations were not statistically significant. Treatment with either drugs or electroconvulsive therapy, alone had an association with recurrence (P = 0.011). In addition, when treatment, drugs and ECT were administered together, they decreased the risk of recurrence.

Discussion

The results of this study revealed that recurrence was associated with various predictors including education, occupation, ethnicity, and type of bipolar disorder according to DSM-IV-TR, type of treatment and cessation of medication.

With increasing age there was an increasing risk of recurrence and this result confirmed the study done in 2006 (13); however, no significant effect was detected for age. In some studies, the reported percentage of hospitalization of men was more than that of women, urban was more than rural and married was more than single or Divorced/ Widowed (14,15). The results of this study confirmed that the percentage of men who were hospitalized was more than that of women. No significant association was found between recurrence and sex, which correspond with the study done by Joy Albuquerque et al. (12). In 2003, Kupka et al. (16) found that the risk of bipolar disorder in women is significantly higher compared to men. Although no significant effects of sex and place

of residence were found, the risk of recurrence among men was more compared to women, and it was more in the urban than in the rural areas. In 2010, Peen et al. (17) indicated a greater prevalence of mood disorders in urban areas compared to the rural. We found that the risk of recurrence was the same in divorced, widowed and married patients.

In a study conducted by Perlis et al. (13), no significant effect was detected between number of recurrence and education. The results of this study revealed that the risk of recurrence decreased in patients with college education. No significant effect was observed for season in patients in this study, but the risk of recurrence was increased in the autumn and summer.

We found a strong association between occupation status and recurrence. Dickerson et al. (18) investigated the association between cognitive functioning and employment status of persons with bipolar disorder and concluded that current employment status was significantly associated with history of psychiatric hospitalization. Lack of previous hospitalizations may indicate a fewer relapses over the history of the illness.

Treatment adherence is an important factor when it comes to bipolar disorder. Many studies have shown that over 60% of the patients did not adhere to treatment. Non-adherence to treatment and discontinuation of mood stabilizers increase the risk of relapse (11). The results of this study is in agreement with previous studies because it showed that the risk of recurrence was higher in patients who stopped drug consumption. In 2006, Altman et al., in a systematic review, assessed the predictors of relapse in bipolar disorder (19). According to their results, the factors associated with longer survival times included psychotherapy, social support and medication adherence.

The risk of recurrence in patients with bipolar I disorder was higher than patients with bipolar II disorder. This can be attributed to more hospitalized patients with bipolar disorder type I than patients with bipolar disorder type II (20).

In this study, by comparing the participants with those patients with manic episodes, we found that the patients with depressed episodes were at higher risk of recurrence; this has been confirmed by previous studies (13). The highest risk of recurrence was observed among those patients who had mixed episodes.

In this study, it was revealed that family history of mood disorders had no association with recurrence. Nevertheless, the risk of recurrence was higher in patients with the family history of mood disorder compared to those without a family history of mood disorder. This can be attributed to the decreased age of onset and increased severity of the disease. A higher likelihood of hospitalization had been found in patients with family history of mood disorders (21).

Kessing et al used frailty models (22) to estimate the effect of the number of episodes on the rate of recurrence taking into account the individual frailty toward recurrence. They concluded the risk of subsequent recurrence increased with the number of episodes. Degenhardt et al (23) used Cox Proportional Hazard models to determine the predictors of relapse/recurrence in bipolar I disorder. In addition, de Dios et al. (15) found the predictors of recurrence in bipolar disorders in Spain using logistic regression analysis. They concluded that the factors significantly related to relapse were living setting and total number of previous episodes.

Medication is an essential component of treatment for patients with bipolar disorder; in addition, psychosocial treatments and electroconvulsive therapy may further improve patients' condition (24, 25). Although in this study patients who received both medication and electroconvulsive therapy had a less risk of recurrence, those patients who received both medication and psychosocial treatments (psychotherapy) had an increased risk of recurrence. This may be due to the fact that most of the patients did not complete psychotherapy as it lasts for a long time and is highly costly in Iran.

Limitations
The limitations of this study were the absence of some data in patients' records and the retrospective design. Despite these limitations, this study revealed some associated variables with recurrence in the target population having an average income. The results may be useful for physicians, psychiatrists and psychologists in preventing relapse.

Conclusion
According to the results, several variables affect recurrence including occupation, type of bipolar disorder according to DSM-IV-TR, and cessation of drugs use. Patients who received both medication and electroconvulsive therapy showed a decreased risk of recurrence.

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Conflict of interest
The authors declare that they have no conflicts of interest.

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