Integrated Family and Individual Therapy for Bipolar Disorder: Results of a Treatment Development Study

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Background: Several studies have established the efficacy of psychosocial interventions as adjuncts to pharmacotherapy in the symptom maintenance of bipolar disorder. This study concerned a new psychosocial approach—integrated family and individual therapy (IFIT)—that synthesizes family psychoeducational sessions with individual sessions of interpersonal and social rhythm therapy.

Method: Shortly after an acute illness episode, 30 bipolar patients (DSM-IV criteria) were assigned to open treatment with IFIT (up to 50 weekly sessions of family and individual therapy) and mood-stabilizing medications in the context of a treatment development study. Their outcomes over 1 year were compared with the outcomes of 70 patients from a previous trial who received standard community care, consisting of 2 family educational sessions, mood-stabilizing medications, and crisis management (CM). Patients in both samples were evaluated as to symptomatic functioning at entry into the project and then every 3 months for 1 year.

Results: Patients in IFIT had longer survival intervals (time without relapsing) than patients in CM. They also showed greater reductions in depressive symptoms over 1 year of treatment relative to their baseline levels. The results could not be explained by group differences in baseline symptoms or pharmacologic treatment regimens.

Conclusion: Combining family and individual therapy with medication may protect episodic bipolar patients from early relapse and ongoing depressive symptoms. Further examination of this integrative model within randomized controlled trials is warranted.

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Bipolar disorder has long been known to be highly recurrent, but the factors that influence its variability over time are only beginning to be identified. Recurrent courses of bipolar illness can often be explained by nonadherence with medications, drug or alcohol abuse, or cycle acceleration attributable to antidepressant treatment.[1–3] There is also increasing evidence that the timing of relapses and the rate of recovery following illness episodes are influenced by psychosocial stress agents.[4–8] Moreover, psychosocial interventions that improve patients' ability to cope with stress enhance the prophylactic value of medications (for reviews, see references 9–11).

Stress in bipolar disorder has been examined in 2 domains: life events and family/marital discord. Regarding the former domain, Ellicott et al.[12] found that bipolar patients with high life stress scores were 4.5 times more likely to have recurrences of mood disorder in a 2-year follow-up than those with medium or low life stress scores. Johnson and Miller[5] showed that bipolar, depressed patients whose episodes were preceded by life

events took longer to recover (median = 395 days) than patients without antecedent life events (median = 112 days).

Malkoff-Schwartz and colleagues[6] found that among bipolar I patients, events with the potential to bring about changes in daily routines and/or sleep/wake cycles (social rhythms) are likely to precipitate manic but not depressive episodes. Examples of social rhythm–disruptive events include travel across time zones, changes in job shift hours, or the onset of a severe illness in a patient's child. Frank et al.[13] have developed a psychotherapy to minimize the effects of life stress on patients' daily routines and resulting mood states. Interpersonal and social rhythm therapy (IPSRT) encourages patients to (1) understand the mutually reciprocal relationships between life stress, environmental context, and the onset of mood disorder symptoms and (2) maintain standardized daily routines and sleep/wake cycles even when faced with events that conspire to change these routines. Preliminary results from a randomized trial indicate that patients treated with standard pharmacotherapy and IPSRT are more likely to maintain stable, euthymic mood states over a year of preventive treatment than those treated with standard pharmacotherapy and intensive clinical management.[14]

The second domain of inquiry—family discord as a trigger for recurrences—has focused on "expressed emotion" (EE) attitudes among caregiving relatives. There is now evidence from 4 studies that patients whose relatives express high-EE attitudes (high criticism, hostility, and/or emotional overinvolvement) in an interview conducted during an acute symptom period have a more pernicious course of illness than patients whose relatives express low-EE attitudes.[7,15–17] High-EE relative/patient pairs have more conflict in laboratory assessments during the post-episode stabilization period than low-EE relative/patient pairs.[18] Furthermore, high-EE relatives of bipolar patients show different patterns of causal attribution about negative patient-related events than low-EE relatives when in face-to-face interaction with the patient during the stabilization period.[19]

Paralleling the research on EE, family interventions have been developed to assist families or couples in negotiating the highly stressful post-episode period. Most of these intervention models have been "psychoeducational" and focus on improving patients' and relatives' coping strategies for managing the cycling of the disorder and building effective communication and conflict resolution skills.[10] Two randomized clinical trials have found that pharmacotherapy and a 9-month regimen of family-focused psychoeducational treatment, consisting of psychoeducation about bipolar disorder, communication enhancement training, and problem-solving skills training, led to delays in relapse and rehospitalization over periods of up to 2 years.[15,20–22]

Despite these promising results, studies of life stress and family discord have largely proceeded independently. No data exist on whether life events and family distress are synergistic in contributing to episodes of bipolar disorder, above and beyond the influences of biological, genetic, or pharmacologic variables. Even more importantly, no treatments have emerged that combine the objectives of the 2 empirically supported treatments linked to these risk factors: individual-interpersonal therapy and family psychoeducational therapy.

