Prevalence, clinical correlates and factors associated with course and outcome of anxiety disorders in youth with bipolar disorder

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PREVALENCE, CLINICAL CORRELATES AND FACTORS ASSOCIATED WITH COURSE AND OUTCOME OF ANXIETY DISORDERS IN YOUTH WITH BIPOLAR DISORDER

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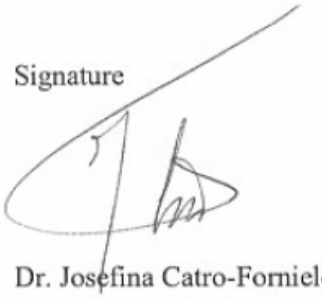
Dr. JOSEFINA CASTRO-FORNIELES,

CERTIFIES that she has supervised and guided the Ph.D. thesis entitled **"PREVALENCE, CLINICAL CORRELATES AND FACTORS ASSOCIATED WITH COURSE AND OUTCOME OF ANXIETY DISORDERS IN YOUTH WITH BIPOLAR DISORDER"** presented by Regina Sala Cassola. She hereby asserts that this thesis fulfils the requirements to be defended for the Degree of Doctor.

Signature



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— Virginia Woolf (To the Lighthouse, 1927)

Contents

Foreword

This thesis, presented to obtain the degree of Doctor by the University of Barcelona, is the result of two different studies carried out at the Department of Psychiatry, Western Psychiatric Institute and Clinic, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA.

The following papers have been published and/or accepted, in international journals with a global impact factor (IF) of 10.046 (ISI of Knowledge, Journal Citation Reports inferred from 2010).

Study I: Salar R, Axelson D, Castro-Fornieles F, Goldstein TR, Ha W, Liao F, Gill MK, Iyengar S, Strober MA, Goldstein BI, Yen S, Hower H, Hunt J, Ryan ND, Dickstein D, Keller MB, Birmaher B. Comorbid anxiety in children and adolescent with bipolar spectrum disorders: prevalence and clinical correlates. Journal of Clinical Psychiatry. 2010 Oct;71(10):1344-50. IF: 5.023

Study II: Salar R, Axelson D, Castro-Fornieles F, Goldstein TR, Goldstein BI, Ha W, Liao F, Gill MK, Iyengar S, Strober MA, Yen S, Hower H, Hunt J, Ryan ND, Dickstein D, Keller MB, Birmaher B. Factors associated with the persistence and the onset of new anxiety disorders in youth with bipolar spectrum disorders. In press at Journal of Clinical Psychiatry, 2011. IF: 5.023

Glossary of Abbreviations

BP Bipolar Disorder

BP-I Bipolar I Disorder

BP-II Bipolar II Disorder

BP-NOS Bipolar Disorder Not Otherwise Specified

DSM-IV Diagnostic Statistic Manual IV

ADHD Attention-Deficit Hyperactivity Disorder

DBD Disruptive Behavior Disorders

SUD Substance Use Disorder

PDD Pervasive Developmental Disorders

PDD-NOS Pervasive Development Disorder Not Otherwise Specified

MDD Major Depressive Disorder

MDE Major Depressive Episode

GAD Generalized Anxiety Disorder

ODD Obsessive Compulsive Disorder

PTSD Posttraumatic Stress Disorder

SAD Separation Anxiety Disorder

Anxiety NOS Anxiety Not Otherwise Specified

CD Conduct Disorder

SSRIs Selective Serotonin Reuptake Inhibitors

COBY Course and Outcome of Bipolar Youth study

K-DSADS-PL Schedule for Affective Disorders and Schizophrenia for School-age Children Present and Lifetime Version

K-MRS Kiddie Mania Rating Scale

CGAS Child Global Assessment Scale

PDS Petersen Pubertal Developmental Scale

SCID-I Structured Clinical Interview I

FHS Family History Screen

LIFE Longitudinal Interval Follow-up Evaluation

PSR Psychiatric Status Rating

OR Odds Ratio

CI Confidence Interval

1. INTRODUCTION

1. INTRODUCTION

Onset of bipolar disorder (BP) during childhood significantly affects an individual's psychosocial development. Moreover, youth with BP are at high risk for suicidal behaviors and completed suicide, substance abuse, and legal problems, and have particularly high rates of health services utilization [1-3]. Youth with BP are among the most psychosocially impaired of psychiatrically ill youth, and the presence of comorbidity compounds disability, complicates treatment, and appears to worsen the prognosis of BP [4]. Comorbid conditions frequently associated with pediatric BP include attention-deficit hyperactivity disorder (ADHD), disruptive behavior disorders (DBD), substance use disorders (SUD), anxiety disorders, and pervasive developmental disorders (PDD) [2].

