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The Influence of Comorbid Disorders on the Episodicity of Bipolar Disorder in Youth

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Abstract

Objective—Bipolar Disorder (BP) frequently co-occurs with other psychiatric disorders. We examine whether course of anxiety disorders (ANX), attention deficit hyperactivity disorder (ADHD), disruptive behavior disorders (DBD), and substance use disorders (SUD) influence likelihood of recovery and recurrence of depression and mania in BP youth.

Method—Weekly ratings of psychiatric disorder intensity were obtained from 413 participants of the Course and Outcome of BP Youth project, followed for an average of 7.75 years. Multiple-event Cox proportional hazards regression analyses examined worsening of comorbid disorders as predictors of mood episode recovery and recurrence.

Results—Increased severity in ANX and SUD predicted longer time to recovery and less time to next depressive episode, and less time to next manic episode. Multivariate models with ANX and SUD found that significant effects of ANX remained, but SUD only predicted longer time to

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Declaration of interests

Doctors Yen, Stout, Weinstock, Topor, Dickstein, Ryan, Sala, Axelson, Heather Hower, Matthew Killam, and Mary Kay Gill report no conflicts of interest.

depression recovery. Increased severity of ADHD and DBD predicted shorter time to recurrence for depressive and manic episodes.

Conclusion—There are significant time-varying relationships between the course of comorbid disorders and episodicity of depression and mania in BP youth. Worsening of comorbid conditions may present as a precursor to mood episode recurrence or warn of mood episode protraction.

Keywords

Bipolar Disorder; comorbidity; child and adolescent psychiatry

Introduction

It is well known that the course of bipolar disorder (BP) can fluctuate widely. Although most patients recover from initial episodes, they remain at substantial risk for later recurrences. This same pattern has been documented in pediatric age patients with BP as well (1-4). In the Course and Outcome of Bipolar Youth (COBY) project, the authors observed previously that nearly 82% of BP youth participants had recovered fully from their index mood episode within 2.5 years of follow-up, with nearly 63% having a syndromal recurrence within 1.5 years of episode offset (4). Recently published data using additional years of follow-up reveals four predominant trajectories of mood episode course with 76% of COBY participants reporting some syndromal mood symptoms over 7+ years follow-up (5). Thus, understanding factors that may contribute to variable course and outcome in this high risk population is important.

As with descriptive studies of comorbidity in adult BP (6, 7) a wide spectrum of non-affective disorders accompany BP in children and adolescents. In the COBY sample at intake, 59.8% of youth were diagnosed with attention deficit hyperactivity disorder (ADHD), 39.5% with oppositional defiant disorder (ODD), 39% with one or more anxiety disorders (ANX), 12.8% with conduct disorder (CD), and 9.1% with one or more substance use disorders (SUD) (8). These rates are generally consistent with, though somewhat lower than, those reported in numerous other studies of pediatric BPs (9-17). While the occurrence of these commordities is widely established, their impact on the disease course has been minimally studied, and none have examined the proximal, time-varying effect of these comorbidities on BP course.

Longitudinal studies on the impact of ANX on BP have been limited by their operationalization of ANX as a lifetime, static variable. A prior report from COBY (18) showed that among participants with at least one ANX at intake or present during follow-up, mean time to depression was lengthened and risk of recurrence was increased over an average of 5 years follow-up. However, this study did not address the proximal effects of ANX on BP mood episodes. In adult studies, ANXs at intake were associated with decreased likelihood of recovery from depressive symptoms, greater illness severity, less time euthymic, poorer functioning and quality of life, as well as a greater likelihood of suicide attempts over follow-up, increased risk of substance abuse, and poor response to treatment (19-24).Results from the Collaborative Depression Study (CDS), which followed participants for 17 years, indicate that baseline ratings of ANX severity, rather than lifetime

comorbidity, was associated with more time in depressive episodes; CDS observed no association between ANX severity and mania/hypomania (25). Importantly, extant studies have examined ANX as a static risk factor; none have examined ANX as a time-varying longitudinal risk factor, in which change in ANX is probed for its potential to have a proximal effect on BP. Longitudinal time-varying analyses provide information about proximal risk and therefore are more likely to provide clinically useful findings than static or lifetime predictor based analyses.

