Published in final edited form as:
Am J Psychiatry. 2014 June 1; 171(6): 658–667. doi:10.1176/appi.ajp.2014.13081130.

Pharmacotherapy and Family-Focused Treatment for Adolescents With Bipolar I and II Disorders: A 2-Year Randomized Trial

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Abstract

Objective—Previous studies have found that family-focused treatment is an effective adjunct to pharmacotherapy in stabilizing symptoms in adult bipolar disorder. The authors examined whether pharmacotherapy and family-focused treatment for adolescents with bipolar disorder was more effective than pharmacotherapy and brief psychoeducation (enhanced care) in decreasing time to recovery from a mood episode, increasing time to recurrence, and reducing symptom severity over 2 years.

Method—A total of 145 adolescents (mean age, 15.6 years) with bipolar I or II disorder and a DSM-IV-TR manic, hypomanic, depressive, or mixed episode in the previous 3 months were randomly assigned, with family members, either to pharmacotherapy and family-focused treatment, consisting of psychoeducation (i.e., recognition and early intervention with prodromal symptoms), communication enhancement training, and problem-solving skills training, delivered in 21 sessions over 9 months; or to pharmacotherapy and three weekly sessions of enhanced care (family psychoeducation). Independent evaluators assessed participants at baseline, every 3 months during year 1, and every 6 months during year 2, using weekly ratings of mood.

Results—Twenty-two participants (15.2%) withdrew shortly after randomization. Time to recovery or recurrence and proportion of weeks ill did not differ between the two treatment groups. Secondary analyses revealed that participants in family-focused treatment had less severe manic symptoms during year 2 than did those in enhanced care.

Conclusions—After an illness episode, intensive psychotherapy combined with best-practice pharmacotherapy does not appear to confer advantages over brief psychotherapy and pharmacotherapy in hastening recovery or delaying recurrence among adolescents with bipolar disorder.

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Half to two-thirds of patients with bipolar disorder have their first mood episode before age 18 (1, 2), and pediatric bipolar disorder is highly recurrent. In a longitudinal follow-up of 115 preadolescents with manic or mixed episodes, 73.3% had recurrences over 8 years (3). Early-onset bipolar illness is associated with a high risk of suicide and considerable psychosocial impairment (3–6).

There is increasing evidence in adult and child samples that bipolar depressive and manic symptoms can be alleviated by a combination of pharmacotherapy and psychosocial intervention (7–13). In a 2-year randomized trial (11), we reported that adolescents with bipolar spectrum disorders who received pharmacotherapy and 9 months of family-focused treatment (psychoeducation, communication training, and problem-solving skills training) had more rapid recoveries from depressive symptoms, more time in remission, and less severe depressive symptoms compared with those who received pharmacotherapy and enhanced care (three sessions of family education). Limitations of the trial included a small sample (N=58), inclusion of patients with subthreshold bipolar disorder, and lack of standardization of pharmacotherapy regimens.

The purpose of the present study was to examine the efficacy of family-focused treatment combined with best-practice pharmacotherapy in improving the symptomatic course of bipolar disorder in adolescents. We made several adjustments to the design of our first trial. First, we examined a larger cohort (N=145) of adolescents with bipolar I or II disorder recruited shortly after a manic, hypomanic, depressive, or mixed episode, and we excluded patients with subthreshold bipolar disorder. Second, study physicians implemented a standardized medication protocol supervised by expert pharmacologists. We hypothesized that adolescents receiving pharmacotherapy and family-focused therapy would have a more rapid recovery from an affective episode at study intake (the primary outcome measure), a longer time to recurrence, and less severe mood symptoms over 2 years when compared with adolescents receiving pharmacotherapy and enhanced care.

In two randomized studies of adult patients (12, 13), we observed that benefits from family-focused treatment were most apparent after patients had completed 9 months of active treatment. In the present study, we explored the secondary hypothesis that patients in family-focused treatment would spend less time ill and more time in remission during the year following active treatment than patients in enhanced care.

Method

Participants

The trial was conducted from August 2006 to July 2010 at the University of Colorado, the University of Pittsburgh School of Medicine, and the Cincinnati Children's Hospital Medical Center. Referrals originated from community practitioners, in-patient and outpatient units, advertisements, and presentations or discussion forums. Inclusion criteria were age between 12 years and 18 years, 1 month; a DSM-IV-TR diagnosis of bipolar I or II disorder based on consensus ratings of separate Schedule for Affective Disorders and Schizophrenia for School-Age Children– Present and Lifetime Version (K-SADS-PL) (14, 15) interviews of the youth and at least one parent, with a manic, hypomanic, or mixed episode lasting at least

1 week or a major depressive episode lasting at least 2 weeks within the previous 3 months; a diagnosis of bipolar I or II disorder by a board-certified psychiatrist, based on a separate evaluation of the child and parent(s); symptoms of at least moderate severity (a score ≥17 on the K-SADS Mania Rating Scale [16] or a score ≥16 on the Depression Rating Scale [14, 15]) for at least 1 week of the previous month; willingness to proceed with pharmacotherapy from a study psychiatrist; and at least one parent willing to participate in family sessions. Participants were excluded if they met DSM-IV-TR criteria for current substance use or a pervasive developmental disorder or were victims of current physical or sexual abuse. Youths who were ineligible for the study were referred to appropriate clinical services.

