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Identifying Some Risk Factors of Time to Recurrent Relapses in Bipolar I Disorder Patients using Frailty Model of Survival Analysis

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Abstract

Objective: Bipolar I disorder patients often experience relapse once and even more with no limit on number of relapses. The time to relapses of these patients are rarely studied particularly considering heterogeneity across individuals. The aim of this study was to identify some risk factors of time to recurrent relapses in bipolar I disorder patients with a recurrent event model in survival analysis.

Methods: In a retrospective longitudinal study, data of medical records of 526 bipolar I disorder patients who had referred to Razi Psychiatric hospital in Tehran from 1993 to 2011 with at least one relapse, with-out relapse in other hospitals or home in this duration, were investigated and time to recurrent relapses were collected in months. Semi-parametric penalized frailty model which consider whit-in subject correlation and heterogeneity across individuals, was applied to identify the risk factors of recurrent time to relapses.

Results: Significant frailty parameter ($p<0.001$) prove presence of heterogeneity among data. In frailty model the effects of substance abuse ($p=0.041$), regular fluctuation ($p=0.002$) and marital status ($p=0.009$) were significant on the hazard of recurrent times to relapses but other variables showed no significant effect.

Conclusions: Substance abuse, marital status and RF are important risk factors in order to plan for postpone the time to next relapses. More studies are required to clear out the effect of other covariates with this model.

Keywords: Bipolar I disorder; Relapses; Recurrent events; Frailty model

Introduction

Bipolar affective disorder, a common and chronic, severe and recurrent, mood and brain disorder that causes unusual shifts in mood, energy, activity levels and ability to carry out day-to-day tasks, is characterized by recurrent episodes of mania and depression [1-4]. Bipolar disorder (BD) remains among the 10 most disabling disorders according to the World Health Organization (WHO) causing a significant amount of disability [5]. Studies have been published before, estimated the prevalence of bipolar disorder in between 1% and 2% [2]. One of the important types of BD is bipolar I disorder with lifetime prevalence of 0.24% [6]. Although BD is often hard to be diagnosed due to its irregular patterns, it can be treated and patients life would be improve [1,7]. Bipolar disorder causes substantial psychosocial morbidity that frequently affects the patient's marriage, children, occupation, and other aspects of the patient's life [8]. Bipolar disorder is the sixth cause of disability in the United States and symptoms can damaged patients relationships, job and school performance, as a consequence, it is one of leading causes of disability which contributes to economic burden of this disorder to society [9,10]. Several studies have reported that 50% to 75% of patients have a recurrence within 4 to 5 years after the first admission [11]. Patients with long duration of illness and highly recurrent course show great impairment of global functioning and number of episodes has been found consistently associated with poor outcome [4]. An important feature of bipolar I disorder is the repetition of relapses over time and up to 90% of BD patients have at least one relapse in their lifetime [12-15]. Information about time to relapse and efficacy of some risk factors in preventing relapses will provide a valuable tool for planning and evaluating the health-outcome results of treatment [16]. There are some studies about relationship of factors and onset of BD but little is known about the factors that may precipitate relapse [10]. Few studies have assessed time to relapse, remission and recovery of patients, using Kaplan-Meier estimator or Cox regression, but most of them failed to account the repeated feature of relapses and correlation caused by recurrent events whit-in subjects [17-23]. In order to study time to relapses, with respect to repeated characteristic of bipolar disorder, we need recurrent event analyzing techniques of survival analysis. Survival analysis typically focuses on time to event data and recurrent event is a multivariate survival analysis in which event occurs more than once per subject over follow-up time such as hospital stays or heart attacks [24,25]. The most important issue in recurrent data is correlation among relapses of each patient. In fact, individuals have varied lifestyles, genetic traits, and experiences which influence the likelihood that they will succumb to disease but either cannot be measured and are unknown. These factors are called latent variable. As a result, some individuals are more prone to experience their next disease relapses more quickly than other individuals. This introduces heterogeneity across individuals and produces within-subject correlation in the timing of recurrent events within a given subject so, response rates can be homogeneous within individuals producing within-subject correlation in event times [26,27]. There is a need for a general and flexible model that simultaneously incorporates the effects of covariates, as well as the effect of latent or unobserved variables [28]. Frailty or random effects models incorporate heterogeneity into the estimator by making assumptions about the frailty distribution and incorporating it into the model estimates

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[29]. Bipolar I disorder is a recurrent disorder for the vast majority of patients, and hospitalization is normally used to control severe symptoms and the goal of treating bipolar I disorder is prevention of relapses/recurrences. In this study, we present a semi-parametric frailty model using penalized approach which accounts for time dependent covariates and heterogeneity in repeated relapses of bipolar I disorder in order to identify some factors that would participate relapses.

