# Is Bipolar Disorder Specifically Associated With Panic Disorder in Youths?

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***Objective:*** To replicate previous findings of high rates of bipolar disorder (BPD) in patients with panic disorder (PD) and determine if youths with both PD and BPD have more severe illness.

***Method:*** 2025 youths aged 5 to 19 years seen at a mood and anxiety specialty clinic were assessed using the Schedule for Affective Disorders and Schizophrenia for School Aged Children, Present Episode, 4th Revision. Diagnoses were made using DSM-III and DSM-III-R criteria and then updated to conform to DSM-IV criteria. Patients were grouped into those with PD (N = 42), those with non-PD anxiety disorders (N = 407), and psychiatric controls with no anxiety diagnosis (N = 1576).

***Results:*** Youths with PD were more likely to exhibit comorbid BPD (N = 8, 19.0%) than youths with either non-PD anxiety disorders (N = 22, 5.4%) or other nonanxious psychiatric disorders (N = 112, 7.1%). The symptoms of PD and mania were not affected by the comorbidity between PD and BPD. Youths with both PD and BPD had more psychotic symptoms and suicidal ideation than patients with PD and other nonbipolar psychiatric disorders and BPD patients with other nonanxious comorbid disorders.

***Conclusion:*** The presence of either PD or BPD in youths made the co-occurrence of the other condition more likely, as has been noted in adults. Patients with both PD and BPD are more likely to have psychotic symptoms and suicidal ideation. In treating youths with PD, clinicians must be vigilant for possible comorbid BPD or risk of pharmacologic triggering of a manic or hypomanic episode. Prospective studies are needed to learn if PD predicts the onset of BPD in children and adolescents.

*(J Clin Psychiatry 2002;63:414–419)*

*Received Sept. 18, 2001; accepted Nov. 27, 2001. From the Western Psychiatric Institute and Clinic, University of Pittsburgh School of Medicine (Drs. Birmaher, Brent, and Axelson); the University of Pittsburgh School of Medicine (Mr. Kennah); and University of Pittsburgh Health System (Dr. Bridge and Ms. Ehmann), Pittsburgh, Pa.*

*Supported in part by Research Units of Pediatric Psychopharmacology (MH 70008) (Dr. Birmaher) and the Child and Adolescent Developmental Psychopathology Research Center for Early-Onset Affective and Anxiety Disorders (MH 55123), Pittsburgh, Pa. (Dr. Brent).*

*In the spirit of full disclosure and in compliance with all ACCME Essential Areas and Policies, the faculty for this CME activity were asked to complete a full disclosure statement. The information received is as follows: Drs. Birmaher, Brent, Bridge, Axelson, and Mr. Kennah and Ms. Ehmann have no significant commercial relationships to disclose relative to the presentation.*

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Anxiety disorders are some of the most common psychiatric illnesses in youths.[1] Panic disorder (PD) represents one of the most extreme manifestations of anxiety in both adults and children. Despite early speculations that PD, by its nature, could not develop in youths, retrospective reports of PD in adults, coupled with clinical case reports of children and adolescents with PD, have led to the general agreement that PD does indeed occur in youths.[2,3] In fact, panic attacks (PAs) have been shown to occur frequently in children and adolescents, with prevalence rates of PAs ranging from 5.4% to 10.2%,[4,5] while PD is less prevalent, ranging from 0.5% to 0.8%,[5,6] with rates for adolescent girls reaching as high as 1.7%.[4,6]

In adults, the association between both PAs and PD and major depressive disorder (MDD) is well documented.[2,7] In addition, in adults, PD has been shown to be associated with bipolar disorder (BPD), with 13% to 23% of adults with PD having comorbid BPD.[8–10] Conversely, in BPD adults, rates of comorbid PD range from 36% to 80%.[11–14] Patients with PAs or PD and comorbid BPD have a more severe disease and are more difficult to treat than patients with PD without BPD.[9,15]

The association between PD and mood disorder has also been shown in youths. In a prospective study of nonreferred high school students, MDD was found in a quarter of subjects diagnosed with PAs.[5] Adolescents with PD, when compared to adolescents with an anxiety disorder