Participants provided written informed consent after receiving a complete description of the study. The study was approved by the human subject review boards of all three institutions.

Diagnostic Evaluation

Participants were prescreened by telephone; those who appeared eligible based on parents' reports were invited for an initial visit in which the K-SADS-PL was administered. The instrument's mood modules were replaced with the K-SADS Mania Rating Scale and Depression Rating Scale, which rate symptoms on 6- or 7-point scales of severity and impairment. Symptom severity was rated for both the most symptomatic week in the past month (baseline rating) and the most symptomatic week in the child's lifetime (see the data supplement that accompanies the online edition of this article). Reliabilities (intraclass r values) across the three sites (12 K-SADS-PL tapes rated by an average of 12 raters each) were 0.89 for Depression Rating Scale scores and 0.81 for Mania Rating Scale scores.

Pharmacological Treatment

Once participants were enrolled in the trial, a data manager at the Pittsburgh site using a modification of Efron's biased coin toss (17) randomly assigned them in a 50-50 proportion to pharmacotherapy plus family-focused treatment or pharmacotherapy plus enhanced care. The groups were balanced on study site, bipolar subtype (I or II), and index episode polarity (depressed, mixed, manic/hypomanic).

Patients in both treatment conditions were pharmacologically managed by board-certified psychiatrists who were supervised monthly by expert pharmacologists (R.A.K., M.P.D., D.A.A.). Pharmacological treatments were standardized using the algorithms of the Child Psychiatric Workgroup on Bipolar Disorder (18) as updated periodically based on literature reviews (e.g., reference 19). The treatment of adolescents in manic, hypomanic, or mixed phases generally began with a second-generation antipsychotic (quetiapine, risperidone, or aripiprazole) or a mood stabilizer (lithium or valproate). Dosages were titrated to clinical response or maximum tolerable dosage. In cases of partial response, treatment was augmented with a combination of a second-generation antipsychotic and a mood stabilizer. Patients with acute bipolar depression had their mood stabilizer and antipsychotic dosages maximized. If they did not respond, a second mood stabilizer (e.g., lamotrigine) or antipsychotic was added (further details are provided in the online data supplement).

Two pharmacotherapy supervisors (D.A.A. and M.P.D.) who were unaware of psychosocial treatment conditions classified 57%–70% of the pharmacotherapy sessions as fully adherent

to the study guidelines, 17%–27% as partially adherent, and 12%–20% as nonadherent (based on 973 ratings across the three sites). Non-adherence often reflected the choices of patients or families regarding specific agents or dosages.

Psychosocial Treatments

Participants in family-focused treatment (patients, parents, and when possible, siblings) were provided 21 family sessions of 50 minutes each over 9 months (12 weekly, then six biweekly, and then every 3 months) in three consecutive modules: psycho-education, communication enhancement training, and problem-solving skills training (see the online data supplement for further descriptions). The three weekly enhanced care sessions were based on an abbreviated version of the family-focused psycho-education manual and focused on monitoring of moods and relapse prevention planning. In both conditions, participants could receive “booster” sessions (i.e., nonprotocol individual or family crisis management) as needed throughout the study.

All clinicians underwent training in both interventions during a 2-day pretrial workshop and received monthly group teleconference supervision during the trial. Treatment fidelity in both conditions was tracked using the 13-item Therapist Competency and Adherence Scale (11, 20). Mean overall fidelity ratings (interrater reliability=0.84), which could range from 1 (nonadherent) to 7 (excellent adherence), did not differ significantly across sites, treatment conditions, or the interaction of sites with treatment conditions (the mean score for the sample was 5.4 [SD=1.3], based on 145 ratings).

Assessment of Outcomes

Independent evaluators who were unaware of treatment assignments interviewed patients and one parent every 3 months during year 1 and every 6 months during year 2 using the Adolescent Longitudinal Interval Follow-up Evaluation (4, 21), with mania/hypomania and major depression assessed on the Psychiatric Status Rating Scales for each week of the previous 13- or 26-week interval. These weekly ratings clarified the timing of recovery (primary outcome) and recurrence events. Cross-site reliability of the 6-point Psychiatric Status Rating Scale scores was 0.74 (intraclass r) for agreement on the highest weekly depression or mania/hypomania scores (see the online data supplement for further details). Evaluators made separate ratings of the worst week of the previous month using the K-SADS Depression and Mania Rating Scale.

