Family-Focused Treatment of Bipolar Disorder: 1-Year Effects of a Psychoeducational Program in Conjunction with Pharmacotherapy

David J. Miklowitz, Teresa L. Simoneau, Elizabeth L. George, Jeffrey A. Richards, Aparna Kalbag, Natalie Sachs-Ericsson, and Richard Suddath

Background: Few studies have examined the combined effects of psychosocial treatment and pharmacotherapy for bipolar disorder. This study used a randomized, controlled design to examine a 9-month, manual-based program of family-focused psychoeducational treatment (FFT).

Methods: Bipolar patients (N = 101) were recruited shortly after an illness episode and randomly assigned to 21 sessions of FFT (n = 31) or to a comparison treatment involving two family education sessions and follow-up crisis management (CM; n = 70). Both treatments were delivered over 9 months; patients were simultaneously maintained on mood stabilizing medications. Patients were evaluated every 3 months for 1 year as to relapse status, symptom severity, and medication compliance.

Results: Patients assigned to FFT had fewer relapses and longer delays before relapses during the study year than did patients in CM. Patients in FFT also showed greater improvements in depressive (but not manic) symptoms. The most dramatic improvements were among FFT patients whose families were high in expressed emotion. The efficacy of FFT could not be explained by differences among patients in medication regimes or compliance.

Conclusions: Family-focused psychoeducational treatment appears to be an efficacious adjunct to pharmacotherapy for bipolar disorder. Future studies should evaluate family treatment against other forms of psychotherapy matched in amount of therapist–patient contact. Biol Psychiatry 2000;48:582–592 © 2000 Society of Biological Psychiatry

Key Words: Bipolar disorder, expressed emotion, family therapy, psychosocial intervention, family-focused treatment, psychoeducation

Introduction

Pharmacotherapy is the first-line offense against episodes of bipolar disorder (American Psychiatric Association 1994). Nonetheless, there is increasing recognition that pharmacotherapy alone forestalls but does not prevent relapses of the disorder: about 40% of medicated bipolar patients relapse in a 1-year period, 60% in 2 years, and almost 75% in 5 years (Gelenberg et al 1989; Gitlin et al 1995; Markar and Mander 1989; Shapiro et al 1989; Tohen et al 1990). Moreover, a substantial proportion of patients (more than 50% in some studies) have significant residual symptoms between illness episodes (Gitlin et al 1995; Harrow et al 1990; Keck et al 1998). The efficacy of medications is limited by the inconsistent adherence common in this population (Keck et al 1998; Jamison and Akiskal 1983; Shaw 1986; Strober et al 1990). Psychosocial treatments that reduce illness morbidity and the severity of symptoms during intermorbid periods and that enhance drug compliance would be welcome additions to outpatient pharmacotherapy regimes.

Despite much scholarly writing on the value of psychotherapy for bipolar patients, it is not clear what kinds of psychotherapies, delivered at what stage of the illness, are most efficacious (Craighead et al 1998). Developing effective psychotherapy treatments begins with understanding the role of psychosocial risk indicators in the course of bipolar disorder. Studies of psychosocial factors have generally focused on life events (Johnson and Roberts 1995) or family or marital discord (Miklowitz 1998). Regarding the latter, four independent studies in three countries (Honig et al 1997; Miklowitz et al 1988; O’Connell et al 1991; Pribe et al 1989) have found that high levels of critical, hostile, or emotionally overinvolved attitudes (high expressed emotion, or EE) in parents or spouses are associated with high rates of relapse, poor symptomatic outcomes, or both in bipolar patients who are followed prospectively. These findings parallel those of numerous studies of family EE in schizophrenia (Butzlaff and Hooley 1998).
The major implication of EE research is that psycho-social interventions targeting the family may enhance the symptomatic adjustment of patients during a postillness aftercare period. Considerable evidence suggests that psychoeducational family interventions delivered during a posthospitalization period, when combined with neuroleptic regimes lead to delays in relapses among schizophrenic patients (Penn and Mueser 1996). Among bipolar patients, Clarkin et al (1998) found that over 11 months of treatment, an outpatient marital psychoeducational program and pharmacotherapy was associated with better global functioning, but not symptom functioning, than medication alone. In a pilot study, Miklowitz and Goldstein (1990) found that acutely ill bipolar patients who received pharmacotherapy and a 9-month outpatient program of family-focused treatment (FFT), consisting of education about bipolar disorder, communication training, and problem-solving skills training, had lower 9-month relapse rates (1 of 9 patients, or 11%) than historical comparison patients (14 of 23 patients, or 61%) given pharmacotherapy without FFT. This was not a randomized, controlled trial, however.

This article reports the results of a randomized trial of FFT with pharmacotherapy for bipolar patients who began in an acute illness episode, compared with a 9-month standard care intervention consisting of education and crisis management (CM) with pharmacotherapy. Patient outcomes at 12 months in these treatments (N = 101) were compared in terms of the frequency and timing of mood disorder relapses and the severity of mania and depression symptoms. Several variables were examined as moderators or mediators of treatment effects, including the pretreatment EE status (high versus low) of the family and the patients’ adherence with mood-stabilizing medications. Thus, the study extended the literature on family treatment as an adjunct to pharmacotherapy for bipolar disorder and examined the conditions under which it achieves its effects.