Method

Participants and procedure

In a retrospective longitudinal study data of 526 bipolar I patients with at least one relapse, who were hospitalized at Razi Psychiatric hospital in Tehran between 1993 and 2011, were collected from their medical records. The first relapse of each patient is considered as entry in to study. Patients relapse has been followed up during this past 10 years. In survival analysis notation, recurrent event was defined as observing bipolar I disorder symptoms in the first re-hospitalization after discharge and following re-hospitalizations. Patients who had been admitted to other hospitals before or had relapses after being discharged from their first hospitalization were excluded from study because we suppose that hospitalization had happened immediately after relapse. The time to recurrent relapses were considered in months. We use the gap time timescale that is most often used timescale in survival analysis: after an event, the subject starts again at time 0 and the time to the next event corresponds to the number of month that it takes to experience the next event [30]. We assessed number of month patients remained to be re-hospitalized as time to event. Right censoring occurs when a subject leaves the study before an event occurs, or the study ends before the event has occurred [31]. Available data fields included: gender, marital status, family history of bipolar disorder (FH), substance abusing, Regular fluctuation (RF), negative life events (NLE) and types of episode. Patients with abusing any kind of drugs other than cigarettes have the positive substance abuse. One of our limitations in this study is, there are some conditions that have been changed in patient life which we could not record them all during this past 10 years. We just consider patients conditions including: marital status, FH, substance abuse and NLE are not changed during this past 10 years. So any change which noticed in each patient condition, by the view of these 4 factors, they are considered to be out of our study in order to have stability in conditions and avoid too many time varying coefficients. There were cases of relapses in some patients during the study that an individual has the mood fluctuations of bipolar disorder but the symptoms do not meet the criteria for any of the other subtypes or the mood changes are abrupt and irregular [32]. RF factor (Regular Fluctuation) was created for this situations. If a patient in one of clients, was cyclothymia, NOS or schizoaffective then RF is negative. NLE and types of episodes defined according to the Diagnostic and Statistical Manual of Mental Disorders book (DSMIV). NLE include stressful life events that often require sweeping readjustments in a person's life such as; death of a loved one, job loss, major illness or injury. There are 3 types of episode in bipolar I disorder (mania, depression, mixed) which could vary in each recurrence of episodes, so we should recognize it as a time varying covariate [33].

Statistical analysis

In many epidemiological and medical studies, the outcome variable of interest is a recurrent event [17]. In these studies each subject is at risk of experiencing repeated events and investigators are interested in evaluating the effects of covariates on the recurrent event times and predicting the developments of future events [34]. An important issue in recurrent events approach is to consider dependency of observations per subjects, called frailty or latent random variable, which is unobservable but influence the model with the meaning that all sampled individuals into the study are not subject in principle under the same risk of disease recurrence [35]. Frailty model that is useful approach to accommodate dependency of the recurrent event times within the same subject has many uses in survival analysis. Frailty models are extensions of well-known Cox (1972) proportional hazards model and are used when proportional assumption holds not true [36,37]. A very common situation in survival analysis is clustered or repeated data. The dependence usually arises because of the recurrence of an event for the same individual. Frailty is a multivariate approach to account the presence of the correlation between the recurrent survival times [38]. In statistical terms, frailty model is a multivariate random effect model for time-to-event data and each individuals repeated relapses are assumed to share the same frailty which is why this model is called shared frailty model [39]. Statistical analysis is complicated by presence of time-dependent covariates, factors that may vary in each relapse of same individual like types of episode in our study [37]. Semi-parametric penalized frailty model is a recurrent frailty model that is suitable when there are time-varying covariates. The advantage of this model is that it can easily evaluate frailty parameter and time varying covariates. R3.2.0 software was used to analyze data. In this software with default packages, results could evaluate without problem.

