Family Treatment for Bipolar Disorder: Family Impairment by Treatment Interactions

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Objective: There is a clear need for psychosocial treatments to supplement pharmacotherapy for bipolar disorder. In this study, the efficacy of 2 forms of adjunctive family intervention were compared to pharmacotherapy alone. In addition to evaluating overall differences between treatments, a chief goal was to examine whether family impairment levels moderated the effects of family intervention on outcome.

Method: Ninety-two patients diagnosed with bipolar I disorder (according to DSM-III-R) were randomly assigned to receive (1) pharmacotherapy alone, (2) family therapy + pharmacotherapy, or (3) multi-family psychoeducational group + pharmacotherapy. Treatments and assessments continued for up to 28 months. Primary outcome measures were number of episodes per year and percentage of time symptomatic throughout the entire follow-up period. The study was conducted from September 1992 through March 1999.

Results: No significant main effects were found for treatment condition. Thus, for the total sample, the addition of a family intervention did not improve outcome. However, there were significant treatment condition by family impairment interactions ($p < .05$). In patients from families with high levels of impairment, the addition of a family intervention (family therapy or psychoeducational group) resulted in a significantly improved course of illness, particularly the number of depressive episodes ($p < .01$) and proportion of time spent in a depressive episode ($p < .01$). These effects were relatively large (Cohen d = 0.7–1.0), with patients receiving either family intervention having roughly half the number of depressive episodes and amount of time spent depressed as those receiving pharmacotherapy alone. In contrast, for patients from low-impairment families, the addition of a family intervention did not improve course of illness.

Conclusions: Our findings build on previous literature suggesting the importance of treatment matching within the mood disorders and suggest that the utility of adding family interventions for bipolar patients and their families may depend upon the family's level of impairment.

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Bipolar disorder is an important mental health problem that occurs in approximately 2% to 4% of the population.[1–3] Perhaps even more critical is that, because of its recurrent nature and substantial impairment,[4] bipolar disorder produces severe consequences for the identified patient, his or her family, and society.[5–7] Furthermore, bipolar disorder is often fatal, with approximately 20% to 50% of patients with bipolar disorder attempting suicide[4,8] and about 10% to 15% of bipolar patients ultimately dying from suicide.[8,9]

While a number of medications have been found to be significantly more efficacious than placebo in treating bipolar disorder,[10,11] many bipolar patients continue to have a pernicious course of illness even with adequate pharmacologic treatment.[12–14] In response to the gaps in treatment efficacy, a number of recent studies have investigated the utility of adding a psychosocial intervention to pharmacotherapy for bipolar patients. Published studies have investigated the efficacy of individual psychotherapies,[15,16] group interventions,[17] and family treatments.[18–21] While the number of available, adequately conducted studies is quite small, in general, the results of these published studies have been largely positive, with the addition of a psychosocial treatment leading to an improved course of illness.[22]

The current study was designed to investigate the efficacy of 2 different adjunctive family treatments (family therapy and multi-family psychoeducational group) as additions to pharmacotherapy alone for bipolar I patients. The family therapy condition used a relatively brief (10- to 15-session), problem-focused family treatment (Problem Centered Systems Therapy of the Family

[PCSTF][23,24]) that has been shown to be efficacious in patients with major depression.[25] The multi-family group was based on the family group interventions developed by Gonzales et al.,[26] McFarlane et al.,[27,28] and Yalom[29] and consisted of 6 psychoeducational sessions with family members from multiple families.[30] Except for the recently published results of the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) trial,[31] previous studies have typically investigated only 1 type of psychosocial intervention. In the current study, the inclusion of 2 different types of family interventions, which differ in intensity and focus, allows exploration of the specificity of the potential effects.

Previous reports from this study have focused on potential differences in categorical variables of recovery[32] and recurrence[33] rates between treatment conditions. These previous reports have found no differences in recovery and recurrence rates between pharmacotherapy alone, family therapy, and multi-family psychoeducational group conditions.

The current report differs from these previous reports in 2 important ways. First, most previous reports of randomized trials for psychosocial interventions for bipolar disorder have focused on proportion or time to recovery, relapse, or recurrence as dependent measures. While the proportions of patients who recover and relapse are certainly important measures, these measures alone do not adequately capture the chronic course of bipolar disorder for many patients, a course characterized by frequently fluctuating episodes of varying polarities and lengths and a high proportion of time with subsyndromal symptoms.[34–36] The limitations of these categorical outcomes of "recovery," "relapse," and "recurrence" have led several investigators to propose that the percentage of time spent at different levels of symptoms over an entire follow-up period may offer a more complete characterization of the course of illness in bipolar disorder.[13,37–39] In the current report, we use these proportional measures of long-term course of illness as the primary outcome variables.

Second, based on previous research suggesting that high levels of family impairment were specifically associated with a poorer course of illness in bipolar disorder,[6,40] this study was designed to assess the hypothesis that family interventions would be more effective for patients from highly impaired families than for those from less impaired families. This interaction hypothesis is conceptually similar to the "deficit-matching" algorithm investigated and found to have modest support in a recent study of patients with major depressive disorder.[25]

METHOD

Subjects

Study subjects included 92 patients with a DSM-III-R diagnosis of bipolar I disorder, according to the Structured Clinical Interview for DSM-III-R Axis I Disorders, Patient Version (SCID-P),[41] and their family members. Additional patient inclusion criteria included (1) current episode of mania, major depression, or mixed episode, (2) age between 18 and 75 years, (3) sufficient reading skills to complete questionnaires in English, and (4) currently living with or in regular contact with a relative or significant other. Patients were excluded from the study if they (1) met DSM-III-R criteria for alcohol or drug dependence during the past year, (2) had a mood disorder secondary to a general medical condition, (3) presented with a medical illness severe enough to contraindicate mood-stabilizing medication, and (4) were pregnant or did not use adequate contraception (in women with childbearing potential). Ninety-two patients who met criteria for current bipolar I disorder were enrolled in this clinical trial. Of these patients, 88 were recruited while hospitalized. This study was approved by the institutional review boards of Butler Hospital and Rhode Island Hospital, and all subjects signed approved informed-consent forms. The study was conducted from September 1992 through March 1999.