Methods and Materials

Subjects

Bipolar patients (N = 101) were recruited from four psychiatric inpatient units in the Boulder/Denver, Colorado, region (n = 82) or were referred to the study as outpatients (n = 19). Inclusion criteria included 1) a DSM-III-R (American Psychiatric Association 1987) diagnosis of bipolar I disorder, manic (n = 51), mixed (n = 35), or depressed episode (n = 15) in the previous 3 months, based on the Structured Clinical Interview for DSM-III-R, Patient Version (SCID-P; Spitzer et al 1992); 2) aged between 18 and 60 years; 3) no neurologic disorder or developmental disability; 4) no DSM-III-R drug or alcohol disorders in the previous 6 months; 5) living with or in regular contact (≥4 hours/week) with close relatives (37 with parents, 56 with spouses, seven with siblings, and one with an adult offspring); 6) willingness to commit to pharmacotherapy involving mood stabilizers or antipsychotic medications; 7) English speaking; and 8) willingness of patients and relatives to provide written informed consent following explanation of the study.

Research diagnosticians administered the SCID-P while patients were in the hospital (if hospitalized) or on an outpatient basis, during or shortly following an acute period of illness. Diagnosticians completed a SCID workshop and were continuously monitored for accuracy throughout the study. Interrater reliabilities (Cohen’s k; Cohen 1960) for SCID-P items ranged from .71 to .87 after training (p < .001).

The 101 participants were drawn from 698 inpatients and outpatients who were screened for the study and whose medical records indicated a primary or rule-out diagnosis of bipolar disorder. Of these 698 patients, 597 were excluded for the following reasons: no regular contact with a family member (n = 181, or 30%), the SCID diagnosis was not bipolar disorder (n = 109, or 18%), aged less than 18 or greater than 60 (n = 77, or 13%), concurrent substance abuse or dependence disorders (n = 68, or 11%), neurologic disorders (n = 53, or 9%), participation refused by the patient or relatives (n = 43, or 7%), lived too far away (n = 24, or 4%), unwilling or unable to take medications (n = 17, or 3%), non-English speaking (n = 5, or 1%), or other reasons (n = 20, 3%).

Treatments

PHARMACOTHERAPY. All patients who were not already engaged in outpatient pharmacologic treatment were referred to a study-affiliated psychiatrist at study entry. The core study questions concerned the efficacy of psychosocial treatment in the context of pharmacotherapy as practiced in community settings. Therefore, physicians adjusted the frequency of psychiatric visits and drug regimes to each patient’s needs. During the first month after study entry and before the initiation of psychosocial treatments (the 1-month pretreatment period), 70 of the 101 patients (69%) were prescribed a primary mood stabilizer (48 lithium carbonate, 13 carbamazepine, five valproate, and four verapamil) and 22 of 101 (22%) were given combinations of mood stabilizers. Of the 92 patients on mood stabilizers, 36 received adjunctive antipsychotics, 17 received antidepressants, and 21 received anxiolytics. Of the remaining nine patients, three were treated without primary mood stabilizers (i.e., antipsychotics only), one refused all medications, and five were lost to follow-up before medication regimes could be determined.

PSYCHOSOCIAL TREATMENT. Within 2 weeks after the SCID intake interview, patients were assigned randomly, using a 1:2 formula, to one of two 9-month psychosocial protocols: FFT with pharmacotherapy (N = 31) or CM with pharmacotherapy (N = 70). This 1:2 randomization strategy, chosen before beginning the trial, was based on a single consideration: case flow estimates in our catchment area indicated that we would encounter a greater number of prospective participants than could be treated with FFT, given the number of available FFT clinicians. Rather than systematically excluding prospective participants (which might have generated unintended selection
biases), we opted to include “all comers.” Choosing this option required assigning more patients to the less intensive crisis management condition (67%) than to the FFT condition (33%).

Patients and family members (parents, spouses, siblings) assigned to FFT with medication received up to 21 one-hour family or marital sessions (mean = 19.4 ± 4.0) over 9 months (weekly for 3 months, biweekly for 3 months, and monthly for 3 months), conducted by a cotherapy team. Clinicians followed an FFT manual (Miklowitz and Goldstein 1990, 1997) in the delivery of sessions. To maximize participants’ compliance, sessions took place in the family’s home.

The first FFT module, psychoeducation, consisted of seven or more sessions in which patients and relatives became acquainted with the symptoms, nature, causes, and treatment of bipolar disorder. The clinicians discussed the disorder’s biological and genetic underpinnings from a vulnerability–stress perspective and emphasized drug compliance. Participants identified the patient’s prodromal signs of illness and developed a relapse prevention plan. In the second module (seven to 10 sessions), patients and relatives learned communication skills for dealing with intrafamilial stress (active listening, requesting changes in others’ behavior, giving positive and negative feedback) using a role-playing/behavior-rehearsal format (Falloon et al 1985; Liberman et al 1981). Finally, in the third module (four to five sessions), participants learned a framework for defining problems and then generating and implementing solutions to those problems related to the postepisode period (e.g., returning to work). Between-session practice assignments facilitated the generalization of communication and problem-solving skills.

CM was designed to emulate standard community care. It was a “treatment as usual” condition with the addition of a limited amount of family education. Over the 9-month treatment interval, project clinicians offered CM patients emergency counseling sessions as needed, typically when suicidal crises or severe family conflicts erupted. At minimum, clinicians telephoned each CM patient monthly to monitor his or her status. To provide family support and increase participants’ cooperation, CM patients and their relatives were also given two home-based sessions of family education covering the same topical areas as FFT, but in abridged form. These sessions were conducted within the first 2 months after entry into the study by the same trained therapists who delivered FFT in the experimental condition. In both FFT and CM, family members and patients were encouraged to contact the clinician if the patient appeared to be relapsing, at which point the clinician arranged appropriate medical services.

**Therapists**

Therapists (n = 19) were on average 30.2 ± 6.7 years old (range 23–46) and had 3.5 ± 3.8 years of clinical experience (range 0–14 years). Of the 19, 15 (79%) were women; three had PhDs in psychology, 14 had MA degrees, and two had BA degrees. There were no differences between patients in FFT and CM in terms of the age, gender, or years of clinical experience of the therapists they were assigned (for all, p > .10).

