Course of Illness in Psychotic Mania

Is Mood Incongruence Important?

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Abstract: Previous research is inconsistent regarding the significance of mood-incongruent psychotic symptoms in relation to the severity and course of bipolar disorder. In the present study, bipolar I patients were assessed at index hospitalization using standardized symptom measures and followed up to 28 months. We contrasted the symptomatic course in patients experiencing mood-congruent versus mood-incongruent psychotic symptoms. Results revealed that patients spent an average of 29% of the time during follow-up in a mood episode, but only 5% of the time with psychotic symptoms. Few differences were found at the index hospitalization and no differences were found on any longitudinal course variables between mood-congruence subtypes. Although experiencing high levels of psychosis at baseline, both subtypes improved considerably following hospitalization, and psychotic symptom levels remained relatively stable. Current results suggest that when provided efficacious treatment, mood-incongruent psychotic mania does not predict a worse symptomatic course of illness.

Key Words: Bipolar disorder, psychotic features, course of illness, hierarchical linear modeling.

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Bipolar disorder (BP) remains a recurrent and severe mental illness for most patients despite advances in pharmacological treatments. Over 70% of patients relapse within 5 years of an index episode (Gitlin et al., 1995), and approximately half of those who do not relapse continue to experience impairing subthreshold mood symptoms (Altshuler et al., 2002; Harrow et al., 1990). Researchers have attempted to identify features of bipolar illness that may be predictive of its severity and course, including the presence of psychotic symptoms during mood episodes. Psychosis is quite common in BP, with approximately 58% of patients possessing a lifetime history of psychotic symptoms during a mood episode (Goodwin and Jamison, 1990).

In their classic paper, Pope and Lipinski (1978) argued that psychosis associated with a severe affective illness is relatively common and not of prognostic significance. Subsequent research has found that psychotic features appear to predict certain outcomes in major depression (e.g., Coryell et al., 1996; Gaudiano et al., 2005). However, results have been more equivocal in studies with BP patients. For example, researchers have reported a variety of conflicting results, including that psychotic features are predictive of worse psychosocial outcome (Rosen et al., 1983; Tohen et al., 1990) but decreased rates of relapse during lithium maintenance therapy (Rosenthal et al., 1979), whereas others have found no relationship whatsoever between psychosis and any long-term outcomes (Goldberg et al., 1995; Harrow et al., 1990; Judd et al., 2002).

In an attempt to improve predictive ability, several studies have examined the relationship between outcome and mood-congruence subtype, as mood-incongruent (MI) psychotic symptoms are believed to signify an illness closer in relation to a primary psychotic disorder (Harrow et al., 2000). BP patients with MI psychosis have been reported to spend a shorter time in remission (Tohen et al., 1992) and have poorer social adjustment and treatment compliance (Miklowitz, 1992) compared with those with mood-congruent (MC) psychosis. In a brief naturalistic study over 8 months by Strakowski et al. (2000), patients with MI psychotic mania had lower Global Assessment of Functioning (GAF) scores at follow-up and spent a higher percentage of time with psychotic symptoms, but spent a similar percentage of time with significant mood symptoms. In contrast, Zemlan et al. (1984) found that MI psychosis in bipolar patients was predictive of a more rapid antipsychotic response to lithium treatment. Most recently, Keck et al. (2003) reported no differences in psychotic symptom subgroups on any demographic, psychosocial, or historical course of illness variables in a large sample of 352 BP outpatients. However, longitudinal outcomes were not assessed in the study.

The DSM-IV-TR (American Psychiatric Association, 2000) requires that mood-congruence subtype be specified AQ:1 when diagnosing mood disorders with psychotic features; however, the aforementioned research does not clearly support the prognostic value of such distinctions. Previous studies of psychosis in BP patients often have examined relapse rates and psychosocial outcomes such as residential or occupational status. However, these variables fail to capture the symptomatic course of BP, including the impact of subsyndromal symptoms. Judd et al. (2002) described the natural course of 146 BP patients by reporting the percentage of

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follow-up weeks spent asymptomatic, subsyndromal, or fully syndromal using the Longitudinal Interval Follow-up Evaluation (LIFE; Keller et al., 1987). This methodology may be useful for examining the course of illness in patients with psychotic mania.