Fewer studies have examined effects of comorbid ADHD or Disruptive Behavior Disorder [(DBD) comprised of ODD and CD] in BP youth longitudinally. In five studies of pediatric BP (2, 15, 26-28), lifetime comorbidity with ADHD was associated with a primarily irritable presentation of mania, greater illness persistence, and poorer psychosocial functioning. As with studies of comorbid ANX, none have examined longitudinal time-varying associations.

While the relationship between SUD and BP course has been studied, the results on the whole have not been consistent. Some studies have reported that SUD was associated with greater BP symptom persistence and a variety of indicators of a more pernicious outcome (29-33), while others found that SUD had no major influence on BP outcomes (34, 35). Some of these studies examined this association for more proximal effects, such as of alcohol or substance use on mood episodes, but here too the field is presented with mixed findings largely based on studies of only the adult BP population (31, 32, 34, 35).

Aims of the study

The aim of this study is to examine the potential influence of comorbid disorders on the course of bipolar disorder in youth. We hypothesize that worsening of comorbid conditions, analyzed in disorder groups, increases the frequency and duration of episodes for both depression and mania.

Material and methods

Participants

Children and adolescents aged 7 to 17 years 11 months (mean±SD age, 13.0±3.1 years) whose primary diagnoses were *DSM-IV* BP-I (n=244) or BP-II (n=28) or an operationalized definition of BPNOS (n=141) were enrolled in the Course and Outcome of Bipolar Youth (COBY) study. Because the *DSM-IV* definition of BP-NOS is vague, BP-NOS was defined as the presence of clinically relevant BP symptoms that did not fulfill the *DSM-IV* criteria for BP-I or BP-II. In addition, participants were required to have a minimum of elated mood plus 2 associated *DSM-IV* symptoms or irritable mood plus 3 *DSM-IV* associated symptoms, along with a change in the level of functioning, duration of a minimum of 4 hours within a 24-hour period, and at least 4 cumulative lifetime days meeting the criteria (1). Diagnostic conversion to BP-I/II occurred in 63 participants (45%), 32 (23%) to BP-I (9 of whom had initially converted to BP-II) and 31 to only BP-II (22%) (36). Participants with current or lifetime diagnoses of schizophrenia, mental retardation, autism, and mood disorders secondary to substance abuse, medical conditions, or use of medications were excluded. Participants were recruited from consecutive admissions to outpatient clinics (65%),

inpatient units (16%), advertisement (11%), and referrals from other physicians (8%) and were enrolled independent of current BP state or treatment status. Participants were enrolled at 3 academic medical centers: Brown University (n=144), University of California at Los Angeles (n=90), and University of Pittsburgh Medical Center (n=204). Informed consent was obtained before initiation of the assessment from the participant's parent or guardian and from participants 14 years or older. The study procedures were explained in age-appropriate language to younger participants, and verbal assent was obtained before the assessment. The institutional review boards at the 3 centers reviewed and approved the study protocol before enrollment of any participant.

Procedures

Assessments were carried out using semistructured interviews of the participant and their parent or primary caregiver, who reported about the participant. Nonmood psychiatric disorders were assessed at intake using the Kiddie Schedule for Affective Disorders and Schizophrenia for School-age Children (KSADS)-Present and Lifetime Version (-PL) (37). Mood symptoms were assessed in follow-up by the adolescent version of the Longitudinal Interval Follow-up Evaluation (A-LIFE) (38), the mood disorders sections of the KSADS-P (Present Episode, fourth revision) (39)and the KSADS Mania Rating Scale (MRS) (40).