Stratification

Patients who met these criteria were subgrouped according to level of family impairment. Using the same procedures as our previous study investigating family by treatment interactions,[25] family impairment levels were determined on the basis of the general functioning scale of the McMaster Clinical Rating Scale (MCRS).[42,43] (We had originally proposed to use both the MCRS and the self-report Family Assessment Device [FAD][43,44] to determine level of family impairment. However, due to the relatively low association between the self-report FAD and the interviewer-rated MCRS [r = –0.43], as well as concerns about the validity of manic patients' self-reports during hospitalization, we decided to use only the MCRS ratings for our stratification.) The MCRS is used to provide ratings of family functioning as assessed by a clinical interviewer. The MCRS includes scales for each of the 6 dimensions of the McMaster Model of Family Functioning,[24] as well as a general functioning scale. For stratification in this study, we used the general functioning scale, which is a 7-point summary scale that takes into account functioning on each of the 6 McMaster dimensions. This scale was rated by a trained clinical interviewer using information gained in a 1- to 2-hour structured interview with the patient and all participating family members.[24,45] Previous studies have demonstrated the reliability, validity, and utility of the MCRS as a measure of family functioning in a variety of populations.[24,43,46–50]

Families were interviewed by experienced master's-level and Ph.D.-level raters who were trained by one of the developers of the MCRS. Training consisted of didactics, role-plays, and supervised interviews/ratings until the interviewers reached an acceptable level of agreement

Table 1. Demographic and Clinical Characteristics of Study Population

Characteristic	Total Sample (N = 91)	Low Family Impairment			High Family Impairment		
		Pharmacotherapy (N = 15)	Family Therapy (N = 7)	Psychoeducational Group (N = 9)	Pharmacotherapy (N = 14)	Family Therapy (N = 25)	Psychoeducational Group (N = 21)
Age, mean (SD), y	39.5 (11.3)	27.9 (10.5)	36.7 (8.0)	33.7 (9.6)	42.3 (11.2)	41.1 (10.9)	40.7 (13.9)
Gender, female, N (%)	39 (42.9)	5 (33.3)	5 (71.4)	3 (33.3)	5 (35.7)	10 (40.0)	11 (52.4)
Education, mean (SD), y	13.3 (2.5)	12.9 (2.4)	13.1 (2.3)	14.0 (1.8)	14.2 (2.9)	13.0 (2.9)	13.2 (2.0)
Polarity of current episode, N							
Manic	68	12	3	6	10	20	17
Depressed	18	2	3	3	2	4	4
Mixed	5	1	1	0	2	1	0
BRMS score, manic only, mean (SD)	26.4 (5.4)	27.0 (6.6)	28.7 (3.5)	26.2 (3.8)	25.4 (6.2)	27.3 (4.7)	25.4 (6.1)
MHRSD score, depressed only, mean (SD)	21.9 (7.7)	23.5 (6.4)	19.7 (11.6)	22.0 (7.5)	25.5 (5.0)	23.5 (11.4)	19.5 (5.9)
No. of previous depressive episodes, mean (SD)	5.0 (8.4)	2.9 (7.8)	5.4 (4.5)	6.0 (8.5)	6.7 (8.9)	3.9 (5.1)	6.7 (12.4)
No. of previous manic episodes, mean (SD)	4.8 (4.8)	3.2 (2.3)	2.4 (1.5)	4.7 (6.9)	5.5 (2.8)	5.4 (6.8)	5.6 (4.2)
No. of previous hospitalizations, mean (SD)	4.7 (4.5)	3.5 (1.0)	3.7 (1.7)	4.8 (1.4)	6.5 (1.1)	4.2 (0.8)	4.4 (0.9)
SCL-90 GSI, primary family member, mean (SD)	0.46 (0.37)	0.34 (0.24)	0.25 (0.22)	0.42 (0.37)	0.55 (0.35)	0.49 (0.38)	0.53 (0.48)

Abbreviations: BRMS = Bech-Rafaelsen Mania Scale, MHRSD = Modified Hamilton Rating Scale for Depression, SCL-90 GSI = Symptom Checklist-90 Global Severity Index.

(90%). Supervision was provided throughout the study; any disagreements in ratings were resolved by consensus. Our group has demonstrated in previous research that even naive raters with minimal training (e.g., college students with < 12 hours of training) can reliably rate the general functioning scale of the MCRS (intraclass correlation coefficient = 0.87).[43]

Since most families with a bipolar member will manifest some dysfunction, particularly during an acute episode,[25,50] we used the median score on the general functioning scale of the MCRS, consistent with the threshold for family impairment used in our previous studies of hospitalized patients with mood disorders.[25,50,51] One family did not complete the MCRS at baseline. Among the remaining 91 families, the median MCRS score was 3.0. Thus, families with an MCRS score of 3 or less were labeled with "high family impairment" (66%, N = 60), and families with a score of 4 or greater were labeled with "low family impairment" (34%, N = 31). Pretreatment patient characteristics can be seen in Table 1.

Treatment Conditions

After informed consent was obtained and baseline assessment was completed, patients were randomly assigned to 1 of 3 treatment conditions: (1) pharmacotherapy alone, (2) family therapy + pharmacotherapy, or (3) multi-family psychoeducational group + pharmacotherapy. Treatments and assessments continued for up to 28 months. Patients were assigned to 1 of these 3 treatments based on an urn randomization model,[52,53] which insured that the treatment conditions were balanced according to (1) polarity (manic, depressed, or mixed), (2) family impairment (high vs. low), (3) living with parent vs. living with another family member or significant other, (4) number of previous mood episodes (1–2 vs. ≥ 3), (5) psychotic symptoms (yes or no), and (6) gender.

