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Patients' Expectancies, the Alliance in Pharmacotherapy, and Treatment Outcomes in Bipolar Disorder

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Bipolar disorder is characterized by a chronic and fluctuating course of illness. Although nonadherence to pharmacotherapy is a frequent problem in the disorder, few studies have systematically explored psychosocial factors related to treatment discontinuation. Previous research with depressed patients receiving psychotherapy has suggested that expectancies for improvement are related to treatment outcomes and that the therapeutic alliance may partially mediate this relationship. The current study found evidence for a similar relationship between patients' initial expectancies for improvement, patient- and doctor-rated alliance, and long-term outcomes in bipolar patients treated with pharmacotherapy for up to 28 months following an acute episode. The results highlight the need for the assessment of expectancies and alliance in bipolar treatment and suggest possible targets for psychosocial interventions.

Keywords: bipolar disorder, expectancies, adherence, pharmacotherapy, alliance

Research has suggested that patients with bipolar disorder spend 47% of the time symptomatically ill over long-term follow-up, with the majority of that time spent in depression (Judd et al., 2002; Miller, Uebelacker, Keitner, Ryan, & Solomon, 2004). In addition, Keck et al. (1998) reported that 53% of bipolar patients initially hospitalized for a manic or mixed episode were partially or fully nonadherent to pharmacotherapy by 1-year follow-up. Research is needed to identify potentially modifiable psychosocial factors related to treatment adherence and outcome in pharmacotherapy that could serve as a focus of assessment and a target of intervention. Previous research has shown that patients' expectancies about treatment are strong predictors of both pharmacotherapy and psychotherapy response in unipolar depressed patients. For example, findings from the Treatment of Depression Collaborative Research Program study indicated that treatment expectancies significantly predicted response across both the psychotherapy and pharmacotherapy conditions (Sotsky et al., 1991). Further, a recent experimental trial of two antidepressants found that 90% of depressed patients who reported high expectancies for improvement at the start of the study responded to treatment, compared with only 33% of those who expected the medications to be "somewhat effective" (Krell, Leuchter, Morgan, Cook, & Abrams, 2004). The effects of expectancies are not limited to those with major depression; Adams and Scott (2000) found that the perceived benefits of medication treatment were predictive of adherence in patients with severe mental disorders.

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Although patients' treatment expectancies predict response to pharmacotherapy and psychotherapy in psychiatric disorders, less research has been conducted on the possible mediating pathways. One potential mediator examined in psychotherapy for depression studies has been the therapeutic alliance. The therapeutic alliance has been shown to be a robust predictor of treatment outcome across different types of treatment (D. J. Martin, Garske, & Davis, 2000). Further, Joyce, Ogrodniczuk, Piper, and McCallum (2003) found that patient- or therapist-rated alliance in short-term psychotherapy accounted for one third of the predictive ability of expectancies on outcome. In addition, Meyer et al. (2002) found that patient and therapist alliance predicted psychotherapy response in the Treatment of Depression Collaborative Research Program study and that patient-rated alliance partially mediated the relationship between patients' expectancies and outcome. Given the high rates of nonadherence to pharmacotherapy and the recurrent nature of bipolar illness, several authors have noted that the therapeutic alliance should be considered an important factor in the treatment of the disorder (e.g., Berk, Berk, & Castle, 2004). Unfortunately, there is a paucity of research in this area to date (Lingam & Scott, 2002). To our knowledge, prior research has not systematically investigated the relationship between patients' expectancies for improvement, the therapeutic alliance in pharmacotherapy, and outcomes in individuals with bipolar disorder.

In the current study, patients diagnosed with bipolar I disorder were treated for up to 28 months with pharmacotherapy following a hospitalization for an acute mood episode. Patients' initial expectancies for improvement were obtained following hospital discharge, and patient- and doctor-rated working alliance in pharmacotherapy was measured early in outpatient treatment. We hypothesized that patients' expectancies and the alliance in pharmacotherapy would predict the number of months patients remained in active study treatment prior to dropout (i.e., overall treatment adherence) and the percentage of time spent depressed or manic over follow-up (i.e., the longitudinal course of illness).

Further, we predicted that the alliance would partially mediate the relationship between expectancies and outcomes.