In the current study, we attempted to improve on methodological limitations in previous research by describing the longitudinal course of illness in a homogenous sample of bipolar I patients with psychotic mania for up to 28 months. Analyses were focused on patients experiencing a manic or mixed episode at the index hospitalization, as psychotic symptoms present during a depressive episode may have different prognostic significance (Coryell et al., 2001). In a previous report from the current dataset, Miller et al. (2004b) expanded on the methodology of Judd et al. (2002) by computing the percentage of time BP patients remained at various symptom levels using valid and widely used measures of depression and mania. However, this report did not examine psychotic symptoms specifically or their potential impact on course of illness in the sample. Further, although Judd et al. reported psychosis severity during follow-up, mood congruence subtypes were not examined in the cohort. Therefore, the aim of the current study was to examine the prognostic validity of MI versus MC subtyping as determined at the index hospitalization.

METHODS

Participants

Participants were recruited to participate in a larger clinical trial assessing pharmacotherapy versus pharmacotherapy plus family therapy for BP (Miller et al., 2004a). Inclusion criteria for the study were as follows: diagnosis of bipolar I disorder (current episode manic, depressed, or mixed) based on structured clinical interview, age 18 to 75, fluency in English, and regular contact with a significant other. Exclusion criteria were 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.

Ninety-two patients meeting study criteria were enrolled in the larger clinical trial; most were recruited during an index hospitalization ($N = 88$). Of the original sample, 74 were in a manic/mixed episode at index hospitalization and therefore included in the current study. In the current sample, 61% were female and 85% were Caucasian. The mean age of the sample was 39 ($SD = 11$), and mean years of education was 13 ($SD = 3$). Most patients were married or cohabitating (72%). Only 7% were in a mixed episode at index hospitalization. Participants had a severe previous course of illness, with 58% and 42% reporting three or more previous manic and depressive episodes, respectively.

Assessments

The Structured Clinical Interview for DSM-III-R (SCID-I/P; Spitzer and Williams, 1988) is a commonly used clinical interview for Axis I disorders and was used to determine diagnostic status at baseline. The LIFE (Keller et al., 1987) is a clinical interview that was used to derive weekly ratings of the presence/absence of psychotic symptoms over follow-up. LIFE assessments were conducted at months 4, 10, 16, 22, and 28 to derive symptom ratings for each week prior to the corresponding assessment point. The Bech-Rafaelsen Mania Scale (BRMS; Bech et al., 1979) is an 11-item interviewer-rated scale used to assess severity of manic symptoms, but does not include items related to psychosis. 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 MHRSD and BRMS were administered at baseline and thereafter on a monthly basis with responses based on the worst previous week. The Brief Psychiatric Rating Scale (BPRS; Lukoff et al., 1986) is a 24-item interviewer-rated instrument used to assess a variety of psychiatric symptoms. The BPRS-Psychosis Subscale, which assesses severity of psychotic symptoms, was administered at baseline, discharge from the hospital, and follow-up months 2, 4, 10, 16, 22, and 28.

All interviewers were trained to proficiency and blind to treatment conditions. Raters were trained to initial reliability (>0.85) with period checks to assure continued reliability. AQ:2
Patients with at least one significant psychotic symptom occurring during a manic episode at the index hospitalization and/or during a previous manic episode were identified using the SCID-I/P at the baseline assessment. Mood-congruence was defined according to DSM-IV-TR (American Psychiatric Association, 2000) criteria and methods used in previous studies (Burch et al., 1994; Keck et al., 2003; Miklowitz, 1992; Strakowski et al., 2000). Mood-incongruence was diagnosed when the content of delusions and/or hallucinations was not related to manic themes of grandiosity, elation, or special powers/relationships. For example, a delusion of persecution attributed to the patient's perceived special powers would be labeled MC. However, delusions such as thought broadcasting/control and other persecutory delusions not related to grandiosity were labeled as MI. When both congruent and incongruent symptoms were present (20% of sample), the interviewer made a judgment based on the frequency and severity. An independent, blind assessor (B. G.) categorized patients based on SCID assessment data into mood-congruence subtypes. Interrater reliability of mood-congruence classification was high (ICC = 0.87, $N = 59$).

