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Family-focused Therapy for Symptomatic Youths at High Risk for Bipolar Disorder
A Randomized Clinical Trial

David J. Miklowitz, PhD; Christopher D. Schneck, MD; Patricia D. Walshaw, PhD; Manpreet K. Singh, MD, MS; Aimee E. Sullivan, PhD; Robert L. Suddath, MD; Marcy Forgey-Borlik, MD; Catherine A. Sugar, MS, PhD; Kiki D. Chang, MD

IMPORTANCE Behavioral high-risk phenotypes predict the onset of bipolar disorder among youths who have parents with bipolar disorder. Few studies have examined whether early intervention delays new mood episodes in high-risk youths.

OBJECTIVE To determine whether family-focused therapy (FFT) for high-risk youths is more effective than standard psychoeducation in hastening recovery and delaying emergence of mood episodes during the 1 to 4 years after an active period of mood symptoms.

DESIGN, SETTINGS, AND PARTICIPANTS This multisite randomized clinical trial included referred youths (aged 9-17 years) with major depressive disorder or unspecified (subthreshold) bipolar disorder, active mood symptoms, and at least 1 first- or second-degree relative with bipolar disorder I or II. Recruitment started from October 6, 2011, and ended on September 15, 2016. Independent evaluators interviewed participants every 4 to 6 months to measure symptoms for up to 4 years. Data analysis was performed from March 13, to November 3, 2019.

INTERVENTIONS High-risk youths and parents were randomly allocated to FFT (12 sessions in 4 months of psychoeducation, communication training, and problem-solving skills training; n = 61) or enhanced care (6 sessions in 4 months of family and individual psychoeducation; n = 66). Youths could receive medication management in either condition.

MAIN OUTCOMES AND MEASURES The coprimary outcomes, derived using weekly psychiatric status ratings, were time to recovery from prerandomization symptoms and time to a prospectively observed mood (depressive, manic, or hypomanic) episode after recovery. Secondary outcomes were time to conversion to bipolar disorder I or II and longitudinal symptom trajectories.

RESULTS All 127 participants (82 [64.6%] female; mean [SD] age, 13.2 [2.6] years) were followed up for a median of 98 weeks (range, 0-255 weeks). No differences were detected between treatments in time to recovery from pretreatment symptoms. High-risk youths in the FFT group had longer intervals from recovery to the emergence of the next mood episode (χ^2 = 5.44; *P* = .02; hazard ratio, 0.55; 95% CI, 0.48-0.92;), and from randomization to the next mood episode (χ^2 = 4.44; *P* = .03; hazard ratio, 0.59; 95% CI, 0.35-0.97) than youths in enhanced care. Specifically, FFT was associated with longer intervals to depressive episodes (log-rank χ^2 = 6.24; *P* = .01; hazard ratio, 0.53; 95% CI, 0.31-0.88) but did not differ from enhanced care in time to manic or hypomanic episodes, conversions to bipolar disorder, or symptom trajectories.

CONCLUSIONS AND RELEVANCE Family skills-training for youths at high-risk for bipolar disorder is associated with longer times between mood episodes. Clarifying the relationship between changes in family functioning and changes in the course of high-risk syndromes merits future investigation.

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Supplemental content

Author Affiliations: Department of Psychiatry and Behavioral Sciences, David Geffen School of Medicine, University of California, Los Angeles (UCLA), Los Angeles (Miklowitz, Walshaw, Suddath, Forgey-Borlik, Sugar); Department of Psychiatry, University of Colorado Anschutz Medical Campus, Denver (Schneck, Sullivan); Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, California (Singh); Department of Biostatistics, Fielding School of Public Health, UCLA, Los Angeles (Sugar); Private practice, Menlo Park, California (Chang).

Corresponding Author: David J. Miklowitz, PhD, Department of Psychiatry and Behavioral Sciences, David Geffen School of Medicine, University of California, Los Angeles, 760 Westwood Plaza, Room A8-256, Los Angeles, CA 90024-1759 (dmiklowitz@mednet.ucla.edu).