Training in FFT proceeded according to a standard protocol, which began when clinicians read the FFT manual, observed videotaped examples of FFT sessions, and attended weekly supervision sessions conducted by the first author. Then, they served as cotherapist to a trained FFT clinician for two family cases. In parallel, the first author trained these same clinicians in the two-session family psychoeducation method of CM and gave them guidelines for and supervised their crisis management of study participants. Clinicians received certification in FFT or CM once the first author judged that they had adhered to the respective manual or guidelines for two consecutive cases. They continued to attend weekly group supervision sessions throughout the study.

Therapy adherence data from independent observers, who applied treatment integrity scales (Weisman et al 1998) to FFT session audiotapes, indicated that clinicians delivered the three FFT modules with consistency. The mean total adherence/competence score, calculated across clinicians and across FFT cases, was 5.1 ± 0.6, on a 1 (very poor) to 7 (excellent) scale. Interrater reliability between three raters on the treatment integrity scales was high (intraclass correlations .64 -.75; ps < .0005).

**Measures**

**EXRESSED EMOTION.** Two weeks (mean = 13.8 days ± 15.4) after the patient’s SCID-P interview, relatives were given the Camberwell Family Interview (Vaughn and Leff 1976), a 1- to 1.5-hour, audiotaped, semistructured interview concerning their emotional reactions to the development of the patient’s bipolar illness. A rater who was unaware of the patients’ psychosocial treatment assignments coded these audiotapes for pretreatment levels of EE. Following the convention in the literature (Butzlaff and Hooley 1998), families were classified as high in EE (n = 41, or 41%) if one or more relatives expressed six or more critical comments toward the patient (interrater reliability [intraclass r] = .82, 10 independent ratings), showed evidence of hostility (personal, generalized criticism; r = .93), or were rated high (4 or 5) on a 0 to 5 scale of emotional overinvolvement (intraclass r = .80; for all, p < .001). Families in which no relative met these criteria were classified as low in EE (n = 59, or 59%). EE data were unavailable for one single-parent family.

**SYMPTOMATIC OUTCOME AND MEDICATION COMPLIANCE.** The primary measure of symptomatic outcome was the interview-based Schedule for Affective Disorders and Schizophrenia, change version (SADS-C; Spitzer and Endicott 1978), which contains 36 Likert-scaled items. Research staff members administered the SADS-C interview at least six times: at the intake SCID-P (covering the development of the acute episode over the preceding 3 months), at the end of the 1-month pretreatment period, at 3, 6, and 9 months (covering the period of active psychosocial treatment), and at 12 months (covering the interval following termination of the psychosocial treatments). Research staff members also conducted interviews spanning the previous 2 weeks if patients were rehospitalized. Interrater reliabilities (intraclass rs, based on a minimum of 10 independent ratings) for SADS-C depression and mania composite scores ranged from .81 to .92 (p < .0001) across 11 rater pairs.
To assess the adequacy of the maintenance pharmacotherapy, patients’ medication regimes at the time of each symptom interview were rated on the Maintenance Treatment Scales (Elliot et al 1990; Gitlin at el 1995; Keller 1988). These scales judge the intensity of drug regimes on a 0 (low)–4 (high) point scale (e.g., for valproate, 0 = no treatment and 4 = 2000 mg/day or more), scored separately for each of the primary mood stabilizers. Combination of mood stabilizers are rated by adding the level assigned to each component medication, up to a maximum total score of 4. Data on serum lithium levels are included in treatment intensity judgements. The mean intensity score during the 1-month pretreatment interval was 2.88 ± 1.2 (median = 3.0); and across the 12-month prospective period, 2.91 ± 0.94 (median = 3.0), indicating moderate to high levels of treatment intensity. Gitlin et al (1995) also reported a median intensity rating of 3 in their 5-year follow-up of bipolar patients at an affective disorders clinic. A regime at this level would include lithium carbonate with serum levels of .70 to .89 mEq/L, valproate at 1250 to 1999 mg/day, or a combination of mood stabilizers reflecting similar treatment intensity.

At each interview, research staff members asked patients to cite any instances of noncompliance with prescribed medications and to recount any instances in which others reported inconsistencies. Patients’ reports were checked against physicians’ observations. Each trimonthly follow-up period was then assigned a 3-point global compliance rating (1 = full compliance, 2 = partial compliance, and 3 = total noncompliance; after Keck et al 1998), based on all available compliance and laboratory blood monitoring data for that interval (lithium ion levels of 0.5–1.5 mEq/L were defined as the therapeutic range). Although all levels of the compliance scale were represented, the average patient was reasonably compliant (mean rating = 1.41 ± 0.49) over the 12-month study period.

Medication intensity and compliance ratings were accomplished by a research assistant who was unaware of the patients’ psychosocial assignments and follow-up symptoms. Interrater reliability between this rater and a secondary rater was .77 for intensity ratings and .86 for compliance ratings (ss; p < .001, n = 12 ratings).

Subject Attrition
Participants were classified as study completers (N = 79) if they participated in research interviews for the 12-month study protocol. Of the remaining 22 patients in the intent-to-treat sample, 17 refused involvement shortly after entering the study (i.e., after randomization), 3 were administratively terminated because of diagnostic ambiguities, and 2 moved away. Dropping out was somewhat more likely to occur in CM (19/70, or 27%) than in FFT [3/31, or 10%; χ²(1) = 3.85, p = .05].