Longitudinal changes in psychiatric symptoms and functioning since the previous evaluation were assessed using the A-LIFE (38). The A-LIFE evaluates the course of ongoing DSM-IV psychiatric disorders and onset of new disorders, with weekly ratings using the A-LIFE Psychiatric Status Rating (PSR) scale. To obtain data for PSR ratings at each follow-up, the interviewer reviews the participant's symptoms reported at the last interview, and then probes for symptoms that were present shortly after the last follow-up, and then for subsequent changes in symptomatology using identifiable anchor points during the interval period such as memorable dates or events (e.g., holidays, school start and end dates, etc.). Although the PSR ratings are made on a week-by-week basis, the participant is not asked how they were feeling during each week; instead, the interviewer rates each week at the same PSR number until there is an identified "change point" in the frequency, duration, or level of impairment associated with a symptom or disorder, and the reported week of that change point will reflect a change in the PSR and that score will be assigned to the subsequent weeks or until the next identified change point. This process occurs iteratively for each "change point" identified. For depression and mania, the PSR scores range on a 6-point scale, from 1 for no symptoms, to 2 to 4 for varying levels of subthreshold symptoms and impairment, to 5 and 6 for full DSM-IV criteria at respectively varying levels of severity and impairment. The disorders that comprise the comorbid disorders groups (ANX, ADHD, DBD, and SUD), were rated on a weekly basis operationalized along a 3-point scale, where 1 = no symptoms, 2 = subthreshold, and 3 = full diagnostic criteria (4, 8). The A-LIFE was administered to adolescents and parents separately; however, when children presented difficulty recalling symptom or mood changes, those under 14 years of age were interviewed in the presence of their parent or caretaker. Any discrepancies between the informants' responses were later discussed with clinical staff, and summary scores based on all available information were determined.

All assessments were completed by research staff who were trained to reliably administer the interview instruments and protocols and the reports that they collected were later presented to child psychiatrists/psychologists who confirmed the diagnoses and ratings. When necessary, participants' medical records were obtained and reviewed for collateral information. The K-SADS kappas for psychiatric disorders were ≥0.8. The A-LIFE intraclass correlations for mood disorders were ≥0.8 (4).

Statistical Analysis

Analyses used Statistical Analysis System (SAS) version 9.2 (SAS Institute Inc., Cary, NC, USA). All p values are based on two-tailed tests with an alpha level set at 0.05.

Multiple-event Cox proportional hazards regression analyses with time-varying covariates were used to predict the time from a PSR increase in a comorbid disorder to recovery and recurrence for depression and mania respectively. Recovery was defined as 8 consecutive weeks with a PSR score of 1 or 2; time to recovery was marked at the first of the 8 consecutive weeks. Recurrence, of a depressive or manic episode, was defined as having followed a period of recovery, and as having again met full diagnostic criteria (i.e., PSR score of 5 or 6) for a minimum duration of 1 week for mania and 2 weeks for depression (4, 8).

The time-varying predictor variables were based on the comorbid PSR ratings, lagged by one week (i.e. a prior week's rating predicting the subsequent week's change in mood disorder severity). For example, week 5 comorbidity PSR was the predictor for the likelihood of a change in mood status in week 6, and week 6's comorbidity PSR was used to predict mood status in week 7. The Cox regression analyses used all available weeks of data for each participant, taking censoring into account.

With the exception of ADHD, the PSR ratings for predictor disorders were combined into three diagnostic groupings (i.e., ANX, DBD, SUD) using the highest (worst) PSR score for each week within the disorder group. Within the ANX group, the highest PSR score for each week may be from Panic Disorder, General Anxiety Disorder (GAD), Agoraphobia, or Social Phobia. Similarly, for SUD the PSR scores for alcohol and non-alcohol abuse and dependence were collapsed with highest PSR scores used in analyses. Within the DBD group, the highest PSR scores were taken from either ODD or CD.

Each Cox proportional hazards regression analysis is based on the PSR for one of the comorbid disorder groups; a participant's inclusion in analysis for a given disorder group required either a history of one of the grouped disorders at intake or onset of a grouped disorder during follow-up. Thus, the analyses for ANX include those who have had one or more ANX at intake or follow-up; likewise for ADHD, DBD, and SUD. Furthermore, for inclusion in the analyses predicting recurrence of a mood episode, participants must have been in a period of recovery from the respective mood episode. Similarly, for the analyses predicting recovery participants must have been experiencing the respective mood episode during the weeks proximal to the worsening of the comorbid disorder group. Therefore, the number of events analyzed in each model varies significantly based on these inherent analytic requirements.

Since a single participant could experience multiple recoveries and recurrences over the years of follow-up, we used the robust sandwich variance estimate recommended by Lin (41) to account for the clustering of events within participants. Analyses were limited to the first five episodes of depression or mania respectively for each participant in order to mitigate undue influence of a few participants having many episodes.

Univariate analyses were conducted initially to assess the time-varying course of comorbid disorders predicting time to recovery and recurrence in mania and depression respectively for ANX, ADHD, DBD, and SUD, individually. Based upon the results of these analyses, multivariate analyses were conducted to test patterns for uniqueness as well as for potential interaction effects.