This article reports results from a treatment development study of integrated family and individual therapy (IFIT), a new psychosocial approach that combines IPSRT with family-focused treatment. In a 12-month treatment protocol, bipolar patients were seen by 2 therapists, one of whom met individually with the patient every 2 weeks and focused on interpersonal problem-solving and social rhythm stabilization. The other therapist met with the patient and his or her significant relatives (spouse or parents) on the alternate weeks and provided education about bipolar disorder and training in communication and conflict resolution skills. Patients received simultaneous treatment with mood stabilizers and adjunctive agents.

Typically, treatment development studies are precursors to randomized trials and are conducted in open rather than controlled fashion. Nonetheless, the effects of a new treatment within an open trial can be assessed relative to a reference group that did not receive the treatment of interest. The goals of the present study were to examine, within an open trial, the clinical effects of IFIT in combination with standard pharmacotherapy. The 1-year outcomes of 30 bipolar patients, who began in an illness episode and received a protocol of IFIT and medications, were compared with the 1-year outcomes of 70 historical controls from an earlier randomized trial.[15] These control patients were selected using similar inclusion criteria, followed over time using an identical outcome assessment battery, and treated with comparable pharmacotherapy. They did not, however, receive an active psychosocial intervention; instead, they received 2 sessions of family education and crisis intervention sessions as needed. This article compares the 2 groups with respect to survival times (intervals prior to relapsing) and the 1-year recovery trajectory of depressive and manic symptoms.

METHOD

Participants

The participants came from 2 sources: (1) patients with bipolar disorder who volunteered for a treatment development study (1996–1999) of IFIT in combination with standard medications (N = 30) and (2) patients who were assigned to the treatment-as-usual condition (crisis

Table 1. Demographic and Illness History Characteristics of 100 Bipolar Patients[a]

Variable	IFIT Group (N = 30)	CM Group (N = 70)	p Value
Age, y, mean ± SD	37.1 ± 11.3	35.6 ± 10.6	NS
Female	14 (47)	46 (66)	NS
Ethnic minority	1 (3)	10 (14)	NS
Family composition			NS
Spousal	21 (70)	37 (53)	
Parental	7 (23)	26 (37)	
Other	2 (7)	7 (10)	
Education, y, mean ± SD	15.9 ± 2.1	13.8 ± 2.2	< .0001
Age at onset, y, mean ± SD	21.4 ± 10.7	24.5 ± 10.1	NS
Time ill, y, mean ± SD	14.9 ± 11.9	10.9 ± 9.3	NS
No. of prior hospitalizations, mean ± SD	1.9 ± 4.5	2.4 ± 2.7	NS
Index episode polarity			< .02
Depressed	11 (37)	9 (13)	
Manic/hypomanic	15 (50)	41 (59)	
Mixed	4 (13)	20 (29)	

[a]Values shown as N (%) unless otherwise noted. All p values pertain to group comparisons using the chi-square or t statistic.
Abbreviations: CM = crisis management, IFIT = integrated family and individual therapy.

management [CM]; N = 70) of an earlier randomized trial of family-focused treatment (1990–1996). Results of this randomized trial—the Colorado Treatment/Outcome Project (CTOP)—have been reported previously.[15] For the present study, the CM patients were used as a reference group against which to evaluate the 1-year effects of IFIT treatment.

Patients in the IFIT sample were located via chart screenings at inpatient facilities within the Boulder/Denver, Colorado, region, or were referred to the program by community psychiatrists. Once a patient was referred to the program, diagnoses were verified through independent evaluations by the research staff, using the Structured Clinical Interview for DSM-IV, Patient Version (SCID-P).[23] Patients had to meet DSM-IV[24] criteria for bipolar I (N = 22) or bipolar II disorder (N = 8), with a manic or hypomanic (N = 15), mixed (N = 4), or depressed (N = 11) episode within the last 3 months.

To be admitted to the IFIT protocol, patients also had to meet the following inclusionary criteria: (1) age between 18 and 60 years; (2) no neurologic disorder or developmental disability; (3) no DSM-IV drug or alcohol disorders in the prior 6 months; (4) living with or in regular contact (≥ 4 hours per week) with close relatives; (5) willingness to be maintained on a drug regimen involving mood stabilizers or, at minimum, antipsychotic agents; (6) English-speaking; and (7) willingness and ability of patients and relatives to provide written informed consent after they had received a thorough explanation of the study procedures.

Patients in the CM control sample also met the requirements for inclusion listed in items 1 through 7 above. Like the IFIT participants, they had experienced an acute episode of bipolar disorder in the 3 months up to entry into the study. However, the CTOP trial was initiated prior to the publication of the DSM-IV. Thus, CM patients originally met the criteria for DSM-III-R[25] bipolar I disorder, as determined from the Structured Clinical Interview for DSM-III-R, Patient Version.[26] CM patients were later rediagnosed by independent raters using DSM-IV criteria, based on audiotape reviews of the SCID interviews. Upon rediagnosis, 1 CM patient originally diagnosed as having DSM-III-R bipolar disorder not otherwise specified was rediagnosed with bipolar II disorder. The remaining CM patients retained their bipolar I diagnosis by DSM-IV criteria.

