A Randomized Study of Family-Focused Psychoeducation and Pharmacotherapy in the Outpatient Management of Bipolar Disorder

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Background: Bipolar patients are at risk for relapses of their illness even when undergoing optimal pharmacotherapy. This study was performed to determine whether combining family-focused therapy (FFT) with pharmacotherapy during a postepisode interval enhances patients' mood stability during maintenance treatment.

Methods: In a randomized controlled trial, 101 bipolar patients were assigned to FFT and pharmacotherapy or a less intensive crisis management (CM) intervention and pharmacotherapy. Outcome assessments were conducted every 3 to 6 months for 2 years. Participants (mean ± SD age, 35.6 ± 10.2 years) were referred from in-patient or out-patient clinics after onset of a manic, mixed, or depressed episode. FFT consisted of 21 sessions of psychoeducation, communication training, and problem-solving skills training. Crisis management consisted of 2 sessions of family education plus crisis intervention sessions as needed. Both protocols lasted 9 months. Patients received pharmacotherapy for 2 study years. Main outcome measures included time to relapse, depressive and manic symptoms, and medication adherence.

Results: Rates of study completion did not differ across the FFT (22/31, 71%) and CM groups (43/70, 61%). Patients undergoing FFT had fewer relapses (11/31, 35%) and longer survival intervals (mean ± SD, 73.5 ± 28.8 weeks) than patients undergoing CM (38/70, 54%; mean ± SD, 53.2 ± 39.6 weeks; hazard ratio, 0.38; 95% confidence interval, 0.20-0.75; P = .003; intent to treat). Patients undergoing FFT showed greater reductions in mood disorder symptoms and better medication adherence during the 2 years than patients undergoing CM.

Conclusion: Combining family psychoeducation with pharmacotherapy enhances the postepisode symptomatic adjustment and drug adherence of bipolar patients.

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Numerous clinical trials indicate that lithium carbonate, anticonvulsants, and antipsychotic agents are effective in stabilizing acute symptoms of bipolar I disorder. However, maintenance drug treatment is associated with less than adequate prevention of recurrences, even when drug regimens are optimized. Up to 60% of patients have recurrences within the 2 years following an acute episode, and at least 50% experience significant interepisode symptoms. Furthermore, bipolar patients have substantial impairments in work, family, or social relationships after their acute symptoms have resolved, even when taking mood stabilizers. Recognizing the limitations of pharmacotherapy alone, a 1996 report by the National Institute of Mental Health, Bethesda, Md, recommended developing adjunctive psychosocial interventions as a central focus for research on bipolar disorder.

New psychosocial interventions have emerged in response to studies that showed associations between socioenvironmental stressors and remission-relapse cycles of the illness. Levels of familial expressed emotion, low parental warmth, and life events that disrupt daily routines or accelerate goal striving have each been found to predict symptom exacerbations among adult- and pediatric-onset bipolar patients. Other psychosocial variables, including lack of social support, single marital status, low education or socioeconomic status, and lack of knowledge about the disorder, influence patients' adherence to drug treatments. Accordingly, the primary objectives of adjunctive psychosocial interventions are to (1) prevent relapses and reduce interepisode symptoms through enhancing patients' ability to cope with stress and (2) encourage consistency with medications through providing illness education and support.

Several manual-based forms of psychosocial therapy have shown promise as adjuncts to pharmacotherapy. Controlled trials indicate that adjunctive family therapy, individual cognitive-
behavioral therapy, and interpersonal and social rhythm therapy are associated with greater stabilization of symptoms than comparison interventions involving medication and active clinical management. The focus of this article is on family-focused therapy (FFT), a 21-session psychoeducation program administered in the 9 months following an episode of bipolar illness. It consists of education for patients and their caregivers about the disorder, communication enhancement training, and problem-solving skills training. Family-focused therapy is an outgrowth of skills-oriented family interventions that, in combination with neuroleptics, have been found to delay relapses of schizophrenia.

We report the 2-year results of a randomized trial in which 101 recently ill bipolar patients were assigned to FFT with mood stabilizers or a less intensive psychoeducational intervention (crisis management [CM]) with mood stabilizers. We hypothesized that patients undergoing FFT would have longer periods of sustained remission and less severe mood symptoms during the 2 years than patients undergoing CM. A secondary hypothesis was that patients undergoing FFT who, along with their relatives, learned of the benefits of long-term medical prophylaxis would be more compliant with drug regimens than patients undergoing CM.