Method

Participants

Participants were recruited into a larger clinical trial assessing pharmacotherapy versus pharmacotherapy plus family intervention for bipolar disorder. Details about study methodology and results can be found in the initial report (Miller, Solomon, Ryan, & Keitner, 2004). Ninety-two patients in an acute episode were enrolled in the larger clinical trial. Inclusion criteria for the study were as follows: diagnosis of bipolar I disorder, age of 18 to 75 years, fluency in English, and regular contact with a significant other. Exclusion criteria were diagnosis of alcohol and/or drug dependence during the past year, a mood disorder secondary to a medical condition, a medical illness severe enough to contraindicate mood stabilizing medication, or pregnancy or inadequate contraception use. The current sample consisted of 61 participants who were retained in study treatment long enough to obtain measures of expectancies and alliance. Regarding the current sample, 43% were male, 57% were female, 92% were Caucasian, 6% were Hispanic, and 2% were African American. The mean age of the sample was 42 ($SD = 12$), and mean years of education was 13 ($SD = 3$). Most patients were married or cohabitating (66%). The vast majority were in a manic or mixed episode at baseline (84%). All were recruited during inpatient treatment for an acute episode. Regarding family involvement, approximately 63% participated with a spouse or partner, 21% with one or both parents, and 16% with an adult child or other family member.

Measures

The Structured Clinical Interview for the *DSM–III–R* (Spitzer & Williams, 1998) was used to determine diagnostic status at baseline. The Bech–Rafaelsen Mania Scale (BRMS; Bech, Bolwig, Kramp, & Rafaelsen, 1979) is an 11-item interviewer-rated scale that was used to assess severity of manic symptoms. The BRMS has been shown to possess excellent interrater reliability and adequate sensitivity to change in clinical trials (Bech, 2002). Internal consistency in the current sample was high (Cronbach's $\alpha = .94$). The 17-item total of the interviewer-rated Modified Hamilton Rating Scale for Depression (MHRSD; Miller, Bishop, Norman, & Maddever, 1985) was used to assess depression severity. The MHRSD is an adapted form of the original Hamilton Rating Scale for Depression (Hamilton, 1960) that includes standardized question prompts to increase reliability. The MHRSD has been shown to possess good interrater reliability and to correlate highly with the original version of the scale. Internal consistency in the sample was high (Cronbach's $\alpha = .92$).

The 4-item Credibility and Expectancy Scale (CES; Borkovec & Nau, 1972) is a widely used measure of treatment-related expectancies and has been shown to be predictive of improvement in clinical trials (Devilly & Borkovec, 2000). The CES was adapted slightly for the current study to assess the treatment of bipolar disorder (e.g., "This treatment will be successful in eliminating symptoms of bipolar disorder"). Items were scored on a scale ranging from 1 (*totally disagree*) to 7 (*totally agree*), and a total score was calculated by summing the items. Higher scores signify greater expectations for improvement. Internal consistency in the current sample was good (Cronbach's $\alpha = .81$), and a principle components analysis indicated only one factor.

The Working Alliance Inventory (WAI; Horvath & Greenberg, 1989) is a 36-item self-report measure rated on a 7-point scale (1 = *never*, 7 = *always*), with higher scores signifying better alliance. Patient- and psychiatrist-rated versions were collected, and questions were reworded slightly to refer to pharmacotherapy. The WAI yields three subscales (Task, Bond, Goal) and a total score. Internal consistency for the total measure has been reported in previous research to be good. Also, the content validity of the WAI has been established through expert ratings and multitrait–multimethod analyses (Horvath & Greenberg, 1989). Internal consistency in the current sample was adequate (Cronbach's $\alpha = .67$). The more commonly used total score was analyzed, as research has been inconsistent in terms of the factor structure of the WAI (Horvath, 1994).

Treatment

Treatment for all patients included semi-structured pharmacotherapy, which was administered by means of a protocol of standardized procedures. Ninety-two percent of participants were prescribed a mood stabilizer, and 94% were judged to have received efficacious administration as determined by independent chart review. Participants met with their psychiatrist once per week for the 1st month and then less frequently on the basis of patient improvement. In addition, some patients were randomized to also receive one of the following family interventions. Family psychoeducation group therapy consisted of six 90-min, multifamily meetings during the first 2 months postdischarge (Keitner et al., 2002). Family therapy was based on the Problem-Centered Systems Therapy of the Family (Ryan, Epstein, Keitner, Miller, & Bishop, 2005). The number of sessions varied on the basis of need, ranging from 6 to 10 sessions of 50-min duration. Approximately 66% of the sample completed at least 6 months of treatment after hospital discharge, and primary analyses revealed no significant differences between treatment conditions on primary outcomes (i.e., time to remission of the acute episode; Miller, Solomon, et al., 2004).

