Clinical variables and implications of the personality on the outcome of bipolar illness: a pilot study

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Abstract: Outcome in bipolar patients is affected by comorbidity. Comorbid personality disorders are frequent and may complicate the course of bipolar illness. This pilot study examined a series of 40 euthymic bipolar patients (DSM-IV criteria) (bipolar I disorder 31, bipolar II disorder 9) to assess the effect of clinical variables and the influence of comorbid personality on the clinical course of bipolar illness. Bipolar patients with a diagnosis of comorbid personality disorder (n = 30) were compared with "pure" bipolar patients (n = 10) with regard to demographic, clinical, and course of illness variables. Comorbid personality disorder was diagnosed in 75% of patients according to ICD-10 criteria, with obsessive-compulsive personality disorder being the most frequent type. Sixty-three per cent of subjects had more than one comorbid personality disorder. Bipolar patients with and without comorbid personality disorder showed no significant differences regarding features of the bipolar illness, although the group with comorbid personality disorder showed a younger age at onset, more depressive episodes, and longer duration of bipolar illness. In subjects with comorbid personality disorders, the number of hospitalizations correlated significantly with depressive episodes and there was an inverse correlation between age at the first episode and duration of bipolar illness. These findings, however, should be interpreted taking into account the preliminary nature of a pilot study and the contamination of the sample with too many bipolar II patients.

Keywords: bipolar disorder, comorbid personality disorder, depressive episode, manic episode, hypomanic episode, obsessive-compulsive personality disorder

Introduction

Among patients with bipolar disorder, comorbid conditions are very common. Comorbidity is associated with a more difficult course of illness (such as longer episodes, shorter time euthymic, and earlier age at onset) and an increase in related problems (such as suicidality and violence) (Vieta et al 2000; Leverich et al 2003; Baldassano 2006). In a cross-national population-based investigation carried out in Canada, rates of chronic fatigue syndrome, migraine, asthma, chronic bronchitis, multiple chemical sensitivities, hypertension, and gastric ulcer were significantly higher in the bipolar disorder group. Chronic medical illnesses were associated with a more severe course of bipolar disorder, increased household and work maladjustment, receipt of disability payments, reduced employment, and more frequent medical service utilization (McIntyre et al 2006).

On the other hand, different studies have shown the high prevalence and negative impact of comorbid alcoholism and anxiety disorders in bipolar subjects (Winokur et al 1995; Sasson et al 2003; Levander et al 2007). Bipolar subjects with a history of comorbid alcohol use disorder are more likely to meet criteria for an axis II diagnosis based on the Structured Clinical Interview for DSM-III-R Personality Disorders (SCID II) compared with bipolar subjects without an alcohol use disorder history (Winokur et al 1995). Cluster A diagnoses are more common in the bipolar/alcohol use disorder group

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(Kay et al 1999). In a recent review of controlled trials, a strong association between bipolar disorder and substance abuse/dependence, anxiety disorders, impulse control disorders, eating disorders, and attention-deficit hyperactivity disorder was found (Singh and Zarate 2006). Comorbidity often complicates the diagnosis and treatment of bipolar disorder and worsens its course of illness and prognosis (McElroy 2004).

Studies in bipolar disorder suggest that personality features are important in predicting outcome. Comorbidity with personality disorders is strongly associated with poor compliance (Colom et al 2000). Co-diagnosis of personality disorder among bipolar patients occurs in 3%–50% of cases (Gonzalez Pinto et al 1997). It has been reported that cluster B and cluster C personality disorders are more common than cluster A (George et al 2003). The presence of a personality disorder may complicate the diagnosis for bipolar disorder. Patients with borderline personality disorder often do not exhibit clinically ascertainable evidence of bipolarity (Deltito et al 2001). On the other hand, personality disorder symptoms are significantly associated with a lower rate of current employment, a higher number of currently prescribed psychiatric medications, and a higher incidence of a history of both alcohol and substance use disorders compared with the bipolar patients without axis II pathology (Hammen et al 2000; Bieling et al 2003). Subjects with co-occurring personality disorder are less likely to achieve recovery and differ from bipolar patients without personality disorders in the severity of residual mood symptoms even during remission (Dunayevich et al 2000; George et al 2003). Comorbid bipolar patients also show a higher number of mixed features, depressive episodes, and suicide attempts (Vieta et al 2001). However, bipolar affective disorder may affect personality traits, determining a lower level of emotional strength and higher levels of introversion (Hirschfeld et al 1986). Obsessive-compulsive personality disorder, borderline personality disorder, and narcissistic personality disorder are more frequent in bipolar patients, whereas avoidant personality disorder is more prevalent in unipolar patients and among depressives (Brieger et al 2003; Rossi et al 2001).