Table 1. Demographics*

| Variable | PD (N = 42) | Non-PD Anxiety (N = 407) | Controls (N = 1576) | Statistic | p Value |
|---|---|---|---|---|---|
| Age, mean (SD), y | 15.3 (2.6)[a] | 13.8 (3.2)[b] | 14.4 (2.8)[c] | ANOVA | < .001 |
| Sex, % female | 66.7 | 59.7 | 56.7 | $\chi^2$ | NS |
| Race, % white | 92.9[a] | 85.8[a] | 77.1[b] | $\chi^2$ | < .001 |
| Socioeconomic status, mean (SD)† | 37.4 (14.6) | 37.9 (13.7) | 37.18 (14.1) | ANOVA | NS |

*For each variable, values with different superscripts differ significantly ($p \leq .05$). Abbreviations: ANOVA = analysis of variance, NS = not significant, PD = panic disorder.
†Socioeconomic status rated using the classification system developed by Hollingshead.[22]



other than PD, have higher depression scores[4] and higher rates of MDD and dysthymia.[16]

While the association between PD and BPD has been studied in adults, similar studies in youths are lacking. Lewinsohn and colleagues,[6] in a community study of high school students with any form of anxiety disorder, reported that anxious youths were 7 times more likely to have comorbid BPD than students without an anxiety disorder. In a longitudinal study, Johnson and colleagues[17] found that adolescents with anxiety disorders had an increased risk of developing BPD in early adulthood. Rao and colleagues[18] in a longitudinal study of depressed adolescents and healthy controls found that 50% of those with comorbid anxiety disorders developed BPD in comparison with 0% of those without any anxiety. There are few studies reported in the literature that have examined the association between PD and BPD in youth. Biederman and colleagues[19] reported significantly high incidence of BPD (52%) in a sample of referred children and adolescents with PD (N = 26) in comparison with psychiatric (N = 372; 15%) and healthy controls (N = 144, 0%). Lewinsohn and colleagues[20] found that community adolescents with BPD had higher prevalence of PD (11%) compared with healthy controls (0.9%), and Wozniak and colleagues[21] reported in a clinical sample that children with BPD had significantly more comorbid PD than children with attention deficit disorder (9% vs. 0.6%, $p \leq .01$).

The present study expands on previous reports noted above. We compared a clinically referred sample of youths with PD, youths with other non-PD anxiety disorders, and psychiatric controls without anxiety disorders. It was hypothesized that (1) youths with PD will have a higher frequency of comorbid BPD than the non-PD anxious and nonanxious psychiatric control groups; (2) youths with PD and BPD will exhibit more severe symptomatology (e.g., panic, suicide) than those with PD alone or comorbid with other psychiatric disorders; and (3) youths with PD and BPD will exhibit more severe symptoms of mania, depression, psychosis, and suicidality than youths with BPD with nonpanic anxious disorders and patients with BPD comorbid with other nonanxious psychiatric disorders.

## METHOD

### Subjects

The sample consisted of 2025 patients (42.5% male and 57.5% female) consecutively referred to an outpatient child and adolescent mood and anxiety disorders clinic between 1986 and 1995. The patients' mean ± SD age was 14.3 ± 2.9 years (range, 5–18.11 years). The mean socioeconomic status (per Hollingshead 1975[22]) was 37.4 ± 17.7 (Social Class III; range, 8 to 66). Seventy-nine percent were white, 17.9% were African American, and 2.9% were from other ethnic backgrounds, primarily biracial.

There were 42 patients with PD, 407 patients with non-PD anxiety disorders, and 1576 psychiatric controls without any anxiety disorder (mainly disruptive and mood disorders; Table 1). The groups differed in age and race, with the non-PD anxious patients being slightly younger and the nonanxious psychiatric control group having fewer white individuals. There were no differences in sex or socioeconomic status.