Youths who develop bipolar I disorder (BD-I) or bipolar II disorder (BD-II) during late adolescence or early adulthood often experience subthreshold mood symptoms in childhood.[1] In the Pittsburgh Bipolar Offspring Study, youths with depression, anxiety, mood instability, and subthreshold manic symptoms who had a parent with childhood-onset BD had a 49% chance of converting to BD-I or BD-II in 8 years compared with 6.8% of youth without these symptom features whose parents had childhood-onset BD.[2] Onset of BD in childhood and delays to first treatment are associated with more time being depressed, less time being euthymic, and poorer functioning in adulthood.[3,4] However, there is little agreement on what treatments are most effective in preventing symptom progression among high-risk children.[4-9]

Psychosocial interventions may facilitate the high-risk youths' acquisition of skills for coping with stress, developing social supports, and achieving autonomy.[10] In a 2-site pilot randomized clinical trial[11] of 40 youths with active symptoms of major depressive disorder (MDD) or unspecified (subthreshold) BD and a family history of BD-I or BD-II, Miklowitz et al[11] found that family-focused therapy (FFT) for high-risk youths, consisting of 12 sessions of family psychoeducation, communication skills training, and problem-solving skills training was associated with more rapid recovery from mood symptoms, more time in remission, and a more favorable trajectory of hypomania symptoms during 1 year compared with brief family education. These findings are consistent with trials showing that FFT and pharmacotherapy are more effective than comparison treatments and pharmacotherapy in enhancing mood stabilization and delaying mood recurrences among adults with BD.[12-15]

We conducted a randomized clinical trial of the effects of FFT compared with standard psychoeducation (enhanced care [EC]) on time to recovery and time to prospectively observed mood episodes among symptomatic high-risk youths. This study expanded on the pilot randomized clinical trial[11] by including 3 sites with a larger number of participants (N = 127) followed up for 1 to 4 years. The duration of the EC treatment was standardized at 4 months to match the duration of FFT. Participants received pharmacotherapy from study psychiatrists (C.D.S., M.K.S., R.L.S., M.F-B., and K.D.C.) using algorithms designed for this population.[16] We hypothesized that high-risk youths receiving FFT would have (1) shorter times to recovery from pretreatment symptoms and longer intervals until their next prospectively observed mood episode (coprimary outcomes), and (2) lower rates of conversion to syndromal BD-I or BD-II and greater improvements in symptom severity over time (secondary outcomes) compared with youths receiving EC.

Key Points

Question Is family-focused therapy for youths at high-risk for bipolar disorder effective in delaying mood disorder episodes?

Findings This 3-site randomized clinical trial included 127 youths (aged 9-17 years) with symptomatic mood disorder and a family history of bipolar disorder. For a mean of 2 years, youths at high-risk for bipolar disorder who received 12 sessions of family-focused therapy (psychoeducation, communication, and problem-solving skills training) with their families had longer well intervals between mood episodes compared with youths who received less intensive family and individual psychoeducation.

Meaning The findings suggest that family-focused therapy is associated with longer times between mood episodes among youths at high risk for bipolar disorder.

Methods

This randomized clinical trial was approved by medical institutional review boards of the University of California, Los Angeles (UCLA), the University of Colorado, Boulder, the University of Colorado Anschultz Medical Center, Aurora, and Stanford University, Stanford, California. After receiving an explanation of the procedures, participants and parents gave written informed assent and consent to participate. The trial protocol is available in Supplement 1.

Participants

Recruitment of participants occurred from October 6, 2011, to September 15, 2016. Data were analyzed from March 13, to November 3, 2019. Participants were clinically referred or learned of the study through online, radio, or print advertisements or public presentations. Eligibility criteria included (1) age between 9 years 0 months and 17 years 11 months; (2) meeting lifetime *DSM-IV* and, later, *DSM-5* criteria[17,18] for unspecified BD or major depressive disorder (MDD) (eMethods in Supplement 2); (3) having at least 1 first- or second-degree relative with a lifetime history of BD-I or BD-II; and (4) a prior week Young Mania Rating Scale (YMRS)[19] score more than 11 or a 2-week Children's Depression Rating Scale, Revised (CDRS-R)[20] score more than 29, indicating at least moderate current mood symptoms. Unspecified BD (formerly BD, not otherwise specified) was defined as distinct periods of abnormally elevated, expansive, or irritable mood and 2 (3, if irritable mood only) symptoms of mania that caused a change in functioning, lasted 1 to 3 days, and occurred for at least 10 days in the child's lifetime.[21,22]

Baseline Assessments

Study diagnosticians administered the Kiddie Schedule for Affective Disorders and Schizophrenia, Present and Lifetime Version (KSADS-PL)[23,24] with the youth and at least 1 parent, with final item ratings based on consensus judgments. Interrater reliability for KSADS Depression and Mania Rating scales[23,25] had means of 0.74 and 0.84 (intraclass correlations) across sites. A trained research assistant interviewed each parent about their own psychiatric history using the MINI International Neuropsychiatric Interview[26] and about psychiatric illnesses in the youth's other first- and second-degree relatives using the Family History Screening instrument.[27]

Study Design and Procedures

Before the study, the independent data core at UCLA created a dynamic random allocation procedure[28] that assigned participants to FFT (n = 61) or EC (n = 66). Assignments were made

separately by site. After a participant was determined to be eligible, the site's principal investigator entered a diagnosis (unspecified BD or MDD), age (<13 years or ≥13 years), and initial medications (mood stabilizers or antipsychotics vs neither) into the algorithm, which then randomly allocated a treatment assignment to minimize imbalances between study arms across these variables.