Treatments

For a more detailed description of the parent clinical trial, refer to Miller et al. (2004a). Pharmacotherapy was administered using a protocol of standardized procedures adapted from the Clinical Management-Imipramine/Placebo Administration Manual (Fawcett et al., 1987). Of the total sample, all were prescribed a mood stabilizer and additional medications (including neuroleptics) were prescribed as appropriate based on the type and severity of symptoms to optimize treatment response. Of patients with psychosis at the index hospitalization, 90% were judged by independent chart review to have received adequate treatment with neuroleptics during the first 4 months of the trial. Participants met with their psychiatrist once per week for the first month, and then

less frequently based on patient improvement. In addition to pharmacotherapy, some patients also received family therapy (Ryan et al., 2005) or a family educational group treatment (Keitner et al., 2002). To ensure the generalizability of findings, assessments were continued when possible even if patients relapsed or dropped out of the study. Of the current sample, 69% completed study treatment through follow-up, with the remaining dropping out of formal study treatment but continuing to participate in at least some additional assessments.

Procedure

Following a complete description of the study, patients and their family members provided written informed consent (based on an Institutional Review Board-approved protocol). After baseline assessment, patients were randomly assigned to one of the three groups: medication alone, medication plus family psychoeducational group, or medication plus family therapy. Family therapy consisted of 12 sessions, and psychoeducational groups were held in six sessions. Follow-up assessments were completed monthly for the next 28 months. Assessments at baseline, discharge from the hospital, and 2, 4, 10, 16, 22, and 28-month follow-ups were conducted in face-to-face interviews. Assessments occurring during the intervening months were conducted via telephone. Previous research has documented the validity of HRSD phone administration (Simon et al., 1993), and scores between face-to-face and phone interviews were highly correlated in the sample (Miller et al., 2004b).

Percent Time Variables

Participants' scores on the MHRSD and BRMS were classified as asymptomatic, partially symptomatic, or fully symptomatic. For the MHRSD and BRMS, categories were based on the criteria established by Frank et al. (1991) and Bech et al. (1986), respectively. Scores of ≤ 7 (MHRSD) and ≤ 5 (BRMS) were considered asymptomatic, 8 to 14 (MHRSD) and 6 to 14 (BRMS) were considered partially symptomatic, and ≥ 15 (MHRSD and BRMS) were considered fully symptomatic. Based on this classification, percent time asymptomatic, partially symptomatic, and fully symptomatic were calculated by dividing the number of months spent in the respective symptom categories by the total number of months for which data were collected in the study (see Miller et al., 2004b, for a detailed description). Percent time variables were computed only for patients with at least 5 months of data available to assure a reasonable period of assessment. Similar to the study by Judd et al. (2002), percent time with psychotic symptoms was computed based on ratings derived using the LIFE. Because of its lack of validated cutoff criteria in patients with BP, the BPRS-Psychosis Subscale was analyzed as a continuous measure to examine overall psychosis severity and to supplement the LIFE ratings.

RESULTS

Presence Versus Absence of Psychosis at Baseline

Primary outcomes (i.e., time to recovery) did not differ between treatment conditions in the parent trial (Miller et al., 2004a).[1] A χ^2 test showed no significant differences for treatment condition by mood congruence subtype proportions ($\chi^2 = 0.97$, $p = 0.62$). Therefore, to maximize power, current analyses were conducted on the full sample regardless of treatment condition as all patients in the study received semistructured pharmacotherapy. Of the total sample in a manic/mixed episode at index hospitalization ($N = 74$), 80% were experiencing psychotic symptoms at baseline assessment. Prevalence and types of psychotic symptoms at baseline are depicted in Table 1. We compared those with ($N = 59$) or without ($N = 15$) psychotic symptoms during mania at hospitalization. As expected, t tests showed that psychotic patients ($M = 21.8$, $SD = 7.2$) had significantly higher baseline BPRS psychosis subscale (BPRS-Psychosis) scores ($t_{1, 72} = 3.87$, $p < 0.001$) compared with nonpsychotic patients ($M = 14.0$, $SD = 5.9$). Also, the psychotic group ($M = 26.5$, $SD = 6.0$) had significantly higher baseline scores on the BRMS ($t_{1, 72} = 2.79$, $p < 0.01$) compared with the nonpsychotic group ($M = 21.4$, $SD = 7.5$). Finally, psychotic patients ($M = 26.1$, $SD = 5.4$) possessed significantly lower baseline GAF scores ($t_{1, 72} = 4.48$, $p < 0.001$) compared with nonpsychotic patients ($M = 33.0$, $SD = 4.8$). T1

