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Twelve Month Outcome of Adolescents with Bipolar Disorder Following First-Hospitalization
for a Manic or Mixed Episode

Melissa P. DelBello, MD

Thesis, Masters of Science

University of Cincinnati

College of Medicine

Department of Environmental Health

Division of Biostatistics and Epidemiology

Thesis Committee Chair: Rakesh Shukla, PhD

Committee Members: Charles R. Buncher, PhD

Jeffrey Welge, PhD

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ABSTRACT

Objective: Although adolescent-onset bipolar disorder is associated with significant morbidity there have been few prospective outcome studies of this population. The aim of this study was to examine the 12-month outcome of adolescents with bipolar disorder following their initial hospitalization for a manic or mixed episode. **Method:** Bipolar adolescents (N=71) were recruited during their first hospitalization for a manic or mixed episode and were evaluated using diagnostic, symptomatic, and functional assessments. Patients were also evaluated at 1, 4, 8, and 12 months after hospitalization to assess syndromic, symptomatic, and functional outcomes. Predictors of each type of outcome were identified. **Results:** Kaplan-Meier estimates of the cumulative probabilities of syndromal, symptomatic, and functional recovery, and syndromic relapse (in adolescents who experienced syndromal recovery) during the first 12-months following initial hospitalization were 0.86, 0.43, 0.41, and 0.48, respectively. Only 35% of bipolar adolescents reported full medication adherence. Individual predictors of syndromic recovery included the absence of co-occurring attention deficit/hyperactivity disorder (ADHD), anxiety disorders, and disruptive behavior disorders, as well as, full psychotropic medication adherence and higher socioeconomic levels. Treatment with an antidepressant and co-occurring alcohol use disorders predicted syndromic relapse. Boys were more than twice as likely as girls to experience symptomatic recovery. Although no predictors of overall functional recovery were identified, predictors of specific domains of functional recovery were explored. **Conclusions:** Most bipolar adolescents experienced syndromic recovery following first hospitalization. However, rates of symptomatic and functional recoveries were much lower. Future studies examining effective treatment strategies for bipolar youth with co-occurring disorder and

investigating the factors that contribute to the development of substance use disorders and treatment adherence in bipolar youth are necessary to improve outcome.

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TABLE OF CONTENTS

Introduction.....	Pages 2-4
Methods.....	Pages 4-9
Results.....	Pages 9-14
Discussion.....	Pages 14-20
Bibliography.....	Pages 21-26
Table 1.....	Page 27
Figures 1-5.....	Pages 28-33
Other Acknowledgements.....	Page 34

LIST OF TABLES AND FIGURES

Table 1. Demographic and clinical variables at index hospitalization among first-hospitalization manic bipolar adolescents (N=71).

Figure 1. Kaplan-Meier estimate of cumulative probabilities of syndromic, symptomatic and functional recoveries during the initial year following first-hospitalization for a manic episode in adolescents with bipolar disorder (N=71).

Figure 2a. Kaplan-Meier estimate of cumulative probability of syndromic recovery at one-year following first-hospitalization for a manic episode in bipolar adolescents with and without ADHD and who were and were not adherent with their prescribed psychotropic medications.

Figure 2b. Kaplan-Meier estimate of cumulative probability of syndromic recovery in bipolar adolescents with and without an anxiety disorder and with and without a disruptive behavior disorder (DBD).

Figure 3. Kaplan-Meier estimate of cumulative probability of syndromic relapse following initial syndromic recovery from first-hospitalization for a manic episode in adolescents with bipolar disorder.

Figure 4. Kaplan-Meier estimate of cumulative probability of syndromic relapse following syndromic recovery during the initial year following first-hospitalization for a manic episode in bipolar adolescents who were and were not prescribed antidepressants and did and did not have a baseline alcohol use disorder.

Figure 5. Kaplan-Meier estimate of cumulative probability of symptomatic recovery during the initial year following first-hospitalization for a manic episode in bipolar adolescents girls and boys.

INTRODUCTION

Although the onset of bipolar disorder most commonly occurs during adolescence,¹⁻² there have been relatively few naturalistic outcome studies of children and adolescents with bipolar disorder.³⁻¹¹ Prospective studies of clinical samples of bipolar youth have reported recovery and relapse rates that range from 14-100% and 35-70%, respectively, during follow-up periods that varied from six months to four years. In general, studies of longer duration, older adolescents, and outpatient samples report higher recovery rates compared with those of shorter duration, prepubescent and early adolescent subjects, and inpatient samples. For example, follow-up studies of *adolescents* with bipolar disorder report recovery and relapse rates of 96-100% and 44-67%, respectively.⁸⁻¹¹ In contrast, rates of recovery in samples that include *prepubescent* bipolar youth are lower. Specifically, Geller and colleagues reported recovery rates of 14%, 37%, 64%, and 87% after 6-, 12-, 24-, and 48-months of follow-up, respectively, and relapse rates in those who recovered of 38%, 55%, and 70% at 12-, 24-, and 48-month follow-up, respectively, in a sample of prepubescent and early adolescent bipolar youth.⁴⁻⁷ Additionally, prior outcome studies have not used consistent definitions of recovery or relapse, which also may have contributed to the wide range of recovery and relapse rates. For example, Geller et al. defined recovery after one-year of follow-up by “no syndromal DSM-IV mania or hypomania for ≥ 2 weeks”⁵ and after two years of follow-up by “8 consecutive weeks without meeting DSM-IV criteria for mania or hypomania”.⁶ Other investigators included the resolution of depressive symptoms, in addition to manic symptoms, in their definitions of recovery.^{3,9}

In general, outcome studies of bipolar youth have not identified consistent predictors of recovery or relapse.^{3,7,10-11} Some studies report that longer index affective episode,^{3,11} index depressive or mixed episodes (vs. pure manic episodes),¹¹ rapid-cycling,¹¹ psychosis,³⁻⁷ low

maternal warmth,⁴⁻⁷ non-intact biological family,⁴⁻⁷ and low socioeconomic status,³ are associated with poor outcome.