Outcome Classification
The 79 study completers were classified as to their 12-month outcomes (relapsed, not relapsed, or unchanged) by two raters (interrater reliability, κ = .88, p < .001) who were unaware of patients’ psychosocial treatment assignments, pharmacotherapy regimes, or family EE status. The raters used an outcome classification system that was validated in a longitudinal study of schizophrenic and bipolar patients (Miklowitz et al 1988; Nuechterlein et al 1992). Of the 79 completers, 35 (44%) met the classification criteria for a mood disorder relapse, 10 with manic relapses (29%) and 25 with depressive relapses (71%). Relapsers achieved a state of full remission (all SADS-C mood disorder items < 3; n = 20, or 25%) or partial remission (one or more items > 4; n = 15, or 19%) at some point during the 12-month study and then shifted to a highly symptomatic state (one or more mood disorder items > 5) for at least 2 weeks.

The 40 patients classified as nonrelapsers (51%) maintained a continuously remitted or a partially remitted clinical state throughout the 12-month prospective period (n = 27, or 34%) or began in a symptomatic state (one or more SADS-C mood disorder items > 4) and then met and maintained remission or partial remission criteria, with no further deterioration (n = 13, or 16%). Four patients (5%) were classified as “unchanged,” with continuously high mood disorder symptoms (one or more items > 5) over the course of the year, but no evidence of relapse or remission.

Data Analysis
First, univariate analyses of variance (ANOVAs) and χ² statistics evaluated whether pretreatment demographic or illness variables distinguished between patients randomly assigned to FFT or CM. Next, survival analyses by the Cox proportional hazards model (Cox 1972) compared the groups on time to relapse, using the intent-to-treat sample (N = 101). Study dropouts (N = 22) were treated as “ensored” at the point of their last follow-up observation (Kleinbaum 1996). For 17 of the 22 study dropouts, this last observation was taken before the 3-month follow-up.

Repeated-measures ANOVAs examined whether FFT with medication led to more pronounced reductions in symptom severity (depression, mania, and total affective symptoms) over the treatment year than CM. The repeated dependent variables were symptom scores obtained at intake into the study (the point at which patients were randomized to treatment), at the 1-month pretreatment assessment, and at the 3-, 6-, 9-, and 12-month evaluations. These comparisons were carried out with participants on whom we had repeated observations of symptoms over the full year (the 79 completers). Thus, we can be less confident that these results generalize to the larger population of bipolar patients. The results from the survival and ANOVA models were reconfirmed in multivariate models that controlled for the effects of episode severity at study entry, the family’s EE status, the patients’ pharmacotherapy regimes, and compliance with drug regimes. Two-tailed tests (α = .05) were used.

Results

Equivalence of Groups at Baseline
Table 1 illustrates that the FFT completers (N = 28), the CM completers (N = 51) and the study dropouts (N = 22) did not differ at study entry on a host of demographic, illness, and pharmacologic variables (for all, p > .10). There were no group differences at the 1-month pretreat-
Table 1. Demographic, Illness, and Treatment Characteristics of 101 Patients with Bipolar Disorder

<table>
<thead>
<tr>
<th>Continuous variables</th>
<th>CM participants (N = 51)</th>
<th>FFT participants (N = 28)</th>
<th>Early terminations (N = 22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>36.1 (10.1)</td>
<td>35.5 (9.2)</td>
<td>34.7 (11.8)</td>
</tr>
<tr>
<td>Socioeconomic status</td>
<td>2.2 (0.9)</td>
<td>2.3 (1.0)</td>
<td>3.1 (1.3)</td>
</tr>
<tr>
<td>Education (years)</td>
<td>14.1 (2.2)</td>
<td>14.0 (2.3)</td>
<td>12.4 (2.4)</td>
</tr>
<tr>
<td>Symptom severity</td>
<td>2.2 (0.6)</td>
<td>2.2 (0.6)</td>
<td>2.3 (0.8)</td>
</tr>
<tr>
<td>Prior episodes</td>
<td>4.0 (3.9)</td>
<td>5.6 (5.6)</td>
<td>5.1 (5.9)</td>
</tr>
<tr>
<td>Prior hospitalizations</td>
<td>2.2 (2.5)</td>
<td>2.9 (3.5)</td>
<td>2.8 (3.1)</td>
</tr>
<tr>
<td>Duration of illness, years</td>
<td>10.9 (9.2)</td>
<td>12.2 (9.0)</td>
<td>11.6 (11.1)</td>
</tr>
<tr>
<td>Drug regime intensity</td>
<td>2.8 (1.2)</td>
<td>2.9 (1.3)</td>
<td>2.9 (1.1)</td>
</tr>
<tr>
<td>Drug compliance, range 0 (low)–4 (high)</td>
<td>1.4 (0.7)</td>
<td>1.3 (0.5)</td>
<td>1.6 (0.5)</td>
</tr>
<tr>
<td>Categorical variables</td>
<td>N % N % N % N %</td>
<td>N % N % N % N %</td>
<td>N % N % N % N %</td>
</tr>
<tr>
<td>Female gender</td>
<td>32 63% 15 54% 17 77%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White race</td>
<td>46 90% 24 86% 15 68%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married/cohabiting</td>
<td>26 51% 19 68% 11 50%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High-EE status family</td>
<td>26 43% 11 39% 8 36%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospitalized at study entry</td>
<td>40 78% 23 82% 19 86%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CM, crisis management; FFT, family-focused treatment; EE, expressed emotion.

*a* Calculated by the Hollingshead and Redlich (1958) criteria.

*b* Participants who dropped from the study differed significantly from FFT/CM completers cases (p < .05); no other contrasts were significant.

*c* Based on the 1-month period before the initiation of psychosocial treatments.