Borderline personality disorder appears to involve affective lability, which may account for efficacy of known treatments for bipolar spectrum disorders (Deltito et al 2001; Henry et al 2001). It has been shown that patients with borderline personality disorder had a significantly higher co-occurrence of bipolar disorder than did patients with other personality disorders; however, this co-occurrence did not appear to affect the subsequent course of borderline personality disorder (Gunderson et al 2006). Moreover, it has been suggested that borderline personality disorder and mood disorders, among which are bipolar disorders, are co-transmitted in families (Henry et al 2001). In contrast, Stone (2006) suggested that patients in whom borderline personality disorder and bipolar disorder co-occur are more apt to be understood as representing an interaction of biological and environmental forces. Premorbid personality associated with bipolar II disorder is characterized as the reward-dependent, passive-avoidant/dependent tendency of personality (Takata and Takaoka 2000).

Many studies have examined the prevalence and predictive validity of axis II personality disorders among unipolar depressed patients, but few have examined these issues among bipolar patients. Axis II pathology seems to complicate the diagnosis and course of bipolar disorder. The purpose of this study was to investigate whether the presence of comorbid personality disorder influences the course of bipolar illness.

Patients and methods

We have collected the first 40 patients referred to the Service of Psychiatry with a DSM-IV diagnosis of bipolar disorder in remission. In these patients, lifetime and current prevalences of comorbid personality disorders were assessed. There were 10 men and 30 women, with a mean (standard deviation, SD) age of 46.1 (12.7) years (range 23–71 years). Patients were recruited from the outpatient clinic of "Virgen del Rocío" mental health center and the Department of Psychiatry of Hospital Virgen Macarena, in Sevilla, Spain. Bipolar I disorder was diagnosed in 31 patients and bipolar II disorder in 9 patients.

All patients were examined for evidence of comorbid personality disorder through the use of a structured diagnostic interview, the Integrated List for the Personality Disorders Diagnostic (ILPDD) (Moreno et al 2002), which is an instrument of easy management and applicability to reach the different kinds of personality disorders diagnoses by the integration of the international classification criteria, both ICD-10 and DSM-IV. The instrument allows a diagnosis of personality disorder in each of the two diagnostic systems (ICD-10 and DSM-IV). The ILPDD questionnaire includes grouping or organization of traits-symptoms according to different spheres (cognitive, exploratory, mental, impulsive, and anxious) in which each item has the peculiarity of being used by the two nosologic systems (ICD-10 and DSM-IV). For description of the items, in some cases the same wording as that found in one of the diagnostic systems has been maintained (eg, item #32 for diagnosis of schizoid

personality disorder is written exactly as appears in criterion #3 of ICD-10, or item #40 for diagnosis of dissocial personality disorder is written exactly as found in criterion #2 of DSM-IV), whereas in other cases, definitions of both systems for the same criterion are integrated in new wordings of the items (eg, item #66 for diagnosis of borderline personality disorder). In order to obtain a specific diagnosis of personality disorder, the questionnaire includes a series of algorithms different for ICD-10 and DSM-IV, which provide a specific diagnosis for each diagnostic system (eg, borderline personality disorder for ICD-10 would be established if three of #19, #53, #63, #66, and #71 criteria would be met, and for DSM-IV if five of the #7, #19, #51, #53, #63, #66, #70, #71, and #78 criteria would be fulfilled).

In all patients the following data were recorded: sex; age; marital status (single, married, widowed, divorced); education level (illiterate, able to read and write, primary school, secondary school, university); job (no profession, housewife, farming, building/industry/services, superior profession); living status (alone, household family, own family, other). Data on bipolar illness were collected from the patient's medical record and included type of bipolar illness, age at onset of the first episode, number and type of affective episodes, duration of bipolar disorder, and number of hospitalizations.

Data analysis

Bipolar patients with a diagnosis of comorbid personality disorder were compared with "pure" bipolar patients for demographic, clinical, and course of illness variables. Continuous variables were analyzed with the Student's *t* test and the relationship between continuous variables with the Pearson product-moment correlation coefficient (r). The SPSS software version 11.0 was used for the analysis of data. A *p* value of 0.05 or less was considered statistically significant.