Table 1 summarizes the similarities and differences between patients from the 2 samples. As indicated, patients in the IFIT and CM series were relatively well-matched despite having been recruited for studies conducted during essentially non-overlapping time periods. Patients in the IFIT sample had had more years of education than those in the CM sample and were more likely to have had a depressive episode at study entry (37% versus 13%). In contrast, the CM patients were more likely than the IFIT patients to have had a mixed episode at study entry (29% versus 13%). Five (17%) of the IFIT cases were rated hypomanic at study entry, versus none of the CM cases.

Diagnostic Evaluation and Reliability

The point of entry into the IFIT and CTOP protocols was the SCID-P diagnostic interview. Research staff members approached potential participants and explained the study. If the patient agreed to an initial evaluation, he or she was asked to sign an informed consent form. If the patient was hospitalized at the time of recruitment, the SCID interview was conducted on an inpatient basis. If not, the interview was scheduled as soon as possible after referral to the program, and always within 3 months after the onset of an acute period of illness. Diagnosticians completed a SCID workshop and were monitored for diagnostic accuracy throughout the study. Interrater reliability was established using the Cohen[27] kappa statistic, which ranged from 0.71 to 0.87 for SCID-P items after training ($p < .001$).

Pharmacotherapy

The core study questions concerned the efficacy of psychosocial treatment in the context of pharmacotherapy as practiced in community settings. Thus, patients in both samples continued to see their preferred provider for outpatient drug treatment. Patients who were not actively engaged in pharmacotherapy sessions were referred to a study-affiliated psychiatrist shortly after recruitment. Physicians adjusted the frequency of psychiatric sessions, drug choice, and drug dosing to fit the requirements of individual patients.

Twelve of the 70 patients assigned to CM left the study before their ongoing drug treatments could be deter-

Table 2. Medication Regimens During the 1-Month Pretreatment Period

	IFIT Group (N = 30)		CM Group (N = 58)	
Medication Regimen	N	%	N	%
Single mood stabilizer only	6	20	21	36
Single mood stabilizer plus antidepressant	6	20	8	14
Single mood stabilizer plus antipsychotic	4	13	14	24
Single mood stabilizer plus antidepressant and antipsychotic	6	20	2	3
Two mood stabilizers only	6	20	1	2
Two mood stabilizers plus antidepressant	0	0	3	5
Two mood stabilizers plus antipsychotic	2	7	6	10
Two mood stabilizers plus antidepressant and antipsychotic	0	0	2	3
Antipsychotic only	0	0	1	2

Abbreviations: CM = crisis management, IFIT = integrated family and individual therapy.

mined. The drug regimens for the remaining 58 CM patients, and the 30 patients assigned to the IFIT protocol, are depicted in Table 2. All regimens pertain to the 1-month period prior to the initiation of psychosocial treatment sessions. During the month preceding the IFIT sessions, 12 (40%) of 30 patients received only mood stabilizers (lithium, divalproex sodium, carbamazepine, or, less frequently, lamotrigine, gabapentin, or calcium channel blockers), either alone or in combination. The remaining 18 (60%) were treated with mood stabilizers with adjunctive antidepressant or antipsychotic agents. For the 1-month period prior to the CM educational sessions (see below), 22 (38%) of the 58 CM patients were maintained on treatment with mood stabilizers only. Of the remaining 36 (62%), 35 were maintained on treatment with mood stabilizers with adjunctive agents, and 1, on treatment with an antipsychotic agent alone.

Patients in the CM series were more likely to be maintained on lithium treatment during the 1-month pretreatment period (N = 42/58, 72%) than patients in the IFIT series (13/30, 43%), perhaps reflecting the different epochs in which the studies were conducted ($\chi^2 = 7.1$, df = 1, $p < .01$). No differences between the groups were found in the likelihood of treatment with carbamazepine or divalproex sodium, either alone or in combination with lithium (for all $p > .10$). The groups also did not differ on the likelihood of adjunctive antidepressant treatment at baseline: 12 (40%) of 30 IFIT patients and 15 (26%) of 58 CM patients began the study on treatment with antidepressants ($\chi^2 = 1.78$, df = 1, $p > .10$).

Of the 37 patients (of 88) who began the study on treatment with antipsychotic medications, 30 (81%) were on treatment with typical antipsychotics (e.g., chlorpromazine) and 7 (19%) were on treatment with atypical antipsychotics (e.g., olanzapine). The likelihood of being treated with an adjunctive antipsychotic did not differ across the groups ($p > .10$). However, patients in IFIT were more likely than those in CM to begin the study on treatment with an atypical than a typical antipsychotic agent ($\chi^2 = 17.99$, df = 1, $p < .0001$), again suggesting the effect of the different study epochs.