METHODS

PARTICIPANTS

The 101 participants (mean±SD age, 35.6±10.2; age range, 18-62 years; 64 women, 37 men) were recruited from 698 consecutively screened inpatients and outpatients whose medical records indicated a working diagnosis of bipolar disorder (Figure 1). All participants met the following eligibility criteria:

- No alcohol or other substance use disorders within the previous 6 months
- Living with or in regular contact (at least 4 hours per week) with a caregiving family member
- English speaking
- Willingness to take mood-stabilizing medications or antipsychotic agents
- Willingness and ability of all patients and relatives to give written informed consent to participate

The sample included 82 patients who were recruited while in the hospital and 19 who were recruited as outpatients following referral from physicians in the Boulder and Denver, Colo, regions. The greater ratio of women to men is consistent with other studies of psychosocial intervention in bipolar disorder that required family participation. The study, begun in 1990, was approved by the University of Colorado's Human Research Committee. All participants gave written informed consent following an explanation of the study procedures.

Participants met the DSM-III-R diagnostic criteria for bipolar disorder (manic, depressed, or mixed episode) in the 3 months that led to the study evaluation. Diagnoses were based on the Structured Clinical Interview for DSM-III-R, Patient Version (SCID-P), which was administered while patients were in the hospital or during an outpatient visit shortly after the onset of an acute episode. Research diagnosticians attended a SCID training workshop and obtained interrater reliabilities for SCID-P items ranging from 0.71 to 0.87 (Cohen χ², P<.001). Throughout the study, one of us (D.J.M.) monitored rater drift through reviewing audiotapes of SCID interviews and providing the diagnosticians with corrective feedback.

The DSM-III-R diagnoses were later confirmed with DSM-IV criteria by independent raters who listened to audiotapes of the original SCID-P interviews. Two patients originally diagnosed as having DSM-III-R bipolar disorder were reclassified with DSM-IV bipolar II disorder (current episode depressed). All others met DSM-IV criteria for bipolar I disorder.

RANDOMIZATION TO TREATMENTS

The allocation to treatments was accomplished through a random number table, which placed 33% of consecutive study admissions into an FFT plus medication group (n=31) and 67%
Family-focused therapy involved all available family members (spouses, parents, or siblings). It was administered in 21 one-hour sessions (12 weekly, then 6 biweekly, then 3 monthly) in 3 consecutive modules: (1) psychoeducation (7 sessions), in which patients and their relatives learned about the signs and symptoms of bipolar disorder, its etiology according to a vulnerability/stress model, and strategies for the family to undertake to prevent relapse (eg, encouraging the patients’ consistency with drug treatments; developing plans for immediate intervention when prodromal symptoms appeared); (2) communication enhancement training (7-10 sessions), in which participants learned, through in-session role-playing and between-session rehearsal, skills for active listening, delivering positive and negative feedback, and requesting changes in each other’s behaviors; and (3) problem-solving skills training (4-5 sessions), in which participants learned to identify specific family problems (eg, a parent’s excessive work stress), brainstorm potential solutions (eg, more equitable sharing of household duties), evaluate the advantages and disadvantages of each proposed solution, and choose and implement one or more solutions.

Psychosocial Treatments

The active period of FFT or CM treatment lasted 9 months. All sessions were conducted in the patients’ or their parents’ homes. The early phases of both protocols consisted of assessments of the patients’ psychiatric history and the family’s or couple’s communication styles. Family-focused therapy involved all available family members (spouses, parents, or siblings). It was administered in 21 one-hour sessions (12 weekly, then 6 biweekly, then 3 monthly) in 3 consecutive modules: (1) psychoeducation (7 sessions), in which patients and their relatives learned about the signs and symptoms of bipolar disorder, its etiology according to a vulnerability/stress model, and strategies for the family to undertake to prevent relapse (eg, encouraging the patients’ consistency with drug treatments; developing plans for immediate intervention when prodromal symptoms appeared); (2) communication enhancement training (7-10 sessions), in which participants learned, through in-session role-playing and between-session rehearsal, skills for active listening, delivering positive and negative feedback, and requesting changes in each other’s behaviors; and (3) problem-solving skills training (4-5 sessions), in which participants learned to identify specific family problems (eg, a parent’s excessive work stress), brainstorm potential solutions (eg, more equitable sharing of household duties), evaluate the advantages and disadvantages of each proposed solution, and choose and implement one or more solutions.

