Research Article

ANXIETY DISORDER COMOBIDITY IN BIPOLAR I DISORDER: RELATIONSHIP TO DEPRESSION SEVERITY AND TREATMENT OUTCOME

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The present study investigated the greater symptom severity and poorer treatment response found in patients with bipolar illness and anxiety comorbidity, and examined depression as a potential mediator of this relationship. The sample consisted of 92 patients in an acute episode of Bipolar I Disorder with a current or past history of an anxiety disorder. Diagnoses were based on structured clinical interview, and participants were assessed at pre-treatment and then randomly assigned to pharmacotherapy alone or pharmacotherapy plus family intervention. Patients were assessed on a monthly basis by blind assessors over 28 months. Compared to patients without anxiety comorbidity, individuals with bipolar disorder and an anxiety disorder possessed greater current symptom severity, even after controlling for depression severity. Logistic regression analysis identified that being female and having higher current depression but not manic severity predicted comorbid anxiety. Comorbid anxiety was associated with poorer treatment response in the sample regardless of treatment type, particularly in subsequent depressive symptoms. Multiple regression analyses indicated that current depression but not manic severity partially mediated the relationship between comorbid anxiety and treatment outcome. Results from the current study investigating comorbid anxiety disorders are consistent with past research limited to anxiety symptoms. Depression only partially accounted for the link between comorbid anxiety and greater symptom severity and poorer treatment response, and examination of other factors is warranted. Because of the clinical relevance of comorbid anxiety in severe affective disorders, treatments designed to specifically address both concerns are needed. Depression and Anxiety 21:71–77, 2005. *© 2005 Wiley-Liss, Inc.*

Key words: *bipolar disorder; anxiety disorders; family therapy; depression; comorbidity; randomized controlled trials*

INTRODUCTION

Bipolar Disorder (BP) is a chronic and debilitating psychiatric illness [Keller et al., 1993; Winokur et al., 1993]. Research is needed into factors contributing to greater severity and poorer prognosis in this population. In numerous studies, individuals with depression and comorbid anxiety have been shown to exhibit greater severity and chronicity of illness [Coryell et al., 1988], more suicidality [Fawcett, 1992], and poorer treatment response to both pharmacotherapy [Frank et al., 2000] and psychosocial interventions [Feske et al., 1998] when compared to those with depression alone. Only recently have researchers begun to investigate the link between BP and comorbid anxiety.

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Preliminary evidence has confirmed that comorbid anxiety also is clinically relevant in bipolar illness. Epidemiologic studies reveal that anxiety disorders co-occur in BP at higher rates than in the general population in the United States [Kessler et al., 1998] and abroad [Szadoczky et al., 1998]. Although prevalence rates vary widely depending on the sample, some epidemiologic evidence suggests that anxiety disorders are more common in bipolar than in unipolar depression [Chen and Dilsaver, 1995].

Studies of treatment-seeking samples show similar comorbidity trends. As in unipolar depression, BP patients with comorbid anxiety show greater symptom severity and chronicity [Frank et al., 2002], more suicidality [Young et al., 1993], and poorer treatment response to pharmacotherapy [Feske et al., 2000; Young et al., 1993] and to combined drug and psychotherapeutic interventions [Frank et al., 2002]. Emerging evidence suggests that BP and comorbid anxiety is associated with family history based on genetic linkage studies [MacKinnon et al., 1998]. Support for the hypothesis that comorbid anxiety disorders are more frequent in patients with BP versus other mental disorders, including unipolar depression, is more equivocal when treatment samples with severe psychopathology are studied [Cosoff and Hafner, 1998; Craig et al., 2002; Simon et al., 2003].

Current studies possess several methodologic weaknesses including small sample sizes, differential and at times nonstandardized methods of assessment, and heterogeneous diagnostic groups [e.g., Yerevanian et al., 2001]. Few quality studies have examined patients who are acutely ill, diagnosed specifically with Bipolar I Disorder, or randomly assigned to pharmacotherapy only versus adjunctive psychotherapy.