A previously published report on the static effect of baseline comorbidities on BP course in the COBY sample identified a number of covariates that were associated with greater likelihood of recovery and recurrence of depression and mania. The identified covariates, which were applied to the present study, include early onset of BP, duration of index episode, family history of mood disorders, low Socio-Economic Status (SES), non-White race, and whether the participant lived with both biological parents (4).

Results

Prevalence and Demographics

Analyses are based on data from 413 participants (mean age 13.0 yrs. ± 3.1 yrs. at intake). After intake, participants were interviewed a mean of 10.0 times (SD = 3.2), on average every 8.7 months (SD = 5.2). The mean duration of follow-up was 93 months (SD = 8.3); 7.75 years. Participants were 221 males (53.5%) and 192 females (46.5%). The majority of the sample was White (81.8%) and non-Hispanic (93.7%), with 7.3% of the sample identifying as Black, 1.2% Asian, 0.2% Native American, 8.5% Biracial, and 0.7% Other. At intake, 244 (59.1%) participants met criteria for BP-I, 28 (4.6%) for BP-II, and 141 (36.3%) for operationally defined BP-NOS (1),(8).

Episodes of recovery and recurrence for depressive and manic episodes by comorbid group

The episode durations reported in the results of this study reflect all episodes (not just the initial one). Over the mean of 7.75 years of follow-up, there were a total of 858 depressive episodes observed in 413 participants, with a median time to depression recovery of 24.2 weeks; 291 participants had at least one recovery. There were 1094 episodes of remission from depression observed in 413 participants, with a median time to depression recurrence of 72.2 weeks; 292 participants had at least one recurrence. With respect to mania, there were 321 episodes observed in 413 participants with median time to mania recovery of 19.3 weeks; 176 participants had at least one recovery. There were 660 episodes of remission from mania observed in 413 participants, with no median time to recurrence, as even after a mean of 7.75 years of follow-up, more than half of the participants did not have a recurrence (157 had at least one recurrence). We limited our analyses to the first five episodes of depression, and the first five episodes of mania, for each participant to mitigate over-

influence of outliers. Only 4% of the sample had more than 5 mania recurrence/recovery episodes, and only 11% had more than 5 depression recurrence/recovery episodes. Table 1 depicts the analyzed number of participants, episodes, and events, by disorder group.

Anxiety Disorders—At intake and during the follow-up, 195 participants (47.2%) met criteria for at least one ANX, including 70 (35.9%) with Panic Disorder, 31 (15.9%) with Agoraphobia, 140 (71.8%) with GAD, and 83 (42.6%) with Social Phobia. In this group, 110 (56.4%) met criteria for BP-I, 19 (9.7%) for BP-II, and 66 (33.9%) for BP-NOS. As shown in Table 2, higher ANX PSR scores predicted significantly longer time to recovery and shorter time to recurrence for depressive episodes, and shorter time to recurrence for manic episodes. Specifically, for participants in a depressive episode, every one point increase in ANX PSR was associated with a 26% decrease in rate of recovery (HR = 0.74, 95% CI [0.65-0.84]), whereas for those not in a depressive episode recurrence risk increased 43% (HR = 1.43, 95% CI [1.24-1.65]). Likewise, for those not in a manic episode, a one point increase in ANX PSR score was associated with a 43% increase (HR = 1.43, 95% CI [1.16-1.75]) in the rate of subsequent recurrence of mania. However, there were no significant associations between worsening of ANX PSR and recovery from a mania episode.

Attention Deficit Hyperactivity Disorder—At intake and during the follow-up, 280 (67.8%) participants met criteria for ADHD. In this group, 163 (58.2%) met criteria for BP-I, 13 (4.6%) for BP-II, and 104 (37.1%) for BP-NOS. As indicated in Table 2, worsening of ADHD (i.e., increase in ADHD PSR score) significantly predicted shorter time to recurrence for depressive and manic episodes. For every one point increase in ADHD PSR rating, for those not in a depressive episode the recurrence risk increased 53% (HR = 1.53, 95% CI [1.25-1.85]). For those not in a manic episode, a one point increase in ADHD PSR score was associated with a 72% recurrence risk increase (HR = 1.72, 95% CI [1.21-2.44]). However, course of ADHD did not significantly predict time to recovery from either depressive or manic episodes.