The CM protocol was designed to emulate standard community care. Therapists conducted 2 one-hour, home-based family education sessions within the first 2 months after study entry. Then, clinicians offered crisis intervention sessions as needed during the remaining 9-month treatment period. These sessions usually focused on relapse prevention and the resolution of immediate family conflicts. At minimum, clinicians telephoned patients once per month to offer support and monitor clinical progress. Regardless of treatment condition, relatives were encouraged to contact the therapist or psychiatrist if the patient developed new symptoms so that emergency services (eg, hospitalization) could be arranged.

Training and Monitoring of Therapists

Therapists were trained in the manual-based FFT protocol by one of us (D.J.M.). Nineteen therapists participated (15 women, 4 men; mean ± SD age, 30.2 ± 6.7 years), 3 with doc-
When clinicians read the FFT manual and observed videotaped examples of family sessions. Next, they served as cotherapists to a trained therapist for 2 family cases, with weekly supervision. One of us (D.J.M.) trained these same clinicians to administer the 2 family educational sessions (following the same didactic format as the FFT sessions) and the follow-up crisis sessions of the CM protocol. Following training, therapists received weekly group supervision in both modalities.

Therapy adherence monitoring was accomplished by independent observers who applied the Therapist Competence and Adherence Scales to session audiotapes. Interrater reliability for these scales was high ($r=0.64-0.73; P<.001$ for all). The mean±SD overall adherence/competence score (n=371) of SADS-C follow-up interview tapes identified by administering any psychosocial treatments, it proved difficult but no evidence of discontinuation), and 3, fully adherent (no inconsistencies).9

Drug treatment intensity and adherence ratings were accomplished by a single rater who was unaware of patients’ psychosocial group assignments or SADS-C outcome data. Reliability ($\kappa$ between this rater and a secondary rater was 0.77 for drug intensity judgments and 0.86 for adherence ratings ($P<.001$ for all, 12 ratings).

STATISTICAL ANALYSIS

The primary study hypotheses concerned the relative efficacy of FFT vs CM on time to relapse and symptom severity during a 2-year interval. Survival time was calculated as the number of weeks between study entry and relapse. Patients who did not experience disease relapse were included in the at-risk sample up to the point of their final research assessment. Survival curves (intent-to-treat sample) were compared using the Kaplan-Meier product-limit formula and, when incorporating covariates, Cox proportional hazards models, with significance set at $P<.05$.64-65 Comparison of the group survival curves indicated that the estimated hazard functions did not differ as a function of time ($\chi^2=0.18, P=.67$).

Repeated-measure, mixed-model analyses of variance (ANOVA) compared the groups on the trajectory of total affective symptom scores, composite depression scores, and composite mania scores across time (intake and 1-month assessments followed by evaluations at 3, 6, 9, 12, 18, and 24 months). Mixed ANOVA models allow the inclusion of data from patients with incomplete observations at follow-up. Secondary analyses examined the effects of covariates found in prior studies to be important predictors of outcome. These included sex, socioeconomic status, baseline symptoms, number of prior illness episodes, medication regimens, and medication compliance (N. F. Watt, PhD, unpublished data, 1976).2,9-12,34-57

RESULTS

OUTCOMES AND ATTRITION

Patients were classified according to their primary outcome status during the 2-year study: terminated early, never experienced disease relapse during their period of follow-up, or experienced relapse at follow-up. Early terminators (n=19) were patients who participated for fewer than 6 months, which was the minimum duration necessary for applying the outcome classification criteria of Nuechterlein et al (Table 2)68,69

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The FFT and CM groups did not differ in early termination: 16 (23%) of the 70 CM patients and 3 (10%) of the 31 FFT patients withdrew before 6 months ($\chi^2 = 2.44, P = .12$). Of the remaining 82 patients, 11 CM patients and 6 FFT patients withdrew between 6 and 24 months (Figure 1). Thus, 43 (61%) of 70 participants assigned to CM and 22 (71%) of 31 assigned to FFT were retained for the full 24 study months ($\chi^2 = 0.85, P = .36$).