Furthermore, data suggest that anxiety symptoms are less prevalent during manic episodes and more prevalent in Bipolar II than in Bipolar I Disorder [Perugi et al., 1999]. In general, little attention has been given to the relationship between anxiety and depression versus mania in patients with BP. Without such information, it is possible that the bipolar–anxiety link may be associated more with depression than with mania per se, similar to that in unipolar depression.

The purpose of the current study was to clarify the relationship between Bipolar I Disorder in patients with or without comorbid anxiety disorders. The study was designed to address three broad questions. First, are comorbid anxiety disorders in patients in an acute episode of illness associated with greater current severity and historical chronicity? Second, are comorbid anxiety disorders in bipolar patients associated with poorer treatment response to pharmacotherapy alone and in combination with family intervention? Third, what role does depression play in the relationship between BP and comorbid anxiety disorders in the above two questions?

SUBJECTS AND METHODS

SUBJECTS

Subjects were recruited to participate in a larger clinical trial [the "parent" study; Miller et al., 2004a] assessing pharmacotherapy versus pharmacotherapy plus family interventions for BP. Inclusion criteria for the study were as follows: diagnosis of Bipolar I Disorder (current episode manic, depressed, or mixed) based on structured clinical interview; aged 18–75 years; fluency in English; and regular contact with a relative or significant other. Exclusion criteria were as follows: diagnosis of alcohol or drug dependence during the past year; a mood disorder secondary to a medical condition; a medical illness severe enough to contraindicate the use of mood stabilizing medication; or pregnancy or inadequate contraception use.

Subjects consisted of 52 women and 40 men. The mean age of the sample was 39 years (standard deviation [*sd*] = 11.5 years) and mean years of education was 13 (*sd* = 2.5). Regarding relationship status, 62% were married, 17% were divorced/separated/widowed, 6% were cohabitating, and 15% were never married. The ethnic makeup of the sample was as follows: 1% Latino, 3% African American, and 96% Caucasian. When admitted to the study, 75% were in a manic episode, 20% were in a depressed episode, and 5% were in a mixed episode; 69% were experiencing psychotic symptoms. The sample was relatively severe, with 16% reporting one or two previous mood episodes, 24% reporting two to six previous episodes, and 60% reporting seven or more past episodes. Mean age of first manic episode was 28 years (*sd* = 10.6 years), and mean number of psychiatric hospitalizations was 4.7 (*sd* = 4.5; range = 1–25). Of the sample, nine were recruited from outpatient settings, with the remaining from inpatient or partial hospitalization settings.

ASSESSMENTS

The Structured Clinical Interview for DSM-III-R [SCID-I; Spitzer and Williams, 1988] is a commonly used semi-structured clinical interview for Axis I disorders and was used to assess diagnostic status. SCID assessments were administered by trained assessors at pre-treatment. The Modified Hamilton Rating Scale for Depression [MHRSD; Miller et al., 1985] is a 25-item interviewer-rated instrument that was used to assess depression severity. The commonly used 17-item total was used in analyses. The Bech-Rafaelsen Mania Scale [BRMS; Bech et al., 1979] is an 11-item interviewer-rated scale used to assess severity of manic symptoms. Suicidal ideation was assessed using the Modified Scale for Suicidal Ideation [MSSI; Miller et al., 1986], which is a 21-item semi-structured interview based on Beck's Scale for Suicidal Ideation. The MHRSD and BRMS were administered at pre-treatment and then on a monthly basis, and responses

were based on the worst previous week. The MSSI was administered at pre-treatment and at Months 4, 10, 16, 22, and 28. Interviewers were trained to proficiency and were blind to treatment condition. The Beck Depression Inventory [BDI; Beck et al., 1988] was used to assess self-reported levels of depressive symptoms and was administered at pre-treatment.