### Procedures

As described in further detail elsewhere,[23,24] subjects were assessed with the Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present Episode, 4th edition (K-SADS-P).[25] The current episode was defined by onset within the past 12 months. The semi-structured interview was performed by a trained clinician (therapist of at least master's level or a psychiatric nurse) who interviewed both the parent or guardian and the child under the supervision of a child psychiatrist. The interviewer determined the onset of the current psychiatric episode and then recorded symptom ratings for the present psychiatric episode and for the week prior to the episode. Past history of bipolarity was recorded using the K-SADS-P, and past history of other disorders was recorded in the medical records, which were reviewed by the authors. The severity of manic, hypomanic, and depressive symptoms was evaluated using the number of positive symptoms and the sum of all the scores rated in each respective section in the K-SADS-P. In addition, the manic/hypomanic symptomatology was assessed using

Table 2. Comorbidity of Psychiatric Disorders for Youths With Panic Disorder (PD), Youths With Non-PD Anxiety Disorders, and Nonanxious Psychiatric Controls*

| Disorder | PD (N = 42) | Non-PD Anxiety (N = 407) | Controls (N = 1576) | Statistic | p Value |
|---|---|---|---|---|---|
| MDD | 50.0[a] | 44.0[a] | 27.0[b] | $\chi^2$ | < .001 |
| Anxiety disorders | | | | | |
| Separation anxiety disorder | 21.4 | 31.2 | NA | $\chi^2$ | NS |
| Agoraphobia | 11.9[a] | 2.7[b] | NA | Fisher | .01 |
| Simple phobia | 11.9 | 12.3 | NA | $\chi^2$ | NS |
| Social phobia | 7.1 | 8.1 | NA | Fisher | NS |
| OCD | 9.5 | 12.5 | NA | $\chi^2$ | NS |
| GAD | 50.0 | 54.5 | NA | $\chi^2$ | NS |
| Conduct disorder | 7.1[ab] | 7.4[a] | 14.8[b] | $\chi^2$ | < .001 |
| ODD | 7.1 | 10.0 | 12.0 | Fisher | NS |
| ADHD | 11.9 | 10.6 | 13.9 | $\chi^2$ | NS |
| Substance abuse/dependence | 9.5 | 6.6 | 6.7 | Fisher | NS |
| Bipolar disorder | 19.0[a] | 5.4[b] | 7.1[b] | Fisher | .01 |

*Values for PD, non-PD anxiety, and control groups shown as percentage of patients with a given disorder. For each variable, values with different superscripts differ significantly (p < .05). Abbreviations: ADHD = attention-deficit/hyperactivity disorder, Fisher = Fisher exact test, GAD = generalized anxiety disorder, MDD = major depressive disorder, NA = not applicable, NS = not significant, OCD = obsessive-compulsive disorder, ODD = oppositional defiant disorder.

the K-SADS-P Mania Rating Scale[26] and Hamilton Rating Scale for Depression extracted from the K-SADS-P.[27]

All diagnoses were made using the *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition (DSM-III),[28] and the revised, DSM-III-R[29] diagnostic criteria. To update the diagnoses for DSM-IV[30] criteria, a computer algorithm was designed to analyze the K-SADS-P symptom ratings and generate diagnoses for schizophrenia, bipolar, depressive, conduct, anxiety, and eating disorders. In general, the severity of an item in the K-SADS-P is rated from 1 to 5 (1 = not present, 2 = slight, 3 = mild, 4 = moderate, 5 = severe). Two psychiatrists (B.B. and D.A.) unanimously agreed on a threshold, at least mild or moderate, that would determine the presence or absence of a symptom. The algorithm arrived at a diagnosis by verifying that the patient exceeded threshold for all symptoms necessary to meet DSM-IV criteria for diagnosis.

Clinically significant psychosis was defined as having at least 1 type of hallucination with a score ≥ 3 (definite) and/or at least 1 delusion with a score ≥ 4 (definite) on the K-SADS-P. Suicidal ideation was defined as a K-SADS-P suicidal ideation item score ≥ 4 or a definite attempt of at least mild lethality.

### Data Analysis

Statistical analyses were performed utilizing the SPSS-PC, version 8.0, statistical package (SPSS, Inc., Chicago, Ill.). Comparisons between groups were performed for categorical data using the chi-square test or the Fisher exact test and for continuous variables using t tests, analysis of variance (ANOVA), and analysis of covariance (ANCOVA). If the ANOVA showed significant difference between the groups, pairwise comparisons were calculated using the method of Scheffé.