Results

Frequencies of all time-independent variables which are fix in each relapses of one individual are shown in Table 1. In studied sample 64.8% (341) of patients were males, 60.4% (318) were single and 58.2%% (306) with-out family history of bipolar disorder. 56.4% (297) of patients did not experience negative life events, 52.4% (276) have substance abuse and 60.0% (316) have not RF (Table 1). The type of episodes that may vary in each relapses of same individual is our only time-dependent variable that is shown in Table 2. Entirely 2889 relapses were registered for 526 patients. 2519 of these were for BP I and 391were for NOS or cyclothymia or schizoaffective. Maximum number of recurrence was 24 but 98.01% of relapses happened up to 9th recurrenc.77.25% of relapses were in mania phase, 3.65% were mixed and 19.09% were depressed (Table 2).

We used semi-parametric penalized frailty model to identify which of these 7 factors could participate next relapse. Usually, it is assumed that the frailty follows a gamma distribution with mean 1 and unknown variance θ. The value θ=0 corresponded to independence and a high value of θ should preferably correspond to a high correlation between

Covariates	Categories	Count (n %)
Sex	Male	341 (64.9)
	Female	185 (35.1)
Family history	No	306 (58.2)
	Yes	220 (41.8)
Substance abuse	No	250 (47.6)
	Yes	276 (52.4)
Negative life event	No	297 (56.4)
	Yes	229 (43.6)
Marital status	Single	318 (60.4)
	Married	208 (39.6)
RF	No	316 (60.0)
	Yes	210 (40.0)

Table 1: Frequency of risk factors in patients with bipolar I disorder.

	Number of Episodes									
Types of Episode	1st (%)	2nd (%)	3rd %)	4th (%)	5th (%)	6th (%)	7th (%)	8th (%)	9th (%)	10th and more
Mania	403 (15.9)	401 (15.9)	387 (15.3)	316 (12.5)	223 (8.8)	94 (3.73)	49 (1.9)	26 (1.0)	17 (0.67)	30 (1.19)
Mixed	16 (0.63)	21 (0.83)	13 (0.51)	7 (0.27)	12 (0.47)	0 (0)	6 (0.23)	5 (0.19)	5 (0.19)	7 (0.27)
Depression	107 (4.24)	98 (3.89)	86 (3.41)	68 (2.69)	41 (1.62)	39 (1.54)	17 (0.67)	7 (0.27)	5 (0.19)	13 (0.51)

Table 2: Frequency of recurrences in 3 types of episodes.

Covariates		Reference Category	β (p-Value)	SE	HR
Gender	Female	Male	0.075 (0.559)	0.128	1.078
Family history	Yes	No	0.073 (0.541)	0.128	1.076
Marital status	Single	Married	0.320 (0.009)	0.123	1.376
Substance abuse	Yes	No	0.795 (0.041)	0.125	1.344
Negative life events	Yes	No	0.085 (0.453)	0.113	1.089
Type of episodes	Mania	Mix	0.006 (0.979)	0.262	1.007
	Depression		-13.416 (0.365)	10.283	1.491
RF	Negative	Positive	0.372 (0.002)	0.125	1.451

θ=0.287 (p<0.001); SE=0.066; LCV=2.949

Table 3: Parameter estimation in semi-parametric penalized frailty model.

the survival times [40]. Results of this analysis are shown in Table 3. Variance of frailty parameter (θ=0.287) is highly significant (p<0.001), suggesting present of heterogeneity among data. In other words in this sample there is correlation between repeated relapses of each patients and with-out considering this frailty of each patients result would be incorrect. Among risk factors, substance abuse (p=0.041), RF (p=0.002) and marital status (0.009) were significant, suggesting these factors have effects to the time of next relapse of patients (Table 3).

Even though frailty is an un-measurable factor but if we have density function of frailty we can have information around heterogeneity of individuals. Shape of shared gamma frailty distribution of our sample is shown in Chart 1. It is a gamma function with mean=0 and variance=0.287. Quartiles are 0.609, 0.906 and 1.287 respectively. We can see that the frailty among patients in our study is not same (Chart 1). Overall hazard function show that hazard increased by time generally. It means with-out considering any covariates in study hazard of next relapse increased by time (Chart 2).

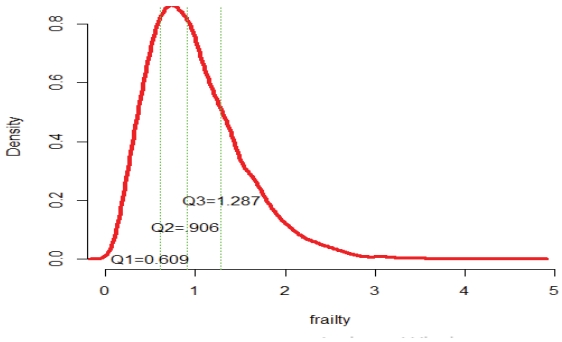

Chart 1: Distribution of frailty.