TREATMENTS

For a more detailed description of treatment conditions, please refer to Miller et al. [2004a]. After pre-treatment assessment, patients were randomly assigned to one of three groups: 29 participants were assigned to medication alone, 30 were assigned to medication plus family psychoeducational group, and 33 were assigned to medication plus family therapy. The number of outpatients assigned to each condition was roughly equivalent.

Pharmacotherapy was administered using a protocol of standardized procedures adapted from the Clinical Management-Imipramine/Placebo Administration Manual [Fawcett et al., 1987]. Ninety-two percent of participants were prescribed a mood stabilizer. Additional medications were prescribed as appropriate based on the type and severity of symptoms to optimize treatment response. Subjects met with their psychiatrist once per week for the first month, and then less frequently based on patient improvement.

Family psychoeducation group therapy [Keitner et al., 2002] consisted of six 90-min, multifamily meetings during the first 2 months post-discharge. Psychoeducation and coping strategies for managing problems associated with bipolar illness were suggested. Sessions were lead by two experienced group psychotherapists. Family therapy was based on the Problem-Centered Systems Therapy of the Family [PCSTF; Epstein and Bishop, 1981; Epstein et al., 1989]. PCSTF is a short-term, present-focused approach that targets current problems in family functioning. Session number varied based on need, ranging from 6 to 10 sessions of 50-min duration. Therapy was delivered by two therapists trained and experienced in the PCSTF approach.

PROCEDURE

Patients in an acute bipolar episode were approached to determine their willingness to participate in a study on the treatment of Bipolar Disorder. After a complete description of the study, patients and their family members provided written informed consent if they agreed to participate and met eligibility criteria. After completing pre-treatment measures, participants were randomly assigned to treatment conditions. Follow-up assessments were completed monthly for the next 28 months.

STATISTICAL ANALYSES

Patients who met criteria for a current or past anxiety disorder diagnosis were included in the comorbid anxiety group. Previous research demonstrates that significant levels of anxiety are related to increased severity and poorer treatment response in bipolar patients. Individuals with a history of an anxiety disorder would be more likely to possess significant anxiety symptoms compared to those without an anxiety disorder. Counting these individuals in the no-anxiety group would likely have resulted in improper categorization of participants. Previous research supports the utility of including participants with a significant lifetime history of anxiety [Feske et al., 1998; Frank et al., 2000, 2002].

Analysis of demographic and pre-treatment variables was used to determine appropriate covariates to include in subsequent analyses. Differences between patients with and without anxiety comorbidity may be accounted for by differences in depression levels. For depression measures, polarity of current episode was used as the covariate, whereas for non-depression measures, depression severity was used as the covariate. Group comparisons were computed based on univariate analyses of covariance. Logistic regression was used to identify variables that predicted comorbid anxiety disorder group membership. A series of regression analyses were conducted to determine if depressive versus manic symptoms mediated the relationship between anxiety comorbidity and treatment outcome. Two-tailed tests were used with α level set at .05.

Treatment outcome was computed in the following way. Subjects' scores on the MHRSD and BRMS were classified as *fully symptomatic* if they possessed scores of 15 or greater on the monthly MHRSD or BRMS. Based on this classification, *percent time symptomatic* was calculated by dividing number of months fully symptomatic by the total number of months for which data were collected in the study [Miller et al., 2004b]. For example, if a patient met criteria for being fully symptomatic according to the MHRSD or BRMS for 10 of 25 months for which data were available, his/her percent time symptomatic would be 40%.