Pharmacotherapy

At baseline, a study psychiatrist conducted a separate medical evaluation of the youth. Participants were offered maintenance pharmacologic care (biweekly and then monthly meetings) when clinically indicated or requested by the youth or parents. Physicians who were unaware of psychosocial assignments followed a pharmacotherapy algorithm for high-risk youths that described medication choices, starting doses, dose ranges, and clinical adjustments to manage mood or comorbid conditions and control adverse effects (trial protocol in Supplement 1 and eResults in Supplement 2).[16,22]

Psychosocial Treatments

All therapists administered both psychosocial treatments. Family-focused therapy involved the high-risk child, parents or stepparents, and when possible, siblings. The protocol consisted of 12 sixty-minute sessions (8 weekly, 4 biweekly) in 4 months of psychoeducation, communication enhancement training (eg, practicing active listening or expressing positive or negative feelings), and problem-solving skills training. The 4-month EC treatment consisted of 3 weekly 60-minute family psychoeducation sessions followed by 3-monthly youth-only sessions that focused on implementing a mood management plan (eMethods and eTable in Supplement 2). Family clinicians were trained in the FFT and EC protocols during a study launch meeting and supervised in monthly teleconferences throughout the study. Clinician fidelity ratings on the Therapist Competence and Adherence Scales[29] indicated high levels of adherence and skill (mean [SD], 5.04 [0.96] on a 7-point scale) in administering both treatments (eMethods in Supplement 2).

Outcome Assessments

Independent evaluators blinded to treatment condition interviewed the youth and at least 1 parent (regarding the youth) at baseline (covering the previous 4 months), every 4 months after randomization in year 1, and every 6 months for up to 4 years. At each assessment, the evaluators administered the Adolescent Longitudinal Interval Follow-up Evaluation (A-LIFE) and associated Psychiatric Status Ratings (PSRs),[30] defined as 1 (asymptomatic) to 6 (fully syndromal, severe), point scales of depression, mania, and hypomania rated for every week of the interval. Interrater reliabilities for 6-point depression PSR was 0.79 (intraclass *r*) and for 6-point mania PSR was 0.76 (intraclass *r*) calculated across evaluators at each study site.

Statistical Analysis

All participants had at least subthreshold mood symptoms (PSR scales ≥3) in the 2 weeks before randomization. The primary analysis was a 2-stage survival model of the coprimary outcomes. Using conventions for the A-LIFE PSRs, we first compared the FFT and EC groups on the number of weeks from treatment assignment to the beginning of a recovery period (all PSR mood scales rated 1 [asymptomatic] or 2 [mildly symptomatic] for ≥8 consecutive weeks).[21,30] For those who recovered from prerandomization symptoms, we next compared treatment arms on time to a new mood episode, defined as either at least 2 weeks with PSR depression ratings of 4 (syndromal with moderately severe), 5 (severe), or 6 (extremely severe symptoms or impairment) or at least 1 week with PSR hypomania or mania ratings of 5 (syndromal with full intensity) or 6 (severe intensity). Reliability between raters for estimating time to recovery was 0.93 and for time to mood episodes was 0.89. Secondarily, we fit individual survival models for time to depressive episodes, time to manic or hypomanic episodes, and time to diagnostic conversion, defined as onset of mood symptoms that changed the diagnosis from MDD or unspecified BD to BD I or BD II (eMethods in Supplement 2).

For the time to event analyses, we obtained Kaplan-Meier estimates of the survival curves for each study arm and used the log-rank procedure (PROC LIFETEST in SAS, version 9.4 [SAS Institute Inc][31]) to test for overall treatment effects. In follow-up analyses, we used Cox proportional hazards regression models (PROC PHREG in SAS[31]) to quantify the treatment effects (via hazard ratio estimates) and to explore the independent effects of specific baseline covariates (site, age, sex, primary and comorbid diagnoses, family history [first- vs second-degree affected relatives], YMRS and CDRS-R scores, and medication regimens) beyond treatment effects.