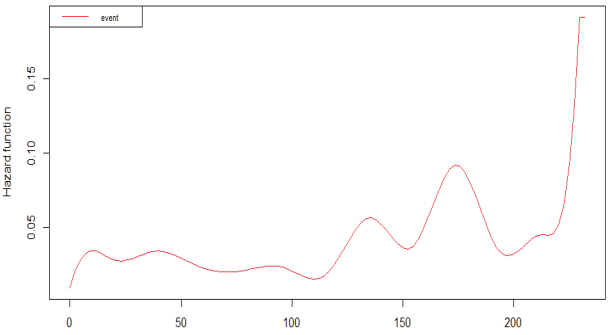

Chart 2: Overall hazard function over time.

Discussion

About 77.25% of episodes were manic, 19.09% depressed and 3.65% mixed (Table 2); these results were close to those of the previews study which reported 74% of index episodes to be mania, 21% to be depressed, and 5% to be mixed [16]. Clearly, unobserved patients characteristics have a very substantial effect on survival so the result will be bias whit out considering individuals heterogeneity. Heterogeneity is considered in terms of frailty and variance of frailty (theta) measures the variability of frailties. If θ differs from zero indicating the presence of unobserved heterogeneity [41], so in the significant level of .05 the frailty should be considered in the model (Table 3). From the shape of frailty distribution (Q1/Q2=.672 and Q3/Q2=1/420) we see that patients with frailty at Q1 have 33% lower risk, and patients with frailty at Q3 have 42% higher risk, than patients with median frailty (Chart 1). However the interpretation of the hazard ratios in the frailty model is slightly different from the other models and the hazard ratios are compared in the given same value of frailty [42]. In semi-parametric penalized frailty model substance abuse have significant effect on hazard rate of relapses and patients with equal frailty who use substance have 0.34 times more chance to have next relapse. Substance abuse may prolong bipolar symptoms, and the behavioral control problems associated with mania can result in a person drinking too much [1] this results support the suggestion that individuals with bipolar affective disorder complicated by substance abuse may have more hospitalizations [43]. Marital status is another effective factor. Single patients have 0.37 times more chance to have next relapse compared to married patients at the same level of frailty although in other studies with cox models, which needs initial assumption that always not hold, marital status was not significant [44]. There is relationship between marital status and substance abuse with onset of bipolar disorder, but our study suggested that these two factors could postpone the time of next relapses. RF factor is also significant. Patients have not RF have 0.45 times more chance to experience next relapse than who have RF. It implies that there should be more attention in treatment procedure and diagnostic criteria in confront

of patients with irregular pattern. We found that type of episodes and sex have no influence on time to relapses in bipolar I disorder patients. Recent study with using Cox regression model in the 12-month follow-up period study, has reported no significant differences in recovery from hospitalization between patients with mania compared with mixed bipolar disorder and another study found that bipolar women experienced an equal greater risk of recurrence than men [45]. Negative life event has not significant effect on outcome although most studies with-out considering frailty have found that negative life events precede episodes of bipolar individuals [46]. It shows that when we consider individuals heterogeneity in model this factor lose its efficiency. It seems negative life events have not direct effect on hazard of next relapse but it depends on each individual to how handle it. Family history has not significant effect on time to relapse although have effect on incident of disorder and children with a parent or sibling who has bipolar disorder are much more likely to develop the illness, compared with children who do not have a family history of bipolar disorder [1]. Single patients with substance abuse and with-out irregular fluctuation have more chance to experience next relapse earlier.

Conclusion

Substance abuse, RF and marital status are important risk factors influencing hazard of time to relapses. Having a good relationship with the spouse and relinquishing addiction could help to postpone the next relapses. Significance of RF factor suggesting further studies around borderlines and treatments of types of bipolar disorder. The course of bipolar I disorder seems to be progressive in nature irrespective of gender, type of disorder, FH and NLE. More studies are required to clear out the effect of other covariates such as place of residence (urban vs. rural), education level, economic status of patients on time to relapses with this model.