RESULTS[1]

PRELIMINARY ANALYSES

Of 92 participants, 28% ($n = 20$) met criteria for at least one current or past anxiety disorder based on

[1]The 17-item HRSD was used to assess depression in the current study because it has been the "gold standard" in clinical trials in this area, permitting easy comparison of results across studies. The measure has been criticized extensively, as it seems to be multi- rather than unidimensional [Babgy et al., 2004]. We therefore explored a possible confound in our analyses that involved comparing the scores of patients with or without an anxiety disorder on a depression scale containing some items related to

SCID-I assessment at pre-treatment. The frequency of specific anxiety disorders was as follows: Panic Disorder with or without Agoraphobia ($n = 14$), Post-traumatic Stress Disorder ($n = 9$), Generalized Anxiety Disorder ($n = 3$), Social Phobia ($n = 2$), Specific Phobia ($n = 1$), and Obsessive-Compulsive Disorder ($n = 1$). Most participants possessed at least one current anxiety disorder ($n = 14$). Ten participants met criteria for more than one current or past anxiety disorder.

Subjects with Bipolar I Disorder and a comorbid anxiety disorder (BP-A group) and those with Bipolar I Disorder only (BP-only group) did not differ in pre-treatment Global Assessment of Functioning scores based on an independent samples t test, or in education level, ethnicity, income, or marital status based on χ^2 analyses. The BP-A group ($M = 35.2$; $sd = 10.1$) was significantly younger than the BP-only group ($M = 40.8$, $sd = 11.4$; $t_{90} = 1.98$, $P = .05$). Polarity of the current BP episode (i.e., manic versus depressed or mixed depressed and manic) also was examined by group. Seventy-eight percent of participants in the BP-only group compared to 65% in the BP-A group were in an acute manic episode. A χ^2 analysis carried out on polarity by group was not significant ($P = ns$).

Furthermore, there were significantly more females than males in the BP-A group (females = 75%; $\chi^2_1 = 5.00$, $P < .05$) compared to in the BP-only group (females = 46%; $P = ns$). Gender was not used as a covariate in the following analyses. It was deemed more appropriate to control for other pre-treatment differences (e.g., depression severity) than for gender per se, as such a procedure would be technically possible but conceptually problematic [Miller and Chapman, 2001].

Finally, there were no differences found between treatment groups in recovery from illness rates in the parent study. Also, drop-out rates did not differ by treatment group. Refer to Miller et al. [2004a] for further information on the overall sample and general treatment outcome findings.

SEVERITY INDICATORS

Historical chronicity. Raw means and standard deviations are depicted in Table 1. Analyses of covariance (ANCOVA) controlling for age revealed that the BP-A group had significantly more depressive episodes within the past year ($F_{1,66} = 5.83$; $P < .05$). Furthermore, the BP-only group had significantly greater number of past manic hospitalizations ($F_{1,66} = 6.79$; $P < .05$). No significant differences were found between the groups in number of manic episodes within the past year or age of first depressive/manic episode (all $P = ns$). In general, the BP-A group showed greater depression chronicity and the BP-only group showed greater manic chronicity historically.

Current severity. ANCOVA controlling for age and polarity showed that the BP-A group had significantly higher scores on the pre-MHRSD ($F_{1,87} = 11.91$; $P = .001$) and the pre-BDI ($F_{3,83} = 6.51$; $P < .001$) than the BP-only group did, but not on the pre-MSSI ($P = ns$). Controlling for MHRSD scores and age, the BP-A group also had significantly higher manic severity according to the BRMS compared to that for the BP-only group ($F_{1,87} = 4.99$; $P < .05$). In general, the BP-A group showed higher levels of current depressive and manic symptoms than did the BP only group, even after controlling for current depression.

PREDICTORS OF ANXIETY COMORBIDITY

Logistic regression analysis was used to identify predictors of anxiety disorder comorbidity in BP participants. The demographic variables of age and gender were entered in the first step as covariates, and the pre-treatment MHRSD and BRMS were entered in the second. In the final equation, gender (Wald $\chi^2_1 = 3.48$; $P < .05$) and pre-MHRSD (Wald $\chi^2_1 = 10.74$; $P < .01$), but not pre-BRMS ($P = ns$) or age ($P = ns$) predicted anxiety comorbidity. Anxiety comorbidity was predicted by greater depression severity ($e^b = 1.18$) and female gender ($e^b = .20$).