Statistical Analysis

We compared the two treatment groups on all demographic, illness history, and medication variables listed in Table 1. Site and pretreatment variables that were imbalanced or that predicted earlier study termination were included as covariates in the statistical models. Time to recovery was calculated as the number of weeks from randomization until weekly Psychiatric Status Rating Scale scores were ≤2 for at least 8 consecutive weeks for depression, mania/hypomania, or both. Time to recurrence was computed as weeks from the point of recovery to the point when the patient had Psychiatric Status Rating Scale scores ≥5 for at least 1 week for mania/hypomania or at least 2 weeks for depression. All randomized patients were included in the at-risk sample; those who did not recover and those who left

the study early were censored at the point of their final research assessment. Survival curves for time to recovery or recurrence were compared across groups using the Kaplan-Meier product-limit equation (22). Cox proportional hazards models (23) were used to control for covariates (site, baseline symptom severity and polarity, and weeks of follow-up, as well as any variables identified in the attrition analyses). With a sample size of 145, a two-sided log-rank test had 90% power to detect a 25% difference in survival proportions, assuming 20% attrition ($p<0.05$).

As in our first trial (11), we compared the groups on proportion of weeks well (weeks with all Psychiatric Status Rating Scale scores ≤2 divided by number of weeks followed) and proportion of weeks depressed (Psychiatric Status Rating Scale depression scores ≥5) or manic/hypomanic (Psychiatric Status Rating Scale mania or hypomania scores ≥5) in each study year. We excluded participants who had ≤6 months of total follow-up. Data were analyzed with mixed-effects models (using Proc Mixed in SAS/ STAT [24]) with time (year 1 or 2) as the within-subject factor, treatment group as the between-subject factor, and a group-by-time interaction, along with baseline covariates and a subject-level random effect to account for correlations between the repeated measurements. With 75 participants per group, the design had >90% power to detect a group-by-time interaction corresponding to a change in effect size of $d=0.56$ ($p<0.05$, two-sided) from baseline to end of study.

Next, to examine more fine-grxained patterns of symptom changes over the 2 years, we fitted analogous mixed models with mean scores for depression or mania/hypomania (on the Psychiatric Status Rating Scale or the K-SADS Depression or Mania Rating Scale), calculated for each 3-month study epoch in months 0–24, as the outcomes. Finally, exploratory general linear mixed models (24) were used to examine whether the groups differed in patterns of medication use (mood stabilizers, second-generation antipsychotics, and antidepressants) over time.

Results

Participants

Participants were 145 adolescents with bipolar I disorder (N=77) or bipolar II disorder (N=68) (mean age, 15.6 years, SD=1.4). A total of 37 patients (25.5%) entered in a bipolar I or II depressed episode, 72 (49.7%) in a manic or hypomanic episode, and 36 (24.8%) in a mixed or sub-threshold mixed (e.g., hypomanic for ≥1 week and depressed for <2 weeks) episode. None of the participants met the DSM-IV-TR course specifier for rapid cycling. The 72 participants in family-focused treatment did not differ significantly from the 73 in enhanced care on any of the variables listed in Table 1. The 145 participants did not differ significantly in sex, age, or race/ethnicity from the 168 screened individuals who were ineligible for the study (Figure 1). (Site differences are explored in the online data supplement.)

Attrition

Of the 145 participants, 123 (84.8%) had at least one follow-up interview. This proportion did not vary significantly across treatment condition, site, sex, bipolar sub-type, or index

episode polarity. However, participants who terminated early had higher baseline K-SADS Mania Rating Scale scores than those who were followed for 2 years (F=5.57, df=1, 143, p=0.02). Participants who lived with both biological parents stayed in the study longer (mean=92.2 weeks, SD=28.3) than those who lived with one biological parent or in another living situation (mean=77.0 weeks, SD=35.9) (F=6.07, df=1, 121, p=0.02). Study site, living situation, baseline K-SADS Mania and Depression Rating Scale scores, and number of weeks of follow-up were included as covariates in the statistical models.

Psychosocial Treatment, Recovery, and Recurrence

During the 2-year study, 87 of the 123 (70.7%) patients for whom follow-up data were available met the 8-week recovery criteria from the index episode; the Kaplan-Meier estimate of cumulative probability of recovery was 87.1% (median time to recovery, 38 weeks, 95% CI=33–46). The 2-year Kaplan-Meier estimate of recovery in family-focused treatment was 85.2% (median time to recovery, 41 weeks, 95% CI=26–54) and in enhanced care, 88.7% (median=36 weeks, 95% CI=25–48; hazard ratio=1.21). In a Cox model that included all covariates, higher baseline K-SADS Depression Rating Scale scores (χ^2=11.37, df=1, p<0.001) and lower Mania Rating Scale scores (χ^2=6.63, df=1, p=0.01) were associated with longer time to recovery; the two treatment arms, however, did not differ in recovery time. (See the online data supplement for survival analyses using a briefer period [≥4 weeks] to define recovery.)

The family-focused treatment and enhanced care groups also did not differ in weeks to recovery from baseline depressive symptoms or from baseline manic/hypomanic symptoms. Furthermore, there was no interaction between treatment group and baseline illness polarity in any time-to-event analysis. Within the mixed (N=36) subgroup, the median time to recovery from the index episode was 42 weeks (95% CI not calculable) for patients in family-focused treatment and 40 weeks (95% CI=23–62) for patients in enhanced care, a nonsignificant difference.