Patients' pharmacotherapy regimens during the 1-month pretreatment period, and at each 3-month interval of the 12-month study protocols, were coded by an independent research evaluator on a 0 (low) to 4 (high) scale of intensity. Ratings were based on a modification for bipolar disorder of the Maintenance Treatment Scales.[12,28,29] These scales enable a numerical comparison of the intensity of drug regimens across patients taking different combinations of mood stabilizers and/or adjunctive agents. First, each individual medication in a regimen is rated on a 0-to-4 scale based on dosage (for example, for divalproex, 0 = no treatment and 4 = 2000 mg/day or more) and, when available, serum drug levels. Then, the overall intensity of the regimen is calculated by adding up the intensity ratings of each individual pharmacologic agent, up to a maximum score of 4. The mean intensity score for the sample as a whole, assessed during the month prior to entry into psychosocial treatment, was 3.1 ± 1.0 (range, 1–4; N = 88). Interrater reliability between the independent evaluator and a secondary rater for these pharmacotherapy intensity ratings was 0.77 (kappa, $p < .001$).

Psychosocial Interventions: The IFIT Model

Patients who entered the IFIT protocol were offered a program of psychosocial therapy involving sessions of individual and family (or couple) therapy for 1 year. Optimally, the protocol called for 25 sessions of individual IPSRT therapy (each delivered every 2 weeks) and 25 sessions of family-focused therapy (given during the alternating weeks). The individual and family therapists were separate clinicians. Because this was a treatment development study, therapists were given considerable latitude in designing the IFIT program to adapt to each patient's needs. For example, some patients did not require 50 sessions; others requested more individual than family sessions, and others requested more family than individual sessions. Some patients required several sessions of individual therapy before initiating the family or couple treatment, or the reverse.

There was significant variability in the number of therapy sessions that patients attended. Of the 30 patients recruited into the study, 6 (20%) received fewer than 10 sessions of individual or family treatment, 4 (13%) received between 11 and 20 sessions, 8 (27%) received between 21 and 30 sessions, 4 (13%) received between 31 and 40 sessions, and 5 (17%) received between 41 and 50 sessions. Three patients (10%) continued their treatment past the 1-year mark and attended more than 50 sessions. The average study patient received 29.4 ± 21.0 IFIT sessions over 39.5 ± 26.4 weeks (18.2 ± 14.6 IPSRT sessions and 11.2 ± 7.8 family sessions).

The individual IPSRT sessions followed the protocol of Frank et al.[13] and consisted of a beginning phase, an intermediate phase, and a maintenance/prevention phase. In the beginning treatment sessions, clinicians took a thorough illness history, with a focus on life events that may have precipitated prior illness episodes. For each patient, clinicians identified 1 or more interpersonal problem areas falling into the domains of grief over loss (including grieving the lost healthy self), role transitions, interpersonal disputes, and interpersonal deficits (for further details, see references 13 and 30). They also introduced the Social Rhythm Metric form, a self-report device by which patients tracked their daily routines and sleep/wake cycles.[31–32]

In the intermediate phases of IPSRT, clinicians assisted patients in managing their symptoms through identifying triggers for social rhythm disruption (e.g., changes in job hours) and attempting to stabilize their daily routines. Clinicians encouraged patients to find an optimal balance between stability in rhythms, sleep, mood, and interpersonal stimulation. Current interpersonal problems (e.g., significant marital conflicts) were explored and, when possible, resolved. Typically, problem resolution required the patient's insight into repeated patterns of interpersonal conflict and the acquisition of new communication strategies for approaching conflicts differently. In the final stages of IPSRT, the focus shifted to relapse prevention: clinicians assisted patients in maintaining social routines, anticipating events that could disrupt these routines, and preventing the reemergence of significant interpersonal problems.

Sessions of family-focused treatment also followed a predetermined structure. In the first phase, patients and their relatives (typically the parents or spouse) were educated about the symptoms, etiology, course, and treatment of bipolar disorder. Clinicians discussed the disorder's biological and genetic underpinnings from a vulnerability/stress framework.[33] They encouraged participants to identify the patient's early warning signs of manic or depressive relapses and develop preventive plans to derail the escalation of emergent symptoms. Clinicians emphasized the recurrent nature of the illness and the necessity of ongoing compliance with pharmacologic treatment.

In the second phase, communication enhancement training, patients and family members learned, via role-playing and behavioral rehearsal, to reduce family or marital conflict through practicing the skills of active listening, delivering positive and negative feedback, and requesting changes in each other's behaviors. In the third phase, problem-solving, participants learned a framework for defining problems (e.g., the patient's becoming exhausted and depressed after social events), brainstorming solutions, evaluating the pros and cons of alternative solutions, and implementing solutions to problems (e.g., using behavioral strategies to cope with overstimulating social situations). Between-session homework assignments helped the participants to generalize the communication and problem-solving skills to the home setting (for a comprehensive review of these procedures, see Miklowitz and Goldstein[22]).

The individual and family clinicians met with each other weekly and were supervised by the first author (D.J.M.). The treatment plan was constructed such that at least 1 week had passed between an individual session and the next family session. Between sessions, each clinician listened to audiotapes or watched videotapes of sessions from the other modality. During supervision meetings, they discussed with each other the content of their previous sessions with the patient and made recommendations for the focus of the next individual or family session (for example, addressing recent life events, work problems, or previously unexplored marital conflicts). Both treatments emphasized the importance of educating oneself about the disorder, social rhythm regularity, mood monitoring, coping with disruptive life events, medication adherence, and keeping the family environment low in conflict.