*d* Mean affective symptom item scores from the Schedule for Affective Disorders and Schizophrenia, change version (Spitzer and Endicott 1978).

Thus, recruitment status was included as a covariate in the primary treatment-outcome analyses.

Relapse

Of the 31 FFT patients in the intent-to-treat sample, eight relapsed, 18 did not relapse, two were unchanged, and three were dropouts during the 12-month study period. Of the 70 CM patients, 27 relapsed, 22 did not relapse, two were unchanged, and 19 were dropouts. Excluding the dropouts, the 1-year survival rates (without relapsing) were 71% in FFT and 47% in CM [χ²(1) = 4.35, p = .037]. Examining the polarity of the relapses indicated that, of 25 patients with depressive relapses, 20 had been assigned to CM and five to FFT [χ²(1) = 4.47, p = .034]; FFT was not differentially associated with reductions in manic relapses [n = 10 [in CM, 3 in FFT]; χ²(1) = 0.80, p = .37].

Treatment group was also predictive of the patients’ 12-month outcome subtypes using the Nuechterlein et al (1992) criteria. Of 20 patients who achieved a full remission and then had a mood disorder relapse, 13 were assigned to CM and seven to FFT. Of 15 who achieved a partial remission and then had a subsequent relapse, 14 were in CM and one in FFT. Of 27 patients who maintained a continuous state of remission or partial remission throughout the 12 months, 17 were in CM and 10 in FFT. In contrast, of 13 patients who began in a symptomatic state and then improved to a state of remission or partial remission (with no further deterioration), five were in CM and eight in FFT. Finally, of four patients judged to be “unchanged,” with continuously high mood disorder symptoms, two were in CM and two in FFT. The group differences in the distribution of 1-year outcomes were statistically significant [χ²(4) = 9.7, p = .046].

Survival Analyses

Survival analyses using the Cox proportional hazards model revealed a superior effect of FFT in forestalling relapses of mood disorder [likelihood ratio χ²(1) = 4.1, p = .042, N = 101; hazard ratio = 1.47; Figure 1]. When survival analyses were carried out in the study completers (N = 79), the between-group difference in survival curves remained significant [χ²(1) = 4.6, p = .032; hazard ratio = 1.5].

In the intent-to-treat sample, treatment group still predicted survival time after covarying the severity of SADS-C depressive symptoms during the acute episode at study entry [χ²(1) = 4.88, p = .027], manic symptoms [χ²(1) = 3.58, p = .059] or total affective (depressive plus manic) symptoms [χ²(1) = 4.68, p = .03]. The main effect of treatment also remained stable after covarying depressive symptoms during the 1-month pretreatment period.
Figure 1. One-year survival curves for bipolar patients in family-focused treatment (FFT) and crisis management (CM). The pretreatment interval spanned weeks 0–4, the active psychosocial treatment period spanned approximately weeks 4–43, and the 12-month posttreatment follow-up spanned weeks 43–52. Comparison of curves by likelihood ratio statistic [intent-to-treat sample, N = 101; χ²(1) = 4.1, p = .042], generalized Savage test [equal weighting of early and late treatment failures; χ²(1) = 3.87, p = .049], and generalized Wilcoxon test [heavier weighting of early treatment failures; χ²(1) = 3.99, p = .046].

The treatment retained its predictive value—albeit at lesser time interaction effects from repeated-measures analyses of variance in which symptom scores were the repeated dependent measures ANOVA on the 79 completers revealed no main effect of psychosocial treatment after covarying EE effects of EE on relapse (p = .65). There was also no treatment by EE interaction (p = .83). Interestingly, the results of studies (Butzlaff and Hooley 1998) showing a relationship between high-EE family attitudes and greater rates of patient relapse were only replicated among patients with parental relatives, and not among patients with spousal relatives (EE × family composition interaction, χ² = 4.69, df = 1, p = .03; log-linear analysis). This effect was independent of treatment group. Relapses were observed in 45% (9 out of 20) of the patients from high-EE parental homes and 19% (3 out of 16) of the patients from low-EE parental homes. Survival times were also nonsignificantly longer among patients in low-EE parental homes (χ² = 3.06, df = 1, p = .08).

**Symptom Severity**

Did patients in FFT and CM differ in the degree to which they achieved stable mood states over the study year? Three SADS-C composite symptom scores were tabulated at intake and at each point during the 12-month evaluation period (Table 2): a total affective symptom score, a depression subscore, and a mania subscore. A repeated-measures ANOVA on the 79 completers revealed no main effect of psychosocial treatment [F(1,77) = 0.01, p = .94], a highly significant effect of time [F(5,385) = 25.86, p < .0001], and a significant treatment by time interaction appeared reasonably robust when evaluated against other explanatory variables.

**Psychosocial Treatment and Expressed Emotion**

A core question was whether the effects of psychosocial treatments depended on the pretreatment EE status of patients’ households. A Cox survival model revealed a main effect of psychosocial treatment after covarying EE (χ² = 3.76, df = 1, p = .05, N = 100), but no main effect of EE on relapse (p = .65). There was also no treatment by EE interaction (p = .83). Interestingly, the results of studies (Butzlaff and Hooley 1998) showing a relationship between high-EE family attitudes and greater rates of patient relapse were only replicated among patients with parental relatives, and not among patients with spousal relatives (EE × family composition interaction, χ² = 4.69, df = 1, p = .03; log-linear analysis). This effect was independent of treatment group. Relapses were observed in 45% (9 out of 20) of the patients from high-EE parental homes and 19% (3 out of 16) of the patients from low-EE parental homes. Survival times were also nonsignificantly longer among patients in low-EE parental homes (χ² = 3.06, df = 1, p = .08).