Pharmacotherapy. The pharmacotherapy condition consisted of regular meetings with 1 of 3 board-certified psychiatrists. Psychiatrists followed a modified version of the clinical management pharmacotherapy manual developed by Fawcett et al.[54] and a semistructured medication protocol designed to optimize treatment response. During each visit, the psychiatrist (1) assessed current symptoms, (2) reviewed medication side effects, (3) provided brief support and advice, and (4) adjusted medications.

Following recommended treatment guidelines, all patients were prescribed a mood stabilizer. In addition, other medications (antidepressants or neuroleptics) were prescribed depending upon the patient's clinical symptoms and history.

Pharmacotherapy visits were scheduled weekly during the first month of study treatment. The subsequent frequency of visits was determined by the patient's clinical course and the psychiatrist's clinical judgment. Typically, patients with continuing symptoms were seen biweekly or monthly, while stable, euthymic patients were seen approximately every 3 months.

Family therapy. Family therapy was conducted according to the PCSTF model.[24,55,56] Based on the McMaster Model of Family Functioning, the PCSTF approach is a short-term, multidimensional, family treatment that emphasizes comprehensive assessment, problem identification, and task-oriented problem-solving. Previous research has found that the inclusion of the

PCSTF family intervention significantly improved outcome in the post–hospital care of severely depressed patients.[25] Sessions were scheduled at the discretion of the family therapist, with a majority of sessions occurring during the first 6 months of treatment and with a general target of 10 to 15 family-therapy sessions during the study period. The family therapy was provided by an M.S.W.-degreed family therapist with 15 years of clinical experience who was certified as competent in PCSTF by one of the developers of the model.

Multi-family psychoeducational group. This intervention consisted of a 6-session multi-family group therapy focused on providing patients and their families with psychoeducational information and coping strategies for bipolar disorder.[30] Each of the 6 group sessions focused on a specific topic, including (1) the signs and symptoms of depression and mania; (2) the experiences of and concerns about living with a family member who has a mood disorder, and potential coping strategies; (3) questions and answers with a psychiatrist regarding pharmacotherapy for mood syndromes; (4) the group members' reactions to the presentation made by the psychiatrist in the previous session, and the notion of taking responsibility for one's actions; (5) the difference in patients' and family members' perspectives and experiences of bipolar disorder and the ways to discuss these perspectives in a constructive manner; and (6) a summary of the main themes of the previous sessions, with a member of a local patient/family mental health support association in attendance. Groups typically consisted of 4 to 6 families and were co-led by a Ph.D.-level clinical psychologist and an M.S.W.-level social worker.

Assessments

Upon admission to the study, patients were administered the SCID-P,[41] the MCRS,[43] the Modified Hamilton Rating Scale for Depression (MHRSD),[57] and the Bech-Rafaelsen Mania Scale (BRMS),[58,59] as well as other measures not included in this report. One family member designated by the patient as "primary" also completed the Symptom Checklist-90 (SCL-90).[60]

The patient version of the SCID[41] was used to assess bipolar I disorder, psychotic symptoms, and clinical-course characteristics. The SCID is a commonly used structured clinical interview that is designed to assess Axis I disorders in adults. The 25-item MHRSD[57] is a commonly used instrument that was used to assess depression severity. For the purposes of this report, we used the 17-item total score. When responding to the MHRSD interviewer, participants were asked to consider the worst week in the past month. The BRMS[58,59] is an 11-item, interview-based scale that was used to assess severity of manic symptoms. As with the MHRSD, participants were asked to consider the worst week in the past month when responding to BRMS questions.

The SCL-90,[60] a 90-item self-report measure designed to assess levels of psychological distress, was administered to the primary family member. For purposes of this study, the SCL-90 Global Severity Index (GSI) was used as an index of global psychopathology.

Trained raters administered all instruments. After a series of didactic presentations on the interview process, manic and depressive symptoms, and specific instruments, interviewers were trained to reliability (≥ 90% agreement) before beginning interviews for the study. All difficult interviews were reviewed by a Ph.D.-level project coordinator, and consensus was reached on any items that were in question. Routine supervision of audiotaped interviews was performed and consensus conferences were held to protect against rater drift. Previous studies conducted by the investigators using these same training procedures have yielded high levels of reliability on these scales.[57,61]

The SCID-P was administered at baseline, and the MHRSD and BRMS were administered at baseline and monthly thereafter. When a patient dropped out of treatment, we made every effort to continue with regular assessments. Assessments at baseline and at months 2, 4, 6, 10, 16, 22, and 28 were conducted in face-to-face interviews; other monthly assessments were conducted over the telephone. Interviewers were unaware of level of family impairment and treatment assignment but were aware of the timing of assessment.

Dependent Measures

Proportional measures. Following recent publications,[13,37–39] in order to characterize the entire course of our 28-month follow-up, we calculated (1) the total number of episodes per year of follow-up and (2) the percentage of time in a mood episode. We further subdivided the number of episodes and percentage of time spent in a mood episode into manic/mixed episode or depressed episode. The specifics of the methods for the development of these measures are presented in Miller et al.[39] and are described briefly here.

Based on the monthly administration of the MHRSD and BRMS, a study month was defined as "fully symptomatic" if either the MHRSD or the BRMS score was ≥ 15. Additionally, "full depressive symptoms" were defined as a month with an MHRSD score ≥ 15 and a BRMS score < 15. Conversely, we defined "full manic symptoms" as a month with a BRMS score ≥ 15 and an MHRSD score < 15. A "full mixed symptoms" month was defined as an MHRSD score ≥ 15 and a BRMS score ≥ 15. However, due to the small number of mixed-symptom months, for this study, the full-manic and full-mixed months were combined into "full manic/mixed symptoms."