RELATIONSHIP TO TREATMENT OUTCOME

Controlling for polarity and age, ANCOVA with treatment type (pharmacotherapy versus family therapy) and anxiety comorbidity (present versus absent) were conducted on percent time symptomatic post-treatment. To aid in the interpretation of significant findings, ANCOVA also were conducted on percent time high (total ≥ 15) on the MHRSD and the BRMS, separately. Significant main effects were found for anxiety comorbidity. The BP-A group spent a significantly higher percentage of time symptomatic ($F_{1,72} = 5.28$; $P < .05$) and high on the MHRSD ($F_{3,50} = 4.55$; $P < .001$), but not high on the BRMS ($P = ns$) compared to the BP-only group. No significant interactions or main effects for treatment type were found (as $P = ns$). In summary, anxiety comorbidity negatively affected treatment outcome, but primarily in depressive in contrast to manic symptoms.

MEDIATION ANALYSES

It was hypothesized that depressive symptoms partially mediated the relationship between comorbid

anxiety. Several authors have presented factor-analyzed versions of the HRSD; however, there is poor agreement across studies regarding the number of factors it contains or which items load onto which factors [e.g., Fleck et al., 1995; Pancheri et al., 2002]. We replicated our analyses by substituting the 15-item MHRSD total score (excluding the two explicitly anxiety-related questions) or the BDI, which is the most widely used self-report depression inventory. In all cases, findings were identical using the BDI or 15-item MHRSD, and therefore these results are not presented in detail. Results using the 17-item MHRSD are reported instead as this was the primary outcome measure used to assess treatment outcome in the parent study [Miller et al., 2004a].

anxiety and treatment outcome. Based on recommendations by Baron and Kenny [1986] for testing mediation hypotheses, three independent regression equations were computed: regressing the mediator (i.e., pre-MHRSD) on the independent variable (i.e., anxiety disorder comorbidity); regressing the dependent (i.e., percent time symptomatic) on the independent variable; and regressing the dependent on both the independent and mediator variables. Mediation occurs if the first two regressions are significant, and in the third equation, the strength of the relationship between the independent and dependent variables is decreased by inclusion of the mediator [see Holmbeck, 2002 for more information].

All the above conditions were met using current depression severity as the mediator (see Table 2). Anxiety comorbidity significantly predicted pre-MHRSD ($P<.05$). Anxiety comorbidity also predicted percent time symptomatic ($P<.01$). Finally, anxiety comorbidity ($P<.05$) and pre-MHRSD ($P<.01$) predicted percent time symptomatic. Testing the standard error of the indirect effect using the Sobel test indicated that pre-MHRSD partially mediated the relationship between anxiety disorder comorbidity and percent time symptomatic ($t_{74}=1.95$; $P=.05$).

In addition, regression analyses were conducted exactly as above to determine if manic severity also mediated the relationship between anxiety comorbidity and percent time symptomatic; however, results did not support manic severity as a mediator. The pre-BRMS was not a significant predictor of anxiety comorbidity ($P=ns$). In summary, depression but not mania mediated the relationship between anxiety comorbidity and treatment outcome.

TABLE 1. Measures in bipolar patients with or without comorbid anxiety disorders

Variables	Bipolar-only ($n=72$)	Bipolar-anxiety ($n=20$)
Pre-treatment severity		
MHRSD	7.6 (8.5)	14.6 (9.9)
BRMS	21.4 (10.5)	20.6 (11.8)
BDI	11.9 (10.3)	19.2 (13.3)
MSSI	4.3 (10.9)	8.0 (12.6)
Historical chronicity		
Age first manic episode (yr)	29.2 (11.3)	25.7 (6.9)
Age first depressive episode (yr)	22.7 (10.5)	18.1 (6.6)
Manic episodes in past year	1.1 (.6)	1.4 (.8)
Depressive episodes in past year	1.3 (1.7)	2.7 (3.3)
Manic hospitalizations	2.9 (2.2)	1.4 (1.4)
Treatment outcome (%)		
Percent time symptomatic	18.2 (25.4)	41.3 (38.2)
Percent time high on MHRSD	12.9 (20.8)	40.8 (38.8)
Percent time high on BRMS	6.0 (16.4)	8.0 (13.7)