MC Versus MI Psychosis at Baseline

Analyses were conducted on patients with a current or past history of psychotic mania, due to the historical chronicity of illness in the sample and to be consistent with previous research in this area (e.g., Keck et al., 2003).[2] Of the total sample ($N = 74$), approximately 86% had a current or past history of psychotic mania. Table 2 depicts the descriptive statistics for baseline variables for those with a history of MC ($N = 40$) or MI ($N = 24$) psychotic symptoms. Based on independent samples t tests or χ^2 tests, no differences were found between groups for ethnicity/race, sex, or years of education. However, the MI group was more likely to be older ($t_{1, 62} = 2.23$, $p < 0.05$) and married/cohabitating ($\chi^2 = 5.43$, $p < 0.05$) compared with the MC group. T2

TABLE 1. Prevalence of Psychotic Symptoms During Hospitalization[a]

Symptom	*N*	%
Delusions		
Grandiose	40	66
Reference	34	56
Persecutory	19	31
Thought broadcasting	10	16
Thought control	9	15
Systematized	5	8
Somatic	4	7
Bizarre	3	5
Hallucinations		
Auditory	25	41
Visual	12	20
Tactile	3	5

[a]Symptoms derived from SCID interviews.

TABLE 2. Descriptive Statistics and Group Differences for Demographic and Baseline Variables

	MC Psychosis ($N = 40$) Mean (*SD*)/Proportion	MI Psychosis ($N = 24$) Mean (*SD*)/Proportion	*t*, *F* or χ^2	*p*
Demographics				
Age	36.9 (10.6)	43.1 (11.1)	2.21	0.03*
Education (years)	13.4 (2.6)	13.2 (2.5)	0.31	0.78
Gender (% women)	60	58	0.02	0.90
Race/ethnicity (% nonwhite)	15	4	1.76	0.19
Marital status (% not married/cohabitating)	40	13	5.43	0.02*
History of illness[a]				
Age of first depressive episode	22.6 (9.1)	22.8 (12.9)	1.17	0.39
Age of first manic episode	27.1 (8.3)	33.3 (14.3)	2.04	0.16
Number of past depressive episodes	2.8 (4.0)	5.3 (12.3)	0.57	0.52
Number of past manic episodes	4.0 (2.9)	4.6 (4.0)	0.05	0.83
Total number of psychiatric hospitalizations	3.8 (2.4)	4.5 (4.2)	0.04	0.85
Baseline severity				
BRMS	27.1 (7.0)	24.3 (5.8)	1.65	0.11
BPRS-Psychosis	20.9 (7.6)	22.0 (7.2)	0.56	0.58
MHRSD	5.7 (5.9)	5.3 (7.0)	0.47	0.84
GAF	27.3 (5.4)	25.5 (6.0)	1.20	0.24

*$p < .05$.
[a]Age used as a covariate in analyses; raw score means (*SD*s) reported.

Using ANCOVAs with age as a covariate, we compared the MC and MI groups on historical course of illness variables, including age of first manic/depressive episode, number of depression/manic episodes, and total number of past hospitalizations. However, no significant differences were found. Further, *t* tests showed no significant group differences on any baseline severity measures: BPRS-Psychosis, BRMS, MHRSD, or GAF. Both groups showed a similar history of illness and symptom severity at baseline, replicating findings by Keck et al. (2003).