A "depressive episode" was defined as the number of consecutive months in which a patient met criteria for full

depressive symptoms. "Manic episode" and "mixed episode" were defined in a similar fashion and, again, were combined for the purposes of this study.* Using these classifications and the number of follow-up months for which data were available, we calculated (1) the number of episodes (depressed, manic/mixed, and total) per year for each patient and (2) the percent of time that each patient spent fully symptomatic (total, depressed, and manic/mixed).

Categorical measures. In addition, for comparison purposes, we also report the percent of patients who recovered and relapsed using standard criteria employed in previous reports from this project.[32,33] Recovery was defined as 2 consecutive months with an MHRSD 17-item score < 7 and a BRMS score < 6. Relapse was defined as an MHRSD 17-item score > 15 *or* a BRMS score > 9 after patients had met criteria for recovery.

Family-member distress. In order to provide a summary measure of family-member distress, we calculated a mean of the SCL-90 GSI index across all available post-treatment assessment points.

Statistical Analyses

The primary analyses were treatment (pharmacotherapy alone vs. family therapy vs. psychoeducational group) by family impairment (high vs. low) using analysis of variance (ANOVA). When overall F values were significant at the $p < .05$ level, a priori, planned comparisons were tested using t tests. Chi-square analyses were used to assess differences in categorical variables. Effect sizes (η^2 for ANOVAs, Cohen d for t tests, and ω for χ^2 tests) are also reported for significant results. All analyses were intent-to-treat using all available data.

RESULTS

Baseline Measures

Sample characteristics and baseline measures can be seen in Table 1. Two-way ANOVAs yielded no significant main effects or treatment by family impairment interactions on these baseline characteristics.

Compliance With Treatment

Nine (10%) of the 91 patients dropped from the study before providing 2 months of assessment data and were not used in subsequent analyses.† Eight of these 9 patients provided no assessment data after hospital discharge. There were no significant differences in proportions of early dropouts between treatment conditions or family impairment groups (Table 2). Sixty-five percent (59/91) of the patients remained in randomized treatment (pharmacotherapy + assigned time period of psychosocial treatment) for at least 6 months, with no differences in compliance among treatment or family impairment groups. Thirty-six percent (33/91) of the patients remained in randomized treatment (pharmacotherapy + assigned course of psychosocial treatment) for the entire 28-month period, again with no significant differences among treatment or family impairment groups.

Treatment Received

The treatment received by patients in the study is summarized in Table 2. Patients received 10 to 15 sessions with psychiatrists during the study. Medication adequacy was rated independently by 2 board-certified psychiatrists who were unaware of treatment condition, family impairment, and patient outcome. The small number of disagreements between psychiatrists were resolved by consensus. As can be seen, a high proportion of patients received adequate trials of mood stabilizers (90%), and substantial proportions received trials of neuroleptics (79%) and antidepressants (51%). There were no significant differences between treatment groups in the proportion of patients who received different types or levels of medication. Patients assigned to the family therapy condition received a mean of 12 family therapy sessions, while patients assigned to the psychoeducational group attended a mean of 4 sessions.

Course of Illness

The unadjusted means and standard deviations of the dependent measures are presented in Table 3. However, because all proportional variables exhibited substantial skew, a square-root transformation was performed on these measures before statistical analyses.

Proportional Measures

Two-way (family impairment by treatment condition) ANOVAs yielded no significant main effects due to family impairment or treatment condition on any variable (all p values > .20). However, significant family impairment by treatment condition interaction effects were found on (1) number of depressive episodes per year ($F = 4.1$, $df = 2,77$; $p < .05$; $\eta^2 = 0.84$), (2) percentage of time in episode ($F = 4.0$, $df = 2,82$; $p < .05$; $\eta^2 = 0.96$), and (3) percentage of time in a depressive episode ($F = 5.2$, $df = 2,82$; $p < .01$, $\eta^2 = 0.93$). No significant effects were

*To be consistent with DSM-IV-TR guidelines,[62] we have defined an episode as the period of time that an individual fully meets symptomatic criteria. The end of an episode was defined by either a monthly assessment that did not meet full symptomatic criteria or a change in the polarity of the symptoms. This time period is distinct from (and shorter than) the period of time between episode onset and full symptom remission. It is also different from our definition of recovery, which requires 2 consecutive months of minimal symptoms. See Miller et al.[39] for a more complete discussion of these definitional issues.

†To evaluate the possibility that the obtained results were due to subjects with a small number of available assessments, we repeated our main analyses, limiting our sample to those with 6 or more months of available data. The effect sizes obtained with this more restricted sample were highly similar to the results with the larger sample.

Table 2. Characteristics of Study Treatment Received

Characteristic	Total Sample (N = 91)	Low Family Impairment			High Family Impairment		
		Pharmacotherapy (N = 15)	Family Therapy (N = 7)	Psychoeducational Group (N = 9)	Pharmacotherapy (N = 14)	Family Therapy (N = 25)	Psychoeducational Group (N = 21)
Early dropout, < 2 months, N (%)	9 (10)	2 (13)	2 (29)	0 (0)	1 (7)	1 (4)	3 (14)
Completed ≥ 6 months of randomized treatment, N (%)	59 (65)	12 (80)	4 (57)	7 (78)	7 (50)	16 (64)	13 (62)
Month of randomized treatment discontinuation, mean (SD)	14.8 (11.5)	17.3 (11.2)	13.6 (13.7)	13.6 (9.7)	11.3 (11.6)	15.4 (11.6)	14.6 (12.0)
Completed 28 months of randomized treatment, N (%)	33 (36)	7 (47)	3 (43)	2 (22)	3 (21)	10 (40)	8 (38)
Mood stabilizer, adequate dose, N (%)	82 (90)	13 (87)	6 (86)	9 (100)	11 (79)	23 (92)	20 (95)
Antidepressant use, N (%)	46 (51)	5 (33)	3 (43)	6 (67)	6 (43)	16 (64)	10 (48)
Neuroleptic use, N (%)	72 (79)	14 (93)	5 (71)	8 (89)	12 (86)	18 (72)	15 (71)
No. of pharmacotherapy visits, mean (SD)	12.8 (8.9)	13.5 (7.7)	16.7 (15.6)	13.0 (7.4)	9.9 (8.4)	13.7 (8.9)	11.3 (8.5)
No. of family therapy visits, mean (SD)	11.9 (12.9)	NA	12.8 (12.1)	NA	NA	11.6 (12.1)	NA
No. of psychoeducational group meetings, mean (SD)	3.9 (2.5)	NA	NA	4.6 (2.2)	NA	NA	3.7 (2.6)

Abbreviation: NA = not applicable.