Values are expressed as mean (*sd*).
Raw data depicted; statistical analyses based on means evaluated at appropriate covariates.
MHRSD, Modified Hamilton Rating Scale for Depression (17-item version); BRMS, Bech-Rafaelsen Mania Scale; BDI, Beck Depression Inventory; MSSI, Modified Scale for Suicidal Ideation. Percent time high on the MHRSD/BRMS = total scores ≥ 15.

DISCUSSION

The present study examined the relationship between Bipolar I and current/past anxiety disorders in patients in an acute episode of illness. Results indicated that comorbid anxiety was related to greater severity in a number of domains, including current severity. Consistent with other studies of BP [Cosoff and Hafner, 1998; Frank et al., 2002], women possessed higher rates of comorbid anxiety disorders than men did. Frank et al. [2002] found similar results in a sample of 66 outpatients divided into low- and high-anxiety groups based on scores from a self-report measure of panic-spectrum symptoms. These authors suggested that categorical classification of anxiety disorders may fail to capture this relationship. The current study replicated and extended these findings in a sample of patients meeting diagnostic criteria for a current/past anxiety disorder.

Furthermore, the clinical significance of the difference in outcome in patients with and without anxiety comorbidity was striking. Bipolar patients with comorbid anxiety disorders were symptomatic an average of 41% of the time whereas bipolar patients without this comorbidity were symptomatic an average of only 18% of the time (see Table 1). Although separate studies investigating treatment response to pharmacotherapy alone or treatment combined with psychosocial interventions have shown that comorbid anxiety is associated with poorer outcome, this investigation is the first to our knowledge to demonstrate the relationship in patients randomly assigned to different types of treatment within a single study. It also is the first study to examine the relationship in those receiving adjunctive family therapy for BP, which failed to reduce the deleterious effects of comorbid anxiety on treatment outcome.

Little previous research has examined the role of depression in the relationship between BP and comorbid anxiety. An evaluation of depression is critical, as the documented association between anxiety and depressive disorders is strong and consistent. In general, differences in depression as opposed to manic severity more clearly separated those with versus those without comorbid anxiety in the current study. In addition, current depression but not mania predicted comorbid anxiety disorders, and poorer treatment response in the BP-A group was restricted to depression but not manic symptoms.

Nevertheless, other results suggested that depression did not account completely for the relationship between mania and anxiety comorbidity. Depression only partially mediated the relationship between

TABLE 2. Multiple regression analyses examining depression as a mediator of the relationship between anxiety disorder comorbidity and treatment outcome

Criterion	Predictor	β	t	P
Equation 1				
Pre-MHRSD	1. Anxiety comorbidity	.28	2.52	.014*
Equation 2				
% Time symptomatic	1. Anxiety comorbidity	.32	2.94	.004**
Equation 3[a]				
% Time symptomatic	1. Anxiety comorbidity	.24	2.07	.042*
	2. Pre-MHRSD	.33	3.06	.003**

[a]Equation 3: $F(2, 74) = 9.31$, $P < .001$.
*$P < .05$; **$P < .01$.
MHRSD, Modified Hamilton Rating Scale for Depression.

comorbidity and treatment outcome; and those with anxiety disorders displayed both greater depression and manic severity currently. Furthermore, the relationship between comorbid anxiety and increased severity remained even after controlling for current depressive symptoms or polarity of episode. These findings raise the possibility that other variables (e.g., comorbid substance use or psychosis) also are associated with poorer outcome and anxiety comorbidity in bipolar patients. As the literature strongly supports the link between depression and anxiety [Frank et al., 2000], as well as high severity and psychiatric comorbidity in general [de Graaf et al., 2004], both of these factors are likely to be relevant in BP as well.