Results

As shown in Table 1, 65% of patients were married, 40% had only primary education, 42% were housewives, and 67% lived with his/her own family. Data on bipolar illness included a mean (SD) age at the first episode of 27.6 (8) years, mean duration of disease of 19.3 (11.8) years, and a mean number of hospitalizations of 4.8 (5.3). On the other hand, the mean number of depressive episodes was 5.4 (5.9), manic episodes 3.2 (3.7), and hypomanic episodes 2.2 (3.1).

Comorbid personality disorder was diagnosed in 30 patients (75%) using the ICD-10 classificatory system and in 28 patients (70%) using the DSM-IV criteria. Subtypes of comorbid personality disorders are shown in Table 2.

Obsessive-compulsive personality disorder was the most frequent axis II disorder (ICD-10, 37.5%; DSM-IV, 32.5%) followed by paranoid personality disorder (ICD-10, 35%; DSM-IV, 27.5%) and anxious (avoidant) personality disorder (ICD-10, 25%; DSM-IV, 27.5%). A single comorbid personality disorder was present in 11 patients and more than one personality disorder in the remaining 19 patients.

When the group of 30 bipolar patients with comorbid personality disorder according to ICD-10 criteria was compared with those without comorbid personality disorder, statistically significant differences for features of the bipolar illness were not observed. However, the group with comorbid personality disorder showed a trend towards a younger age at onset, more depressive episodes, and longer duration of bipolar illness (Table 3).

The relationships between clinical variables and characteristics of bipolar disorder in the 10 patients without comorbid personality disorder showed statistically significant associations in the following data: age at onset of the first episode with depressive episodes, duration of bipolar illness with both manic and depressive episodes, number of hospitalizations with manic, hypomanic and depressive episodes, depressive episodes with both manic and hypomanic episodes, and manic episodes with hypomanic episodes (Table 4). In the group of 30 patients with comorbid personality disorder, statistically significant relationships were observed between depressive episodes and hypomanic episodes, and between depressive episodes and number of hospitalizations (Table 4). Patients with only one comorbid personality disorder showed a significant association between age at the onset of the first episode and number of depressive episodes as well as duration of bipolar disorder and number of hospitalizations (Table 4). In contrast, patients with more than one comorbid personality disorder showed statistically significant relationships between hospitalizations and depressive episodes, depressive episodes and hypomanic episodes, and an inverse correlation between age at the first episode and duration of disease (Table 4).

Discussion

The present study was performed in a sample of bipolar patients with particular sociocultural characteristics. Most patients were women, who were married, housewives, of low education level, and living with their own family. For clinical features of the bipolar illness, bipolar I disorder was the most frequently diagnosed (77.5% of cases) and the first episode did not occur at a younger age (mean age 27.6 years). Relevant findings related to the course of bipolar disorder

Table 1 Characteritics of 40 patients with bipolar disorder

Data	No (%)	Mean ± SD (range)
Sex		
Males	10 (25)	
Females	30 (75)	
Age, years		46.10 ± 12.7 (23–71)
Marital status		
Single	9 (22.5)	
Married	26 (65.0)	
Widowed	3 (7.5)	
Divorced	2 (5.0)	
Education level		
Illiterate	2 (5.0)	
Able to read and write	11 (27.5)	
Primary school	16 (40.0)	
Secondary school	5 (12.5)	
University	6 (15.0)	
Job		
No profession	7 (17.9)	
Housewife	17 (42.5)	
Farming	2 (5.1)	
Building/industry/services	10 (25.6)	
Superior profession	4 (10.3)	
Living status		
Alone	3 (7.5)	
Original household family	9 (22.5)	
Own family	27 (67.5)	
Other	1 (2.5)	
Bipolar I disorder	31 (77.5)	
Bipolar II disorder	9 (22.5)	
Age at the first episode, years		27.64 ± 8.03 (16–50)
Duration of disease, years		19.26 ± 11.83 (2–41)
Hospitalizations		4.8 ± 5.3 (0–23)
Depressive episodes		5.4 ± 5.9 (1–30)
Manic episodes		3.2 ± 3.7 (0–18)
Hypomanic episodes		2.2 ± 3.1 (0–15)