Methodological differences among, and limitations of, prior studies may have contributed to the failure to identify consistent predictors of outcome in prior studies of bipolar youth. First, previous studies have not reported information regarding adherence to medication, despite the strong association found between treatment adherence and high rates of recovery in studies of bipolar adults.¹² Second, although some studies were naturalistic,³⁻⁷ several included a majority of patients who were systematically treated with lithium,^{8-9, 11} limiting the ability to generalize their findings. Third, few studies have included bipolar youth close to their onset of illness^{9, 11} and to our knowledge, no study has examined outcome exclusively in a sample of adolescents hospitalized for their first manic episode. Studying patients early in their illness course permits identification of factors associated with recovery that may be difficult to detect in samples of patients who have had multiple affective episodes, where illness chronicity may become the most significant predictor of outcome.^{3, 12-13} Finally, prior investigations of bipolar youth have not distinguished among syndromic, symptomatic, and functional outcomes, an important step in clarifying unique factors that differentially contribute to specific aspects of recovery.¹² In fact, there has been only one study to examine functional impairment in children and adolescents with bipolar disorder.¹⁴ In this study, compared with healthy controls and children and adolescents with attention-deficit/hyperactivity disorder (ADHD), bipolar youth had significantly greater tension with their parents and impairment in peer relationships and maternal-child warmth. However, this study was cross-sectional and thus the functional outcome of children and adolescents with bipolar disorder remains unknown.

With these considerations in mind, the aim of this study was to investigate the 12-month outcome of adolescents with bipolar disorder following their initial hospitalization for a manic or mixed episode. Specifically, we examined the rates of syndromic, symptomatic, and functional recoveries as well as syndromic relapse. As a secondary aim of this study we examined whether there are distinct predictors of syndromic, symptomatic, and functional outcomes. Based on prior studies of children, adolescents, and adults with bipolar disorder,^{3-7, 11-12, 15-16} we hypothesized that psychosis, socioeconomic status; poor medication adherence, and co-occurring substance use disorders would predict worse outcome in first-hospitalization adolescents with bipolar disorder.

METHODS

Study Participants

Adolescents admitted for their first hospitalization for bipolar disorder, type I, manic or mixed (N=71) were recruited from consecutive inpatient admissions to the Adolescent Psychiatric Unit at Cincinnati Children's Hospital Medical Center between July 1, 1999-December 1, 2003. Patients were included in the study if they were 12 years-17 years 11 months, met DSM-IV criteria for bipolar disorder, type I, currently mixed or manic, and had no prior treatment with anticonvulsant, antidepressant, or antipsychotic medications. Patients who had been treated with psychostimulants were included in order to maximize the generalizability of our findings since many had been treated for presumed pre-existing attention deficit hyperactivity disorder (ADHD). Exclusion criteria for potential subjects were a diagnosis of mental retardation (IQ<70) or a manic or mixed episode resulting entirely from an unstable medical or neurological disorder or acute intoxication or withdrawal from drugs or alcohol, as determined by symptom resolution within 72 hours.

Adolescents provided written assent and their legal guardians provided written informed consent after study procedures were fully explained. This study was approved by the University of Cincinnati and the Cincinnati Children's Hospital Medical Center Institutional Review Boards.

Index Diagnostic and Demographic Assessments

Diagnoses were established using the Washington University at St. Louis Kiddie-Schedule for Affective Disorders and Schizophrenia (WASH-U-KSADS) (17) administered by trained child and adolescent psychiatrists with good diagnostic reliability ($\kappa=0.94$).¹⁸ Adolescents and their primary caregivers were interviewed separately and responses were combined in order to ascertain diagnoses. All diagnoses were reviewed in a conference, attended by the WASH-U-KSADS interviewer and at least one other child and adolescent psychiatrist and from which a consensus diagnosis was made for each patient. The Young Mania Rating Scale (YMRS),¹⁹⁻²⁰ the 17-item Hamilton Depression Rating Scale (HDRS),²¹⁻²² and the Scale for the Assessment of Positive Symptoms (SAPS)²³ were performed at the time of index hospitalization by trained psychiatrists (ICC >0.8 for all ratings scales)¹⁵ to assess severity of manic, depressive, and psychotic symptoms, respectively. Demographic information, including age, sex, and ethnicity, was obtained by interviewing the adolescent and their legal guardian. Socioeconomic status (SES) was ascertained using the 4-factor Hollingshead Scale.²⁴ Age at onset of bipolar disorder was defined as the age at which a DSM-IV affective episode initially occurred and was determined using the WASH-U KSADS, information from medical records, personal recall and/or family corroboration.¹⁸