**Table 2. Effects of Psychosocial Treatment on the Course of Bipolar Disorder: Mean Symptom Scores over 1 Year**

<table>
<thead>
<tr>
<th>Symptoms (SADS-C)</th>
<th>Treatment</th>
<th>Intake (acute episode)</th>
<th>1 month (pretreatment)</th>
<th>3 months</th>
<th>6 months</th>
<th>9 months</th>
<th>12 months</th>
<th>F</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total affective symptoms</td>
<td>CM</td>
<td>2.8 (0.7)</td>
<td>2.2 (0.6)</td>
<td>2.3 (0.7)</td>
<td>2.2 (0.8)</td>
<td>2.2 (0.8)</td>
<td>2.2 (0.8)</td>
<td>2.19</td>
<td>.05</td>
</tr>
<tr>
<td></td>
<td>FFT</td>
<td>3.1 (0.8)</td>
<td>2.2 (0.6)</td>
<td>2.4 (0.8)</td>
<td>2.2 (0.9)</td>
<td>1.9 (0.6)</td>
<td>2.0 (0.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>CM</td>
<td>2.6 (1.1)</td>
<td>2.4 (0.9)</td>
<td>2.5 (1.1)</td>
<td>2.4 (1.0)</td>
<td>2.4 (1.0)</td>
<td>2.3 (1.0)</td>
<td>2.36</td>
<td>.04</td>
</tr>
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<td></td>
<td>FFT</td>
<td>3.0 (1.1)</td>
<td>2.5 (0.9)</td>
<td>2.7 (1.0)</td>
<td>2.4 (1.1)</td>
<td>2.0 (0.8)</td>
<td>2.2 (1.0)</td>
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<tr>
<td>Mania</td>
<td>CM</td>
<td>3.1 (1.2)</td>
<td>1.8 (0.6)</td>
<td>2.0 (0.9)</td>
<td>1.8 (1.0)</td>
<td>1.8 (0.8)</td>
<td>2.1 (1.0)</td>
<td>0.74</td>
<td>.59</td>
</tr>
<tr>
<td></td>
<td>FFT</td>
<td>3.3 (1.3)</td>
<td>1.9 (0.6)</td>
<td>2.0 (0.8)</td>
<td>2.0 (1.0)</td>
<td>1.8 (0.9)</td>
<td>1.8 (0.7)</td>
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Means for depression subscores are calculated from 11 SADS-C items that can each range from 1 to 6 or 1 to 7. Means for mania subscores are calculated from seven SADS-C items that can each range from 1 to 6. Means for total affective symptoms are calculated from the 18 SADS-C items that compose the depression and mania subscores. The F values refer to treatment × time interaction effects from repeated-measures analyses of variance in which symptom scores were the repeated dependent variables. SADS-C, Schedule for Affective Disorders and Schizophrenia, Change Version (Spitzer and Endicott 1978); CM, crisis management (n = 51); FFT, family-focused treatment (n = 28).
Repeted-measures ANOVAs revealed significant effects of time on depression scores \(F(5,385) = 7.1, p < .0001\) and mania scores \(F(5,385) = 27.66, p < .0001\), indicating that patients in both treatments improved over the study year; however, the degree of improvement in depression scores was uncorrelated with the degree of improvement in mania scores \((r = -.02, p = .86, n = 79)\). Paralleling the findings regarding relapse, FFT was associated with greater stabilization of SADS-C depression symptoms than CM [treatment by time interaction, \(F(5,385) = 2.36, p = .04\), but not mania symptoms \(F(5,385) = 0.74, p = .59\)]. The results of these analyses were confirmed in repeated-measures mixed ANOVA models (Laird and Ware 1982; SAS Institute 1992), which allow one to include cases with incomplete longitudinal data (intent-to-treat sample). These models also revealed a treatment by time interaction favoring FFT for total affective symptoms \([F(5,498) = 2.25, p = .048]\) and depressive symptoms \([F(5,498) = 2.54, p = .028]\) over 12 months.

Were the effects of FFT on depression outcomes attributable to pretreatment illness variables? First, covarying inpatient/outpatient recruitment status of the patients did not weaken the psychosocial treatment by time interaction for depression severity scores \([F(5,380) = 2.5, p = .03]\). No effect of inpatient/outpatient status on depression outcome scores was found \([F(5,380) = 1.5, p = .18]\). Second, the FFT and CM groups did not differ at the intake assessment \([F(1,77) = 2.09, p = .15]\) or at the 1-month pretreatment assessment \([F(1,77) = 0.04, p = .84]\) in the severity of depressive symptoms; however, pretreatment depression robustly predicted depressive symptoms over the 12-month study period (for both, \(p < .0005\)). The psychosocial treatment by time interaction for follow-up depression scores was weakened but not fully compromised by covarying the two pretreatment depression scores \([F(3,225) = 2.45, p = .06]\). The effects of FFT on depression outcomes were most pronounced at the 9-month evaluation, even after covarying pretreatment depression scores \([F(1,75) = 6.3, p = .014]\).

Did improvements in depression vary as a function of the EE status of the family? An analysis of covariance, with depression intercept scores (levels of depression at baseline) as the covariate, revealed a robust effect of baseline depression \([F(1,74) = 29.05, p < .0001]\), a moderate main effect of psychosocial treatment group \([F(1,74) = 4.45, p = .038]\), and a treatment by EE interaction effect \([F(1,74) = 4.28, p = .042]\) on depression slope scores calculated over 12 months. No main effect of EE was found \([F(1,74) = 1.44, p = .23]\). The variance in depression slope scores accounted for by this model was \(41 (R^2)\).