In secondary analyses examining the differential effects of FFT vs enhanced care on the trajectory of mood symptoms over time, we computed a maximum PSR mood (depression, mania, or hypomania) severity score for each week of follow-up and then averaged these weekly maximum scores (range, 1-6) in each 4- to 6-month study interval for up to 48 months. We fit a mixed effect regression model (in PROC MIXED in SAS[31]) with mean maximum PSR scores as the outcome, treatment as the between-persons effect, time as the within-persons effect, and treatment-by-time interaction terms. We used a piecewise linear segmentation of time, allowing for a change in slope at 8 months because we expected faster improvements during and immediately after the acute treatment period followed by a leveling after treatment as the corresponding skills learned in treatment were consolidated.

For all analyses, we initially included site and its interactions with group and time to ensure that differential implementations of the interventions were not affecting observed results. Because there was no evidence of any site effects, we present the final results for models with site terms removed. Statistical significance was set at 2-sided $P < .05$.

Table. Demographic and Illness History Features of High-risk Youths Receiving Family-focused Therapy or Enhanced Care[a]

Variable	Family-focused Therapy (n = 61)	Enhanced Care (n = 66)	Total (N = 127)
Age, mean (SD), y	13.2 (2.7)	13.3 (2.5)	13.2 (2.6)
Socioeconomic status, mean (SD)[b]	3.7 (0.8)	4.1 (0.8)	3.9 (0.8)
Young Mania Rating Scale at baseline, mean (SD)	12.8 (6.8)	12.5 (7.7)	12.6 (7.3)
Children's Depression Rating Scale–Revised at baseline, mean (SD)	46.3 (13.5)	48.3 (15.5)	47.3 (14.5)
Children's Global Assessment Scale in the last 2 wk at baseline, mean (SD)	52.7 (9.8)	52.2 (22.5)	52.5 (10.6)
Children's Global Assessment Scale, most severe past episode, mean (SD)	44.5 (7.6)	42.8 (8.5)	43.6 (8.1)
Female	37 (60.7)	45 (68.2)	82 (64.6)
Nonwhite race	12 (19.7)	10 (15.2)	22 (17.3)
Hispanic ethnicity	15 (24.6)	8 (12.1)	23 (18.1)
Primary diagnosis			
Major depressive disorder	37 (60.7)	38 (57.6)	75 (59.1)
Bipolar disorder, not otherwise specified	24 (39.3)	28 (42.4)	52 (40.9)
Mood polarity at study entry			
Depression, no mania or hypomania	27 (44.3)	31 (47.0)	58 (45.7)
Hypomania, no depression	0	1 (1.5)	1 (0.8)
Depression, subthreshold mania or hypomania	24 (39.3)	26 (39.4)	50 (39.4)
Hypomania, subthreshold depression	3 (4.9)	3 (4.5)	6 (4.7)
Subthreshold depression and mania or hypomania	7 (11.5)	5 (7.6)	12 (9.4)
Comorbid disorders[c]			
None	6 (9.8)	11 (16.7)	17 (13.4)
Internalizing disorders only	21 (34.4)	26 (39.4)	47 (37.0)
Externalizing disorders	13 (21.3)	14 (21.2)	27 (21.3)
Internalizing and externalizing disorders	21 (34.4)	15 (22.7)	36 (28.4)
Baseline medications			
None	23 (37.7)	33 (50.0)	56 (44.1)
Lithium	1 (1.6)	0	1 (0.8)
Antipsychotic	13 (21.3)	17 (25.8)	30 (23.6)
Anticonvulsant	10 (16.4)	8 (12.1)	18 (14.2)
Antidepressant	27 (44.3)	20 (30.3)	47 (37.0)
Anxiolytic	2 (3.3)	2 (3.0)	4 (3.1)
Psychostimulant or other ADHD agent	12 (19.7)	14 (21.2)	26 (20.5)
Family composition			
Both biological parents, intact family	32 (52.5)	30 (45.5)	62 (48.8)
Both biological parents, joint custody	6 (9.8)	5 (7.6)	11 (8.7)
1 Biological parent without stepparent	7 (11.5)	14 (21.2)	21 (16.5)
1 Biological parent plus stepparent	9 (14.8)	11 (16.7)	20 (15.7)
Grandparent	2 (3.3)	1 (1.6)	3 (2.4)
Other relative	5 (8.2)	5 (7.6)	10 (7.9)
Family history of bipolar disorder			
Youths with first-degree relatives only	35 (57.4)	47 (71.2)	82 (64.6)
Youths with second-degree relatives	10 (16.4)	9 (13.6)	19 (15.0)
Youths with first- and second-degree relatives	16 (26.2)	10 (15.2)	26 (20.5)

Abbreviation: ADHD, attention-deficit/hyperactivity disorder.