Index Functional Assessment

Premorbid psychosocial function during the year prior to index hospitalization was assessed using the functional rating scales of the Longitudinal Interval Follow-up Examination (LIFE).²⁵⁻²⁶ The interview occurred near the end of hospitalization and information was obtained from the adolescents, as well as their primary caregivers and medical records. Trained raters with good interrater reliability ($\kappa > 0.75$) evaluated four major areas of functioning: role performance, interpersonal relationships, recreational enjoyment, and sexual activity.²⁶

Outcome Assessments

Patients were reassessed at 1, 4, 8, and 12 months following discharge from the hospital. The outcome assessments have been described elsewhere^{13,25-28} and are based on the NIMH Multi-site Collaborative Study.²⁹ At each follow-up visit, the investigators reviewed affective symptoms during the prior interval, week-by-week, with the adolescent and their primary caregivers. Particular attention was given to periods of changing affective symptoms during the interval, using the methodology of the LIFE. Each follow-up interview included every item of the symptom ratings scales (YMRS, HDRS, SAPS) at each week. Additionally, the affective and psychotic disorders sections of the diagnostic interviews were repeated at each follow-up visit. For each week an overall rating of symptom severity was made based on the scores of the rating and diagnostic instruments using a 0-6 scale: 6=Full syndrome, severe: meets several DSM-IV criteria more than the minimum required for a manic, hypomanic, mixed or major depressive episode; 5=Full syndrome, mild to moderate: meets minimal DSM-IV criteria bipolar disorder required for a manic, hypomanic, mixed or major depressive episode; 4=Marked symptoms: does not meet full affective syndrome criteria, but has several DSM-IV affective syndrome criteria scored greater than mild on the HDRS or YMRS; 3=Partial remission: no DSM-IV affective syndrome criteria are rated greater than mild on the HDRS or YMRS, but total HDRS score >

10, YMRS score > 5 or any SAPS global item score > 2 ; 2=Residual symptoms: one or more mild symptoms, but YMRS ≤ 5 and HDRS ≤ 10 and SAPS global item scores are all ≤ 2 ; 1=Usual self: no significant symptoms.

From these ratings, syndromic and symptomatic recovery and syndromic recurrence were identified and the percent of weeks without symptoms (1 or 2), with subsyndromal symptoms (3 or 4) and with a full syndrome (5 or 6) were calculated.^{12-13, 15, 27-28} Syndromic and symptomatic recoveries and syndromic relapse were defined *a priori* as eight contiguous weeks during which the patient no longer met criteria for a manic, mixed, or depressive episode, operationalized as 8 weeks with a LIFE overall score of ≤ 4 and as eight contiguous weeks during which the patient experienced minimal to no psychiatric symptoms, operationalized as 8 weeks with a LIFE overall score of ≤ 2 , respectively.^{12-13, 15, 27-28} Syndromic relapse was defined by any week during which the patients re-experienced a manic, mixed, hypomanic or depressive episode following syndromic recovery, operationalized as 1 week (2 weeks for depression) with a LIFE overall score of ≥ 5 which occurred any time after 8 weeks of a LIFE overall score of ≤ 2 .^{12,13, 15, 27-28}

Functional recovery was defined based on prior studies by achieving a rating equal to or better than baseline in all four of the areas of functioning on the LIFE for at least 8 contiguous weeks.²⁶ To assess functional recovery, at each follow-up visit the four major areas of function (role performance, interpersonal relationships, recreational enjoyment, and sexual activity) were rated for each 4 week period during the follow-up interval.

Treatment Assessments

This study was naturalistic and therefore the investigators were not involved in treatment decisions for the adolescents. Medications that were prescribed during each follow-up period were reviewed with the adolescents and their primary caregivers. Medical records from treating

clinicians were also obtained as necessary. Treatment adherence for each medication during each interval period was assessed by reviewing weekly medication use with the adolescent, and separately with their primary caregiver. Adherence for each medication was characterized as full adherence (the medication was taken $> 75\%$ of the time as prescribed), non-adherence (the medication was taken $< 25\%$ of the time as prescribed), or partial non-adherence (the medication was taken between 25% and 75% of the time as prescribed). The percent of follow-up in which each patient exhibited each category of adherence was determined for each prescribed psychotropic medication and an average score across medications was used for analyses.¹² Medications were categorized into mood stabilizers (anticonvulsants and lithium), antipsychotics, antidepressants, or psychostimulants.

Statistical Analysis

Statistical analyses were performed using the Statistical Analysis System for the PC, Windows Version 8.02 (SAS Institute, Cary, NC 2003). The cumulative probabilities of syndromal, symptomatic, and functional recovery, as well as syndromic relapse (in adolescents who experienced syndromal recovery) during the first 12-months following initial hospitalization were estimated using the Kaplan-Meier method (30). Based on existing literature, the individual effect of each *a priori* determined potential predictor on each outcome event (syndromic, symptomatic, and functional recoveries and syndromic relapse) and time to each outcome event were evaluated using Kaplan-Meier estimates and Cox proportional hazards modeling (31), respectively. Additionally, using Cox proportional hazards modeling, predictors were entered by stepwise selection if associated with the event at a significance level of $p < 0.1$.