Among the 87 patients who recovered, 50 (57.5%) had a recurrence during the 2-year study. The Kaplan-Meier estimate of cumulative probability of recurrence was 65.1%, with a median time to recurrence of 37 weeks (95% CI=18–55). Of the 50 participants with recurrences, eight had manic, 11 had hypomanic, three had mixed, and 28 had depressive recurrences. Of 39 participants in family-focused treatment who recovered, 25 had recurrences (Kaplan-Meier probability estimate, 74.4%; median time to recurrence, 27 weeks, 95% CI=16–55). Of 48 in enhanced care who recovered, 25 had recurrences (Kaplan-Meier estimate, 58.8%; median time to recurrence, 37 weeks, 95% CI not calculable). In a Cox model that included all demographic and baseline illness scores as covariates, treatment condition was not associated with time to any recurrence, time to depression recurrence, or time to manic or hypomanic recurrence.

Adolescents who lived with both biological parents had a longer time to manic recurrence than those living in another arrangement (χ^2= 3.69, df=1, p=0.05). There were no interactions of treatment group, site, and living situation on time to recovery or recurrence.

Number of Treatment Sessions

Across sites, patients in family-focused treatment attended a mean of 15.4 (SD=7.3) of 21 expected protocol therapy sessions and a mean of 2.0 (SD=5.5) extra (non-protocol) sessions. In enhanced care, patients attended a mean of 2.5 (SD=1.1) of three expected protocol sessions and 0.8 (SD=2.3) nonprotocol sessions. The number of nonprotocol sessions did not differ across treatment conditions or sites. Inclusion of a therapy contact ratio (number of psychosocial contacts to number of expected sessions in each treatment) in the survival models did not alter the null effects of treatment condition on time to recovery or recurrence.

Longitudinal Trajectory of Mood Symptoms

There were no treatment group differences in the percentage of weeks free of mood symptoms (Psychiatric Status Rating Scale scores ≤2) or the percentage of weeks with acute mood symptoms (Psychiatric Status Rating Scale scores ≥5) across study years 1 and 2 (Table 2). There were also no main effects of treatment group or treatment group-by-time (year 1, year 2) interactions on percentage of weeks with depressive symptoms. However, adolescents in family-focused therapy showed a greater increase from year 1 to year 2 in proportion of weeks without mania/ hypomania symptoms compared with those in enhanced care ($F=4.02$, $df=1, 87$, $p=0.048$).

Patients in family-focused treatment did not differ in mean Psychiatric Status Rating Scale scores for depression across the 3-month study epochs. However, patients in family-focused treatment showed greater improvements in mean Psychiatric Status Rating Scale scores for mania/ hypomania across 3-month intervals than did patients in enhanced care ($F=1.98$, $df=8, 742$, $p=0.046$) (Figure 2). This treatment-by-time interaction remained significant when covarying site, baseline K-SADS Mania Rating Scale score, and living situation. There was no treatment-by-baseline K-SADS Mania Rating Scale score interaction on Psychiatric Status Rating Scale scores across the 3-month epochs, and there were no treatment effects or treatment-by-time interactions on K-SADS Depression or Mania Rating Scale scores across the study epochs.

Effects of Comorbid Disorders

Patients with comorbid anxiety disorders (N=57; Table 1) had earlier mood recurrences (median=19 weeks, 95% CI=13–42) than patients without anxiety disorders (median=67 weeks, 95% CI not calculable) ($\chi^2=6.62$, $df=1$, $p=0.01$). Patients with comorbid attention deficit hyper-activity disorder (ADHD) (N=48) had earlier mood recurrences (median=17 weeks, 95% CI=11–25) than patients without ADHD (N=97; median=53 weeks, 95% CI not calculable) ($\chi^2=4.39$, $df=1$, $p=0.04$). In a Cox model that included treatment group, site, living situation, and baseline symptom scores, only concurrent anxiety disorders remained strongly associated with time to mood recurrence ($\chi^2=7.65$, $df=1$, $p=0.006$).

Pharmacotherapy Regimens

The number of pharmacotherapy visits during the trial (mean=11.6, SD=6.9) did not differ between treatment groups and did not predict time to recovery or recurrence. Participants in the two groups did not differ in the mean number of medications prescribed at baseline

(family-focused treatment: mean=2.0, SD=1.0; enhanced care: mean=1.6, SD=0.9) or at the 12-month or 24-month follow-ups (Table 3). The two groups also did not differ in the likelihood of taking lithium (compared with other mood stabilizers), second-generation antipsychotics (considered individually or as a class), or adjunctive antidepressants, psychostimulants, or anxiolytics at any point in the trial, or in having a mood stabilizer or antidepressant added or discontinued (Table 3). When dichotomous variables indicating the presence or absence of each class of medications were included in Cox survival models, no effects emerged for psychosocial treatments on time to recovery or recurrence.

Discussion

In five controlled trials involving adult patients with bipolar I or II disorder (8, 12, 13, 25, 26), family-focused treatment was associated with more rapid recovery from depressive episodes, longer intervals to recurrences, and less severe mood symptoms over 1–2 years than pharmacotherapy and brief psychoeducation (enhanced care) or active clinical management. Unlike in our previous randomized trial of adolescents with bipolar spectrum disorders (11), we observed no differences in adolescents with bipolar I or II disorder between family-focused treatment and enhanced care on time to recovery or severity of mood symptoms over 2 years.