All analyses were done with and without controlling for age and race. Because no differences were found, results are presented without controlling for these variables.

Values are reported as mean ± SD. p Values are based on 2-tailed tests with $\alpha = .05$.

## RESULTS

### Psychiatric Diagnoses

Patients with PD showed significantly more comorbid BPD (19.0%) than the patients with non-PD anxiety disorders (5.4%) and the nonanxious psychiatric controls (7.1%) (p = .01, odds ratio [OR] = 4.1 and p = .01, OR = 3.1, respectively; Table 2). There were no differences in the prevalence of BPD between the youths with non-PD anxiety disorders and the psychiatric controls (p = .3).

As depicted in Table 2, youths with PD and non-PD anxiety disorders were equally likely to have comorbid MDD, and both showed significantly more comorbid MDD than the nonanxious psychiatric controls (p < .001). As expected, patients with PD had significantly more agoraphobia than those with non-PD anxiety disorders (p = .01). The patients with nonanxious psychiatric disorders had significantly more conduct disorder than the non-PD anxious group. There were no other differences in the rates of psychiatric disorders among the 3 groups.

### Symptom Severity

To assess the effects of the comorbid PD on bipolar symptomatology and vice versa, we first compared patients with PD and BPD (N = 8) with patients with PD and other nonbipolar disorders (N = 34). Subsequently, within the patients with BPD, we compared those with BPD and PD (N = 8) with BPD patients with non-PD anxiety disorders (N = 22) and BPD patients with nonanxious psychiatric disorders (N = 112) (Table 3).

The severity of panic symptoms, as recorded using the K-SADS-P, did not differ between youths with PD and BPD in comparison with those with PD and no BPD (2.8 ± 0.60 vs. 2.7 ± 0.63, t = 0.211, df = 40, p = .8). Also, there were no significant differences between each of the DSM-IV panic symptoms between these 2 groups. Significantly more patients with PD and BPD had psychotic symptoms than PD patients with other nonbipolar comorbid disorders (50.0% vs. 8.8%; Fisher exact test, p = .02). There were no differences in the prevalence of suicidal attempts between these 2 groups (37.5% vs. 20.6%, NS), but significantly more patients with PD and BPD had

**Table 3. Symptomatology for Youths With Panic Disorder (PD) and Bipolar Disorder (BPD), Youths With BPD and Non-PD Anxiety Disorders, and Youths With BPD and Nonanxious Psychiatric Disorders***

| Variable | PD + BPD (N = 8) | BPD + Non-PD Anxiety (N = 22) | BPD + Nonanxious Disorders (N = 112) | Statistic | p Value |
|---|---|---|---|---|---|
| Depressive symptoms | | | | | |
| No. of DSM-IV MDD symptoms | 6.4 (2.1)[a] | 6.0 (1.7)[a] | 4.3 (2.3)[b] | ANOVA | .001 |
| K-SADS-P rating for depressive symptoms | 3.2 (0.8)[a] | 2.9 (0.7)[a] | 2.3 (0.9)[b] | ANOVA | .001 |
| HAM-D score | 22.5 (8.9)[a] | 20.4 (6.6)[a] | 15.1 (6.7)[b] | ANOVA | < .001 |
| Manic symptoms | | | | | |
| K-SADS-P rating for manic symptoms | 2.6 (0.6) | 2.9 (0.4) | 2.7 (0.6) | ANOVA | NS |
| No. of DSM-IV hypomanic symptoms | 4.1 (1.6) | 4.6 (1.3) | 4.3 (1.5) | ANOVA | NS |
| No. of DSM-IV manic symptoms | 2.6 (1.3) | 2.4 (1.7) | 2.4 (1.8) | ANOVA | NS |
| K-SADS-P Mania Rating Scale score | 31.9 (7.4) | 34.5 (5.6) | 32.4 (6.6) | ANOVA | NS |
| Psychosis/suicide, % yes | | | | | |
| Psychosis | 50.0[a] | 18.2 | 12.5[b] | Fisher | .02 |
| Suicide attempt | 37.5 | 22.7 | 25.9 | Fisher | NS |
| Suicidal ideation (≥ moderate) | 87.5 | 63.6 | 49.1 | Fisher | NS (.07) |