Sex, ethnicity, SES status, baseline alcohol and cannabis use disorders, affective state (manic versus mixed), psychosis, treatment adherence, and treatment with specific classes of

psychotropic medications, as well as co-occurring attention deficit hyperactivity disorder (ADHD), conduct disorder, oppositional defiant disorder, and anxiety disorders were assessed as predictors of each of the four outcome variables (syndromic, symptomatic, and functional recovery and syndromic relapse). The results of all analyses were unchanged by combining co-occurring oppositional defiant disorder or conduct disorder into one predictor variable called disruptive behavior disorders (DBD). All independent variables were examined to ensure that they met the proportional hazards assumption, and none exhibited statistically significant deviation from this assumption. Adjusted hazard ratios and their 95% confidence intervals were calculated for each predictor for each outcome variable. Other statistical analyses were performed as necessary.

RESULTS

Baseline Demographic and Clinical Characteristics

The demographic and clinical variables at initial hospitalization for all adolescents are listed in Table 1. Additional clinical characteristics of the sample are described below. The index hospitalization was the result of the initial affective episode in 60 (85%) of the adolescents. However, eleven (15%) of the adolescents had a prior episode of major depression for which they had not received psychotropic medications or been hospitalized. The mean (SD) duration of the index affective episode was 29 (31) weeks. Mood incongruent psychosis was present in half of the adolescents with psychosis (15/29, 52%). Nine (13%) adolescents had a co-occurring substance use disorder (either abuse or dependence) at initial hospitalization. Of the nine adolescents with a substance use disorder, 2 (22%) were diagnosed with polysubstance dependence, 3 (33%) with a cannabis use disorder only, and 4 (44%) with an alcohol use disorder only. Twenty-one (30%) of the adolescents were also diagnosed with co-occurring

conduct disorder (CD), 33 (46%) with oppositional defiant disorder (ODD), and 36 (51%) with CD, ODD, or both (any disruptive behavior disorder, DBD).

Sixty-two of the 71 (87%) adolescents were interviewed at all follow-up intervals. There were no statistically significant differences in demographic, clinical, or outcome variables between patients with (N=62) and without (N=9) 12 months of follow-up ($p>0.1$). Of the subjects who did not complete all 12 months of follow-up, most (7/9, 78%) completed at least 8 months and all had at least one follow-up interview.

Pharmacological Treatment and Adherence

During the initial year following first hospitalization for mania, 42 (59%) of the adolescents were treated with at least one mood stabilizer, 47 (66%) with an atypical antipsychotic, 24 (34%) with an antidepressant, and 19 (27%) with a psychostimulant. Twenty-five (35%) of the adolescents reported full adherence, 30 (42%) reported partial adherence, and 16 (23%) reported non-adherence. Similar to the findings of prior studies of bipolar adults, the results of all analyses were unchanged by combining the partially adherent and non-adherent groups into a non-adherent group (taking psychotropic medication $\leq 75\%$ of the time as prescribed).¹²

Logistic regression analyses revealed that co-occurring ADHD [$F(1,70)=9.7$, $p=0.003$] and low SES level [$F(1,70)=4.5$, $p=0.04$] were associated with medication non-adherence. Specifically, bipolar adolescents without co-occurring ADHD were more likely to be adherent to their medications than bipolar adolescents with ADHD [20 (50%) vs. 5 (16%), $\chi^2=8.9$ $df=1$, $p=0.003$]. SES level was significantly higher in bipolar adolescents who were medication adherent compared with those who were partially or non-adherent to medications [mean (SD)=3.1 (3.0) vs. 2.1 (2.0), $t=-2.1$, $p=0.04$]. There was also a non-statistically significant trend

for an association between baseline alcohol use disorders and medication non-adherence.

Specifically, none of the adolescents with an alcohol use disorder (N=6) were fully adherent to their medications as compared to 25 (38%) of the adolescents without an alcohol use disorder (N=65, $\chi^2=3.8$, $df=1$, $p=0.06$). There were no statistically significant associations among any class of medications prescribed during the initial year following hospitalization and medication adherence [$F(1,36)=0.96$, $p=0.3$].

Syndromic Recovery and Relapse

Sixty (85%) of the 71 adolescents had a syndromic recovery from the index affective episode during the first year following initial hospitalization. The Kaplan-Meier estimate of cumulative probability of syndromic recovery during the first year was 0.86 [95% confidence interval (CI)=0.78-0.94], with a mean (SD) time to syndromic recovery of 20 (13) weeks (Figure 1).

Estimates using Kaplan-Meier analyses revealed that the absence of an anxiety disorder (log-rank $\chi^2=6.3$, $df=1$, $p=0.01$), a disruptive behavior disorder (log-rank $\chi^2=7.1$, $df=1$, $p=0.007$), and ADHD (log-rank $\chi^2=13$, $df=1$, $p=0.0003$), as well as full adherence with prescribed medications (log-rank $\chi^2=3.8$, $df=1$, $p=0.05$) were significantly associated with syndromic recovery within the initial year following first hospitalization for mania (Figures 2a and 2b). Furthermore, Cox regression analysis revealed that the absence of ADHD (hazard ratio=2.4, 95% CI=1.4-4.0, $\chi^2=9.8$, $df=1$, $p=0.002$), full adherence (hazard ratio=1.7, 95% CI=1.0-2.9, $\chi^2=4.2$, $df=1$, $p=0.04$), and higher SES level (hazard ratio=1.2, 95% CI=1.0-1.3, $\chi^2=4.6$, $df=1$, $p=0.002$) were associated with shorter time to syndromic recovery. ADHD was the only predictor that remained statistically significantly associated with syndromic recovery in the stepwise Cox regression analysis ($p<0.02$) as well as in regression models examining the effect of ADHD and

medication adherence, ADHD and SES level, and ADHD, medication adherence, and SES level on syndromic recovery ($p < 0.02$, hazard ratios=1.8-1.9, CI=1.01-1.10 to 3.23-3.33) (Figures 2a and 2b).