[a] Data are presented as number (percentage) of participants unless otherwise indicated.

[b] Higher values for socioeconomic status indicate higher educational level and occupation.

[c] Internalizing disorders include all anxiety disorders and eating disorders. Externalizing disorders include ADHD, conduct disorder, oppositional defiant disorder, and disruptive mood dysregulation disorder.

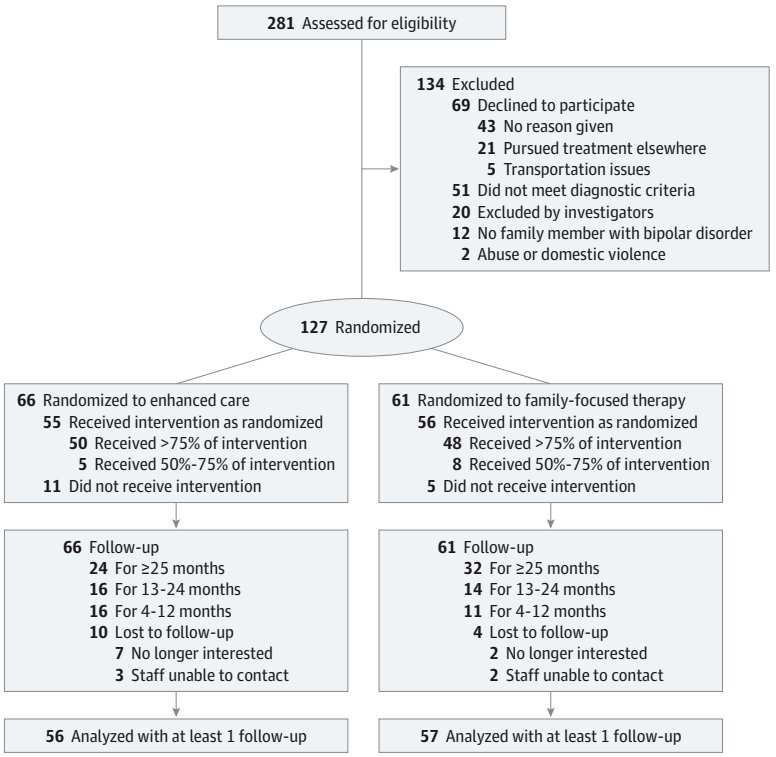
Results

Participants

Participants were 127 youths (82 female [64.6%]; mean [SD] age, 13.2 [2.6] years; range, 9.0-17.9 years.), including 75 youths with MDD (59.1%) and 52 youths with unspecified BD (40.9%). The FFT participants did not differ from the EC participants on any baseline characteristic overall or by site (**Table**). The final sample of 127 participants did not differ in sex, age, or race/ethnicity from 134 candidates who were screened and found ineligible or who refused to participate in the study (**Figure 1**).

Participants were in the study for a median of 98 weeks (range, 0-255 weeks); 14 (11.0%) were lost to follow-up (10 in

Figure 1. CONSORT Diagram



The participants allocated to interventions were enrolled at UCLA (n = 56), University of Colorado (n = 44), or Stanford University (n = 27) Schools of Medicine.

EC and 4 in FFT) shortly after randomization (Figure 1). Duration of follow-up did not differ significantly across psychosocial treatments (FFT: median, 114 weeks; range, 0-255 weeks; EC: median, 92.5 weeks, range, 0-221 weeks; survival analysis log-rank $\chi^2 = 2.78$; $P = .10$) nor as a function of baseline depression (CDRS-R) or mania or hypomania (YMRS) scores, study site, sex, age, family history, or primary or comorbid diagnoses. Patients in FFT and EC groups attended the same proportion (91.7%) of protocol therapy sessions (FFT: mean [SD], 11.0 [3.4] of 12.0; EC: mean [SD], 5.5 [2.4] of 6.0), and the proportion of participants who dropped out during the 4-month treatment period did not differ significantly across groups (8.2% vs 16.7%; $\chi^2 = 2.07$; $P = .15$). Additional checks of the potential impact of follow-up duration on the primary outcome results are presented in the eResults in Supplement 2.