Table 3. Treatment Outcome Data Over 28-Month Follow-Up Period

Variable	Total Sample[a] (N = 82)	Low Family Impairment			High Family Impairment		
		Pharmacotherapy (N = 13)	Family Therapy (N = 5)	Psychoeducational Group (N = 9)	Pharmacotherapy (N = 13)	Family Therapy (N = 24)	Psychoeducational Group (N = 18)
No. of months of data, mean (SD)	18.1 (10.8)	23.9 (9.6)	13.4 (12.5)	17.4 (11.1)	15.2 (11.0)	15.6 (11.3)	21.3 (8.0)
Total no. of episodes per year, mean (SD)	1.8 (2.2)	1.0 (1.4)	1.7 (1.7)	1.7 (1.8)	2.8 (2.1)	2.1 (3.1)	1.1 (1.4)
No. of depressive episodes per year, mean (SD)	1.1 (1.4)	0.6 (0.8)	1.5 (1.6)	1.0 (0.9)	2.1 (1.5)	1.2 (1.9)	0.7 (0.9)
No. of manic/mixed episodes per year, mean (SD)	0.6 (1.9)	0.4 (1.0)	0.2 (0.4)	0.7 (1.2)	0.7 (1.4)	0.9 (2.0)	0.4 (0.8)
Percent of time fully symptomatic, mean (SD)	24 (30)	12 (18)	44 (46)	30 (35)	34 (22)	28 (35)	20 (27)
Percent of time with full depressive symptoms, mean (SD)	19 (28)	9 (15)	42 (47)	22 (31)	30 (21)	23 (32)	14 (24)
Percent of time with full manic symptoms, mean (SD)	7 (16)	4 (9)	4 (6)	10 (21)	6 (7)	9 (18)	6 (14)
Percent of time symptom-free, mean (SD)	50 (35)	59 (32)	48 (45)	49 (33)	34 (35)	47 (40)	49 (31)
Recovered, % (N/N)	62 (51/82)	85 (11/13)	40 (2/5)	78 (7/9)	39 (5/13)	50 (12/24)	78 (14/18)
Relapsed, percent of recovered, % (N/N)	63 (32/51)	64 (7/11)	50 (1/2)	57 (4/7)	60 (3/5)	67 (8/12)	64 (9/14)
SCL-90 GSI, primary family member, mean (SD)	0.38 (0.37)	0.26 (0.39)	0.34 (0.22)	0.42 (0.39)	0.25 (0.21)	0.53 (0.51)	0.40 (0.28)

[a]Total sample with ≥ 2 months of data.
Abbreviation: SCL-90 GSI = Symptom Checklist-90 Global Severity Index.

found for other measures. However, there was a nonsignificant trend for an interaction effect for the total number of mood episodes per year ($F = 2.64$, $df = 2,77$; $p = .08$; $\eta^2 = 0.81$).

Among patients with high family impairment, planned comparisons indicated that when compared to patients in the pharmacotherapy-alone condition, the patients who were assigned to the psychoeducational group had significantly (1) fewer depressive episodes per year ($t = 2.7$, $df = 27$, $p < .01$, $d = 1.0$), (2) lower percentage of time in any mood episode ($t = 2.2$, $df = 29$, $p < .05$, $d = 0.82$), (3) lower percentage of time in a depressive episode ($t = 2.8$, $df = 29$, $p < .01$, $d = 1.0$), and (4) fewer total mood episodes per year ($t = 2.4$, $df = 27$, $p < .05$, $d = 0.92$). Patients who received family therapy had significantly fewer depressive episodes per year than patients who

received pharmacotherapy alone ($t = 2.0$, $df = 33$, $p < .05$, $d = 0.70$). There were also nonsignificant trends for the patients in the family therapy condition to have spent a lower proportion of time in any mood episode ($t = 1.7$, $df = 35$, $p < .10$, $d = 0.58$) and in a depressive episode ($t = 1.9$, $df = 35$, $p < .10$, $d = 0.64$).

Conversely, among patients with low-impairment families, no significant differences were found. However, nonsignificant trends were found for patients in the pharmacotherapy-alone condition to spend a lower percentage of time in any mood episode than patients in family therapy ($t = 1.80$, $df = 16$, $p < .10$, $d = 0.90$) or the psychoeducational group ($t = 1.75$, $df = 20$, $p < .10$, $d = 0.78$) and less time in a depressive episode than patients who received family therapy ($t = 2.07$, $df = 16$, $p < .10$, $d = 1.0$).

No significant differences were found on proportional measures between patients assigned to family therapy or psychoeducational group from either high- or low-impairment families.

Categorical Measures

We found no significant differences in recovery or relapse rates between treatment conditions among patients from high- or low-impairment families. However, among patients from high-impairment families, there was a nonsignificant trend ($\chi^2 = 5.5$, $df = 2$, $p < .10$, $\omega = 0.51$) for patients receiving the multi-family group intervention to have higher recovery rates (78%) than those receiving pharmacotherapy alone (39%).

Family-Member Distress

We found no significant differences between treatment conditions nor between members of high- and low-impairment families on the averaged SCL-90 GSI score. We also found no differences in SCL-90 scores when each assessment time was analyzed separately.