Disruptive Behavior Disorders—At intake and during the follow-up, 260 (63.0%) participants met criteria for a DBD, 47 (18.1%) with CD, and 159 (61.2%) with ODD. In this group, 151 (58.1%) met criteria for BP-I, 10 (3.9%) for BP-II, and 99 (38.1%) for BPNOS. As seen in Table 2, higher DBD PSR scores significantly predicted shorter time to recurrence for both depressive and manic episodes. For every one point increase in DBD PSR rating, for those not in a depressive episode the recurrence risk increased 22% (HR = 1.22, 95% CI [1.04-1.44]). For those not in a manic episode, a one point increase in DBD PSR score was associated with a 67% recurrence risk increase (HR = 1.67, 95% CI [1.29-2.16]). Course of DBD did not significantly predict recovery from either depressive or manic episodes.

Substance Use Disorders—At intake and during the follow-up, 154 (37.3%) participants met criteria for a SUD, 105 (68.2%) with alcohol abuse disorder, 60 (39.0%) with alcohol dependence, 110 (71.4%) with non-alcohol substance use abuse, and 89 (57.8%) with non-alcohol substance dependence. In this group, 86 (55.8%) met criteria for

BP-I, 12 (7.8%) for BP-II, and 56 (36.4%) for BP-NOS. As shown in Table 2, higher SUD PSR scores significantly predicted shorter time to recurrence for both depressive and manic episodes, as well as longer time to recovery from a depressive episode. For every one point increase in SUD PSR rating, for those in a depressive episode, rate of recovery from depressive episode dropped by 19% (HR = 0.81, 95% CI [0.68-0.97]), while for those not in a depressive episode the rate of recurrence increased 21% (HR = 1.21, 95% CI [1.01-1.44]). In addition, for those not in a manic episode, a one point increase in SUD PSR score was associated with a 46% (HR = 1.46, 95% CI [1.09-1.96]) increase in the recurrence risk. Course of SUD did not significantly predict recovery from mania episodes.

Multivariate Analyses—Two patterns of similar influence emerged in the results of our univariate analyses and warranted further investigation. First, both ANX and SUD were found to exert a similar influence on mood, where each predicted shorter time to recurrence of depression and mania, and longer time to recovery from depression. Second, we saw that both ADHD and DBD each predicted shorter time to recurrence of depression and mania. To test these patterns for their uniqueness as well as for potential interaction effects we computed post-hoc multivariate time-varying Cox multiple regression analyses.

As shown in Table 3, in this post-hoc multivariate model containing both PSR scores for ANX and SUD as well as a priori specified baseline covariates, ANX continued to have a significant main effect in predicting shorter time to recurrence of depression and mania, as well as longer time to depression recovery. SUD no longer significantly predicted time to recurrence of depression or mania. The only significant effect of SUD to remain was in predicting longer time to depression recovery. There was no significant interaction effect between ANX and SUD.

As shown in Table 4, in the multivariate model containing both PSR scores for ADHD and DBD, as well as a priori specified baseline covariates, there were both significant main and interaction effects. With regard to predicting time to recurrence of depressive episodes, a significant subadditive interaction effect was found. Each disorder group by itself is associated with 55-56% ($\beta = 0.43$ for ADHD, $\beta = 0.44$ for DBD) increased risk of recurrence, and if each contributed independently to risk of recurrence, having both would increase the risk by a factor of almost 2.4 (combined $\beta = .87$, HR = 2.39). However, the interaction indicates a somewhat lower but still substantial risk (combined $\beta = .72$, HR = 2.05). With regard to predicting time to recurrence of mania, the main effect results for ADHD and DBD remained, and there was no interaction effect between the two disorder groups. Of note, in the COBY sample utilized for this study, there were no participants who were diagnosed with only ODD (and not ADHD).

Discussion

To summarize, we found two main patterns by which comorbidity influenced the course of BP. First, for anxiety and substance use disorders, a worsening course of these comorbidities predicted a longer time to recovery from a depressive episode as well as increased risk of both depressive and manic episode recurrences. This increased likelihood of recurrence of both depressive and manic episodes was more robust for anxiety disorders. Second, for

ADHD and DBD, worsening of symptoms significantly increased the probability of recurrence for both depressive and manic episodes. Overall, deterioration in comorbid symptomatology consistently increased the risk for mood episode recurrence, while only ANX and SUD prolonged recovery.