Effects of Treatment on Time to Recovery

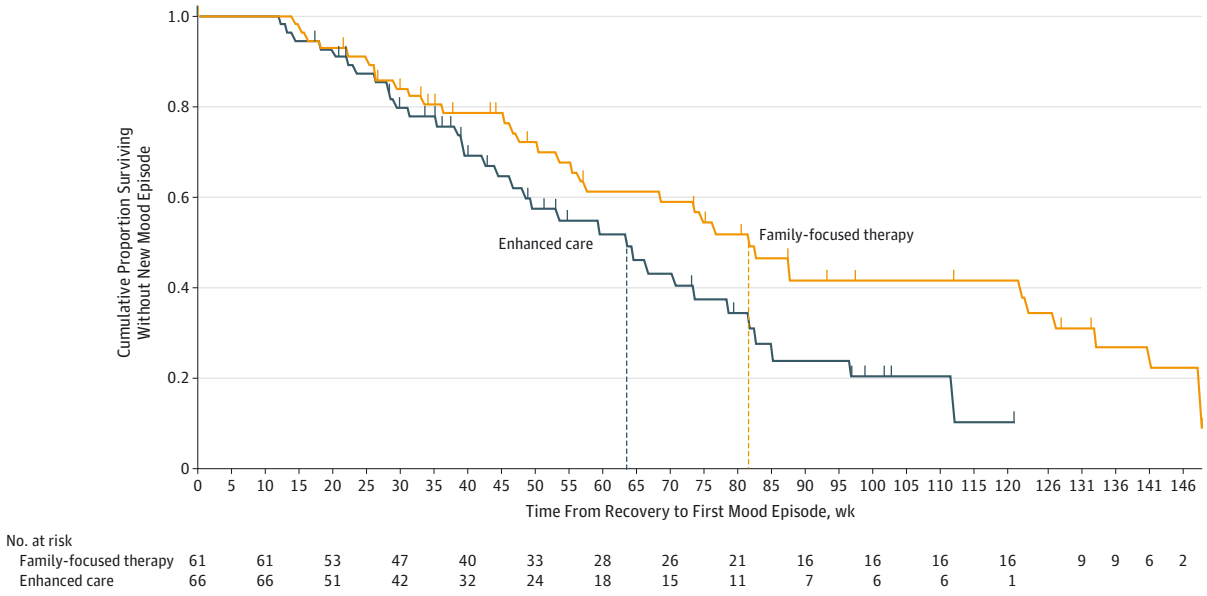
Of the 127 participants, 90 (70.9%) met the 8-week mood recovery criteria at some point during follow-up, 23 (18.1%) did not, and 14 (11.0%) withdrew at baseline. In the FFT group, 47 of 61 participants (77.0%) recovered in a median of 24 weeks (95% CI, 17-33 weeks) compared with 43 of 66 (65.2%) in the EC group in 23 weeks (95% CI, 17-29 weeks) (log-rank $\chi^2 = 0.01$; $P = .93$; unadjusted hazard ratio [HR] for FFT vs EC, 1.02; 95% CI, 0.67-1.54). In a Cox proportional hazards regression model that examined baseline covariates, lower CDRS-R depression scores (Wald $\chi^2 = 7.59$; $P = .006$; HR, 0.98; 95% CI, 0.96-0.99) and male sex (Wald $\chi^2 = 5.57$; $P = .02$; HR, 1.81; 95% CI, 1.11-2.96) were independently associated with shorter time to mood recovery.

Effects of Treatment on Prospectively Observed Mood Episodes

Among the 90 participants who recovered, new mood episodes were observed in 71 (78.9%) during follow-up; 70 of 90 participants (77.8%) had new episodes of major depression and 12 (13.3%) had new episodes of mania (n = 7; 3 with mixed episodes) or hypomania (n = 5) at follow-up. In the FFT group, new mood episodes occurred in 37 of 47 recovered participants (78.7%) compared with 34 of 43 (79.1%) in the EC group. The survival analysis of time from recovery to recurrence indicated that FFT participants experienced longer times without a new mood episode than EC participants (log-rank $\chi^2 = 5.44$; $P = .02$; HR, 0.55; 95% CI, 0.48-0.92).