References

1. Angst J, Cassano G (2005) The mood spectrum: improving the diagnosis of bipolar disorder. Bipolar Disord 7: 4-12.
2. Sajatovic M (2005) Bipolar disorder: disease burden. Am J Manag Care 11: S80-S84.
3. Ketter TJ, Houston JP, Adams DP, Risser RD, Meyers AL, et al. (2006) Differential efficacy of olanzapine and lithium in preventing manic or mixed recurrence in patients with bipolar I disorder based on number of previous manic or mixed episodes. J Clin Psychiatry 67: 95-101.
4. Di Marzo S, Giordano A, Pacchiarotti I, Colom F, Sanchez-Moreno J, et al. (2006) The impact of the number of episodes on the outcome of bipolar disorder. Eur J Psychiat 20: 21-28.
5. Rathod S, Kingdon D, Pinninti N, Turkington D, Phiri P (2015) Bipolar Affective Disorder. Cultural Adaptation of CBT for Serious Mental Illness: A Guide for Training and Practice. John Wiley & Sons, Ltd, Chichester, UK.
6. Perälä J, Suvisaari J, Saarni SI, Kuoppasalmi K, Isometsä E, et al. (2007) Lifetime prevalence of psychotic and bipolar I disorders in a general population. Arch Gen Psychiatry 64: 19-28.
7. Cha B, Kim JH, Ha TH, Chang JS, Ha K (2000) Polarity of the First Episode and Time to Diagnosis of Bipolar I Disorder. Psychiatry Investig 6: 96-101.
8. Zarate CA Jr, Tohen M, Land M, Cavanagh S (2000) Functional impairment and cognition in bipolar disorder. Psychiatr Q 71: 309-329.
9. Müller-Oerlinghausen B, Berghöfer A, Bauer M (2002) Bipolar disorder. The Lancet 359: 241-247.
10. Altman S, Haeri S, Cohen LJ, Ten A, Barron E, et al. (2006) Predictors of relapse in bipolar disorder: a review. J Psychiatr Pract 12: 269-282.
11. Kemner SM, van Haren NE, Bootsman F, Eijkemans MJ, Vonk R, et al. (2015) The influence of life events on first and recurrent admissions in bipolar disorder. Int J Bipolar Disord 3: 6.
12. Kessler RC, McGonagle KA, Zhao S, Nelson CB, Hughes M, et al. (1994) Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. Results from the National Comorbidity Survey. Arch Gen Psychiatry 51: 8-19.
13. Bebbington P, Ramana R (1995) The epidemiology of bipolar affective disorder. Soc Psychiatry Psychiatr Epidemiol 30: 279-292.
14. Merikangas KR, Akiskal HS, Angst J, Greenberg PE, Hirschfeld RM, et al. (2007) Lifetime and 12-Month Prevalence of Bipolar Spectrum Disorder in the National Comorbidity Survey Replication. Arch Gen Psychiatry 64: 543-552.
15. Grant BF, Stinson FS, Hasin DS, Dawson DA, Chou SP, et al. (2005) Prevalence, Correlates, and Comorbidity of Bipolar I Disorder and Axis I and II Disorders: Results From the National Epidemiologic Survey on Alcohol and Related Conditions. J Clin Psychiatry 66: 1205-1215.
16. Gitlin MJ, Swendsen J, Heller TL, Hammen C (1995) Relapse and impairment in bipolar disorder. Am J Psychiatry 152: 1635-1640.
17. Leelahanaj T, Kongsakon R, Choovanichvong S, Tangwongchai S, Paholpak S, et al. (2013)Time to relapse and remission of bipolar disorder: findings from a 1-year prospective study in Thailand. Neuropsychiatr Dis Treat 9: 1249-1256.
18. Wang MC, Chang SH (1999) Nonparametric Estimation of a Recurrent Survival Function. J Am Stat Assoc 94: 146-153.
19. Twisk JW, Smidt N, de Vente W (2005) Applied analysis of recurrent events: a practical overview. J Epidemiol Community Health 59: 706-710.
20. Yang H, Lu LH, Wu M, Stevens M, Wegbreit E, et al.(2013) Time course of recovery showing initial prefrontal cortex changes at 16 weeks, extending to subcortical changes by 3 years in pediatric bipolar disorder. J Affect Disord 150: 571-577.
21. Johnson SL, Miller I (1997) Negative Life Events and Time to Recovery From Episodes of Bipolar Disorder. J Abnorm Psychol 106: 449-457.
22. Lin CH, Chen MC, Chou LS, Lin CH, Chen CC, et al. (2010) Time to rehospitalization in patients with major depression vs. those with schizophrenia or bipolar I disorder in a public psychiatric hospital. Psychiatry Res 180: 74-79.
23. Lin CH, Kuo CC, Liu RY, Huang CW, Chen CC (2009) Factors affecting time to rehospitalization for Chinese patients with bipolar I disorder in Taiwan. Aust Nz J Psychiat 43: 927-933.
24. Cumming RG, Kelsey JL, Nevitt MC (1990) Methodologic issues in the study of frequent and recurrent health problems: falls in the elderly. Ann Epidemiol 1: 49-56.
25. Glynn RJ, Stukel TA, Sharp SM, Bubolz TA, Freeman JL, et al. (1993) Estimating the variance of standardized rates of recurrent events, with application to hospitalizations among the elderly in New England. Am J Epidemiol 137: 776-786.
26. Oakes D (1992) Frailty models for multiple event times. In: Survival Analysis, State of the Art. Klein JP, Goel PK (eds) , Nato Science Series.
27. Therneau TM, Grambsch PM (2000) Modeling Survival Data: Extending the Cox Model. In: Gail M, Samet JM, Tsiatis A, Wong W (eds) Statistics for Biology and Health. Springer: New York USA.
28. Peña EA, Slate EH, González JR (2007) Semiparametric Inference for a General Class of Models for Recurrent Events. J Stat Plan Inference 137: 1727-1747.
29. Box-Steffensmeier JM, De Boef S (2006) Repeated events survival models: The conditional frailty model. Stat Med 25: 3518-3533.
30. Duchateau L, Janssen P, Kezic I, Fortpied C (2003) Evolution of recurrent asthma event rate over time in frailty models. J Roy Stat Soc C-App 52: 355-363.
31. Kleinbaum, DG, Klein M (2012) Survival Analysis A Self-Learning Text. (3rd edn), Statistics for Biology and Health, Springer.
32. Cavendish M (2008) Diseases and disorders. Marshall Cavendish Corporation, New York, USA.
33. Keith SD (2010) Handbook of Cognitive-Behavioral Therapies. (3rd edn), Guilford Press, New York, USA.
34. Glynn R, Buring JE (1996) Ways of measuring rates of recurrent events. BMJ 312: 364-366.
35. Wienke A (2003) Frailty Models. Max Planck Institute for Demographic Research, Germany.