The strongest co-variation observed was between worsening of both anxiety symptoms and depressive episodes. Consistent with this observation, others (22, 25) have noted the cooccurrence of anxiety with both unipolar and bipolar depressions, and a previous study from COBY reported that participants with ANX exhibited more syndromal mood recurrences, longer times to recovery, less time euthymic, and a disproportionately greater number of mixed/cycling and depressive episodes, compared to those without ANX (18). Results from the present study thus extend these findings by identifying a temporal relationship. Moreover, in noting the time-varying associations between these disorders, the findings may lend further support to the idea that these phenotypes are linked to a broader biologically driven dimension of negative affectivity (42-44). Furthermore, our study and those aforementioned suggest that the presence of subthreshold anxiety spectrum symptoms, as indicated by a PSR between 2 and 4 in our study, is sufficient to affect the course of mood episodes.

Additionally, we found that worsening or new onset of ANX predicted time to recurrence of a manic episode. Compared to the research on anxiety and depressive episodes, notably less attention has been paid to the relationship between anxiety and manic episodes, even though it has been reported that ANX comorbidity, specifically Panic Disorder and Social Phobia, is higher in those with BP compared to unipolar depression (45, 46). Our study adds specificity to the limited body of research by finding an increased risk for mania recurrence, but no significant effect on mania recovery. Clearly, more research is needed to elucidate the specific impact of each anxiety disorder on mania; however, taken together these results and those of extant studies suggest the possibility of specific and differential associations between each particular anxiety disorder and mania.

The association of SUD with episode recurrence appeared to be accounted for by the co-presence of anxiety symptoms. This observation is unsurprising considering the frequent comorbidity of anxiety and substance use disorders, the role of substance use in mitigating anxiety, and evidence of a common mode of familial transmission of the two (47). Even after controlling for anxiety, this study offered the robust finding that SUD continued to predict a longer time to recovery from depression. However, it is difficult to draw implications from this specific finding given the potential for co-occurring substance use to complicate pharmacological interventions for depression, either through reluctance to prescribe pharmacotherapy to patients who are actively abusing substances, compromised medication adherence, or substance-medication interactions that may interfere with the efficacy of pharmacotherapy (48, 49).

Both ADHD and DBD symptoms significantly hastened time to recurrence of depressive and manic episodes. With regard to depression recurrence, the interaction effect found in the multivariate model suggests that worsening course of either disorder significantly increases risk for depression, but also that having both comorbid disorders dramatically increases that

risk. Even with respect to mania, worsening of either ADHD or DBD predicted increased risk of recurrence. Due to the high rates of co-occurrence between ADHD and DBD, it is difficult to disentangle specific disorder effects, particularly as they share common elements such as impulse control deficits. It is also possible that CD and ODD may exert different effects upon BP, one longitudinal study observed that CD but not ODD significantly increased risk for BP (50). However, our DBD subsample was predominantly represented by those meeting criteria for ODD. Future studies that separate out the impact of CD and ODD may better disentangle specific effects of each disorder.

Our results must be viewed in light of several important limitations. Our study is based on retrospective follow-up interview data, which is subject to recall bias, and the possibility of a halo effect. Also, study participants were predominantly White, and were recruited from clinical settings, thus limiting generalizability. Nevertheless, course and morbidity in non-clinically referred pediatric BP youth have been shown to be similar to those in referred populations (51).

While the COBY project utilizes a large sample of pediatric BP youth, each of the data analyses performed in this study utilized only the subsets of participants who had at least one respective comorbid condition in a given grouping. It is possible that our analyses were underpowered to find effects from some specific comorbidities; this can be seen particularly in SUD comorbidity, which may have been underpowered due to sample age. Our decision to group disorders together was based on a number of conceptual and statistical power considerations.

Conceptually, given the multiple disorders assessed by COBY and the complexity of weekly longitudinal data, our group made the decision to have one initial “overview” comorbidity paper, with future papers that might examine the role of specific disorder comorbidities. For example, a prior COBY paper (18) presented an examination of the effect of comorbid anxiety disorders at baseline. While the categorization strategy utilized in the present analyses potentially masks individual disorder-level relationships, the *time-varying* relationships of individual anxiety disorders and mood episodes will need to be examined in a separate follow-up manuscript due to the large number of analyses it would entail and due to the complexity of the current manuscript.