Procedure

Procedures were as follows. After a complete description of the study, patients and their family members provided written informed consent (using a protocol approved by the Institutional Review Board). Following baseline assessments, patients were randomly assigned to one of the three groups: pharmacotherapy alone ($n = 19$), pharmacotherapy plus family psychoeducational group ($n = 23$), or pharmacotherapy plus family therapy ($n = 19$). The CES was administered after patients were informed of their randomized condition and received their first outpatient pharmacotherapy session following hospital discharge. The WAI was completed after the CES, but early ($Mdn = 2$ months) in outpatient pharmacotherapy. MHRSD and BRMS assessments were completed monthly for up to 28 months. All interviewers were blind to treatment conditions and were trained to initial reliability (>.85) with periodic checks. 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. Scores between face-to-face and phone interviews were highly correlated in the sample (Miller, Uebelacker, et al., 2004). To ensure the generalizability of findings, we continued assessments when possible even if patients relapsed or dropped out of study treatment. Forty-one percent of the current sample was retained in study treatment over the full 28-month follow-up period, with those remaining dropping out but continuing with the assessments for at least 1 additional month.

The primary outcome measure in the current study was the number of months in study treatment (up to 28 months). In addition, course of illness was measured by computing percentage of time fully symptomatic in depression or mania up to 28 months. Scores greater than 14 on the MHRSD or BRMS were used to designate fully symptomatic status on the basis of the criteria established by Frank et al. (1991) and Bech, Kastrup, and Rafaelsen (1986), respectively. As in procedures used in other studies of bipolar disorder (Judd et al., 2002; Strakowski et al., 2000), percentage of time fully symptomatic in depression or mania was calculated by dividing the number of months spent in the respective symptom categories by the total number of months for which data were available in the study (Miller, Uebelacker, et al., 2004). The current sample comprised patients

Table 1
Correlations and Descriptive Statistics for Study Variables

Measure	1	2	3	4	5	6	7
1. CES	—	.42***	.54***	.32*	−.22†	−.09	−.19
2. WAI-P		—	.31*	.48***	−.37**	.05	−.06
3. WAI-D			—	.38**	−.33**	.05	−.20
4. Months in study treatment				—	−.33**	−.26*	.11
5. % time depressed (MHRSD)					—	.22†	.12
6. % time manic (BRMS)						—	−.10
7. Discharge GAF							—
M	19.8	180.5	190.7	19.9	15.4	4.8	40.1
SD	4.0	37.1	30.0	10.0	21.7	10.6	11.6
Range	9–28	61–232	106–237	1–28	0–100	0–64	21–70

Note. $n = 61$. CES = Credibility and Expectancy Scale; WAI-P/WAI-D = Working Alliance Inventory Patient or Doctor Version; MHRSD = Modified Hamilton Rating Scale for Depression; BRMS = Bech–Rafaelsen Mania Scale; GAF = Global Assessment of Functioning Scale.
† $p < .10$. * $p < .05$. ** $p < .01$. *** $p < .001$.

with 9 or more months of data available for computing percentage of time variables.

Results

Descriptive statistics and Pearson correlations for study variables are displayed in Table 1.[1] The results showed moderately strong correlations between the CES, WAI-P (patient version), and WAI-D (doctor version). Further, the CES was significantly related to months in treatment but only marginally significantly related to percentage of time depressed. Both the WAI-P and WAI-D were associated with months in treatment and percentage of time depressed but not manic. Overall severity of illness according to the Global Assessment of Functioning Scale (GAF) at hospital discharge was not associated with other study variables. As expected, months in treatment and percentage of time depressed or manic were negatively correlated. In summary, the results suggested that patients' expectancies and the therapeutic alliance were associated with outcomes. Severity of illness was not confounded with expectancies or alliance. Treatment adherence was associated with less time spent symptomatic.

Next, we examined whether the early working alliance in pharmacotherapy predicted outcomes independent of initial treatment expectancies (see Table 2). A hierarchical multiple regression analysis was conducted, entering the CES in the first step and the WAI-P and WAI-D in the second step to predict months in study treatment. Results showed that the WAI-P and WAI-D predicted treatment dropout after controlling for the CES. Although the CES was a significant predictor in the first step, this variable was no longer significant when the working alliance variables were entered into the equation. Similar analyses were conducted predicting percentage of time symptomatic on the MHRSD and the BRMS separately. The working alliance variables predicted percentage of time depressed independent of the expectancies variable, which was marginally significant in the first step. No variables significantly predicted percentage of time manic.