36. Zeng D, Lin DY (2008) Semiparametric Transformation Models with Random Effects for Joint Analysis of Recurrent and Terminal Events. Biometrics 65: 746–752.

37. Nosyk B, MacNab YC, Sun H, Fischer B, Marsh DC, et al. (2009) Proportional hazards frailty models for recurrent methadone maintenance treatment. Am J Epidemiol 170: 783-792.

38. Miller RG Jr (2011) Survival analysis. John Wiley & Sons, New Jersey, USA.

39. Therneau TM, Grambsch PM, Pankratz VS (2003) Penalized survival models and frailty. J Comput Graph Stat 12: 156-175.

40. Parner E (1998) Asymptotic theory for the correlated gamma-frailty model. Ann. Statist 26: 183-214.

41. Yashin AI, Iachine IA, Begun AZ, Vaupel JW (2001) Hidden frailty: myths and reality. Department of Statistics and Demography, Odense University, CRC Press, Florida, USA.

42. Sonne SC, Brady KT, Morton WA (1994) Substance abuse and bipolar affective disorder. J Nerv Ment Dis 182: 349-352.

43. Perlis RH, Ostacher MJ, Patel JK, Marangell LB, Zhang H, et al. (2006) Predictors of recurrence in bipolar disorder: primary outcomes from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). Am J Psychiatry 163: 217-224.

44. Goes FS, Zandi PP, Miao K, McMahon FJ, Steele J, et al. (2007) Mood-Incongruent Psychotic Features in Bipolar Disorder: Familial Aggregation and Suggestive Linkage to 2p11-q14 and 13q21-33. Am J Psychiatry 164: 236-47.

45. Kessing LV (1998) Recurrence in affective disorder. II. Effect of age and gender. Br J Psychiatry 172: 29-34.

46. Alloy LB, Abramson LY, Urosevic S, Walshaw PD, Nusslock R, et al. (2005) The psychosocial context of bipolar disorder: Environmental, cognitive, and developmental risk factors. Clin Psychol Rev 25:1043-1075.

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