Furthermore, statistical power limitations precluded us from conducting multivariate analyses with four groups of disorders in one model at the same time. These analyses would require the imputation of more than 50% of the (PSR) data points (because, e.g., study youth participants who may have ADHD PSR data may not have SUD, or vice versa). This extraordinary amount of imputation would compromise the integrity of the analyses.

Analyses were limited to the first five episodes (of each depression and mania) for any given participant in order to mitigate undue influence of a few participants having many episodes. However, comorbidity may exert differing effects at different points in the course of BP among youth, or during the course of youth development, yet these factors were beyond the scope of this study.

Due to the complexity of the current set of analyses, we did not analyze potential effects of treatment. As COBY is a naturalistic study, there is extreme variability and heterogeneity in types and intensity of treatment utilized, or abstained from, by our participants (52). To operationalize this as a covariate would require excessively reductionistic approaches and would introduce even greater statistical complexity; therefore the variable of treatment was deemed well beyond the scope of the present study. Nor did we examine bidirectional effects (i.e. mood episodes effecting comorbidity). While a transactional effect is highly plausible, this was also beyond the scope of the present study.

Among the strengths of the COBY study is its large sample of participants, drawn from geographically disparate regions of the US, who at intake underwent detailed assessments for pediatric BP. Similarly, detailed assessments continued as these participants were followed naturalistically, with weekly ratings assigned for depression, mania/hypomania, and their comorbid disorders. The wealth of data amassed in this manner has allowed for the ability to examine time-sensitive proximal changes on both a subsyndromal and syndromal level from which we can ascertain with greater confidence the extent to which worsening of comorbid disorders influences the course of each BP mood state. These analyses have the potential to assist in the identification of antecedents to deteriorating course in BP mood states, thereby providing information that will allow clinicians to offer not only earlier interventions, but also interventions that have accounted for the likely influence of comorbid conditions. These data point to the necessity of properly diagnosing and treating comorbid conditions, and early recognition of deterioration in those conditions, particularly as they are shown to increase probability of recurrence of depressive and manic episodes in patients with BP.

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Significant Outcomes

- Worsening presentation of ANX and SUD predicted that preexisting depressive episodes were protracted, and in the absence of depression the worsening of ANX and SUD symptoms increased the probability of a proximal recurrence of both depressive and manic episodes. In a multivariate analysis of ANX and SUD the effects for ANX remained significant, however SUD only predicted extended time to recovery from depression.
- Disorders of executive functioning and behavior (ADHD and DBD) exerted similar effects on the course of BP. Worsening of symptoms of these disorders was found to significantly increase the probability of a proximal recurrence of both depressive and manic episodes.

Limitations

- The prospective cohort study design employed and the intermittent follow-up interview method of data collection introduce the potential for recall bias and the possibility of halo effect.
- To diminish the influence of a small number of participants higher episodicity, analyses were restricted to the first five mood episodes per participant.
- The potential effects of mood episodes upon comorbid conditions was not examined in the current study.

Table 1

Episodes of recovery and recurrence for depressive and manic episodes by comorbid group.

	ANX (n=195)	ADHD (n=236)	DBD (n=260)	SUD (n=154)
N at intake	83	43	191	32
New onsets f/u	112	193	69	122
Recovery Depression				
N eligible	174	211	192	133
Episode eligible	508	510	479	380
Recovery	358	432	394	199
Recurrence Depression				
N eligible	194	276	256	154
Episode eligible	579	659	621	449
Recurrence	363	444	405	204
Recovery Mania				
N eligible	98	134	122	79
Episode eligible	208	251	232	146
Recovery	153	241	198	74
Recurrence Mania				
N eligible	195	279	259	154
Episode eligible	372	487	456	284
Recurrence	142	216	179	70

ANX = Anxiety Disorders, ADHD = Attention Deficit Hyperactivity Disorder, DBD = Disruptive Behavior Disorders (ODD and CD), SUD = Substance Use Disorders (Substance Abuse and Substance Dependence)

Table 2

Multivariate Analyses

Time-varying course of comorbid disorders predicting time to recovery and recurrence in mania and depression respectively (restricted to a maximum of 5 episodes).