The comparable efficacy of the two treatments did not appear to be due to unique characteristics of this study's population. The 2-year rates of recovery (87%) and recurrence (57.5%) were comparable to the rates observed in the Course and Outcome of Bipolar Youth Study (81.4% and 62.5%, respectively over a mean of 123.7 weeks) (4) and the Geller et al. follow-up study of prepubertal and early adolescents with mania (65% and 55% over 2 years) (27). Compared with the participants in our first adolescent trial, however, those in the present study were more likely to have bipolar II disorder (47% compared with 10%), manic or mixed episodes at intake (65% compared with 26%), and comorbid anxiety disorders (33.1% compared with 3.5%). Although baseline depression severity and comorbid anxiety disorders were independently associated with time to recovery and recurrence, respectively, they did not moderate the efficacy of psychosocial treatments.

There were important design differences between the two trials that may partially explain the different results. In the present study, participants in the three-session enhanced care condition received at least monthly sessions of medication management from study psychiatrists, regular clinical monitoring by an independent evaluator, and booster sessions as needed for 2 years. Enhanced care psychoeducation sessions were closely monitored by supervisors to ensure that fidelity to the clinician manuals was equivalent across sites and conditions. Thus, enhanced care was more regulated than in our first trial and may have been more effective as a result.

Similarly, oversight of pharmacological management was more intensive in this study than in our first study. When the first trial was initiated, there were no published pharmacotherapy guidelines for pediatric bipolar disorder. In the present study, pharmacologists were supervised by experts in the implementation of standardized treatment guidelines (28) and rated for guideline adherence. It is possible that the quality of

pharmacotherapy in this trial limited the degree to which the effects of psychotherapy could be observed over and above medication effects.

A secondary analysis revealed that family-focused treatment was associated with lower mania severity ratings during year 2 of the study and with greater increases from year 1 (active intervention period) to year 2 (follow-up) in the proportion of weeks without mania symptoms. Two previous trials found that differences in outcome between family-focused treatment and comparison conditions became statistically significant only during a posttreatment follow-up (12, 13). The emphasis in family-focused treatment on early recognition of mood changes (see the Patient Perspective) and communication and problem-solving skills may not translate into clinical benefits for patients until families have implemented these strategies during new cycles of illness.

Comparing results of the present trial to those from adult samples raises the question of whether family-focused treatment is developmentally attuned to the needs of adolescents. The emphasis on family relationships may neglect the role of peer and romantic relationships in symptom exacerbation. Adolescents respond with greater emotional intensity to evaluative scrutiny from peers than do children or adults (29). We found in previous work (30) that adolescents with bipolar spectrum disorders who reported higher levels of stress in peer or romantic relationships showed less improvement in family treatment over 12 months. The overall effects of family intervention on the course of adolescent bipolar disorder may be enhanced by a greater focus on skills for managing peer aggression, peer rejection, and relationship stress.

Two secondary findings merit discussion. First, consistent with naturalistic studies of children and adolescents (4) and of adults (31–35), the polarity of the index episode was strongly associated with more severe symptoms of the same polarity at follow-up. As found in adult treatment trials (36), more severe depressive symptoms at intake were associated with longer time to recovery. Thus, in both adults and adolescents with bipolar disorder, fully stabilizing the current episode is an important consideration for effective prophylaxis.

Second, adolescents who lived with both biological parents had a longer time to manic recurrence than those living with one biological parent. An association between having an intact biological family and shorter time to recovery has been observed in children and adolescents with mania (37). It is not clear whether the effects of family structure on outcome can be attributed to genetic factors (i.e., higher genetic load in divorced pairs), stress attributable to custody arrangements or financial difficulties, prior traumatic experiences (e.g., domestic violence; 38), or differences in medication compliance or access to treatment. Nonetheless, clinicians may need to take a more active role in monitoring treatment consistency and response in youths with mood disorders in single-parent families.

Acknowledgments

Dr. Miklowitz has received research funding from NIMH, NARSAD, the Attias Family Foundation, the Danny Alberts Foundation, the Carl and Roberta Deutsch Foundation, the Kayne Family Foundation, and the Knapp Foundation and book royalties from Guilford Press and John Wiley & Sons. Dr. Schneck has received research support from NIMH, the Crown Family Philanthropies, and the Ryan White HIV/ AIDS Treatment Extension Act. Dr. Birmaher has received support from NIMH and has received royalties from Random House, Lippincott

Williams & Wilkins, and UpToDate. Dr. Kowatch has served as a consultant for Forest Pharmaceuticals, AstraZeneca, Sunovion, and the REACH Foundation. Dr. DelBello has served as a consultant or speaker for Bristol-Myers Squibb, Dey, Lundbeck, Otsuka, Pfizer, and Sunovion. The other authors report no financial relationships with commercial interests.

Supported by NIMH grants R01 MH073871 and R34MH077856 to Dr. Miklowitz, grant R01MH073817 to Dr. Axelson, and grant R01MH074033 to Dr. Kowatch.