Psychosocial Interventions: The Crisis Management Model

Patients who had been randomly assigned to the crisis management condition of the CTOP study received a protocol that emulated standard community care. To provide support and increase cooperation, each participating family received 2 home-based sessions of education about bipolar disorder, conducted within 2 months after the patient's entry into the study. These sessions covered the same topical areas as family-focused treatment, but in abbreviated form. Then, over the next 9 months, project clinicians offered the patient emergency counseling sessions as needed, which typically were required when the patient had symptomatic exacerbations, suicidal crises, or severe family or marital conflicts. Patients and relatives were encouraged to contact the CM clinician immediately if the patient appeared to be relapsing, at which point the clinician conducted an assessment and helped arrange emergency medical intervention (including hospitalization if necessary). At minimum, clinicians contacted patients by phone at least once a month to monitor their progress.

Therapists

Therapists who conducted the individual and family IFIT sessions, and the family educational sessions of the CM protocol, were graduate students and postdoctoral fellows in clinical psychology at the University of Colorado. All participating clinicians administered both the individual and family therapy components of IFIT for different treatment cases, but never served as both indi-

vidual and family therapist for the same patient. They were trained to standard levels of adherence and competence for each treatment modality and were supervised closely to minimize drift from the respective treatment manuals.

Follow-Up Procedures

Independent research evaluators interviewed patients in the IFIT and CM protocols as to symptom status, first during the initial SCID interview (spanning the 3 months prior to entry into the study protocols, including the acute period of illness), again at the end of a 1-month pretreatment assessment period, and then at least once every 3 months during the next 12 months. Research interviews spanning the prior 2 weeks were scheduled between these 3-month assessments if the patient had been hospitalized or otherwise appeared to be relapsing.

The primary measure of symptomatic outcome was the Schedule for Affective Disorders and Schizophrenia, Change Version (SADS-C), a 36-item interview and rating scale.[34] From the independent evaluators' ratings of this interview, composite scores were calculated for total mood disorder symptoms (the sum of all depression and mania items), for depressive symptoms only (e.g., depressed mood, self-reproach, suicidality, insomnia), and for manic symptoms only (e.g., elevated mood, grandiosity, increased activity). The composite scores tabulated at each point of follow-up reflected the worst period of symptomatic functioning during the preceding 3-month interval. Interrater reliability between rater pairs (intraclass correlations, calculated from at least 10 SADS-C interview ratings for each evaluator) ranged from 0.81 to 0.92 for SADS-C depression and mania composite scores.

Patients were classified as to 1-year outcome status (relapsed versus nonrelapsed) only if they participated in research interviews for at least 9 of the 12 months of each study protocol (N = 72). The remaining 28 patients ended their participation in the protocols before a determination of 1-year outcome status could be made. Most of these patients left the study prior to the 3-month assessment point. Of the 30 IFIT patients, 21 (70%) completed the longitudinal assessments. Of the 70 CM patients, 51 (73%) completed the assessments, a nonsignificant difference in attrition rates ($p > .10$)

The 1-year outcomes of the study completers were judged by 2 raters who had been trained in the relapse classification system of Nuechterlein et al.[35] Raters classified the patients without knowledge of which psychosocial or medical treatments had been assigned. The relapse classification system, validated in longitudinal studies of schizophrenic and bipolar patients,[7,35] contains 9 categories of outcome that are reduced to the general categories of relapse, nonrelapse, or "unchanged" (continuous, highly persistent symptoms from baseline to follow-up, without relapse or remission). Interrater reliability for this tripartite distinction was high for the present samples ($\kappa = 0.88$, $p < .001$).

Statistical Analyses

Data analyses compared the longitudinal outcomes of the patients in IFIT treatment with the outcomes of the patients in the CM group. First, analyses of variance compared patients' symptom status at study intake (the 3 months up to and including the SCID assessment) and at the end of a 1-month baseline assessment period prior to the initiation of psychosocial treatments. The dependent variables were composite mood disorder severity scores, depression scores, and mania scores from the SADS-C.

Second, comparisons on time to relapse over the course of the 12-month research protocols were conducted using Cox survival models.[36–38] It appeared that the estimated hazard functions of the IFIT and CM groups differed as a function of time ($\chi^2 = 5.2$, df = 1, $p = .02$). Thus, a treatment group–by-time interaction term was included in an extended Cox regression model to account for the time dependence of the hazard ratios. Inclusion of this interaction term improved the fit of the Cox survival model ($p = .01$) over a standard model that assumed constant proportionality. All survival models were tested using PROC PHREG from the Statistical Analysis System.[39]