DISCUSSION

The results of this study suggest that the utility of adding family interventions for bipolar patients and their families depends upon the level of family impairment as well as the type of outcome assessed. For patients with high levels of family impairment, adding a family intervention to pharmacotherapy produced significant improvements in subsequent course of illness, particularly in the number of depressive episodes and proportion of time spent in a depressive episode. These effects were relatively large ($d = 0.7–1.0$); patients who received either family intervention were rated as having roughly half the number of depressive episodes and amount of time spent depressed as those receiving pharmacotherapy alone. No significant differences were found for the categorical variables of recovery and recurrence, although there was a nonsignificant trend for the patients assigned to the multi-family group to have higher rates of recovery. Thus, our data suggest that patients from families with high levels of family impairment benefit from family interventions, particularly when outcome is assessed through more proportional variables that capture the level of symptoms over time rather than at a singular point in time.

Conversely, among patients with families rated as having low levels of impairment, the addition of a family intervention did not produce improved course of illness on any measure. In fact, there were nonsignificant trends for patients from low-impairment families who received additional family interventions to have a worse subsequent course of illness than those who received pharmacotherapy alone. However, because the sample sizes for these comparisons were quite small, these results should be considered quite cautiously. Our data suggest that providing family interventions for bipolar disorder when the families are already functioning well does not appear to produce significant benefits.

Our findings concerning an interaction of family impairment by treatment are parallel with findings reported in several previous studies of mood-disordered patients. Miklowitz et al.[63] reported that the effectiveness of family-focused treatment for bipolar disorder was especially pronounced among patients with high family impairment, as indexed by high levels of expressed emotion. Similarly, Jacobson et al.[64] reported that marital therapy was specifically effective for patients with major depression who had high levels of marital dysfunction. Finally, in another study of patients with major depression, Miller et al.[25] found modest support for a treatment-matching algorithm that included a family impairment by treatment interaction as one of the 2 matching factors. Given the consistent results for family impairment to be a significant predictor of the course of illness in bipolar disorder[6] and major depression,[50,65,66] this growing evidence for the specific efficacy of family treatment for highly impaired families may represent an important clinical prescriptive factor in the treatment of patients with mood disorders.

The effectiveness of family interventions for patients from high-impairment families was especially pronounced for patients assigned to the multi-family psychoeducational group. While no significant differences were found between patients assigned to the individual family therapy condition and those assigned to the multi-family psychoeducational group, the patients who were assigned to the multi-family group manifested improved course of illness relative to the pharmacotherapy-alone condition on a more consistent basis than the family-therapy condition. Thus, despite the fact that the multi-family psychoeducational group patients received a mean of only 4 group sessions, compared to a mean of 12 sessions of individual family therapy, patients in the multi-family psychoeducational group had equivalent or even better

course of illness. Thus, similar to research on multi-family groups in other disorders,[27] the addition of a multi-family psychoeducational group intervention appears to be a very efficacious and cost-effective addition to pharmacotherapy for bipolar disorder.

What might account for the relative success of the multi-family psychoeducational group? As noted previously, the multi-family psychoeducational group provided a large amount of psychoeducation coupled with an opportunity to interact with other families with bipolar members. Although the family-therapy intervention did provide some psychoeducation, it was not as structured or intensive as the psychoeducation provided in the multi-family group. Since psychoeducation is an important aspect of other empirically supported treatments for bipolar disorder,[15,16,20] this emphasis may have been particularly important. Similarly, the sense of sharing and support from other families has also been described as one of the most important ingredients of the success of multi-family groups.[27]

Previous studies of family interventions for bipolar patients have reported largely beneficial effects upon rates of recovery, relapse, and recurrence,[19–21] although there have been exceptions.[18,67] In contrast, we found no main effects for our family treatments on these variables. The reasons for this discrepancy are not clear and may be due to cross-study differences in family treatments, patient samples, intervention timing, or other factors. For example, the studies of Miklowitz et al.[19,20,63] and Rea et al.[21] evaluated the efficacy of family-focused treatment,[68] which consisted of 21 sessions of family therapy conducted in the patient's home by 2 therapists with a specific focus on psychoeducation, problem-solving, and communication. Conversely, the PCSTF family intervention used in this study consisted of 12 sessions of family therapy conducted in an outpatient clinic by a single therapist with a focus on assessment and resolution of important family issues. Similarly, the patients in the Rea et al.[21] study had a mean age of 26 years, 15% were married, and 40% were in their first manic episode, whereas the patients in the current study had a mean age of 39 years, 67% were married, and only 10% were in their first episode. The Miklowitz et al.[19,20,63] studies began randomized treatment after a stabilization period, while the present study, as well as Rea et al.,[21] began randomized treatment immediately following an acute episode. Thus, these differences in multiple aspects of treatment, patient samples, and timing between studies do not allow easy identification of reasons for differential overall efficacy of family treatments. Given the very small number of studies of psychotherapeutic interventions for bipolar disorder, more research is clearly needed to begin to explore the reasons for these discrepancies.

While it might be expected that family members would derive substantial benefits from family treatments, we found no significant differences in levels of family-member distress among groups. However, it should be noted that family members did not report very high levels of emotional distress at baseline. Thus, the lack of significant differences between groups may represent a floor effect for family-member distress level.

Finally, we found greater differences among treatment conditions on the proportional measures of percent of time symptomatic and number of episodes per year over the follow-up period rather than on more traditional categorical outcome measures of recovery and recurrence. Given the highly variable and fluctuating course of bipolar disorder, outcome measures that summarize level of illness across the entire length of follow-up may offer a more sensitive measure of course of illness.