Of the 60 adolescents who had syndromic recovery, 28 (47%) had at least one syndromic relapse within the first year following initial hospitalization. The Kaplan-Meier estimate of cumulative probability of syndromic relapse following syndromic recovery during the first year of follow-up was 0.48 (95% confidence CI=0.38-0.66), with a mean (SD) time to syndromic relapse of 41 (8) weeks (Figure 3). Kaplan-Meier estimates revealed that treatment with an antidepressant (log-rank $\chi^2=4.0$, $df=1$, $p=0.04$) and a co-occurring alcohol use disorder (log-rank $\chi^2=3.7$, $df=1$, $p=0.05$) were associated with syndromic relapse (Figure 4). Using Cox regression analyses, there were no statistically significant predictors of time to syndromic relapse.

Symptomatic Recovery

During the initial year of follow-up, bipolar adolescents spent 38% of the time with an affective episode (of which 63% was spent with a mixed episode, 22% with mania or hypomanic, and 15% with depression), 46% of the time with subsyndromal symptoms, and only 16% of the time asymptomatic. Twenty-eight (39%) of the 71 adolescents achieved symptomatic recovery during the initial year following first hospitalization for mania. The Kaplan-Meier estimate of cumulative probability of symptomatic recovery during the first year of follow-up was 0.43 (95% confidence CI=0.31-0.55), with a mean (SD) time to symptomatic recovery of 35 (13) weeks (Figure 1, because of definitions in outcome measures there are no effects on figures during the initial 8 weeks). Kaplan-Meier estimates revealed that boys had a greater cumulative probability of recovery as compared to girls (log-rank $\chi^2 = 4.4$, $df=1$, $p=0.03$) (Figure 5). Specifically, 29% of the girls as compared to 53% of the boys had symptomatic recovery

($\chi^2=4.2$, $df=1$, $p=0.04$). Moreover, Cox regression analysis revealed that boys had a shorter time to symptomatic recovery than girls (hazard ratio=2.2, 95% CI=1.1-4.7, $\chi^2=4.3$, $df=1$, $p=0.04$).

Functional Recovery

Twenty-eight (39%) of the 71 adolescents achieved functional recovery during the initial 12-months following first hospitalization for mania. The Kaplan-Meier estimate of cumulative probability of functional recovery during the first 12-months of follow-up was 0.41 (95% CI=0.29-0.53), with a mean (SD) time to functional recovery of 38 (16) weeks (Figure 1). Kaplan-Meier estimates and Cox regression analyses revealed no statistically significant predictors of functional recovery (smallest p value=0.16 for ADHD, greatest hazard ratio= 1.7, 95% CI=0.85-3.3 for ADHD).

However, examination of each of the individual subscales of functional recovery revealed that Kaplan-Meier estimate of cumulative probability of recovery was 0.97 [95% CI=0.93-1.0, mean (SD) time= 11 (8) weeks] for sexual activity, 0.92 [95% CI=0.84-0.98, mean (SD) time= 17 (13) weeks] for role performance, 0.80 [95% CI=0.71-0.89, mean (SD) time= 20 (16) weeks] for recreational enjoyment, and 0.73 [95% CI=0.62-0.84, mean (SD) time= 24(18) weeks] for interpersonal relationships. Kaplan-Meier estimates revealed that bipolar adolescents without co-occurring ADHD ($\chi^2=4.4$, $df=1$, $p=0.04$, Cox regression hazard ratio= 2.0, 95% CI= 1.2-3.3 , $p=0.01$) or DBD ($\chi^2=3.8$, $df=1$, $p=0.05$, Cox regression hazard ratio=1.8, 95% CI=1.1-2.9, $p=0.03$) were more likely to achieve recovery in the area of role performance, bipolar adolescents who were not prescribed stimulants ($\chi^2=4.0$, $df=1$, $p=0.04$, Cox regression hazard ratio=1.9, 95% CI=0.93-3.6, $p=0.08$) were more likely to achieve recovery in the area of interpersonal relationships, and bipolar adolescents who were younger (Cox regression hazard ratio=1.2, 95% CI=1.0-1.4, $\chi^2=4.3$, $df=1$, $p=0.04$) were more likely to achieve recovery in the area of

recreational enjoyment.

There were no statistically significant differences between the rate of functional recovery between adolescents who did (25/60, 42%) and did not (3/11, 27%) have syndromic recovery ($\chi^2=0.8$, $df=1$, $p=0.37$), nor between the rate of functional recovery between adolescents who did (14/28, 50%) and did not (14/43, 33%) have symptomatic recovery ($\chi^2=2.2$, $df=1$, $p=0.14$), although the estimated proportions show interesting differences. .