Strengths of the current study that constitute improvements in previous research include examination of a sample of exclusively Bipolar I patients in an acute episode, use of standardized and blinded assessment procedures, random assignment of patients to treatment groups, longitudinal assessment, long-term follow-up, and analysis of clinically significant outcomes. Potential limitations also exist. First, the study did not include a standardized measure of anxiety severity but was limited to examination based on diagnostic status. Although dimensional versus categorical examination of anxiety is likely to yield a richer picture of the relationship between anxiety and BP, this study found largely similar results when compared to previous research using continuous measures [Frank et al., 2002]. One could argue that diagnostic status is a clinically important variable to examine as this information is likely to be more widely available to treatment providers. Furthermore, results suggest that even a past history of an anxiety disorder may help predict current treatment response to pharmacologic or combined treatments.

Another potential limitation of the study was that the investigation of adjunctive psychosocial treatments was based on family interventions only. Because studies have found mixed results regarding the benefit of family therapy for acutely ill patients with BP [Miller et al., 2004a], it is unclear whether other psychosocial treatments could help ameliorate the negative effects of comorbid anxiety on treatment outcome found in this study. To our knowledge, the relationship between comorbid anxiety and treatment response with interventions other than family and interpersonal therapy has not yet been investigated in this population.

Our sample size of comorbid anxiety patients was only modest, potentially limiting the generalizability of results. Furthermore, cell sizes for treatment type by anxiety comorbidity may have been underpowered to detect any differences between treatments. However, even with the modest sample size the number and magnitude of significant results suggest that anxiety comorbidity in bipolar patients is a robust and important clinical feature. In addition, as is the case with any randomized, controlled trials, treatment provided and patient characteristics may be somewhat unrepresentative of general community samples and standards. For example, patients with recent substance use dependence were excluded from the study and treatment was delivered by specialists using standardized protocols.

Finally, one possible explanation for findings explored further was whether the relationship found between anxiety disorder comorbidity and depression severity was spurious, as the MHRSD contains some items related to anxiety. Analyses were rerun by substituting the BDI or 15-item MHRSD (excluding anxiety-related questions) for the 17-item MHRSD and showed the same results. Additionally, results remained significant even when the full MHRSD was used as a covariate in certain analyses. Furthermore, bipolar patients were compared based on the presence of anxiety *disorder* comorbidity, and not simply based on the presence of anxiety-related symptoms, which are quite common in depression in general.

Overall, results of the current study suggest that anxiety disorder comorbidity is most associated with depression compared to manic severity in patients with BP. Future studies should examine whether variables other than depression, such as psychotic severity or other psychopathology, also mediate the relationship between anxiety comorbidity and severity. Interestingly, Cosoff and Hafner [1998] found no differences in severity between those with comorbid anxiety who were hospitalized with bipolar versus a psychotic disorder. Although it is clear that anxiety comorbidity is associated with greater severity and poorer outcome in BP patients, the exact mechanisms of action will remain unknown until future research systematically examines several potential mediators within the same study.

Regardless of mechanisms of action, it is evident that comorbid anxiety is a clinically relevant factor in patients experiencing a bipolar illness. In typical clinical settings, intervention tends to focus on treatment of the acute episode, and little effort is made to treat comorbid psychopathology after patients are stabilized [Cosoff and Hafner, 1998]. Results from

the current study using pharmacotherapy plus family intervention, and others involving adjunctive interpersonal therapy [Frank et al., 2002], demonstrate that those with comorbid anxiety demonstrate a poorer response to treatment. Adjunctive treatments specifically designed to address anxiety comorbidity in individuals with severe affective disorders are greatly needed.

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