The treatment by EE interaction indicated that the most dramatic improvements in depression scores were among patients from high-EE families who participated in FFT. These patients showed greater negative slopes for depression scores over the study year (mean = \(-.029 \pm .023\); \(n = 11\)) than patients in high-EE families who received CM (mean = \(-.002 \pm .015\); \(n = 22\)) or patients in low-EE families who received FFT (mean = \(-.006 \pm .017\); \(n = 17\)) or CM (mean = \(-.007 \pm .022\); \(n = 29\)).

**Effects of Pharmacotherapy Regimes and Compliance**

Could the effects of FFT on relapse or symptom severity be attributed to group differences in pharmacotherapy? Alternatively, did the greater educational emphasis of FFT improve drug compliance, which in turn accounted for the higher survival rates?

There was no effect of psychosocial treatment \([F(1,77) = 1.42, p = .24]\) or time \([F(4,308) = 0.3, P = .85]\) and no treatment by time interaction \([F(4,308) = 0.6, p = .65]\) in predicting pharmacotherapy intensity ratings over the year. No differences in intensity ratings were found between the psychosocial groups at the 1-, 3-, 6-, 9-, or 12-month evaluations (for all, \(p > .10\)). There were also no group differences in the frequency of patients’ visits to the treating psychiatrist during any 3-month interval (for all, \(p > .10\)).

Psychosocial treatment group still predicted survivorship when mean drug intensity ratings (calculated over the 12 months) were covaried in Cox Proportional Hazards models, in both the intent-to-treat sample \([\chi^2(1) = 4.47, p = .034]\) and the completer sample \([\chi^2(1) = 4.8, p = .028]\). Marginally significant effects of drug intensity ratings were noted in these analyses (\(p = .09\) and \(p = .11\), respectively). Furthermore, after covarying drug intensity scores, there remained a significant effect of psychosocial treatment in predicting linear changes in total affective symptoms \([F(1,76) = 5.3, p = .024]\) but no separate effect of intensity scores \([F(1,76) = 0.06, p = .81]\).

We considered the possibility that the effects of FFT on depression outcome scores were due to systematic differences between the treatment groups in adjunctive antidepressant use; however, mirroring the lack of group differences in medication intensity ratings, there was no evidence that patients in FFT were more likely than those in CM to be prescribed antidepressants, either at the 1-month pretreatment assessment \([\chi^2(1) = .12, p = .72]\) or at the 3-, 6-, 9-, or 12-month evaluations (for all, \(\chi^2 < 1.0, p > .10\)). To examine the longitudinal effects of antide-
pressant usage, we conducted a repeated-measures mixed ANOVA, using treatment group as a predictor of depression scores over the 12 study months. Adjunctive antidepressant usage, with values coded for each 3-month study interval (yes vs. no), was treated as a repeated covariate. As expected, patients who were given antidepressants had significantly higher depression scores during follow-up than those who were not given antidepressants \( F(1,77) = 11.36, p = .001 \). The ANOVA model also revealed a psychosocial treatment by time interaction (favoring FFT) on depression outcome scores, however, even after statistically adjusting for antidepressant usage \( F(5,77) = 2.32, p = .05; N = 79 \). Results were similar when this analysis was carried out in the intent-to-treat sample [main effect of antidepressants, \( F(1,91) = 13.99, p = .0003 \); psychosocial treatment by time interaction, \( F(5,91) = 2.46, p = .039 \)].

There was no main effect of psychosocial treatments \( F(1,74) = 1.59, p = .21 \), no effect of time \( F(4,296) = 0.1, p = .97 \), and no group by time interaction \( F(4,296) = 0.13, p = .97 \) in predicting medication compliance scores (a 1–3 scale) over the 12 months (compliance data were missing on three patients). FFT still led to longer survivorship in the intent-to-treat \( \chi^2(1) = 3.42, p = .06 \) and the completer samples \( \chi^2(1) = 3.73, p = .05 \) after covarying mean compliance levels over the 12-month study. No effects of compliance were found on survivorship \((ps = .70 \text{ and } .65, \text{ respectively})\).

The pattern of results was different when we considered the relation of drug compliance to composite symptom scores. Better drug compliance was associated with greater improvement in mania slope scores over the year than was poorer compliance \((r = .27, p = .018, N = 79)\). This effect did not extend to depression slope scores \((r = .13, p = .25)\). Multiple regression analyses revealed that the effect of psychosocial treatment on depression slope scores remained significant \( t(76) = 2.0, p = .049 \) with mean compliance ratings covaried [compliance effect, \( t(76) = 0.91, p = .37 \)]. In parallel, the effect of drug compliance on mania slope scores remained robust \( t(76) = 2.34, p = .022 \) with psychosocial treatment group covaried, but there was no psychosocial effect \( t(76) = 0.41, p = .69 \). Thus, drug compliance affected the manic pole of the illness more than the depressive pole, whereas the reverse was true for psychosocial treatment.

**Discussion**

This study examined the efficacy of a 9-month program of family-focused psychoeducational treatment (FFT) and pharmacotherapy versus standard community care (CM) and pharmacotherapy for bipolar patients who began in an acute state of illness. Over the 12-month study interval, FFT provided greater prophylaxis against mood disorder (notably depressive) relapses than did CM. The results were not substantially altered by covarying the pretreatment symptom status of patients or their history of mood disorder episodes. The findings are consistent with those of previous studies suggesting that family psychoeducation is an efficacious adjunct to pharmacotherapy for patients with major, recurrent psychiatric disorders (Clarkin et al 1998; Goldstein and Miklowitz 1995; Penn and Mueser 1996). Results of a longer term follow-up of the patients in this study (in progress) will reveal whether the protective effects of FFT are enduring or whether they are limited to the intervals during which patients are in treatment.