The authors thank Adrine Biuckians, Jedediah Bopp, Victoria Cosgrove, L. Miriam Dickinson, Dana Elkun, Jessica Lunsford, Chris Hawkey, Zachary Millman, Aimee Sullivan, and Marianne Wamboldt of the University of Colorado for their assistance.

Clinicaltrials.gov identifier: NCT00332098.

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Patient Perspective

"Kristin," a 16-year-old girl with a 2-year history of bipolar I disorder, entered the trial after a severe mixed episode. Her parents explained that her mood episodes were always mixed, characterized by periods of considerable anger and hostility in which she destroyed property, cut herself, and in one case chased her brother with a knife. During those phases, she also slept less, had more energy, and reported a speeding up of her thoughts. Between mood episodes, her mother described Kristin as "sweet" and even-tempered but still prone to "minor rages" when things did not go her way. Family treatment sessions included her two parents, her older brother, and her younger sister. Kristin was able to articulate the stages of her escalation, beginning with a trigger (for example, being teased by her brother), followed by a feeling that "something isn't right." Her father noticed that her speech would become "clipped" and "curt"; he would intervene by attempting to calm her down, but this typically led to further escalation. She would try to calm herself by telling everyone to leave her alone, but she would often slam a door or knock something off of a shelf. At that point, her father would lose his temper and follow her out of the room, calling her derogatory names. At this point, she entered her "red zone," where "I kind of check out" and "I'm no longer responsible for myself."

Psychoeducation sessions focused on what she and the family could do to alter this predictable escalation pattern. Her psychiatrist prescribed an extra dosage of risperidone for intervals in which she felt agitated or easily provoked. She also agreed to track her mood and sleep/wake patterns using a daily mood chart. During a family session, her parents wrote down a set of predictable behaviors that, they agreed, marked the beginning of Kristin's mood escalations. During communication training sessions, Kristin role-played making *positive requests*: asking her father to give her more room when she was upset and requesting that her brother "back off" when she'd had enough teasing. Her father practiced expressing his own frustration with her behavior without becoming provoked. Family members were given homework assignments to practice these skills in real-life situations. Finally, Kristin suggested that at the beginning of an argument, her family members should allow her to "escape to my room" so that she could "scream into my pillow." These options were summarized in a written mood management plan and revisited later in treatment as further mood events occurred.