Assignments of relapse or nonrelapse status were made for the 82 participants (54 undergoing CM, 28 undergoing FFT) with at least 6 months of follow-up. Two independent raters who were unaware of therapy assignments or medication regimens sorted participants’ longitudinal SADS-C data into 1 of 9 categories of outcome, including 3 categories of relapse, 5 categories of nonrelapse, and 1 category indicating unchanged status (high persisting symptoms throughout follow-up; Table 2). Interrater reliability ($\kappa$) for these classifications, based on ratings of all study cases, was 0.75 ($P < .001$).

Of the 82 patients, 28 had their conditions classified as never relapsed at follow-up (34%) and 5 (6%) as unchanged. A total of 49 patients (60%) had at least 1 relapse during the prospective period (Table 2), 19 (39%) of whom experienced relapse within the first 6 months, 16 (33%) between months 6 and 12, and 14 (29%) between months 12 and 24. Hospitalization occurred in 17 (35%) of the 49 patients who experienced disease relapse and in 6 (12%) of the 52 patients who did not experience relapse or terminated prematurely ($\chi^2 = 7.69, P = .006$).

**TREATMENT OUTCOME**

**Relapse and Survival Time**

Of the 70 patients assigned to CM, 38 (54%) experienced disease relapse during the 2-year follow-up, 12 (17%) survived without disease relapse, 4 (6%) were unchanged, and 16 (23%) terminated prematurely (Table 2). Of the 31 FFT patients, 11 (35%) experienced disease relapse at follow-up, 16 (52%) survived without disease relapse, 1 (3%) was unchanged, and 3 (10%) terminated prematurely. The group differences in relapse and nonrelapse rates were significant ($\chi^2 = 13.03, P < .005$). Survival analyses using the Kaplan-Meier method revealed that the conditions of patients undergoing FFT had longer survival intervals without experiencing disease relapse than patients undergoing CM (Wilcoxon $\chi^2 = 8.71, P = .003$).

Comparison of the curves revealed that patients undergoing FFT had longer survival intervals without experiencing disease relapse than patients undergoing CM (Wilcoxon $\chi^2 = 8.71, P = .003$). The pretreatment assessment interval spanned weeks 0 to 4; the active period of psychosocial intervention, weeks 4 to 43; and the posttreatment follow-up interval, weeks 44 to 104.

None of the following pretreatment variables altered the effects of psychosocial treatment on survival time: SADS-C total affective symptom scores (or mania or depression composite scores) at study intake or at the 1-month pretreatment assessment, baseline pharmacotherapy intensity scores, polarity of the index study episode, age or sex, socioeconomic status, number of prior episodes, age at illness onset, or inpatient vs outpatient status at entry. The SADS-C total affective symptoms at 1 month were independently associated with more rapid relapse ($\chi^2 = 4.82, P = .03$; hazard ratio, 1.57; 95% CI, 1.0-2.3).
Symptom Type and Severity

A repeated-measure, mixed-model ANOVA revealed a main effect of time on total affective symptom scores \((F_{7.54}=18.37; \ P<.001; \ N=101)\), indicating that patients, on average, improved significantly during the 24 months. There was no main effect of psychosocial treatment group \((F_{1.03}=0.45; \ P=.50)\) in predicting total affective symptoms, but there was a statistically reliable treatment group \(\times\) time interaction \((F_{7.54}=2.81; \ P=.007)\). As indicated in Figure 3, patients in the FFT group had equivalent affective symptom scores to patients in the CM group for the first 6 study months but then stabilized at lower levels of symptom severity. This treatment group \(\times\) time interaction remained robust after covarying patients’ total affective symptoms during the intake study episode \((F_{7.55}=2.88; \ P=.006)\) or at the 1-month pretreatment assessment \((F_{7.54}=2.57; \ P=.01)\).

A close examination of the polarity of symptoms revealed a treatment \(\times\) time interaction on SADS-C depression scores at follow-up \((F_{7.55}=2.91; \ P=0.005)\). This interaction remained statistically reliable after covarying depression symptoms at intake \((F_{7.55}=3.05; \ P=.004)\) and at 1 month \((F_{7.56}=2.65; \ P=.01)\). Family-focused therapy patients also had lower average mania scores across time than CM patients, a main effect of treatment group that approached significance \((F_{1.84}=3.52; \ P=.06)\). The magnitude of this group difference was not diminished by covarying mania scores at study intake \((F_{1.85}=4.01; \ P=.049)\) or at the 1-month pretreatment assessment \((F_{1.84}=3.06; \ P=.08)\). Finally, the effects of psychosocial treatment on depression and mania scores were not explained by patients’ sex, socioeconomic status, number of prior episodes, or age at onset.