DISCUSSION

To our knowledge, this is the first report to examine the illness course of bipolar adolescents following their initial manic or mixed episode. Consistent with the findings of most,^{3, 8-9, 11} but not all⁴⁻⁷ prior outcome studies of bipolar adolescents, the results of our study indicate that a large majority (85%) of bipolar adolescents experienced syndromic recovery during the initial 12 months following their first manic or mixed episode. Although prior outcome studies of bipolar youth have not limited inclusion to first-episode patients, in general, syndromic recovery rates are greater in studies that included more first-episode patients (8-11) than in studies which had fewer first episode patients (3-7) implying that illness duration may be a negative predictor of outcome.

Similar to prior studies,^{3, 10-11} we found that 45% of bipolar adolescents who experienced syndromic recovery had a syndromic relapse within 12 months. However, this relapse rate is greater than that reported in another 12-month outcome study of bipolar youth,⁵ prompting one suggestion that our sample of hospitalized adolescents may be more severely ill than the other sample, which was of outpatients. Alternatively, other factors, such as the relatively higher rates of substance use reported in our sample may have contributed to the greater relapse rate.

Despite the high rate of syndromic recovery in our study, a majority of the adolescents

did not experience symptomatic (61%) or functional (61%) recovery, particularly in the area of interpersonal relationships. Furthermore, we found that only 20% of bipolar adolescents experienced all three types of recovery, indicating that most bipolar adolescents continued to have impairment in at least one domain during the first year following initial hospitalization. These results also emphasize the importance of assessing symptomatic and functional recoveries in outcome studies of bipolar youth. However, most prior outcome studies of bipolar youth have exclusively examined syndromic recovery and relapse.

In a recent outcome study of bipolar youth, Birmaher and colleagues³ compared their findings to an outcome study of bipolar adults that used comparable methodology,³² and concluded that bipolar youth have a more severe illness course. Comparison between the results of our study and those of similar studies of bipolar adults revealed conflicting findings.^{12, 16} Specifically, Tohen and colleagues reported that within two years following initial hospitalization for a manic episode, 98% of bipolar adults experienced syndromic recovery, 72% experienced symptomatic recovery, and 43% experienced functional recovery.¹⁶ These results suggest that bipolar adolescents may have lower rates of syndromic and symptomatic recovery than adults. Indeed, we also found that bipolar adolescents spent only 16% of the time asymptomatic, compared with bipolar adults who were found to be asymptomatic during 53% of the follow-up period in an outcome study.³² Alternatively, the longer duration of the adult study¹⁶ likely contributed to the higher recovery rates.

In contrast, Keck and colleagues reported that during the 12 months following hospitalization for a manic episode only 48% of adults experienced syndromic recovery, 26% experienced symptomatic recovery, and 24% experienced functional recovery. However, in this study patients were not excluded for having prior manic or mixed episodes.¹² Together, these

studies provide additional support that longer illness duration may be a negative predictor of outcome in bipolar patients.^{12, 16} Indeed, Birmaher and colleagues found that for every year of illness, bipolar youth had a 10% lower likelihood of recovery.³

The effects of treatment adherence on outcome in bipolar youth are largely unknown. Recently, in one of the only published studies to examine treatment adherence, Coletti and colleagues found that 34% of bipolar adolescents reported full medication adherence during a 1-month assessment period.³³ This study also reported that patients with optimal medication adherence were diagnosed more recently (1.06 years) than those who had missed one or more medication doses (3.12 years). The authors concluded that early in illness course bipolar adolescents may be more treatment adherent than later in illness course.³³ However, despite using a more lenient definition for full medication adherence (taking psychotropic medication as prescribed >75% of the time) than Coletti and colleagues, the findings from our study did not support this premise. In fact, we found that only 35% of first-episode manic bipolar adolescents reported full psychotropic medication adherence during the follow-up period, indicating that self-report non-adherence rates for bipolar adolescent are high, even early in illness course. Factors associated with poor medication adherence included co-occurring ADHD or alcohol use disorders and low family SES levels. Although our study can not determine the causal relationships amongst these factors, we speculate that patients with ADHD are more likely to forget to take their medications and patients in families of lower SES levels may have limited access to prescribed medications. Prior studies have identified an association between substance use disorders and medication adherence in bipolar adults.¹² However, the causal relationship between these variables remains unknown. Specifically, prior studies have been unable to determine whether bipolar patients with substance use disorders were more likely to become

non-adherent to medications or whether bipolar patients who are medication non-adherent are more likely to subsequently develop substance use disorders. Our finding of higher non-adherence in first episode manic adolescents who were diagnosed with an alcohol use disorder at baseline suggests that alcohol use may be a risk factor for poor medication adherence in bipolar adolescents.