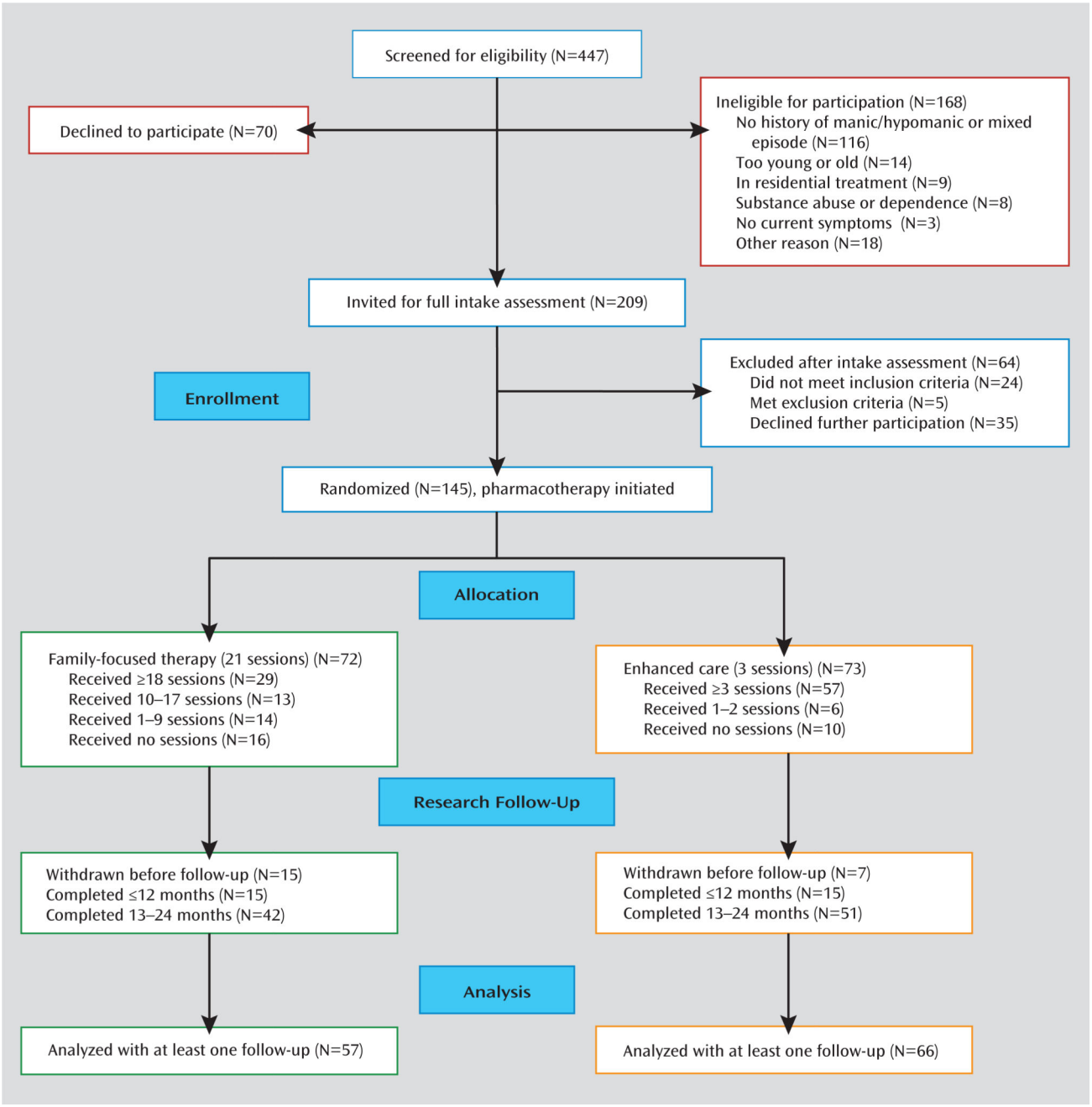

FIGURE 1.

CONSORT Flow Diagram for a 2-Year Randomized Trial in Adolescents With Bipolar I or II Disorder Receiving Pharmacotherapy With Either Family-Focused Treatment or Enhanced Care

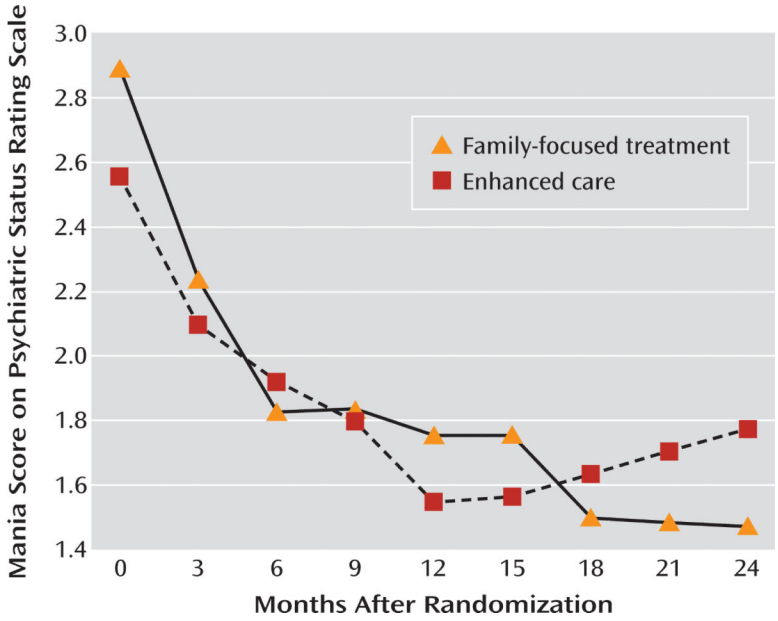

FIGURE 2.

Mania/Hypomania Severity Scores Across Time in Adolescents With Bipolar I or II Disorder Receiving Pharmacotherapy With Either Family-Focused Treatment or Enhanced Care[a]

[a] Weekly Psychiatric Status Rating Scale mania scores were obtained from the Adolescent Longitudinal Interval Follow-Up Evaluation and averaged across 3-month intervals. Family-focused treatment for adolescents (N=72) was associated with lower mean mania/hypomania severity scores than enhanced care (N=73) during year 2 (treatment-by-time interaction, F=1.98, df=8, 742, p=0.046). Means are adjusted for prerandomization Mania Rating Scale scores from the Schedule for Affective Disorders and Schizophrenia for School-Age Children, for study site, and for living situation (with two biological parents or not).

TABLE 1

Demographic and Clinical Characteristics of Adolescents With Bipolar I or II Disorder Receiving Pharmacotherapy With Either Family-Focused Treatment or Enhanced Care

Characteristic[a]	Family-Focused Treatment (N=72)		Enhanced Care (N=73)	
	N	%	N	%
Female	36	50.7	43	58.1
Nonwhite	12	16.9	12	16.2
Hispanic	7	9.7	5	6.8
Lives with both biological parents	23	32.4	27	37.0
Bipolar I disorder	40	55.6	37	50.7
Manic/hypomanic	21	29.2	16	21.0
Depression	8	11.1	10	13.7
Mixed	11	15.3	11	15.1
Bipolar II disorder	32	44.4	36	49.3
Hypomanic	16	22.2	19	26.0
Depressed	9	12.5	10	13.7
Subthreshold mixed[b]	7	9.7	7	9.6
Current comorbid disorders[c]				
Anxiety disorder	27	37.5	30	41.1
Attention deficit hyperactivity disorder	25	34.7	23	31.5
Oppositional defiant or conduct disorder	28	38.9	28	38.4
Study site				
Colorado	26	48.2	28	51.9
Pittsburgh	23	52.3	21	47.7
Cincinnati	23	48.9	24	51.1

	Mean	SD	Mean	SD
Age (years)	15.5	1.4	15.7	1.5
Socioeconomic status (class 1–5)[d]	3.6	1.3	3.7	1.1
Children's Global Assessment Scale score				
Most severe past episode	41.2	7.7	40.8	7.7
Highest in previous year	61.1	8.5	61.2	8.1
Depression Rating Scale score[e]				
Current	24.2	10.7	26.8	10.8
Most serious lifetime	30.4	10.3	32.3	9.7
Mania Rating Scale score[e]				
Current	29.1	12.0	28.3	10.7
Most serious lifetime	32.0	11.4	31.9	9.9
Weeks of follow-up	82.1	34.7	83.1	33.6

[a] No significant difference on any variable between groups or sites, based on Mantel-Haenszel chi-square and two-way analysis of variance tests.