This conditional analysis included only participants who recovered (n = 90) and was therefore not randomized. Because the 2 groups did not differ on time to recovery, we conducted an intent-to-treat analysis of time from randomization until the first observed mood episode to assess whether participants in FFT had longer periods of remission. The estimated median time from randomization to a new mood episode was 73 weeks (95% CI, 55-82 weeks) in the intent-to-treat sample (n = 127), with a median of 81 weeks (95% CI, 56-123 weeks) for those in the FFT group and 63 weeks (95% CI, 44-78 weeks) for those in the EC group. Patients in the FFT group had longer intervals of wellness before new mood epi-

Figure 2. Family-focused Therapy vs Enhanced Care for Youths at High Risk for Bipolar Disorder



Effect of treatment condition on time to mood episode (χ^2 = 4.44, *P* = .03; hazard ratio, 0.59 [95% CI, 0.35-0.97]). All patients (N = 127) began with at least subthreshold symptoms. Time to episode was calculated from the date of randomization to the beginning of the first prospectively observed mood episode. Dashed vertical lines indicate group medians.

sodes than patients in the EC group (χ^2 = 4.44; *P* = .03; HR, 0.59; 95% CI, 0.35-0.97) (**Figure 2**). In a Cox proportional hazards regression model, there were no independent effects of baseline covariates on time to mood episodes, whereas the effect of treatment group in this analysis remained robust (Wald χ^2 = 8.58; *P* = .003; HR, 0.39; 95% CI, 0.21-0.74).

Because of the large proportion of participants lost to follow-up at the Stanford University site (eResults in Supplement 2), we also constrained the survival models to the UCLA and Colorado sites only (n = 100). In the 2-site subsample, we observed a stronger effect of FFT vs EC on time to new mood episodes (log-rank χ^2 = 6.08; *P* = .01; HR, 0.50; 95% CI, 0.28-0.88), suggesting that the 3-site comparison was more conservative.

Of 61 participants in the FFT group, 36 (59.0%) experienced recovery and then had new depressive episodes in a median of 87 weeks (95% CI, 73-127 weeks) compared with 34 of 66 EC participants (51.5%) in 63 weeks (95% CI, 44-78 weeks), indicating longer well intervals before recurrences of depression in the FFT group (log-rank χ^2 = 6.24; *P* = .01; HR, 0.53; 95% CI, 0.31-0.88). Base rates of hypomanic and manic episodes after recovery were lower. Of 61 youths in the FFT group who recovered, 9 had manic or hypomanic episodes in a mean (SE) of 140.6 (5.7) weeks (median not estimable because of number of events). Of 66 EC participants, 3 had manic or hypomanic episodes in a mean (SE) of 133.6 (2.9) weeks (log-rank χ^2 = 2.43; *P* = .12).

Conversion to BP-I or BP-II Disorder

Of 127 participants, 9 (7.1%) had manic or mixed episodes at follow-up, resulting in a change from unspecified BD (n = 6) or MDD (n = 3) to BD-I; 9 (7.1%) had hypomanic episodes resulting in a change from unspecified BD (n = 4) or MDD (n = 5) to BD-II. One participant progressed from unspecified BD to schizoaffective disorder, depressed type (eMethods in Supplement 2). In the FFT group, 11 participants converted in a mean (SE) of 135.5 (6.6) weeks, whereas in the EC group, 8 converted in a mean (SE) of 91.4 (4.0) weeks (medians not estimable because of low number of events) (log-rank χ^2 = 0.17; *P* = .68). Only baseline YMRS scores were independently associated with risk of conversion (Wald χ^2 = 3.84; *P* = .05; HR, 1.08; 95% CI, 1.00-1.16).

Effects of Treatment on Symptom Trajectories

In secondary analyses, we examined whether youths in FFT had a more favorable trajectory of mood symptom scores than youths in EC in up to 48 months of follow-up. In mixed effect regression models, with time treated as piecewise linear, the longitudinal patterns of mean maximum PSR mood scores did not differ by group (likelihood-ratio test comparing models with and without the group-by-time interaction terms, χ^2 = 0.50; *P* = .78). However, each of the time components was statistically significant (*P* < .001), with FFT participants and EC participants showing a decline in symptoms during the first 8 months, followed by a substantial leveling off during the follow-up period (eFigure in Supplement 2).

Effects of Pharmacotherapy

We detected no differences between treatment arms in the frequency of antipsychotic, mood stabilizer, antidepressant, anxiolytic, or psychostimulant use at baseline (Table) or at any follow-up point. In Cox proportional hazards regression models, there were no relationships between baseline medications and time to recovery or time to diagnostic conversions, nor any ef-

fects of medications on time to mood recurrences beyond psychosocial treatment (eResults in Supplement 2).