In general, distinct predictors were associated with each of the outcome measures. Specifically, higher SES level and medication adherence, as well as the absence of co-occurring ADHD, anxiety disorders, and disruptive behavior disorders were associated with syndromic recovery. After controlling for the other predictors, ADHD was the only risk factor that remained significantly associated with longer time to syndromic recovery. However, we were unable to determine the independent effects of poor medication adherence, SES level, and ADHD because of the high colinearity among these risk factors. *Post-hoc* exploratory analyses of the associations among these factors suggests that independent of ADHD status, medication adherence had a greater impact on time to syndromic recovery in bipolar adolescents of higher SES levels (11 vs. 17 weeks in bipolar adolescents without ADHD and with and without medication adherence, respectively and 21 vs. 31 weeks in bipolar adolescents with ADHD and with and without medication adherence, respectively) than in those of lower SES levels (17 vs. 18 weeks in bipolar adolescents without ADHD and with and without medication adherence, respectively and 27 vs. 31 weeks in bipolar adolescents with ADHD and with and without medication adherence). Although additional studies are needed, these findings imply that the quality of care varies among bipolar adolescents of different SES levels.

Consistent with outcome studies of bipolar adults^{12, 15, 34-35} we found that alcohol use was associated with a greater risk of relapse, highlighting the importance of educating adolescents

with bipolar disorder about the negative impact of substance use on illness outcome.

Additionally, these findings stress the importance of developing effective treatment strategies for adolescents with co-occurring bipolar and substance use disorders.

Although treatment in this study was naturalistic, our data suggest that antidepressants and psychostimulants may be associated with greater syndromic relapse and poorer recovery of interpersonal relationships, respectively. Prior studies have described the negative impact of antidepressants and psychostimulants on illness course in bipolar youth.^{18, 36} However, other studies have reported that, in combination with mood stabilizers, antidepressants and psychostimulants may be useful for the treatment of bipolar youth.³⁷⁻³⁹

Recently, Birmaher and colleagues reported that bipolar girls have poorer outcomes than bipolar boys. Consistent with this, we found that boys were twice as likely as girls to experience symptomatic recovery. Future studies are needed to confirm these results and examine whether gender differences in treatments, medication adherence, co-occurring psychiatric disorders, and other clinical characteristics may contribute to these findings.

Inconsistent with prior studies of bipolar youth,^{3, 7} our results did not reveal that psychosis was predictive of any outcome measure. A possible explanation for this finding is that psychosis has been a marker of illness severity in prior studies that have included samples of both inpatients and outpatients. In contrast, our sample was recruited exclusively from an inpatient setting and therefore, the patients may have been more severely ill than those of prior studies.

In summary, our findings indicate that adolescent-onset bipolar disorder is associated with high rates of co-occurring psychiatric disorders, poor medication adherence and persistent affective symptoms and functional impairment. However, there are several limitations that

should be considered when interpreting the results of our study. First, our sample was recruited from a single inpatient site, which may limit the ability to generalize our findings. Second, although our study is a prospective study, adolescents and their family members were separately interviewed retrospectively at each follow-up visit which might have limited their ability to accurately recall mood symptoms. However, in order to improve the accuracy of the information obtained, subjects and their primary caregivers were each interviewed, interviews were performed frequently (at 1-, 4-, 8- and 12-month), and all subjects were reminded of anchor time points (i.e. holidays, birthdays, and school events) that occurred during each follow-up period. Third, although our study is the first to assess treatment adherence as a predictor of outcome in bipolar youth, we based adherence ratings on patient reports and independent information ascertained from their family members. Measurement of serum concentrations of prescribed medications may be a more valid method for assessing medication adherence. Fourth, we used first hospitalization for mania as a proxy for illness onset. However, some of the patients in our study had prior untreated depressive episodes. Despite these limitations, our findings suggest that most adolescents with bipolar disorder will experience poor outcome following their initial manic episode and in general, that specific outcome measures are associated with distinct predictors. Future studies of longer duration are needed to determine whether adolescents with bipolar disorder ultimately progress into adults with bipolar disorder.

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Table 1. Demographic and clinical variables at index hospitalization among first-hospitalization manic bipolar adolescents (N=71).

Variable	Bipolar adolescents (N=71)	
Age, mean (SD), years	15.2	(1.9)
Socioeconomic status (SES), mean (SD)	3.3	(1.7)
Age at onset, mean (SD), years	13.5	(10.9)
Sex, females, N (%)	41	(58)
Ethnicity, Caucasian, N (%)	54	(76)
Psychosis, N (%)	29	(41)
Mood incongruent psychosis, N (%)	15	(21)
Mixed (vs. manic) episode, N (%)	52	(73)
Co-occurring Diagnoses		
Attention deficit hyperactivity disorder, N (%)	31	(44)
Disruptive behavior disorder, N (%)	36	(51)
Anxiety disorder, N (%)	16	(23)
Alcohol use disorder, N (%)	6	(8)
Cannabis use disorder, N (%)	5	(7)
Rating Scales		
Hamilton Depression Rating Scale, mean (SD)	17.2	(6.5)
Young Mania Rating Scale, mean (SD)	28.0	(7.6)
Scale for the Assessment of Positive Symptoms, mean (SD)		
Hallucinations	1.2	(1.7)
Delusions	1.7	(1.6)
Bizarre behavior	1.1	(1.5)
Thought disorder	0.8	(1.2)

Figure 1. Kaplan-Meier estimate of cumulative probabilities of syndromic [cumulative probability=0.86, 95% confidence interval (CI)=0.78-0.94], symptomatic (cumulative probability=0.43, 95% confidence CI=0.31-0.55) and functional (cumulative probability=0.41, 95% CI=0.29-0.53) recoveries during the initial year following first-hospitalization for a manic episode in adolescents with bipolar disorder (N=71).