Patients in FFT showed greater improvement than did CM patients in depressive symptoms, although this treatment effect was of modest size. Comparable effects of FFT on manic symptoms were not observed. Preliminary results of another maintenance trial (Frank 1999) found that interpersonal psychotherapy and medication were superior to intensive clinical management and medication in preventing bipolar depressive symptoms but not manic symptoms. In contrast, the literature on lithium carbonate and the anticonvulsants suggests that these agents have greater stabilizing effects on manic symptoms than on depressive symptoms (Keck and McElroy 1996). Possibly, mood stabilizers and psychosocial treatment are complementary treatment approaches that, if administered conjointly during the postepisodic period, can address fluctuations in both poles of the disorder.

Could the superior performance of FFT be attributed less to its ameliorative properties than to the poor showing of patients in CM? There are two arguments against this position. First, the 1-year relapse rate among CM patients, 53%, and the sample rate of 44%, are comparable to what has been found in other prospective studies of bipolar patients in which 1-year rates have ranged from 37% to 67% (Gelenberg et al 1989; Gitlin et al 1995; Goldberg et al 1995; Markar and Mander 1989; Miklowitz et al 1988; O’Connell et al 1991; Shapiro et al 1989; Tohen et al 1990). Second, patients in CM were not sampled from a more severely ill population than were patients in FFT: the two groups were indistinguishable in pretreatment levels of symptoms and lifetime histories of mood disorder episodes. Nonetheless, we cannot rule out the possibility that the CM and FFT patients differed during the study’s prospective period on other uncontrolled variables. Although the frequency of medication visits was comparable across conditions, participating in a more intensive treatment program such as FFT may provide more opportunities for therapists, physicians, and family members to collaborate to prevent a patient’s relapses. Our results await replication in trials that match psychotherapy treatments on the amount and intensity of therapist–patient contact.

The effects of psychosocial treatment could not be
attributed to differences in patients’ medication regimes or their compliance with these regimes, either at study entry or at any point during the study year. Nonetheless, as is typical of community outpatient samples, there was considerable variability in drug regimes. Our results might have been different had we required that physicians follow a pharmacotherapy protocol that specified the frequency or duration of medication visits, limited the choice of mood stabilizers or adjunctive antidepressants, or dictated the frequency of blood monitoring. Counter to this argument is the position that management trial studies, in which medication decisions are based on clinician judgements rather than controlled research protocols, more accurately represent the treatments that bipolar patients receive in community settings (Harrow et al 1990; Sackett and Gent 1979).

Drug compliance had its own predictive validity, independent of psychosocial treatment. Specifically, better compliance with lithium or anticonvulsant regimes predicted greater stabilization of mania symptoms among patients at follow-up. Our results, like those of other investigators (Jamison and Akiskal 1983; Keck et al 1998; Shaw 1986; Strakowski et al 1998; Strober et al 1990) underline the protective effects of drug adherence during the intervals following mood disorder episodes. Possibly, we have underestimated the strength of the compliance effect, given that on average patients were consistent with their medication regimes, in contrast to our previous study of first- and second-episode bipolar patients (Miklowitz et al 1988).

We found only weak support for the often-replicated association between high-EE family attitudes and greater relapse rates among patients. Levels of EE were only predictive of relapse among patients who were in close association with parental relatives. Perhaps the EE construct does not adequately measure the variety of emotional reactions that spouses experience in coping with the fluctuations of bipolar disorder; however, ours was not a naturalistic study and therefore not optimally designed to test the EE-relapse association. In fact, the provision of family education in both treatment groups may have altered marital relationships to the extent that the prognostic effects of EE were blunted (see also Hogarty et al 1986).

Interestingly, patients from FFT-treated, high-EE families began with the highest depression scores at entry into the study but also showed the most dramatic symptom improvement. These results, although based on secondary exploratory analyses, suggest that bipolar, depressed patients from high-EE families are particularly good candidates for FFT. Possibly, depression symptoms and intrafamilial conflicts become intertwined in bipolar disorder, and ameliorating the latter through family intervention may help bring about improvements in the former. An analysis of data from a subset of families in this study ($N = 44$) indicated that posttreatment family interactions—those of parent–offspring pairs as well as spousal pairs—were more positively toned after FFT than after CM (Simoneau et al 1999). These results suggest that family members and patients incorporate many of the communication and problem-solving skills targeted in FFT. Nonetheless, in the absence of multiple, repeated assessments of family communication and patients’ symptoms, we cannot disentangle the directional relationship between the two.

As administered in the context of this study, FFT was relatively labor-intensive (21 sessions) and given in family’s homes. Applying this approach in clinical-commumity settings, where health care costs must be minimized, would require developing streamlined versions of the core FFT modules and, in all likelihood, moving to a clinic-based model. A preliman report from a randomized trial of FFT at the University of California, Los Angeles, indicated high rates of treatment completion among patients who received family intervention in an outpatient clinic (Goldstein et al 1996; Miklowitz and Goldstein 1997); however, the clinical efficacy results of this study are still pending. Clearly, research that examines the effectiveness of FFT in “real-world” clinical settings with limited financial resources will be necessary to address these issues.

Finally, the issue of differential attrition deserves comment. Perhaps due to the lesser amount of psychotherapy offered to the CM group, and the resulting lack of ongoing contact with a family clinician, the rate of attrition in CM was higher than in FFT (27% vs. 10%). We were also less successful in retaining lower SES patients in the study protocol, regardless of the treatment condition. Thus, our treatment/outcome results may not generalize to bipolar patients who are more difficult to retain in longitudinal programs. Because of these and the aforementioned design limitations, our study should be viewed as one in a series that would be required to validate family treatments as effective adjuncts to pharmacotherapy for bipolar patients.

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