Discussion

In a 2-site randomized clinical trial,[11] youths at clinical and familial risk for BD who received 4 months of FFT had more favorable mood trajectories (faster episode recovery, more time in remission, and lower mania or hypomania scores) during 1 year compared with youths in a 1 to 2 session EC treatment. In the present study, a randomized clinical trial with a larger sample, 3 sites, a more intensive EC comparator (6 sessions during 4 months), and a longer follow-up period (average of 2 years), we observed no difference between FFT and EC in recovery times. However, FFT was associated with longer well intervals from randomization to new mood episodes (median, 81; 95% CI, 56-123 weeks) than EC (median, 63; 95% CI, 44-78 weeks), suggesting that FFT may have uniquely enduring effects that extend into the maintenance phase of treatment. This study extends the results of other randomized clinical trials indicating effects of family psychoeducation and skill training on the long-term trajectory of depressive symptoms in pediatric mood disorders (eDiscussion in Supplement 2)[32-34] as well as trials indicating enduring effects of cognitive behavioral therapy (given acutely) on recurrence among adult patients with depression.[35,36]

Of 7 randomized clinical trials of adult and pediatric BD, 5 indicated stronger effects of FFT on depressive symptoms than manic or hypomanic symptoms,[11,12,14,37,38] whereas 2 indicated stronger effects of FFT on manic or hypomanic symptoms.[13,39] Because the FFT protocols in these 7 trials were similar, we suspect that differences between study populations in the polarity of baseline symptoms influenced whether treatment effects were specific to one pole vs the other. Of note, 85% of youths in the present study enrolled while in a depressed state, and treatment effects were primarily for time to depressive episodes.

Contrary to one of our hypotheses, the treatment groups did not differ on the trajectory of mood severity scores during 1 to 4 years of follow-up. Of interest, both groups showed significant mood improvement during the treatment period and 4 months after treatment, followed by a leveling of symptoms (with intermittent fluctuations) for the remainder of the follow-up period (eFigure in Supplement 2). This pattern of immediate symptom improvement followed by a leveling of symptoms has been observed in previous trials of FFT in BD.[12,37-39] The longer-term period of follow-up may be the time when the relevant behavioral skills learned in treatment are consolidated.

The FFT and EC groups did not differ in the rate of conversions to syndromal BD. In secondary analyses, baseline levels of mania and hypomania emerged as the only factors associated with diagnostic conversion. Subthreshold mania symptoms are a key component of risk calculation algorithms for onset of BD in high-risk youths, especially when combined with early indicators of depression, anxiety, and mood instability.[2,7,40-42] In clinical practice, measuring subthreshold manic symptoms can be accomplished with child- and parent-report questionnaires.[43]

Limitations

This trial has limitations. First, the EC condition was matched to the FFT condition in duration (4 months) but not number of sessions (12 vs 6 sessions). Thus, group differences in symptom outcomes could have been attributable to more opportunities for FFT clinicians to observe symptom changes in patients and arrange preventative interventions. Second, although the treatment groups did not differ significantly on time in study, the estimated median follow-up time in the FFT group (114.0 weeks) was numerically longer than that in the EC group (92.5 weeks). We did not find any effects of study site, sex, age, baseline symptoms, or other covariates on time in study, and the treatment effects on time to new mood episode remained significant after controlling for these factors. Moreover, there were no indications that participants in the EC group who were doing well initially were more likely to drop out early. Thus, the pattern of data loss did not appear to be informative in a way that would bias the results in favor of FFT (eResults in Supplement 2).

Third, families in the FFT and EC groups completed the same proportion of protocol therapy sessions (91.7%) and did not differ significantly in rates of treatment discontinuation, reflecting the substantial outreach to families by clinical and research staff. We did not, however, examine whether youths and families in the FFT group developed stronger relationships with their assigned study staff than those in the EC group, leading to longer study participation and perhaps better outcomes. Examining this question would require measuring therapeutic alliance as an intervening variable in the relationship between treatment and clinical outcomes. Such a study is currently underway.[44] Participant attrition should also be examined in community care settings where treatment costs are higher, travel to clinics more expensive, and socioeconomic status more variable than in this study.

In addition, previous trials have shown that FFT is associated with increases in constructive family communication and decreases in criticism or conflict compared with comparison treatments.[45-48] The present study's design did not enable us to examine the temporal relationship between changes in family communication and symptom changes in patients, such as whether (1) incorporating communication skills reduces adversity in family interactions and contributes to symptom regulation in patients or (2) stabilization of symptoms enables patients to downregulate their reactions to critical comments by family members. These questions are important to elucidating the mechanisms by which family interventions are associated with clinical improvements among patients.

Conclusions

Among youths with a family history of BD who show early signs of depression or subthreshold mania or hypomania, mood disorder episodes may be delayed through participation in a

4-month program of FFT. Delaying or preventing episodes of mood disorder may have enduring effects on psychosocial functioning for youths with high-risk syndromes, as well as among parents in terms of the considerable burden of caregiving for a young person with early-onset BD.[4,49]

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