Previous analyses demonstrated that expectancies significantly predicted treatment dropout, but not after controlling for alliance. Therefore, we formally examined whether early doctor- or patient-rated working alliance in pharmacotherapy mediated the relationship between initial treatment expectancies and long-term treatment adherence. Statistical procedures outlined by Baron and Kenny (1986) were used to examine mediation hypotheses. Secondary analyses were conducted on the basis of procedures used in previous studies examining similar variables (Joyce et al., 2003; Meyer et al., 2002). Mediation occurs if the strength of the relationship between the independent (i.e., CES) and dependent variables (i.e., treatment dropout, percentage of time symptomatic) is significantly decreased by the inclusion of the mediator (i.e., WAI-P/WAI-D).

First, patient-rated working alliance was tested as a mediator of months in treatment. All conditions for mediation were met (see Figure 1). The CES predicted the WAI-P, $t(59) = 3.54$, $p = .001$. Also, the WAI-P predicted treatment dropout, $t(59) = 2.60$, $p = .012$. When the WAI-P and CES were included together in the regression equation, the WAI-P predicted treatment dropout, $t(58) = 3.30$, $p = .002$, but the CES did not ($p = .25$). Testing the standard error of the indirect effect (Goodman, 1960) indicated that patient-rated working alliance partially mediated the relationship between treatment expectancies and treatment dropout ($z = 2.45$, $p = .014$). In addition, regression analyses were conducted to determine if doctor-rated working alliance mediated the relationship between patient expectancies and months remaining in treatment. All conditions were met (see Figure 2). In the final regression, the WAI-D significantly predicted months in treatment, $t(58) = 2.09$, $p = .042$, but the CES did not ($p = .27$). Testing the standard error of the indirect effect indicated that doctor-rated working alliance partially mediated the relationship between patient expectancies and treatment dropout ($z = 1.99$, $p = .047$).

[1] The expectation-maximization (EM) algorithm was used to impute randomly missing data (15%) for nonoutcome-related measures (i.e., CES, WAI, GAF) to obtain a consistent sample for each analysis (see Hill, 1997). EM is a recommended method for imputing missing values and has been shown to be superior to simple regression imputation techniques (Graham & Donaldson, 1993). In brief, the EM algorithm computes missing values on the basis of maximum likelihood estimates using known participant variables in an iterative process that preserves variability (Demster, Laird, & Rubin, 1977). Findings using nonimputed data produced the same pattern of effects or trends, but low statistical power was an issue in some analyses.

Table 2
Hierarchical Multiple Regression Analyses of Treatment Expectancies and Working Alliance Predicting Outcomes

Predictor	Dependent variable: Δ *F*	*p*	Δ R^2	β	*t*[c]	*p*
No. of months in study treatment						
Step 1[a]	6.77	<.05				
CES			.10	.32	2.60	.01
Step 2[b]	7.47	<.001				
CES			.19	.02	0.15	*ns*
WAI-P				.39	3.15	.00
WAI-D				.25	1.89	.06
% time depressed (MHRSD)						
Step 1[a]	2.94	.09				
CES			.05	−.22	−1.71	.09
Step 2[b]	5.08	<.01				
CES			.14	.06	0.34	*ns*
WAI-P				−.31	−2.34	.02
WAI-D				−.27	−1.90	.06
% time manic (BRMS)						
Step 1[a]	0.43	*ns*				
CES			.01	−.09	−0.66	*ns*
Step 2[b]	0.55	*ns*				
CES			.02	−.19	−1.15	*ns*
WAI-P				.09	0.63	*ns*
WAI-D				.12	0.76	*ns*

Note. $n = 61$. CES = Credibility and Expectancy Scale; WAI-P/WAI-D = Working Alliance Inventory Patient or Doctor Version; MHRSD = Modified Hamilton Rating Scale for Depression; BRMS = Bech–Rafaelsen Mania Scale.
[a] *df*s = 1 and 59. [b] *df*s = 2 and 57. [c] *df* = 1.