Course of Mood Symptoms

Table 3 depicts the percentage of time patients with a history of psychosis during mania spent at various symptom levels over the 28 months of follow-up for which sufficient data were available (at least 5 months of follow-up data; $N = 51$). Overall, patients spent approximately 29% of time fully symptomatic (depression and/or mania), 20% of time partially symptomatic, and 51% of time fully asymptomatic. Table 3 also depicts percent time variables according to mood-congruence subtype. *t* Tests revealed no significant

TABLE 3. Percent Time Spent at Each Symptom Level During 28-Month Follow-Up

	Any Psychosis Total Sample ($N = 51$)		MC Psychosis ($N = 30$)		MI Psychosis ($N = 21$)		
	Mean (*SD*)	Median (range)	Mean (*SD*)	Median (range)	Mean (*SD*)	Median (range)	Effect Sizes[a]
Percent time asymptomatic	51 (34)	56 (0–100)	50 (34)	50 (0–100)	55 (35)	63 (0–96)	0.14
Percent time partially symptomatic							
Depression only	20 (18)	15 (0–70)	19 (19)	13 (0–70)	20 (18)	18 (0–61)	0.05
Mania only	5 (6)	4 (0–20)	5 (6)	4 (0–20)	4 (5)	4 (0–18)	0.18
Mixed: depression and mania	4 (8)	0 (0–50)	4 (6)	0 (0–20)	5 (12)	0 (0–50)	0.11
Percent time fully symptomatic							
Any episode	29 (20)	25 (0–78)	28 (20)	24 (0–78)	29 (21)	25 (0–71)	0.05
Pure depression only	10 (14)	4 (0–45)	13 (15)	7 (0–45)	7 (12)	0 (0–40)	0.44
Depression with hypomanic symptoms	4 (12)	0 (0–80)	4 (15)	0 (0–80)	3 (8)	0 (0–33)	0.08
Pure mania only	2 (7)	0 (0–32)	3 (8)	0 (0–32)	2 (4)	0 (0–18)	0.16
Mania with depressive symptoms	2 (6)	0 (0–36)	2 (4)	0 (0–20)	2 (8)	0 (0–36)	0.00
Mixed: depression and mania	1 (4)	0 (0–20)	1 (2)	0 (0–10)	2 (5)	0 (0–20)	0.26
Psychotic symptoms	5 (13)	0 (0–74)	6 (15)	0 (0–74)	3 (8)	0 (0–34)	0.25

[a]Cohen *d* computed between mood congruence subtypes; all effects nonsignificantly different from zero.

differences between the groups on any variables. Further, we computed effect size estimates between groups based on the Cohen (1988) *d* statistic to examine whether low power accounted for the null findings. Differences were in the small range ($d < 0.20$) and none were statistically significant as confidence intervals (not depicted) for all comparisons included zero.

We also conducted a stepwise multiple regression analysis for patients in a manic episode at index hospitalization to test whether initial level of psychosis predicted future severity of illness ($N = 59$). We entered baseline severity measures (BRMS, MHRSD, BPRS-Psychosis) as predictors of percent time fully symptomatic over the follow-up period. In the final model, the BRMS ($t = 2.34$, $p < 0.05$) and MHRSD ($t = 3.46$, $p = 0.001$) but not the BPRS-Psychosis Subscale ($p = 0.49$) emerged as significant predictors ($F_{2, 56} = 6.51$, $R^2 = 0.19$, $p < 0.01$). Only higher scores on the BRMS ($\beta = 0.31$) and MHRSD ($\beta = 0.46$) at baseline were predictive of greater time spent in a mood episode during the follow-up period.

Course of Psychotic Symptoms

We also were interested in specifying the course and severity of psychotic symptoms experienced in the sample over the follow-up period to understand better its relationship to mood symptoms. First, we computed the percent of time spent with psychotic symptoms based on weekly LIFE ratings (Table 2). On average, patients spent a relatively low amount of time with active psychotic symptoms (5%) over the 28 months of follow-up. A *t* test revealed no differences between rates of psychosis between MC (6%) and MI (3%) groups.

To provide a more detailed description of psychosis severity, we examined BPRS-Psychosis scores between MC and MI groups at baseline, discharge from the hospital, and follow-up months 2, 4, 10, 16, 22, and 28. Hierarchical linear modeling was used to analyze change in psychotic symptoms, as it accommodates for missing data in repeated measurements using empirical Bayesian estimates (Singer and Willett, 2003). First, we examined the overall pattern of change for the entire sample of patients with a history of psychosis. In the second set of analyses, we examined whether mood-congruence subtype accounted for differential symptom change over time.