Pharmacotherapy Regimens and Adherence

The 2 psychosocial groups (FFT and CM) could not be distinguished on drug treatment intensity scores (0-4 scale) at study entry, the 1-month pretreatment assessment, or any point of follow-up \((F_{1.37}=1.06; \ P=39)\). The groups were also equivalent at all time points on the frequency of psychiatry visits, the use of lithium carbonate vs the anticonvulsants, or the use of adjunctive antidepressants or antipsychotics \((P>.10\) for all).

In contrast, patients undergoing FFT had higher mean drug adherence scores (1-3 scale) during the follow-up \((2.77 \pm 0.43)\) than patients undergoing CM \((2.56 \pm 0.48; \ F_{1.79}=4.48; \ P=.04)\). This finding raised the possibility that drug adherence mediated the effects of FFT and CM on the trajectory of mood disorder symptoms. To examine this possibility, we used repeated-measure, mixed-model ANOVAs to examine treatment group as an independent variable, depression and mania scores as repeated dependent variables, and medication adherence scores at each point of follow-up as time-dependent covariates.\(^7^0\) These analyses revealed no effect of drug adherence on depression scores at follow-up \((F_{14.48}=1.26; \ P=.23)\), but the psychosocial treatment-by-time interaction remained reliable \((F_{7.39}=2.52; \ P=.02)\). In contrast, patients who were more medically adherent had consistently lower mania scores over time than patients who were less adherent \((F_{14.60}=3.64; \ P<.001)\). Furthermore, the main effect of psychosocial treatments on mania scores disappeared once drug adherence scores were covaried \((F_{1.79}=0.6; \ P=.43)\), suggesting that adherence mediated the effects of the psychosocial interventions on mania symptoms.

Figure 3. Mean total affective symptom scores throughout 24 study months among patients in family-focused treatment (FFT) and medication or crisis management (CM) and medication (intent-to-treat analysis, N=101). Total affective symptoms were calculated by averaging 18 items from the Schedule for Affective Disorders and Schizophrenia, Change Version,\(^1^8\) which measured depressive symptoms and manic symptoms. A repeated-measure, mixed-model analysis of variance revealed a treatment \(\times\) time interaction \((F_{7.42}=2.81; \ P=.007)\), indicating that patients undergoing FFT showed greater reductions in total affective symptoms over time than patients undergoing CM.

COMMENT

This study demonstrates that a 9-month program of FFT, administered with pharmacotherapy and initiated during the postepisode phases of bipolar I disorder, is associated with longer relapse-free intervals during 2 years than a less intensive psychoeducational intervention (CM) and pharmacotherapy. The hazard ratio of 0.38 reflects a 3-fold higher rate of survival in the FFT group (52%) than the CM group (17%), a 35% reduction in relapse rates (35% in FFT vs 54% in CM), and an average duration of survival almost 5 months longer in FFT (73.5 weeks) vs CM patients (53.2 weeks). The benefits of family intervention extended beyond the 9-month period of active treatment: patients undergoing FFT showed greater stabilization of mood disorder symptoms, particularly depression, during the 2 years. Similar benefits of family psychoeducation during 18- to 24-month periods are found in schizophrenia studies,\(^7^1\) especially when maintenance family sessions are given during the posttreatment intervals.

How do the present findings compare with the results of other randomized trials of psychosocial intervention in bipolar I disorder? In a 1-year trial, Lam et al\(^3^5\) found a lower rate of relapse (21/48, 44%) among bipolar patients treated with medication and individual cognitive-behavioral therapy (average, 16 sessions) than among patients treated with medication and clinical management (36/48, 75%). Their observed hazard ratio (0.40; 95% CI, 0.21-0.74) was nearly identical to ours. In an 18-month randomized study of 69 patients, Perry et al\(^3^6\) reported a 30% reduction in manic relapses from a com-
combination of drug treatment and individual psychoeducation (7-12 sessions) when compared with drug treatment and routine care. It seems that adjunctive psychosocial interventions, both individual and family, decrease relapse risk in bipolar disorder by 30% to 40% during intervals that range from 12 to 24 months.