The proportion of variance explained by the mediators can be represented as a ratio between the variance explained by the mediation effect relative to the direct effect of expectancies on adherence (Joyce et al., 2003). Patient-rated working alliance accounted for approximately 53% of the variance in the prediction of months in treatment by patient expectancies. Further, doctor-rated working alliance accounted for approximately 50% of the variance. For full mediation, the working alliance would have had to explain 100% of the variance in the predictor, a condition considered rare in the social sciences. However, results show that alliance accounted for a substantial proportion of the variance in the prediction of treatment adherence.

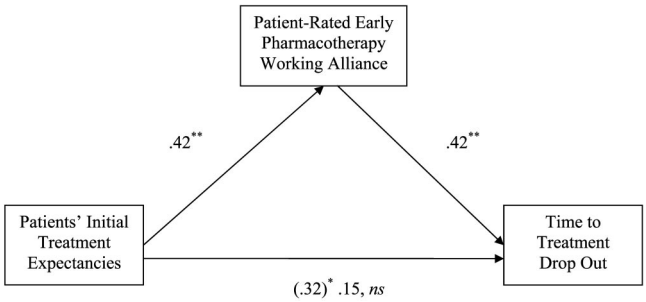

Figure 1. Patient-rated working alliance partially mediates the relationship between patients' expectancies and treatment dropout. Values presented are standardized regression coefficients (βs). The value in parentheses represents the coefficient for the direct (i.e., unmediated) path. There was a significant decrease in the direct path when the alliance variable was included in the regression equation ($p < .05$). *$p < .05$. **$p < .01$.

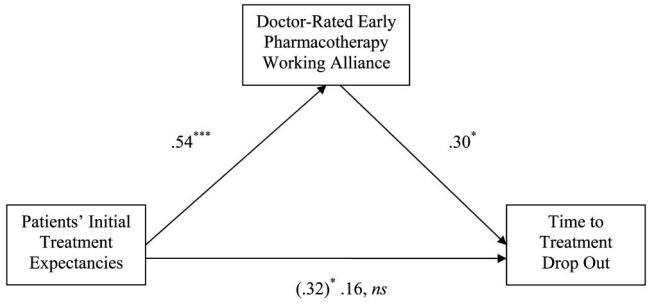

Figure 2. Doctor-rated working alliance partially mediates the relationship between patients' expectancies and treatment dropout. Values presented are standardized regression coefficients (βs). The value in parentheses represents the coefficient for the direct (i.e., unmediated) path. There was a significant decrease in the direct path when the alliance variable was included in the regression equation ($p < .05$). *$p < .05$. ***$p < .001$.

Finally, a series of hierarchical regression analyses was conducted to examine whether the associations between expectancies, alliance, and treatment outcomes differed by treatment condition (i.e., the addition of family therapy). Treatment condition was dummy coded and multiplied separately by expectancies and alliance (after each was centered) to form interaction terms. Hierarchical regression equations were conducted, entering main effects in the first step and interaction terms in the second to predict either months in study treatment or percentage of time symptomatic. None of the interaction terms in these regressions were significant (*p*s > .10), suggesting that the addition of family therapy did not differentially influence the relationships between expectancies, alliance, and outcomes demonstrated in previous analyses.[2]

Discussion

The results were largely consistent with the hypothesis that patients' treatment expectancies and therapeutic alliance in pharmacotherapy are predictive of outcomes in bipolar disorder. Although similar findings have been demonstrated in psychotherapy research with unipolar depressed patients, to our knowledge this is the first study to provide specific support for this phenomenon in a bipolar sample receiving medication treatment. In the current study, expectancies and alliance were most consistently predictive of the number of months remaining in treatment. Further, the relationship between patients' expectancies and overall treatment dropout was mediated by patient- and doctor-rated alliance. Al-

[2] To further explore potential moderation effects, we examined whether history of illness variables (e.g., number of past depressive or manic episodes) were associated with expectancies or alliance. However, Pearson correlations between these variables were small in magnitude and not statistically significant.

though alliance was also predictive of percentage of time spent depressed, expectancies were only marginally significantly predictive of this outcome. In addition, neither expectancies nor alliance was predictive of percentage of time spent manic. Results did not suggest that the effects of expectancies and alliance were explained by initial severity of illness. Further, the addition of family therapy did not differentially influence the effects of alliance and expectancies on outcomes.