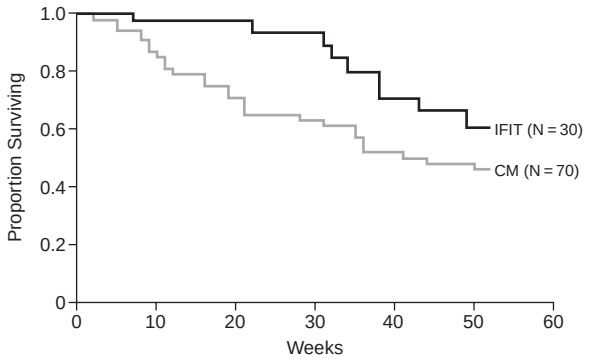
Third, group differences in the trajectory of individual symptom clusters were compared as a function of time, using repeated measure mixed analysis of variance (ANOVA) models. The survival analyses and mixed ANOVA models included data on participants for whom there were incomplete observations at follow-up (intent-to-treat analyses). Secondary analyses examined the effects of significant covariates, including baseline symptom status and medication regimens. All statistical tests were 2-tailed.

RESULTS

Comparisons of the Treatment Groups at Baseline

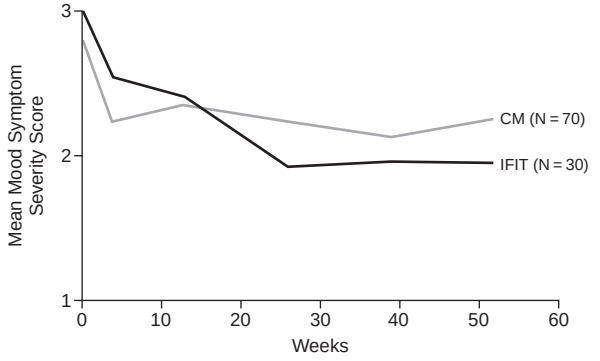
Patients in IFIT and CM did not differ in the severity of total mood disorder symptoms (the mean of all depression and mania items) in the 3 months prior to and including the intake SCID assessment ($F = 1.51$, df = 1,95; $p > .10$). There was, however, a statistical trend for patients in IFIT to be more symptomatic during the 1-month pretreatment period than those in CM ($F = 3.7$, df = 1,85; $p = .058$; 1-month SADS-C data were available for 87 of the 100 patients). Examination of the polarity of these symptoms indicated that during the pretreatment period, IFIT patients had more severe depression symptoms than CM patients ($F = 6.73$, df = 1,85; $p = .01$), but not mania symptoms ($F = 0.46$, df = 1,85; $p > .10$). IFIT patients also had correspondingly higher medication regimen intensity scores during the pretreatment period ($t = 1.95$, df = 86, $p = .05$).

Figure 1. One-Year Survival Curves for Patients Receiving Integrated Family and Individual Therapy (IFIT) and Crisis Management (CM)[a]



[a]Survival curves adjusted for polarity of the illness episode at study intake (manic, depressed, mixed), composite depressive symptoms (from the Schedule for Affective Disorders and Schizophrenia, Change Version) and medication treatment intensity scores during a 1-month pretreatment baseline period, and number of years of education. Treatment with IFIT was associated with longer survival intervals than treatment with CM after adjusting for covariates ($\chi^2 = 5.97$, df = 1, p = .02; hazard ratio = 0.07).

Figure 2. Psychosocial Treatment and the Trajectory of Bipolar Mood Symptoms Over 1 Year[a]



[a]Mean mood symptom severity scores were calculated as an average of all depression and mania symptom items on the Schedule for Affective Disorders and Schizophrenia, Change Version. Symptom item scores could range from 1 to 6 or 1 to 7. The interaction between treatment group (integrated family and individual therapy [IFIT], crisis management [CM]) and time was highly significant (F = 3.49, df = 5,381; p < .005).

Effects of Psychosocial Treatment on Survival Time

Of the 72 study completers, 36 were classified as having had a relapse. Of these, 24 were depressive relapses, 10 were manic relapses, and 2 were of mixed polarity. The remaining 36 patients were judged not to have relapsed, including 33 patients who were classified as having stable (full or partial) remissions throughout follow-up and 3 who were designated as unchanged from baseline. For the purposes of the survival analytic models, the stable remission and unchanged groups were combined into a single "nonrelapsing" group.

Mood disorder relapses were observed in 27 (39%) of the 70 CM patients by the 12-month follow-up and in 9 (30%) of the 30 IFIT patients, a nonsignificant difference ($\chi^2 = 0.67$, df = 1, p > .10). Of the 27 relapsing patients in CM, 16 (59%) had depressive episodes, 9 (33%) had manic episodes, and 2 (7%) had mixed episodes. Of the 9 relapsing patients in IFIT, 8 (89%) had depressive episodes and 1 (11%) had a manic episode. The distributions of relapse polarities did not differ across the groups ($\chi^2 = 2.76$, df = 2, p > .10).

A survival analysis using an extended Cox model (see above), which included data on the study dropouts, revealed that IFIT led to greater delays in mood disorder relapses than CM ($\chi^2 = 5.63$, df = 1, p < .02; hazard ratio = 0.078). The mean (SE) survival interval for IFIT patients was 42.5 (2.2) weeks and for CM patients, 34.5 (2.5) weeks.