Number remaining without recovery:

Syndromic	71	..	71	...	44	...	39	...	33	...	27	...	24	...	16	..	15	..	14	...	12	...	9	...	9	...	7
Symptomatic	71	..	71	...	65	...	63	...	59	...	54	...	53	...	46	..	43	..	36	...	34	...	32	...	32	...	32
Functional	71	..	71	...	63	...	59	...	57	...	56	...	51	...	51	..	45	..	44	...	42	...	40	...	37	...	37

X=censored data

Figure 2a. Kaplan-Meier estimate of cumulative probability of syndromic recovery at one-year following first-hospitalization for a manic episode in bipolar adolescents with (N=31, cumulative probability=0.75, 95% CI=0.61-0.91) and without (N=40, cumulative probability=0.95, 95% CI=0.87-1.0) ADHD and who were (N=25, cumulative probability=0.95, 95% CI=0.86-1.0) and were not (N=46, cumulative probability=0.83, 95% CI=0.71-0.94) adherent with their prescribed psychotropic medications.

Number remaining without syndromic recovery:

No ADHD	40	...	40	...	17	...	15	...	12	...	10	...	9	...	4	...	4	...	4	...	4	...	2	...	2	...	1
ADHD	31	...	31	...	27	...	24	...	21	...	17	...	15	...	12	...	11	...	10	...	8	...	7	...	7	...	6
Non-adherent	46	...	46	...	33	...	30	...	25	...	20	...	18	...	12	...	12	...	12	...	10	...	8	...	8	...	7
Adherent	25	...	25	...	11	...	9	...	8	...	7	...	6	...	4	...	3	...	3	...	2	...	2	...	1	...	0

X=censored data

Figure 2b. Kaplan-Meier estimate of cumulative probability of syndromic recovery at one-year following first hospitalization for a manic episode in bipolar adolescents with (N=16, cumulative probability=0.79, 95% CI=0.57-1.0) and without (N=55, cumulative probability=0.89, 95% CI=0.78-0.94) an anxiety disorder and with (n=36, cumulative probability=0.85, 95% CI=0.73-0.97) and without (N=35, cumulative probability=0.87, 95% CI=0.75-0.99) a disruptive behavior disorder (DBD).

Number remaining without syndromic recovery:

No anxiety d/o	55	...	55	...	29	...	25	...	21	...	18	...	16	...	11	...	11	...	10	...	9	...	6	...	6	...	5		
Anxiety d/o	16	...	16	...	15	...	14	...	12	...	9	...	8	...	5	...	4	...	4	...	3	...	3	...	3	...	2		
No DBD	35	...	35	...	15	...	12	...	11	...	9	...	8	...	6	...	6	...	6	...	6	...	6	...	4	...	4	...	3
DBD	36	...	36	...	29	...	27	...	22	...	18	...	16	...	10	...	9	...	8	...	6	...	5	...	5	...	4		

X=censored data

Figure 3. Kaplan-Meier estimate of cumulative probability of syndromic relapse following initial syndromic recovery from first-hospitalization for a manic episode in adolescents with bipolar disorder (N=60) (cumulative probability=0.48, 95% confidence CI=0.38-0.66).

Number remaining without syndromic relapse:

60...60...60...59...56...52...49...46...44...36...30...26...25...23

X=censored data

Figure 4. Kaplan-Meier estimate of cumulative probability of syndromic relapse following syndromic recovery during the initial year following first-hospitalization for a manic episode in bipolar adolescents who were (N=16, cumulative probability=0.14, 95% CI=0-0.32) and were not (N=44, cumulative probability=0.34, 95% CI=0.20-0.48) prescribed antidepressants and did (N=6, cumulative probability=0.17, 95% CI=0-0.47) and did not (N=54, cumulative probability=0.59, 95% CI=0.45-0.73) have a baseline alcohol use disorder.

Number remaining without syndromic relapse:

No antidepressants	44	...	44	...	44	...	43	...	41	...	39	...	37	...	35	...	35	...	28	...	24	...	20	...	20	...	18
Antidepressants	16	...	16	...	16	...	16	...	15	...	13	...	12	...	11	...	9	...	8	...	6	...	6	...	5	...	5
No alcohol d/o	54	...	54	...	54	...	53	...	51	...	49	...	47	...	44	...	43	...	39	...	35	...	34	...	32	...	28
Alcohol d/o	6	...	6	...	6	...	6	...	6	...	6	...	5	...	5	...	4	...	4	...	3	...	1	...	1	...	1

X=censored data

Figure 5. Kaplan-Meier estimate of cumulative probability of symptomatic recovery during the initial year following first-hospitalization for a manic episode in bipolar adolescents girls (N=41, cumulative probability=0.32, 95% CI=0.17-0.47) and boys (N=30, cumulative probability=0.57, 95% CI=0.39-0.75).

Number remaining without symptomatic recovery:

Boys	30 . . . 30 . . . 27 . . . 25 . . . 22 . . . 20 . . . 20 . . . 15 . . . 14 . . . 12 . . . 12 . . . 11 . . . 11 . . . 11
Girls	41 . . . 41 . . . 38 . . . 38 . . . 37 . . . 34 . . . 33 . . . 31 . . . 29 . . . 24 . . . 22 . . . 21 . . . 21 . . . 21

X=censored data

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