[b] Adolescents with subthreshold mood episodes had at least 1–2 weeks with Psychiatric Status Rating Scale scores of 3 or 4 for mania or depression in the past 3 months, as assessed with the Adolescent Longitudinal Interval Follow-up Evaluation.

[c] Comorbid disorders that were present in less than 10% of participants are not listed.

[d] Higher values indicate higher education and occupation; a value of 3 indicates middle class.

[e] Depression and Mania Rating Scale scores were based on the Schedule for Affective Disorders and Schizophrenia for School-Age Children interview at intake into the study, covering the worst 1–2 week period in the previous 3 months.

TABLE 2

Percent of Weeks in Remission, in Subthreshold States, or in Episode During Study Years 1 and 2 for Adolescents With Bipolar Disorder Receiving Pharmacotherapy With Either Family-Focused Treatment or Enhanced Care[a]

Clinical State	Family-Focused Treatment				Enhanced Care				p		
	Year 1 (N=53)		Year 2 (N=40)		Year 1 (N=58)		Year 2 (N=49)				
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Treatment	Time	Treatment by time
Euthymic	47.1	25.9	56.4	32.0	51.2	27.7	57.6	28.9	0.56	0.01	0.63
Subthreshold mood (depressed or manic/hypomanic)	36.1	20.7	26.3	22.5	33.1	20.8	30.4	24.8	0.90	0.02	0.17
Syndromal mood (depressed or manic/hypomanic)	16.9	12.2	17.0	19.3	15.7	15.0	12.1	12.9	0.19	0.33	0.28
No depressive symptoms	63.0	27.9	63.4	32.0	62.7	29.4	69.1	25.8	0.56	0.25	0.31
Subthreshold depressive symptoms	25.8	21.2	22.1	21.3	25.3	22.5	21.5	20.3	0.89	0.11	0.99
Syndromal depressive episode	11.2	10.5	14.4	19.3	12.0	13.9	9.3	11.7	0.30	0.87	0.07
No manic/hypomanic symptoms	71.7	25.2	85.4	18.9	78.1	21.6	82.4	22.8	0.66	<0.001	0.048
Subthreshold manic/hypomanic symptoms	22.4	21.9	11.5	17.6	17.2	14.9	14.2	22.4	0.70	0.004	0.09
Syndromal manic/hypomanic episode	6.0	8.2	3.0	5.0	4.7	9.1	3.3	6.9	0.69	0.03	0.40

[a]Treatment effects are based on mixed-effects regression models with time (year 1 or 2) as the within-subject factor, treatment group as the between-subject factor, a group-by-time interaction, and a subject-level random effect to account for correlations between the repeated measurements. Covariates included study site, baseline Mania or Depression Rating Scale scores from the Schedule for Affective Disorders and Schizophrenia for School-Age Children, living situation (with two biological parents or not), and number of weeks of follow-up. Means, standard deviations, and p values are adjusted for covariates. Analyses excluded participants who had less than 6 months of follow-up.

TABLE 3

Medications Over Time in Adolescents With Bipolar Disorder Receiving Pharmacotherapy With Either Family-Focused Treatment or Enhanced Care[a]

Medication	Baseline Assessment				12-Month Assessment				24-Month Assessment			
	Family-Focused Treatment (N=72)		Enhanced Care (N=73)		Family-Focused Treatment (N=49)		Enhanced Care (N=52)		Family-Focused Treatment (N=26)		Enhanced Care (N=31)	
	N	%	N	%	N	%	N	%	N	%	N	%
Lithium	15	21	11	15	14	29	12	23	5	19	9	29
Anticonvulsant	23	32	21	29	21	43	25	48	12	46	14	45
Antipsychotic	58	81	58	79	41	84	42	81	20	77	25	81
Antidepressant	21	29	12	16	10	20	9	17	8	31	4	13
Psychostimulant	13	18	10	14	11	22	10	19	6	23	5	16
Anxiolytic	2	3	0	0	3	6	0	0	2	8	1	3
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Number of medications	2.0	1.0	1.6	0.9	2.1	1.0	2.0	0.9	2.2	1.1	2.0	1.1

[a]Antipsychotics included both first- and second-generation agents. Anticonvulsants included valproate, lamotrigine, carbamazepine, oxcarbazepine, and topiramate. There were no differences between the treatment groups or treatment-by-time interactions in the proportion of patients taking each medication or in the mean number of medications per patient.