Some of the most common comorbid disorders among youth with BP are the anxiety disorders [4] . However, the presence of anxiety disorders in patients who suffer from BP has been under-recognized and understudied [4]. Since anxiety disorders are also accompanied by significant impairment in the psychosocial functioning of the child [5], it is important to evaluate the prevalence, clinical correlates and factors associated with course and outcome of anxiety disorders in youth with BP.

1.1. Clinical Characteristics

1.1.1. DSM-IV Criteria

It is clear from the work of several groups that some children and adolescents meet the full *DSM-IV* criteria for BP, despite the fact that the criteria were not specifically adapted for use in the pediatric population [1, 6]. When examining the *DSM-IV* criteria for a Manic **(Box 1)** or Hypomanic **(Box 2)** episode, it is obvious that normal children can exhibit many of these features to some degree, especially in certain situations or environments. Therefore it is of utmost importance to evaluate whether the mood and symptoms are abnormal or clearly different from child's usual mood and behavior the given the context and the child's level of development [2].

Box 1. *DSM-IV* criteria for a manic episode

***DSM-IV* criteria for a manic episode**
A. A distinct period of abnormally and persistently elevated, expansive, or irritable mood for at least 1 week (or any duration if hospitalization is necessary). B. During the period of mood disturbance, three (or more) of the following symptoms have persisted (four if the mood is only irritable) and have been present to a significant degree: (1) inflated self-esteem or grandiosity (2) decreased need for sleep (e.g., feels rested after only 3 hours of sleep) (3) more talkative than usual or pressure to keep talking (4) flight of ideas or subjective experience that thoughts are racing (5) distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli) (6) increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation (7) excessive involvement in pleasurable activities that have a high potential for painful consequences (engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments)

C. The symptoms do not meet criteria for a Mixed Episode.

D. The mood disturbance is sufficiently severe to cause marked impairment in occupational functioning or in usual social activities or relationships with others, or to necessitate hospitalization to prevent harm to self or others, or there are psychotic features.

E. The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication, or other treatment) or a general medical condition (e.g., hyperthyroidism).

Note: Manic-like episodes that are clearly caused by somatic antidepressant treatment (e.g., medication, electroconvulsive therapy, and light therapy) should not count toward a diagnosis of bipolar I disorder.

Box 2. *DSM-IV* criteria for a hypomanic episode

***DSM-IV* criteria for a hypomanic episode**
A. A distinct period of persistently elevated, expansive, or irritable mood, lasting throughout at least 4 days, that is clearly different from the usual nondepressed mood.
B. Same as B criterion for Manic Episode.
C. The episode is associated with an unequivocal change in functioning that is uncharacteristic of the person when not symptomatic.
D. The disturbance in mood and the change in functioning are observable by others.
E. The episode is not severe enough to cause marked impairment in social or occupational functioning, or to necessitate hospitalization, and there are no psychotic features.
F. The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication, or other treatment) or a general medical condition (e.g., hyperthyroidism).
Note: Hypomanic-like episodes that are clearly caused by somatic antidepressant treatment (e.g., medication, electroconvulsive therapy, light therapy) should not count toward a diagnosis of bipolar II disorder.

The distinction between a Manic and Hypomanic Episode can be difficult, but also must be taken in a developmental context. Beyond the differences in minimum duration, Manic Episodes require marked impairment, which should be measured against what would be the expected level of functioning for a child given his/her chronological age and intellectual capabilities, in the psychosocial domains that are relevant to youth (e.g. school, family, peers, etc.). A Hypomanic Episode does not require impairment, although there must be an unequivocal change from usual functioning and the mood and functional changes must be observable by others. Given that lack of insight can be associated with mania or hypomania, it is imperative to obtain information from caregivers or other significant adults in the child's or adolescent's life in order to accurately assess symptoms and potential change in functioning [2] .

1.2. Mood Symptomatology

Kowatch et al., (2005) [6] conducted a literature review and meta-analysis of seven reports describing the phenomenology of pediatric BP. The weighted average rates of irritable mood (81%) and euphoria/elated mood (70%) found in the studies was not statistically different. However, there was statistically significant heterogeneity in the rates of irritability and euphoria/elated mood among the individual studies. For instance the rate of euphoria/elation ranged from 14% to 89%. Grandiosity was present in an average of 78% of subjects. Increased energy was on average the most common presenting symptom of mania, occurring in an average of 89% of cases across the samples. Distractibility and pressured speech were nearly equally common. Racing

thoughts, decreased need for sleep, and poor judgment were all displayed by around 70% of youths with mania. Hypersexuality was significantly less common than any other symptom or associated feature of mania, and it manifested in fewer than half of all cases in all samples with relevant data. Flight of ideas was the second rarest symptoms, appearing in an average 56% of cases **(Table 1)**. These patterns of symptom presentation also appear to be consistent with recent analyses of a large group of children and adolescents with bipolar spectrum disorders [1] and a report on the phenomenology of cases with early onset BP in Europe [7] .