Table 2 Comorbid personality disorders in 40 patients with bipolar illness

Personality disorder	Classificatory system	
	ICD-10 criteria (n = 30)	DSM-IV criteria (n = 28)
Paranoid	14 (35)[a]	11 (27.5)
Schizoid	5 (12.5)	7 (17.5)
Schizotypical	8 (20)	5 (12.5)
Dissocial	2 (5)	5 (12.5)
Borderline	6 (15)	5 (12.5)
Unstable	7 (17.5)	
Histrionic	6 (15)	6 (15)
Narcissistic		1 (2.5)
Anxious	10 (25)	11 (27.5)
Dependent	9 (22.5)	10 (25)
Obsessive-compulsive	15 (37.5)	13 (32.5)

[a]Percentages in parenthesis.

Table 3 Differences between patients with bipolar illness with and without comorbid personality disorder

Bipolar disorder	Comorbid personality disorder		Statistics
	Present, n = 30	Absent, n = 10	
Age at the first episode	26.61 (7.50)	31.63 (9.29)	t = 1.605, d.f. = 37, p = ns
Depressive episodes	5.58 (6.21)	4.88 (5.41)	t = 0.293, d.f. = 37, p = ns
Manic episodes	2.81 (3.07)	5.13 (5.87)	t = 1.554, d.f. = 37, p = ns
Hypomanic episodes	1.90 (2.47)	3.75 (4.92)	t = 1.509, d.f. = 37, p = ns
Duration of disease	21.07 (12.32)	12.50 (6.72)	t = 1.881, d.f. = 37, p = ns
Hospitalization	4.71 (4.80)	5.75 (5.75)	t = 0.489, d.f. = 37, p = ns

include a duration of disease of about 19 years, a mean of 5 depressive episodes, 4 manic episodes, and 3 hypomanic episodes, and an average of 5 occasions in which admission to the hospital for in-patient care was needed. This indicates that, in general, we studied a population of bipolar patients with a long-standing disorder and torpid clinical course, which in turn is adequate to assess comorbidity.

The incidence of comorbid personality disorder in the present sample of 40 euthymic patients with bipolar illness was very high either according to ICD-10 criteria (75%) or DSM-IV criteria (75%). These figures are greater than those reported by others (Gonzalez-Pinto et al 1997). However, the high rate of co-occurrence of personality disorders may be related to the long clinical course of bipolar illness in the

Table 4 Relationships between clinical variables and characteristics of the bipolar disorder in patients with and without comorbid personality disorder

	Depressive	Manic	Hypomanic	Age at onset	Duration disease	Hospitalizations
Bipolar disease without comorbid personality disorder (n = 10)						
Depressive		r = 0.896*	r = 0.835*	r = 0.652†	r = 0.679†	r = 0.815*
Manic	r = 0.896*		r = 0.946*	ns	r = 0.680†	r = 0.967*
Hypomanic	r = 0.835*	r = 0.946*		ns	ns	r = 0.969*
Age at onset	r = 0.652†	ns	ns		ns	ns
Duration disease	r = 0.679†	r = 0.680†	ns	ns		ns
Hospitalizations	r = 0.815*	r = 0.967*	r = 0.969*	ns	ns	
Bipolar disease with comorbid personality disorder (n = 30)						
Depressive		ns	r = 0.392†	ns	ns	r = 0.531*
Manic	ns		ns	ns	ns	ns
Hypomanic	r = 0.392†	ns		ns	ns	ns
Age at onset	ns	ns	ns		ns	ns
Duration disease	ns	ns	ns	ns		ns
Hospitalizations	r = 0.531*	ns	ns	ns	ns	
Bipolar disease with one comorbid personality disorder (n = 11)						
Depressive		ns	ns	r = 0.620†	ns	ns
Manic	ns		ns	ns	ns	ns
Hypomanic	ns	ns		ns	ns	ns
Age at onset	r = 0.620†	ns	ns		ns	ns
Duration disease	ns	ns	ns	ns		r = 0.718†
Hospitalizations	ns	ns	ns	ns	r = 0.718†	
Bipolar disease with more than one comorbid personality disorder (n = 19)						
Depressive		ns	r = 0.474†	ns	ns	r = 0.671*
Manic	ns		ns	ns	ns	ns
Hypomanic	r = 0.474†	ns		ns	ns	ns
Age at onset	ns	ns	ns		r = −0.556†	ns
Duration disease	ns	ns	ns	r = −0.556†		ns
Hospitalizations	r = 0.671*	ns	ns	ns	ns	