REFERENCES

1. Kessler RC, McGonagle KA, Zhao S, et al. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States: results from the National Comorbidity Survey. Arch Gen Psychiatry 1994;51:8–19
2. Robins L, Helzer J, Weissman M, et al. Lifetime prevalence of psychiatric disorders in three sites. Arch Gen Psychiatry 1984;41:949–958
3. Kessler RC, Berglund P, Demler O, et al. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry 2005;62:593–602
4. Goodwin F, Jamison K. Manic-Depressive Illness. New York, NY: Oxford University Press; 1990
5. Dion G, Tohen M, Anthony WA, et al. Symptoms and functioning of patients with bipolar disorder six months after hospitalization. Hosp Community Psychiatry 1988;39:652–657
6. Miklowitz D, Goldstein M, Nuechterlein K, et al. Family factors and the course of bipolar disorder. Arch Gen Psychiatry 1988;45:225–231
7. Miller IW, Kabacoff RI, Keitner GI, et al. Family functioning in the families of psychiatric patients. Compr Psychiatry 1986;27:302–312
8. Hawton K, Sutton L, Haw C, et al. Suicide and attempted suicide in bipolar disorder: a systematic review of risk factors. J Clin Psychiatry 2005;66:693–704
9. Harris E, Barraclough B. Suicide as an outcome for mental disorders: a meta analysis. Br J Psychiatry 1997;170:205–208
10. McElroy SL, Keck PE Jr. Pharmacologic agents for the treatment of acute bipolar mania. Biol Psychiatry 2000;48:539–557
11. Tondo L, Baldessarini RJ, Hennen J, et al. Lithium maintenance treatment of depression and mania in bipolar I and bipolar II disorders. Am J Psychiatry 1998;155:638–645
12. Prien RF. Maintenance treatment of depressive and manic states. In: Georgotas A, Cancro R, eds. Depression and Mania. New York, NY: Elsevier; 1988:439–451
13. Judd LL, Schettler PJ, Akiskal HS, et al. Long-term symptomatic status of bipolar I vs bipolar II disorders. Int J Neuropsychopharmacol 2003;6:127–137
14. Solomon DA, Keitner GI, Miller IW, et al. Course of illness and maintenance treatments for patients with bipolar disorder. J Clin Psychiatry 1995;56:5–13
15. Frank E, Kupfer DJ, Thase ME, et al. Two-year outcomes for interpersonal and social rhythm therapy in individuals with bipolar I disorder. Arch Gen Psychiatry 2005;62:996–1004
16. Lam DH, Watkins ER, Hayward P, et al. A randomized controlled study of cognitive therapy for relapse prevention for bipolar affective disorder: outcome of the first year. Arch Gen Psychiatry 2003;60:145–152
17. Bauer MS, McBride L, Chase C, et al. Manual-based group psychotherapy for bipolar disorder: a feasibility study. J Clin Psychiatry 1998;59:449–455
18. Clarkin JF, Carpenter D, Hull J, et al. Effects of psychoeducational intervention for married patients with bipolar disorder and their spouses. Psychiatr Serv 1998;49:531–533