Examination of the empirical growth plots of the raw data suggested that it would be important to model two phases separately (inpatient: from intake to discharge; and outpatient: from discharge to month 28). That is, there was a clear discontinuity in the slope of BPRS scores over time from one treatment phase to the next, with the inpatient phase involving a very steep negative slope, and the outpatient phase having a much shallower slope over time. Using methods described by Singer and Willett (2003), we next constructed a hierarchical linear model, with BPRS scores as a function of time, which allowed for a discontinuity in slope between inpatient and outpatient phases. We examined a random intercept model involving three fixed parameters: the intercept, the inpatient slope (coefficient = −0.074, $SE = 0.73$, $t = -9.75$, $p < 0.001$), and the outpatient slope (coefficient = 0.018, $SE = 0.01$, $t = 1.86$ $p < 0.10$). As expected, this model suggested that during the inpatient phase, there was a steep decrease (i.e., significant improvement) in BPRS scores, but during the outpatient phase, BPRS scores remained relatively stable.

In the second set of analyses, we examined whether mood-congruence subtype accounted for differential symptom change over time. That is, we examined whether subtype predicted intercept (i.e., baseline scores), inpatient slope, or outpatient slope. We found that subtype was not a significant predictor of the intercept (coefficient = 1.37, $SE = 0.54$, $t = -0.89$, NS), inpatient slope (coefficient = 1.80, $SE = 1.45$, $t = 1.24$, NS), or outpatient slope (coefficient = 0.01, $SE = 0.02$, $t = 0.75$, NS), suggesting that the improvement in BPRS-Psychosis scores was similar between groups over time.

DISCUSSION

The DSM-IV-TR (American Psychiatric Association, 2000) requires that psychotic features occurring in the context of a mood episode be classified as MC or MI, based on the assumption that incongruent symptoms are predictive of greater severity and a poorer prognosis. Therefore, we contrasted patients with a history of MC versus MI psychotic features to examine the prognostic value of this subtyping in relation to symptomatic outcome. Consistent with previous research, psychotic features in mania were quite common in the current sample. Approximately 86% of patients who were manic at baseline had a lifetime history of psychotic mania. Of those with a history of psychosis, approximately 38% had psychotic symptoms that were classified as MI according to DSM-IV-TR (American Psychiatric Association, 2000) criteria. Patients with psychotic symptoms at index hospitalization possessed more severe forms of illness as represented by significantly higher levels of psychosis, mania, and overall functional impairment compared with those without psychotic symptoms. However, when psychotic patients were compared according to their mood-congruence subtype, only age and marital status differed between groups. No group differences were found in baseline symptom severity or in the historical course of bipolar illness, similar to results reported by Keck et al. (2003).

We also described the long-term symptomatic course in the sample. Overall, total time spent fully or partially symptomatic over the 28-month follow-up period was substantial (49%). However, classification of psychotic symptom history in terms of mood-congruence failed to be predictive of any longitudinal course of illness variables. The lack of significant findings was unlikely to be due to low power, as effect size differences between groups were small in magnitude and not consistently in one direction. Mood severity but not level of psychosis at baseline predicted the percent of time patients spent in a mood episode during follow-up, similar to findings reported by Judd et al. (2002).

The overall lack of differences between mood-congruence subtypes became clearer when severity of psychosis during the follow-up period was examined. Although experiencing initial high levels of psychosis at baseline, patients showed substantial improvement that, on average, was sustained during the 28-month follow-up period. This is an

important finding because previous naturalistic course of illness studies finding psychosis predictive of outcome often have reported concurrent elevated levels of psychotic symptoms in patients during follow-up. For example, Strakowski et al. (2000) assessed bipolar manic patients for up to 8 months in a naturalistic study. Their results showed that the percent of weeks symptomatic did not differ between MI (31%) and MC/no psychosis groups (29%). It is important to note that we replicated this finding, as the rates by Strakowski et al. (2000) were similar to those found in the current study (29%). Strakowski et al. (2000) only found differences between the groups on follow-up GAF scores and percent time with any psychosis (MI group = 49% vs. combined MI/no psychosis group = 10%). In contrast, the current study found low levels of psychosis during 28-month follow-up (5%), and no differences between mood-congruence subtypes. The study by Strakowski et al. (2000) reported low rates of medication adherence during follow-up. The stability of psychotic symptoms found in the current study over follow-up may have been the result of effective symptom management during outpatient treatment based on involvement in a clinical trial.