	Mania (Maximum 5 Episodes)					Depression (Maximum 5 Episodes)				
	Event n	**HR**	**p**	**95% CI**		**Event n**	**HR**	**p**	**95% CI**	
ANX PSR										
Recovery	153	0.89	0.22	0.73 -	1.07	358	0.74	<.0001	0.65-	0.84
Recurrence	142	1.43	<.001	1.16 -	1.75	363	1.43	<.0001	1.24-	1.65
ADHD PSR										
Recovery	241	1.49	0.15	0.86 -	2.58	432	0.83	0.15	0.64 -	1.07
Recurrence	216	1.72	<.0001	1.21 -	2.44	444	1.53	<.0001	1.25 -	1.85
DBD PSR										
Recovery	198	0.99	0.92	0.72 -	1.34	394	0.89	0.19	0.74 -	1.06
Recurrence	179	1.67	<0.001	1.29-	2.16	405	1.22	0.02	1.04 -	1.44
SUD PSR										
Recovery	74	0.84	0.19	0.61-	1.10	199	0.81	0.02	0.68 -	0.97
Recurrence	70	1.46	0.01	1.09-	1.96	204	1.21	0.04	1.01 -	1.44

Notes:

The above analyses included covariates: BP age of onset, living with biological parents, race, SES, BPNOS status at intake, family history of mania, and duration of illness.

ANX = Anxiety Disorders, ADHD = Attention Deficit Hyperactivity Disorder, DBD = Disruptive Behavior Disorders (ODD and CD), SUD = Substance Use Disorders (Substance Abuse and Substance Dependence).

Table 3

Multivariate Analyses

Time-varying course of ANX and SUD and interaction predicting time to recovery and recurrence in mania and depression respectively (restricted to a maximum of 5 episodes).

	Mania (Maximum 5 Episodes)					Depression (Maximum 5 Episodes)				
	Event n	HR	p	95% CI		Event n	HR	p	95% CI	
ANX PSR										
Recovery	194	1.10	0.60	0.76 -	1.59	449	0.70	0.0012	0.56 -	0.87
Recurrence	180	1.49	0.04	1.01 -	2.18	456	1.44	0.0044	1.12 -	1.84
SUD PSR										
Recovery	194	0.93	0.74	0.62 -	1.41	449	0.73	0.01	0.57 -	0.94
Recurrence	180	1.34	0.14	0.90 .	1.98	456	1.01	0.95	0.77 -	1.31
ANX. × SUD										
Recovery	194	0.94	0.54	0.77 -	1.15	449	1.04	0.52	0.92 -	1.18
Recurrence	180	0.94	0.54	0.77 -	1.15	456	1.05	0.46	0.92 -	1.20

Notes:

The above analyses included covariates: BP age of onset, living with biological parents, race, SES, BPNOS status at intake, family history of mania, and duration of illness.

ANX = Anxiety Disorders, SUD = Substance Use Disorders (Substance Abuse and Substance Dependence).

Table 4

Multivariate Analyses

Time-varying course of ADHD and DBD predicting time to recovery and recurrence in mania and depression respectively (restricted to a maximum of 5 episodes).

	Mania (Maximum 5 Episodes)					Depression (Maximum 5 Episodes)				
	Event n	HR	p	95% CI		Event n	HR	p	95% CI	
ADHD PSR										
Recovery	275	0.58	0.0233	0.36 -	0.93	510	0.76	0.20	0.50 -	1.15
Recurrence	249	1.94	0.0360	1.03 -	3.62	527	1.55	0.0067	1.12 -	2.10
DBD PSR										
Recovery	275	0.46	0.06	0.21 -	1.02	510	0.82	0.42	0.50 -	1.34
Recurrence	249	2.14	0.0324	1.06 -	4.33	527	1.56	0.0204	1.07 -	2.25
ADHD × DBD										
Recovery	275	1.36	0.0350	1.03 -	1.78	510	1.05	0.59	0.88 -	1.25
Recurrence	249	0.80	0.10	0.62 -	1.04	527	0.86	0.0414	0.75 -	0.99

Notes:

The above analyses included covariates: BP age of onset, living with biological parents, race, SES, BPNOS status at intake, family history of mania, and duration of illness.

ADHD = Attention Deficit Hyperactivity Disorder, DBD = Disruptive Behavior Disorders (ODD and CD).