To further examine this result, 4 variables that had distinguished between the treatment groups at baseline were included as covariates in a single extended Cox survival model. Three of these variables measured baseline clinical state: polarity of the acute episode at study entry, and baseline SADS-C depression scores and medication regimen intensity scores during the 1-month pretreatment period. We also examined the contribution of 1 antecedent demographic variable: years of education. Possibly, the lower education level of the CM patients placed them at higher risk for an early return of symptoms.[40]

The Cox survival model revealed an even stronger impact of IFIT versus CM in delaying mood disorder relapses after statistically equating the groups on these pretreatment variables ($\chi^2 = 5.97$, df = 1, p = .01; hazard ratio = 0.07). None of the covariates in the model were individually associated with time to relapse (p > .10). The survival curves for the 2 treatment groups, corrected for baseline clinical state variables and education, are depicted in Figure 1.

Effects of Psychosocial Treatment on the Severity of Ongoing Mood Disorder Symptoms

A repeated-measure mixed ANOVA model (intent-to-treat sample) indicated that patients in both psychosocial conditions showed reductions in symptom severity over the course of the study (intake assessment followed by the 1-, 3-, 6-, 9-, and 12-month reassessments). The effect of time on total mood symptoms was highly significant (F = 23.3, df = 5,381; p < .0001), as was the interaction between treatment group (IFIT, CM) and time (F = 3.49, df = 5,381; p < .005). This interaction indicated greater improvement in IFIT patients than CM patients (Figure 2).

The effects of psychosocial treatment were mainly observable for SADS-C composite depression scores. Reductions in mean depression scores from study intake

to 12-month follow-up were more pronounced for IFIT than CM patients ($F = 5.44$, $df = 5,376$; $p < .0001$). In contrast, a significant effect of time was found for improvements in SADS-C mania scores over the study year ($F = 20.46$, $df = 5,386$; $p < .0001$), but no effect of psychosocial treatment or treatment by time interaction (for both, $p > .10$).

The average IFIT patient showed a 33% reduction in SADS-C total depression scores over the year-long follow-up interval, whereas the average CM patient showed an 11% reduction. When considering the 1-to-6 Likert-type dimension of severity on which most SADS-C items are scaled, these changes translated into a mean 1-point reduction in depression scores for the IFIT group and a mean 0.25-point reduction for the CM group. For example, on the item "depressed mood," a typical IFIT patient would have changed over the study year from a rating of moderate ("most of the time feels depressed") to a rating of mild ("often feels somewhat depressed").

Because the IFIT patients were more depressed than the CM patients during the pretreatment period, we examined whether their greater improvement in depression symptoms was attributable to "regression to the mean." A repeated-measures mixed ANOVA model, using treatment group (IFIT, CM) as the independent variable and intake and 1-month pretreatment depression scores as covariates, once again revealed an effect of treatment group on follow-up depression scores ($F = 14.2$, $df = 1,85$; $p < .0005$). Thus, the groups still differed on follow-up depression scores after being statistically equated on baseline depression. Independent of treatment group, the patients who were the most depressed during the 1-month pretreatment period were also the most depressed at follow-up ($F = 34.5$, $df = 1,75$; $p < .0001$).

Finally, we examined whether the effects of psychosocial treatment on follow-up depression scores were a function of differences in medications between the 2 groups. As indicated earlier, there were no group differences during the 1-month pretreatment interval in the likelihood of adjunctive antidepressant treatment. As expected, patients on antidepressant treatment had higher depression scores over the 12-month study period than patients who did not require antidepressant treatment ($F = 17.72$, $df = 1,84$; $p < .0001$). Nonetheless, the psychosocial treatment–by-time interaction on follow-up depression scores remained robust after covarying the use of antidepressants ($F = 5.28$, $df = 5,375$; $p < .0001$). Likewise, covarying medication regimen intensity scores during the pretreatment period, or more specifically, the use of lithium versus anticonvulsants, did not affect the psychosocial treatment–by-time interaction for depression scores (for both, $p < .0001$). The results were virtually identical after covarying the use of atypical versus typical antipsychotic agents ($F = 5.19$, $df = 5,374$; $p < .0001$).

DISCUSSION

The present study examined the 1-year outcomes of bipolar patients treated openly with integrated family and individual therapy (IFIT group) and mood-stabilizing medications within the context of a treatment development study. The comparison patients were historical controls who received non-intensive psychoeducation, crisis management, and mood-stabilizing medications (CM group). The IFIT model synthesized 2 empirically supported psychosocial interventions for bipolar disorder—family-focused psychoeducation and interpersonal and social rhythm therapy. Patients treated with IFIT and medication showed longer delays prior to relapses and greater improvement in depression symptoms than CM patients over a year of treatment and follow-up. The effects of IFIT on survival time and ongoing depressive symptoms could not be explained by individual variability in the severity of depressive symptoms at entry into the treatment protocols, nor by differences in medication regimens.