The present study has several limitations. First, it compares a relatively intensive outpatient program (21 home-based family sessions) to treatment with less frequent therapist-patient contact (2 home-based family sessions and follow-up crisis intervention). This design was chosen because at the study’s inception, there were no empirically supported individual or group treatments for bipolar disorder that could serve as credible comparisons. Instead, we chose a treatment-as-usual comparison that reflected what many bipolar patients received in the community. The CM condition provided a control for the frequency of research assessments, the passage of time, and nonspecific factors such as the coordination of emergency interventions by therapists and physicians. Nonetheless, the superior effects of FFT may have been due to its greater frequency and, by extension, the greater opportunity for clinicians or caregivers to intervene when prodromal symptoms of relapse appeared.

Relevant to these design considerations are the results of another 2-year randomized trial, which assigned 53 bipolar, manic patients to FFT and medication or to equally intensive (21 sessions) individual educational therapy and medication, administered in an outpatient clinic setting. Patients undergoing FFT had lower rates of relapse (28%) and rehospitalization (12%) than patients in individual therapy (60% and 60%, respectively) but only during a 1-year posttreatment interval. These results suggest that the effects of FFT are not simply due to its frequency and duration. They also suggest that families require a period of absorption of new skills and coping strategies before the benefits of family therapy relative to comparably paced individual interventions can be observed.

A second study limitation was the lack of control over patients’ drug regimens. This study was a management trial, in which pharmacotherapy was delivered according to clinicians’ judgments rather than predetermined drug decision trees administered under controlled conditions. The latitude given physicians did not seem to benefit one psychosocial group over the other. Nonetheless, evaluating psychosocial interventions as a function of specific medication options (eg, mood stabilizers vs without antidepressants) or dosing strategies, as is being done in the Systematic Treatment Enhancement Program for Bipolar Disorder, should strengthen the internal validity of future trials.

By what mechanisms do family interventions contribute to more benign outcomes of bipolar disorder? A secondary hypothesis was that family psychoeducation, because of its focus on the biological underpinnings of bipolar disorder and the critical role of medication in prophylaxis, would enhance patients’ drug adherence. We also predicted that regular participation of caregivers would increase the likelihood that instances of noncompliance would be identified early and derailed. Indeed, FFT patients were more consistent with their medications than CM patients.

Several randomized trials involving schizophrenia patients found that the clinical effects of family interventions are independent of their effects on drug compliance, although not all trials have examined this issue directly. In the present study, compliance with mood stabilizers mediated the effects of family intervention on bipolar, manic symptoms but not depressive symptoms. This pattern of results is consistent with the observation that mood stabilizers are more effective in controlling manic than depressive symptoms. However, we cannot conclude that medical adherence was causally related to lower manic symptoms in the FFT group, because data on adherence and mood symptoms were collected during retrospective intervals. Thus, the reemergence of manic symptoms may have contributed to poorer drug adherence in the same or the following study interval. Intervention studies that include daily diaries of moods and drug compliance during prospective periods may help to disentangle the direction of these relationships.

Possibly, mania is a more purely biologically driven phenomenon than bipolar depression, with onsets more readily attributable to medication inconsistency, sleep deprivation, circadian disruption, or behavioral activation. In contrast, social and familial support has been found to protect against depression in bipolar and unipolar affective disorders, but the role of these variables in manic recurrences is unclear. An analysis of laboratory interactional data from a subset of 44 families in this sample revealed that treatment-related improvements in family communication skills were more closely associated with reductions in patients’ depressive than manic symptoms. This may be because different sets of risk and protective factors. Possibly, medication and family intervention are complementary approaches that, if administered together, lead to greater control over fluctuations of both poles of the disorder.

Psychosocial interventions are by no means substitutes for pharmacotherapy, but they may augment mood stabilizers in protecting patients from symptom deterioration as well as enhance compliance with maintenance treatments. Studies of the cost-effectiveness of manual-based psychosocial approaches in socioeconomically diverse settings, which include bipolar patients with a broader range of illness presentations, are essential to extending these observations beyond the laboratory.

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