The current study is not without potential limitations. Generalizability of findings may be limited as the current sample was drawn from only one site and the participation of a significant other was required. However, the symptomatic course reported in our sample matches that described in other studies. In addition, some patients also received family therapy after hospital discharge, but results in the clinical trial did not demonstrate clear superiority in outcomes for those receiving additional therapy (Miller et al., 2004a). AQ:3

Unfortunately, data were not available on mood-congruence subtype of psychotic symptoms during the follow-up phase of the study. Some patients with MC psychotic symptoms at the index assessment may have later developed MI symptoms, thus obscuring differences. However, such high variability in mood-congruence would still signify the poor prognostic validity of DSM subtyping. Further, the current study emphasized symptomatic course of illness, and it is possible that differences between mood-congruence groups may be present on other variables (e.g., psychosocial outcome).

It also is possible that modifying criteria for defining mood-incongruence may result in better differentiation for prognostic purposes. For example, Tohen et al. (1992) only found worse outcomes in those with MI psychosis when modifying DSM guidelines for subtyping. However, the purpose of the current study was to test the prognostic validity of standard DSM diagnostic rules. Finally, sample size was not large enough to compare those with or without any history of psychosis on longitudinal outcome measures, and therefore it is unknown whether the overall presence of psychosis was predictive of a worse course of illness in the sample. Nevertheless, it is important to consider that severity of psychosis at baseline was not predictive of percent time symptomatic during the follow-up period, which replicated the findings of Judd et al. (2002) that included nonpsychotic patients.

The lack of differentiation between mood-congruence subtypes found in the current study and previous research is consistent with data indicating that psychosis is relatively common in mania (Goodwin and Jamison, 1990; Pope and Lipinski, 1978) and that patients often experience both MC and MI psychotic features within the same episode or among different episodes (Burch et al., 1994; Tohen et al., 1992). Review of the literature suggests that it is difficult to differentiate true from pseudo psychotic symptoms as they likely fall along a continuum of severity (Allen et al., 2006; Bak et al., 2003; Verdoux and van Os, 2002). Further, studies examining internally versus externally perceived hallucinations have not supported the validity of this distinction (Copolov et al., 2004). Research also has failed to support consistently the special prognostic significance of Schneiderian first-rank symptoms in bipolar patients (Abrams and Taylor, 1981). Our results support the notion that MI psychotic symptoms during mania are relatively common, but when treated are not prognostic of a worse long-term symptomatic course of illness. Future research should continue to investigate modified classification rules for defining mood-incongruence to attempt to improve prognostic validity.

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END NOTES

[1]In the parent trial, there was some evidence of interaction effects between family functioning and treatment conditions on symptomatic outcomes (Miller et al., 2006). Patients in the adjunctive family therapy conditions showed better depression outcomes only if they exhibited initial high levels of family dysfunction. Secondary analyses were conducted to examine the possible effects of baseline family functioning in the present study. However, χ^2 tests showed no significant differences between rates of high versus low baseline family functioning (according to the McMaster Clinical Rating Scale-Global Functioning; Miller et al., 1994) and psychosis versus no psychosis ($\chi^2 = 0.07$, $p = 0.79$) or mood congruence subtypes ($\chi^2 = 0.62$, $p = 0.43$). Controlling for the simple effects of family functioning and mood congruence subtype, multiple regression failed to reveal significant interactions between mood congruence subtype and level of family functioning on percent time symptomatic variables (p values = 0.70–0.73). Therefore, only analyses based on the entire sample are reported in detail.

[2]We ran secondary analyses on the subsample of patients with psychotic mania at the index hospitalization only. No differences were found between the MC and MI groups on any measures (all p values >0.05). Therefore, only the primary analyses are reported in detail in the text.

AUTHOR QUERIES

AUTHOR PLEASE ANSWER ALL QUERIES **1**

AQ1---Citation correct?

AQ2---Should "period" be changed to "periodic"?

AQ3---Correct to change date to 2004a as in reference list?

AQ4---Citations of "Coyrell" are spelled "Coryell" in text. Please check spelling and make consistent.

AQ5---Please provide place of publication.