*Values shown as mean (SD) unless otherwise noted. For each variable, values with different superscripts differ significantly ($p < .05$).
Abbreviations: ANOVA = analysis of variance, Fisher = Fisher exact test, HAM-D = Hamilton Rating Scale for Depression, K-SADS-P = Schedule for Affective Disorders and Schizophrenia for School Aged Children–Present Episode, MDD = major depressive disorder, NS = not significant.



suicidal ideation (87.5% vs. 44.7%; Fisher exact test, $p = .05$).

As shown in Table 3, within the BPD patients there were no significant differences in manic and hypomanic symptoms. The depressive symptoms, as measured by the number of DSM MDD symptoms, the number of K-SADS-P depressive symptoms, and the HAM-D, were similar between patients with BPD and PD and those with other non-PD anxiety disorders, but both groups showed greater depressive symptomatology than the nonanxious BPD subjects ($p < .001$). Patients with BPD and PD had a significantly higher rate of psychotic symptoms (50.0%) compared with the BPD patients with other nonanxious psychiatric disorders (12.5%) ($p = .02$). They also had more psychosis than the BPD patients with other non-PD anxiety disorders (18.2%) but this difference did not reach statistical significance. There were no differences in the prevalence of suicidal attempts among the 3 BPD groups, but there was a trend ($p = .07$) for more suicidal ideation in the BPD patients with PD.

## DISCUSSION

In this study, we found that youths with PD showed a higher rate of BPD than youths with either non-PD anxiety disorders or youths with other nonanxious psychiatric disorders. Youths with both PD and BPD had more psychotic symptoms and suicidal ideation than patients with PD and other non-bipolar psychiatric disorders and BPD patients with other nonanxious comorbid disorders. The youths with PD and BPD did not exhibit more severe symptoms of mania than youths with BPD comorbid with other non-PD disorders, although youths with BPD and any anxiety disorder had more severe depressions. Finally, youths with PD and BPD did not have more severe panic symptoms than those with PD alone.

Before discussing the results further, it is important to take into account the limitations of this study. We assessed present psychopathology and not lifetime disorders or lifetime suicidal attempts. The version of K-SADS-P used did not include DSM-IV diagnoses for attention-deficit/hyperactivity disorder, oppositional defiant disorder, or substance abuse, and these diagnoses were based on the psychiatrists' DSM-III and DSM-III-R diagnoses on the diagnosis summary sheet. The use of a computer algorithm allows for improved diagnostic uniformity, but it also removes the ability to exercise clinical judgment and synthesize the entire clinical presentation. However, the rates of agreement with the clinician summary sheet diagnoses were high (κ values ranging from 0.5 to 0.6).[26] The sample included only outpatient youths referred for treatment, so findings may not generalize to the overall population. Finally, despite a large sample, the subgroup of those with PD was small, with only 8 subjects in the PD with BPD subgroup.

Similar to findings in the adult literature,[8–11,13] PD conveyed about a 3- to 4-fold increased risk for BPD patients compared to other clinic patients, occurring in about 1 in 5 PD patients. Biederman and colleagues[19] also reported a specific association between PD and BPD in children and adolescents, but at a much higher rate (56%). However, in contrast to our report, which mainly focused on current disorder, Biederman and colleagues examined lifetime diagnoses, which would be expected to yield higher individual rates as well as higher rates of comorbidity. It is not clear why PD subjects are more likely to have comorbid BPD, but this specific association has been consistently reported in the adult PD[8–10] and BPD literature.[11–14] While this could be an artifact of using a referred sample, the association between mood and panic disorder has been reported in adult and adolescent community samples.[11,20]