Strengths of the current study included the use of a homogenous sample of patients diagnosed with bipolar I disorder and hospitalized after an acute episode. Also, all patients received semistructured and efficacious pharmacotherapy while in the study. Further, patients who dropped out of study treatment prior to completing the full 28 months continued to be assessed on a monthly basis when possible, which allowed for sufficient variability to test study hypotheses. Although most previous research has examined expectancies using a single Likert scale question (e.g., Meyer et al., 2002), the current study employed the commonly used 4-item CES. Symptomatic outcome in the current study was measured in a clinically relevant manner that has been successfully used in previous studies investigating long-term outcome in bipolar samples (e.g., Judd et al., 2002; Miller, Uebelacker, et al., 2004). Finally, alliance was measured from both patients' and doctors' perspectives and results were consistent across measures, suggesting the robust nature of the alliance in predicting outcomes.

It is interesting to note that results for expectancies, alliance, and symptomatic outcome were more equivocal, especially with respect to mania. The lack of significant findings for mania was most likely explained by the fact that patients spent much less time manic than depressed over follow-up, possibly because of efficacious medication treatment. Findings in the current sample are consistent with past research showing that bipolar patients spend more time depressed than manic (Judd et al., 2002; Miller, Uebelacker, et al., 2004). Therefore, sufficient variability in this outcome may not have been present and should be explored further in future research.

Potential limitations of the current investigation include the modest sample size and the inclusion criterion for the clinical trial requiring that patients enrolled in the study have a family member or close friend also willing to participate. We estimate that approximately 20% of potential participants did not meet this inclusion criterion, which may limit the generalizability of our findings for bipolar patients with low levels of social support in the community. However, it should be noted that the course of illness in the current sample (Miller, Uebelacker, et al., 2004) was very similar to that obtained in a larger, longitudinal study of bipolar patients in which significant-other contact was not an inclusion criterion (Judd et al., 2002). Further, the study also permitted psychiatric comorbidity and suicidality, allowed for continued assessment of patients who dropped out of study treatment, and did not require that patients receive any one medication, which helped to assure that study participants were more comparable to patients in general clinical practice.

Although measured as a continuous variable, another potential weakness of the study was that we were only able to assess overall treatment adherence according to the number of months patients remained in pharmacotherapy. It is possible that those remaining in the study could have been at least partially nonadherent to medication regimens or that those who dropped out of the study but continued assessments could have been adherent to other community treatments. Nevertheless, time spent in treatment was deemed appropriate in the current investigation because therapeutic alliance as measured in the study was predictive of patients choosing to continue treatment with their specific study psychiatrist. Finally, expectancies were only marginally significantly predictive of time spent depressed, and thus we did not formally test the mediational role of alliance on this outcome. However, it should be noted that time spent in study treatment was inversely correlated with time spent symptomatic over follow-up.

Overall, results of the current study demonstrate that expectancies and alliance are not just important predictors in psychotherapy for unipolar depression, but in pharmacotherapy for bipolar disorder as well. Expectancies for improvement appeared to influence how well patients worked with their psychiatrists, which in turn influenced their continued participation in the study's pharmacotherapy. Further, longer treatment adherence was associated with less time spent symptomatic over long-term follow-up. Results suggest that psychiatrists may be able to improve adherence to pharmacotherapy by explicitly inquiring about bipolar patients' beliefs and expectations about medications. In addition, findings suggest that expectancies should not merely be viewed as a "nuisance" variable to be assessed and controlled for in clinical trials but may represent an important and potentially modifiable target of intervention. For example, Cochran (1984) randomly assigned 28 bipolar patients receiving lithium to a cognitive–behavioral intervention or no added treatment. The intervention group showed superior medication adherence at posttreatment and at 6-month follow-up. However, several studies of psychosocial interventions for bipolar disorder have found mixed results regarding their efficacy for increasing treatment adherence (Bauer, 2001). A better understanding of the interactions between expectancies, alliance, and outcomes may prove useful in the treatment development and testing process.

The findings of the current study are consistent with previous proposals suggesting that expectancies exert their effects on outcome largely through indirect pathways (P. J. Martin, Moore, Friedmeyer, & Claveaux, 1977). Although we examined one possible mediating variable, it will be essential for future research to assess other theoretically relevant psychological factors, including self-efficacy, insight into illness, treatment preferences, and interpretations of side effects, as they are likely to impact patients' expectancies for improvement, and vice versa. Therefore, additional research is needed to replicate current findings and to extend them by investigating the relative impact of other potential mediating variables to develop better targets of intervention.

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