*p < 0.05; †p < 0.01.

study population. On the other hand, it has been shown that bipolar subjects with co-occurring personality disorder have a poorer outcome and a worse psychosocial adaptation (Colom et al 2000) as well as a higher number of affective episodes (Vieta et al 2001). In the present study, however, there were no significant differences in the clinical course and history of bipolar illness between bipolar patients with and without comorbid personality disorder. This finding might indicate that the presence of comorbid personality disorder does not essentially modify the course of bipolar illness in terms of the number of affective episodes (depressive, manic, and hypomanic), duration of disease, and number of hospitalizations. In addition, age at first episode was not significantly different between the groups of bipolar subjects with and without comorbid personality disorder. These data are not in agreement with data reported by Vieta et al (2001) who found that comorbidity had a clear relevance to the course and outcome of bipolar illness, which may be explained by the size of our study sample.

However, when subsamples of patients with and without comorbid personality disorders are independently analyzed, significant correlations between clinical data and outcome were observed. Patients without comorbid personality disorder showed a significant correlation for a higher number of admissions to the hospital with a greater number of affective episodes (depression, mania, and hypomania). Moreover, there was a direct correlation among the number of affective episodes themselves, particularly between hypomanic episodes and depressive and manic episodes. Additionally, age at first episode and the number of depressive episodes showed a statistically significant relationship, that is, patients of an older age at the onset of bipolar illness showed a higher number of depressive episodes. These results emphasize the importance of the clinical course of the disease (ie, affective episodes) as the most important reason for in-patient care as well as the strong interrelationships of manic, hypomanic, and depressive episodes.

Patients with only one comorbid personality disorder showed a significant association between age at onset of the first episode and the number of depressive episodes, a similar finding to that observed in bipolar patients without comorbid personality disorder. When the personality disorder is more complex, that is, when patients meet diagnostic criteria for more than one comorbid personality disorder, there was a statistically significant inverse correlation between age at first episode and duration of disease, that is, the younger the patient at the first episode of bipolar illness the longer the course of the disorder.

On the other hand, there was a significant association between depressive episodes and hospitalizations. In these patients, in-patient care might be more strongly related to personality disorder-associated characteristics than to the bipolar illness itself.

In agreement with data reported by others (Rossi et al 2001; Brieger et al 2003), obsessive-compulsive personality disorder was the most frequent axis II disorder in our study, with cluster C (obsessive-compulsive and anxious) and cluster A (paranoid) personality disorders as the most common types. In the series of 52 euthymic male bipolar patients reported by Kay et al (2002), cluster A and cluster B disorders were the most frequent, whereas in the study of George et al (2003), cluster B and cluster C personality disorders were more common than cluster A. Comorbid personality disorder observed in our patients may be a consequence of the bipolar illness as argued by Hirschfeld et al (1986), which may affect personality by decreasing the emotional strength and favoring anancastic, anxious, and paranoid aspects of the patient's personality traits.

In summary, in a series of 40 euthymic patients with bipolar illness, comorbid personality disorder was diagnosed in 75% of patients with obsessive-compulsive personality disorder being the most frequent type. Sixty-three per cent of subjects had more than one comorbid personality disorder. The number of hospitalizations correlated significantly with depressive episodes and there was an inverse correlation between age at first episode and duration of bipolar illness. These findings, however, should be interpreted taking into account the preliminary nature of a pilot study and the contamination of the sample with too many bipolar II patients.

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References

Baldassano CF. 2006. Illness course, comorbidity, gender, and suicidality in patients with bipolar disorder. *J Clin Psychiatry*, 67 (Suppl 11):8–11.

Bieling PJ, MacQueen GM, Marriot MJ, et al. 2003. Longitudinal outcome in patients with bipolar disorder assessed by life-charting is influenced by DSM-IV personality disorder symptoms. *Bipolar Disord,* 5:14–21.

Brieger P, Ehrt U, Marneros A. 2003. Frequency of comorbid personality disorders in bipolar and unipolar affective disorders. *Compr Psychiatry*, 44:28–34.

Colom F, Vieta E, Martinez-Aran A, et al. 2000. Clinical factors associated with treatment noncompliance in euthymic bipolar patients. *J Clin Psychiatry,* 61:549–55.

Deltito J, Martin L, Riefkohl J, et al. 2001. Do patients with borderline personality disorder belong to the bipolar spectrum? *J Affect Disord,* 67:221–8.