This study had several limitations. First, it was not a randomized controlled trial of IFIT but rather an open treatment trial compared with a matched historical comparison group. Replication within randomized trials would be essential to ensure confidence in the findings. Second, the IFIT and CM groups were not matched on number of psychotherapy contact hours: on average, IFIT treatment was 29 sessions long, whereas only 2 psychosocial sessions were offered to the CM group. As a result, we cannot determine whether the specific components of IFIT led to greater clinical improvement among patients or simply that patients in IFIT received more intensive therapy than patients in CM.

Future randomized studies should go beyond standard community care as the comparison condition. To evaluate the potential influence of amount of therapy contact, and to determine whether there is in fact a synergy between individual and family treatment, IFIT would need to be evaluated against its component treatments (family-focused therapy and IPSRT), each delivered with the same level of treatment intensity (frequency and duration) as the fully integrated model.

Third, and related to the above, this study did not include an analysis of treatment costs versus benefits. Although we would assume that over a lengthier follow-up, the delays in relapse and reductions in depressive symptoms observed in IFIT would translate into greater savings in health care costs (for example, rehospitalizations) and improvements in quality of life, we did not test these assumptions directly. It is possible that the economic and health benefits of IFIT relative to CM would have been offset by its greater treatment costs.

A fourth study limitation was that patients varied in their acceptance of IFIT treatment. Few patients availed

themselves of weekly psychotherapy sessions for a full year. An advantage of treatment development studies is that the investigator can learn, before submitting an intervention to a randomized trial, the extent to which patients accept and make use of the proposed model. The results suggest that IFIT treatment should be tailored to the needs of individual patients, with the expectation that most patients will not opt for intensive, weekly treatment. Alternatively, some patients may be too unstable after an acute episode to commit to weekly sessions of both individual and family therapy.

Fifth, the present study did not include measures of mediating mechanisms (active agents of therapeutic change). Identifying mechanisms of change is an important step in developing treatments with enduring clinical effects.[41] Relevant to this issue are prior studies conducted on the mechanisms of action of IPSRT and family-focused treatment. In the Pittsburgh Maintenance Therapies trial conducted by Frank et al.,[42] IPSRT was associated with greater stabilization of patients' social routines and sleep/wake rhythms than intensive clinical management over as long as 52 weeks of treatment. In the CTOP study, family-focused therapy was associated with greater increases than crisis management in the spontaneous expression of positive communication behaviors among patients and relatives, as evaluated over a 9-month pretreatment/posttreatment interval.[43] We do not know whether IFIT has a similar impact on these variables or whether other protective influences—such as the quality of social supports, medication adherence, or the ability of the patient or family to identify and manage prodromal symptoms—are enhanced through this integrated model.

Consistent with prior psychosocial treatment studies, IFIT had a greater impact on depressive than manic symptoms. The previously cited CTOP study,[15] which used the same comparison group as the present study, found that patients treated with family psychoeducation and medication had less severe depressive symptoms and fewer depressive relapses than patients treated with CM and medication; the effects of family treatment did not extend to mania symptoms or relapses. In the Pittsburgh Maintenance Therapies trial, patients treated with IPSRT and medication were more likely to maintain euthymic moods and less likely to develop depressive states during the first year of preventive maintenance than patients treated with intensive clinical management and medication.[14]

Possibly, the greater efficacy of psychosocial treatment in controlling bipolar depressive symptoms is a by-product of the greater efficacy of mood-stabilizing medications in controlling manic symptoms.[44] Depressive symptoms are more likely to persist after an acute episode has been stabilized with pharmacotherapy, and adjunctive psychotherapy is correspondingly more likely to focus on ongoing depressive symptoms as targets for change. In interpersonal and family therapies for bipolar disorder, residual symptoms of depression are addressed through exploratory and skill-building strategies that promote effective disease management, interpersonal communication, problem-solving, and alliances with family members. Notably, social and familial support are significant protective factors against depression in unipolar and bipolar patients.[7,45–47]

The present study adds to the growing literature suggesting that outpatient psychosocial intervention is an important adjunct to pharmacotherapy in delaying relapses and enhancing the symptomatic functioning of bipolar patients. The empirical literature consistently recommends that patients be engaged in psychosocial interventions during the post-episode stabilization period, but the optimal length and frequency of these interventions have not been determined. It is also unclear whether the benefits of psychosocial intervention are achieved during the period of active intervention or whether the interventions must be "absorbed" before their clinical effects can be observed. Several studies find that improved patient outcomes attributable to active psychosocial interventions are apparent only once these interventions have been completed or tapered to maintenance levels.[14,15,21,48]

Finally, empirically supported psychosocial treatments remain unavailable to the majority of bipolar patients, notably treatment-refractory, diagnostically complicated patients who often appear in mental health centers but not in experimental trials. Effectiveness studies that establish methods for transporting manual-based psychosocial interventions into community settings are essential to moving this field forward.

Drug names: carbamazepine (Carbatrol, Tegretol, and others), chlorpromazine (Thorazine, Sonazine, and others), divalproex sodium (Depakote), gabapentin (Neurontin), lamotrigine (Lamictal), olanzapine (Zyprexa).

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