The association between PD and BPD raises an important question of phenomenology and etiology. This association may signify that one represents a prodrome of the other, that the two are part of the same shared diathesis, or that one condition predisposes to the second by making it more likely to occur. MacKinnon and colleagues[31] have reported that, in relatives of adult probands with both PD and BPD, PD cosegregated with BPD significantly more often than predicted by chance. MacKinnon and colleagues[32] also reported that linkage studies for the 18q marker loci were highest in families of BPD probands with PD and lowest with BPD probands without PAs. This has led to the hypothesis that BPD comorbid with PD may represent a highly familial subtype of BPD.[32]

The combination of PD and BPD may have clinical implications, insofar as patients with both disorders present with a problematic clinical picture. Patients with both PD and BPD are more difficult to treat,[9,15] and their comorbidity signifies a poorer outcome in the acute treatment of BPD.[15]

A third implication relates to the prognosis of PD. It is reasonable to hypothesize that youths with PD will be at higher risk for the development of BPD, although no such prospective studies have yet been conducted. If PD is a marker of risk for BPD, then when PD patients are treated with antidepressants, a personal and family history of BPD should be elicited, and they should be closely monitored for the emergence of mania.[33,34]

Because children with PD often have somatic complaints such as shortness of breath or chest pain, they often present first to primary care or specialty physicians. When treating patients who present in the primary care sector, the challenge is 2-fold: making the diagnosis and, if pharmacotherapy is initiated, carefully monitoring for the onset of manic symptoms. Therefore, any physician who makes a diagnosis of PD must make a conscious effort to rule out BPD before medication is initiated or risk exacerbating a "hidden" manic/hypomanic state.[35]

Youths with PD and BPD did not report more severe symptoms of panic than youths with nonbipolar PD. While other studies examining the impact of comorbid BPD on panic severity have not been conducted, there have been reports in adults showing that PD comorbid with MDD resulted in greater severity of both conditions. For example, Noyes et al.[36] reported that adults with both PD and MDD exhibited more severe anxiety symptoms and were likely to exhibit extensive phobic avoidance than adults with PD alone, whereas we did not find an effect of MDD on PD severity in this sample.

Counter to hypothesis, youths with PD and BPD did not exhibit more severe symptoms of mania than youths with BPD with other anxiety and other nonanxious psychiatric disorders. To the best of our knowledge, the severity of the manic symptoms between patients with PD and bipolar patients with non-PD anxiety and nonanxious disorders has not been addressed in previous studies. In contrast, as it has been reported in the adult literature, the BPD patients with comorbid PD and other anxiety disorders had more severe depression.[10,15,37]

PD was associated with a greater risk for BPD, which in turn was associated with higher rates of psychosis and suicidal ideation. In fact, of the 8 patients with PD and BPD, 4 (50%) exhibited definite suicidal symptoms and 7 had clinically significant suicidal ideation. These associations appear attributable to the combination of PD and BPD because youths with PD and other non-BPD disorder and youths with BPD and other non-PD disorders have lower rates of psychosis and suicidal ideation. Cassano and colleagues[38] and Dilsaver and colleagues[13] also reported PD to be associated with psychotic features, but in adult patients with mood spectrum disorders. Other studies, but not all, have also found increased suicidality in patients with PD,[24,37,39–41] but it is not clear if this association is due to the PD or the comorbid BPD or MDD.

In conclusion, we have demonstrated a specific association between PD and BPD in a clinically referred sample. The presence of either disorder should lead to a careful assessment for presence of the other condition. The pharmacologic treatment of PD may result in manic symptomatology, although this needs to be verified by clinical and longitudinal studies. Conversely, because panic symptoms are a significant source of morbidity, patients with BPD should be carefully assessed as to the presence of PD, and appropriate intervention undertaken. It is important to carefully assess youths with PD for comorbid BP disorder because the pharmacologic treatment of PD may increase the risk for a manic episode or rapid cycling in those patients with both disorders. Further research should be aimed at studying how the association between PD and BPD affects the course of both illnesses and determine whether or not the two combined represent a specific subtype of disease. Also, more work should be directed at improving the outcome in individuals who exhibit both disorders.

*Disclosure of off-label usage:* The authors have determined that, to the best of their knowledge, no investigational information about pharmaceutical agents has been presented in this article that is outside U.S. Food and Drug Administration–approved labeling.

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