Dunayevich E, Sax KW, Keck PE Jr, et al. 2000. Twelve-month outcome in bipolar patients with and without personality disorders. *J Clin Psychiatry,* 61:134–9.

George EL, Miklowitz DJ, Richards JA, et al. 2003. The comorbidity of bipolar disorder and axis II personality disorders: prevalence and clinical correlates. *Bipolar Disord,* 5:115–22.

Gonzalez-Pinto A, Ibarrola E, Garcia-Godoy MJ, et al. 1997. Curso y evolución del trastorno bipolar. In Gutierrez M, Ezcurra J, Pichot P, (eds). Ediciones en Neurociencias, p 227–40.

Gunderson JG, Weinberg I, Daverswa MT, et al. 2006. Descriptive and longitudinal observations on the relationship of borderline personality disorder and bipolar disorder. *Am J Psychiatry,* 163:1173–8.

Hammen C, Gitlin M, Altshuler L. 2000. Predictors of work adjustment in bipolar I patients: a naturalistic longitudinal follow-up. *J Consult Clin Psychol,* 68:220–5.

Henry C, Mitropoulou V, New AS, et al. 2001. Affective instability and impulsivity in borderline personality and bipolar II disorders: similarities and differences. *J Psychiatr Res,* 35:307–12.

Hirschfeld RM, Klerman GL, Keller MB, et al. 1986. Personality of recovered patients with bipolar affective disorder. *J Affect Disord,* 11:81–9.

Kay JH, Altshuler LL, Ventura J, et al. 1999. Prevalence of axis II comorbidity in bipolar patients with and without alcohol use disorders. *Ann Clin Psychiatry,* 11:187–95.

Kay JH, Altshuler LL, Ventura J, et al. 2002. Impact of axis II comorbidity on the course of bipolar illness in men: a retrospective chart review. *Bipolar Disord,* 4:237–42.

Levander E, Frye MA, McElroy S, et al. 2007. Alcoholism and anxiety in bipolar illness: Differential lifetime anxiety comorbidity in bipolar I women with and without alcoholism. *J Affect Disord,* doi:10.1016/j.jad.2006.11.023.

Leverich GS, Altshuler LL, Frye MA, et al. 2003. Factors associated with suicide attempts in 648 patients with bipolar disorder in the Stanley Foundation Bipolar Network. *J Clin Psychiatry,* 64:506–15.

McElroy SL. 2004. Diagnosing and treating comorbid (complicated) bipolar disorder. *J Clin Psychiatry,* 65 (Suppl 15):35–44.

McIntyre RS, Konarsky JZ, Soczynska JK, et al. 2006. Medical comorbidity in bipolar disorder: implications for functional outcomes and health service utilization. *Psychiatr Serv*, 57:1140–4.

Moreno MJ, Medina A, Lillo R, et al. 2002. Lista integrada para el diagnóstico de los trastornos de personalidad (LIDTP). *An Psiquiatr,* 18:359–68.

Rossi A, Marinangeli MG, Butti G, et al. 2001. Personality disorders in bipolar and depressive disorders. *J Affect Disord,* 65:3–8.

Sasson Y, Chopra M, Harrari E, et al. 2003. Bipolar comorbidity: from diagnostic dilemmas to therapeutic challenge. *Int J Neuropsychopharmacol,* 6:139–44.

Singh GH, Zarate A Jr. 2006. Pharmacological treatment of psychiatric comorbidity in bipolar disorder: a review of controlled trials. *Bipolar Disord,* 8:696–709.

Stone MH. 2006. Relationship of borderline personality disorder and bipolar disorder. *Am J Psychiatry*, 163:1126–9.

Takata T, Takaoka K. 2000. Bipolar II disorder and its premorbid personality. *Psychopathology,* 33:86–93.

Vieta E, Colom F, Corbella B, et al. 2001. Clinical correlates of psychiatric comorbidity in bipolar I patients. *Bipolar Disord,* 3:253–8.

Vieta E, Colom F, Martínez-Arán A, et al. 2000. Bipolar II disorders and comorbidity. *Compr Psychiatry,* 41:339–43.

Winokur G, Coryell W, Akiskal HS, et al. 1995. Alcoholism in manic-depressive (bipolar) illness: familial illness, course of illness, and the primary-secondary distinction. *Am J Psychiatry,* 152:365–72.