19. Miklowitz DJ, Goldstein MJ. Behavioral family treatment for patients with bipolar affective disorder. Behav Modif 1990;14:457–489
20. Miklowitz DJ, George EL, Richards JA, et al. A randomized study of family-focused psychoeducation and pharmacotherapy in the outpatient management of bipolar disorder. Arch Gen Psychiatry 2003;60:904–912
21. Rea MM, Tompson MC, Miklowitz DJ, et al. Family-focused treatment versus individual treatment for bipolar disorder: results of a randomized clinical trial. J Consult Clin Psychol 2003;71:482–492
22. Jones S. Psychotherapy of bipolar disorder: a review. J Affect Disord 2004;80:101–114
23. Epstein N, Bishop D. Problem Centered Systems Therapy of the Family. J Marital Fam Ther 1981;7:23–31
24. Ryan C, Epstein N, Keitner G, et al. Evaluating and Treating Families: The McMaster Approach. New York, NY: Rutledge; 2005
25. Miller IW, Keitner GI, Ryan CE, et al. Treatment matching in the post-hospital care of depressed inpatients. Am J Psychiatry 2005;162: 2131–2138
26. Gonzalez S, Steinglass P, Reiss D. Family-Centered Interventions for the Chronically Disabled: The 8-Session Multiple Family Discussion Group Program [treatment manual]. Washington, DC: George Washington University Rehabilitation Research and Training Center; 1987
27. McFarlane W. Multifamily Groups and the Treatment of Schizophrenia and Other Psychiatric Disorders. New York, NY: Guilford Press; 2002
28. McFarlane WR, Lukens E, Link B, et al. Multiple-family groups and psychoeducation in the treatment of schizophrenia. Arch Gen Psychiatry 1995;52:679–687
29. Yalom I. The Theory and Practice of Group Psychotherapy. New York, NY: Basic Books; 1995
30. Keitner GI, Drury LM, Ryan CE, et al. Multifamily group treatment for major depressive disorder. In: McFarlane WR, ed. Multifamily Groups in the Treatment of Severe Psychiatric Disorders. New York, NY: Guilford Press; 2002:244–267
31. Miklowitz D, Otto M, Frank E, et al. Psychosocial treatments for bipolar depression: a one year randomized trial from the Systematic Treatment Enhancement Program. Arch Gen Psychiatry 2007;64: 419–427
32. Miller IW, Solomon DA, Ryan CE, et al. Does adjunctive family therapy enhance recovery from bipolar I mood episodes? J Affect Disord 2004;82:431–436
33. Solomon DA, Ryan CE, Keitner GI, et al. Recurrence of bipolar I mood episodes and hospitalization: pharmacotherapy plus family psychotherapy versus pharmacotherapy alone as prophylaxis. Presented at the 45th annual meeting of the New Clinical Drug Evaluation Unit, National Institute of Mental Health; June 6–9, 2005; Boca Raton, Fla
34. Keitner GI, Solomon DA, Ryan CE, et al. Prodromal and residual symptoms in bipolar I disorder. Compr Psychiatry 1996;37:362–367
35. MacQueen GM, Marriott M, Begin H, et al. Subsyndromal symptoms assessed in longitudinal, prospective follow-up of a cohort of patients with bipolar disorder. Bipolar Disord 2003;5:349–355
36. Altshuler LL, Gitlin MJ, Mintz J, et al. Subsyndromal depression is associated with functional impairment in patients with bipolar disorder. J Clin Psychiatry 2002;63:807–811
37. Judd LL, Akiskal HS, Schettler PJ, et al. The long-term natural history of the weekly symptomatic status of bipolar I disorder. Arch Gen Psychiatry 2002;59:530–537
38. Judd LL, Akiskal HS, Schettler PJ, et al. A prospective investigation of the natural history of the long-term weekly symptomatic status of bipolar II disorder. Arch Gen Psychiatry 2003;60:261–269
39. Miller IW, Uebelacker LA, Keitner GI, et al. Longitudinal course of bipolar I disorder. Compr Psychiatry 2004;45:431–440
40. Miller I, Johnson S, Keitner G, et al. Family functioning in bipolar disorder [paper]. Presented at the 7th annual meeting of the Society for Research in Psychopathology; Nov 12–15, 1992; Palm Springs, Calif
41. Spitzer RL, Williams JBW. Structured Clinical Interview for DSM-III-R, Patient Version. New York, NY: Biometrics Research, New York State Psychiatric Institute; 1987
42. Epstein N, Baldwin L, Bishop D. The McMaster Clinical Rating Scale. Providence, RI: Brown University Family Research Program; 1982
43. Miller I, Kabacoff R, Bishop D, et al. The development of the McMaster Clinical Rating Scale. Family Process 1994;33:53–69
44. Epstein N, Baldwin L, Bishop D. The McMaster Family Assessment Device. J Marital Fam Ther 1983;9:171–180
45. Bishop D, Epstein N, Keitner G, et al. The McMaster Structured Interview for Family Functioning. Providence, RI: Brown University; 1980
46. Dickstein S, Seifer R, Hayden L, et al. Levels of family assessment, 2: impact of maternal psychopathology on family functioning. J Fam Psychol 1998;12:23–34
47. Hayden L, Schiller M, Dickstein S, et al. Levels of family assessment, 1: family, marital and parent-child interaction. J Fam Psychol 1998;12:7–22
48. Maziade M, Capéraà P, Laplante B, et al. Value of difficult temperament among 7-year-olds in the general population for predicting psychiatric diagnosis at age 12. Am J Psychiatry 1985;142:943–946
49. Maziade M, Cote R, Boutin P, et al. Temperament and intellectual development: a longitudinal study from infancy to four years. Am J Psychiatry 1987;144:144–150
50. Miller I, Keitner G, Whisman M, et al. Dysfunctional families of depressed patients: description and course of illness. J Abnorm Psychol 1992;101:637–646
51. Uebelacker LA, Keitner GI, Ryan CE, et al. Characterizing the long-term course of individuals with major depressive disorder. J Nerv Ment Dis 2004;192:65–68
52. Stout RL, Wirtz PW, Carbonari JP, et al. Ensuring balanced distribution of prognostic factors in treatment outcome research. J Stud Alcohol Suppl 1994;12:70–75
53. Wei I. Application of an urn model to the design of sequential controlled clinical trials. J Am Stat Assoc 1978;73:559–563
54. Fawcett J, Epstein P, Fiester SJ, et al. Clinical management—imipramine/placebo administration manual: NIMH Treatment of Depression Collaborative Research Program. Psychopharmacol Bull 1987;23:309–324
55. Epstein NB, Bishop DS. Problem Centered Systems Therapy of the Family. In: Gurman AS, Kniskern DP, eds. Handbook of Family Therapy. New York, NY: Brunner/Mazel; 1981:444–482
56. Epstein NB, Bishop DS, Keitner GI, et al. A systems therapy: Problem Centered Systems Therapy of the Family. In: Wells RA, Giannetti VJ, eds. Handbook of the Brief Psychotherapies. New York, NY: Plenum Publishing; 1990:405–436
57. Miller IW, Bishop S, Norman WH, et al. The Modified Hamilton Rating Scale for Depression: reliability and validity. Psychiatry Res 1985;14:131–142
58. Bech P, Bolwig T, Kramp P, et al. The Bech-Rafaelsen Mania Scale and the Hamilton Depression Scale: Evaluation of homogeneity and interobserver reliability. Acta Psychiatr Scand 1979;59:420–430
59. Bech P, Rafaelsen O, Kramp P, et al. The mania rating scale: scale construction and inter-observer agreement. Neuropharmacology 1978;17: 430–431
60. Derogatis L. The SCL-90 Manual: Scoring, Administration and Procedures for the SCL-90R. Baltimore, Md: Clinical Psychometric Research; 1977
61. Johnson SL, Winett CA, Meyer B, et al. Social support and the course of bipolar disorder. J Abnorm Psychol 1999;108:558–566
62. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision. Washington, DC: American Psychiatric Association; 2000
63. Miklowitz DJ, Simoneau TL, George EL, et al. Family-focused treatment of bipolar disorder: 1-year effects of a psychoeducational program in conjunction with pharmacotherapy. Biol Psychiatry 2000;48: 582–592
64. Jacobson N, Dobson K, Fruzzetti A, et al. Marital therapy as a treatment for depression. J Consult Clin Psychol 1991;59:547–557
65. Hooley JM, Teasdale JD. Predictors of relapse in unipolar depressives: expressed emotion, marital distress and perceived criticism. J Abnorm Psychol 1989;98:229–235
66. Keitner G, Ryan C, Miller I, et al. 12-Month outcome of patients with major depression and comorbid psychiatric or medical illness. Am J Psychiatry 1991;148:345–350
67. Honig A, Hofman A, Rozendaal N, et al. Psychoeducation in bipolar disorder: effect on expressed emotion. Psychiatry Res 1997;72:17–22
68. Miklowitz DJ, Goldstein MJ. Bipolar Disorder: A Family-Focused Treatment Approach. New York, NY: Guilford Press; 1997