Table 1. Symptoms of mania from meta-analysis of pediatric BP studies

Symptom	Weighted Rate (%)	95% CI (%)
Increased energy	89	76-96
Distractibility	84	71-92
Pressure speech	82	69-90
Irritability	81	55-94
Grandiosity	78	67-85
Racing thoughts	74	51-88
Decreased need for sleep	72	53-86
Euphoria/elation	70	45-87
Poor judgment	69	38-89
Flight of ideas	56	46-66
Hypersexuality	38	31-45

Data from Kowatch RA, Youngstrom EA, Danielyan A, et al. Review and meta-analysis of the phenomenology and clinical characteristics of mania in children and adolescents. Bipolar Disorder 2005; 7:483-96.

Though there is less published research on the phenomenology of depression in BP youth, depressive symptoms appear to be quite common. BP youth are frequently described as having mixed states of manic and depressive symptoms or very rapid

cycling between mania and depression [8]. Rates of mixed episodes vary among different studies of bipolar youth. Some groups have reported chronic mixed state lasting years in duration and rapid cycling between mania and depression as frequently as several times per day [9-12] . The issue is complicated by the fact that there are no clear boundaries that delineate a mixed state from an actual switch in episode polarity, or from mood lability and/or transient dysphoria occurring in the midst mania. It is not clear whether the reports of multiple mood cycles in a day represent periods where the child switches from meeting the full criteria of the manic syndrome to a period where they are completely depressed or whether they are manifestations of mood lability within the manic state. However, the evidence does indicate that the majority of BP youth have symptoms of depression interspersed in some manner with manic symptoms [13].

Bipolar children and adolescents can have clear periods of depression that met the full criteria for a Major Depressive Episode (MDE); over 50% of BP youth had a prior history of a MDE in a recent report [1]. A major depressive episode may precede the onset of manic symptomatology, so that some children and adolescents who appear to have unipolar depression may actually have BP with depression as the initial presentation [2]

Psychotic symptoms are frequently present in youth with BP. In the Kowatch meta-analysis, hallucinations and/or delusions were present in an average for 42% of BP youth; however there was substantial heterogeneity in the rates of psychosis across the different studies [6]. The presence of hallucinations or delusions in a youth should trigger careful evaluation for mood disorder, for even though pediatric BP uncommon, it has a

significantly higher prevalence than early-onset schizophrenia or other potential causes of psychotic features in children.

1.3. Controversies Regarding the Diagnosis of Pediatric BP

The diagnosis of children with BP disorder may be difficult because pediatric bipolar disorder usually manifests with rapid mood changes and therefore many children do not have the currently required *DSM-IV* duration of symptoms to fulfill diagnosis for bipolar I disorder (BP-I) or bipolar II disorder (BP-II). According to McClellan et al. (2007) [8], the most common presentation among youth with BP in community settings is characterized by "outbursts of mood lability, irritability, reckless behavior, and aggression". Shifts in mood state are short-lived [14] and irritability, rather than euphoria, tends to be the predominant and most impairing mood state [10]. Furthermore, developmental issues influencing the clinical pictures bipolar disorder in youths, the difficulties children and adolescents have in verbalizing their emotions, and the high rates of comorbid disorders with symptoms that overlap with BP account for the complexity and current controversies in diagnosing children and adolescents with BP [2] .

One factor that may contribute to the difficulty of diagnosing BP in youth is that the most common symptoms of pediatric mania from the meta-analysis by Kowatch et al., (2005) [6] also happen to be frequently present in other pediatric psychiatric disorders. A recent study comparing the phenomenology of bipolar disorder and ADHD found that there were no significant differences between the BP vs. the ADHD subjects in the rate of

irritability (98% BP vs. 72% ADHD), accelerated speech (97% vs. 82%), distractibility (94% vs. 96%) or unusual energy (100% vs. 95%) [15]. The lack of specificity makes it problematic to diagnose mania by simply counting the presence or absence of symptoms. Symptoms expressions concerning inflated self-esteem and increased goal-directed activity are best judged in the context of the child's history because behaviors in isolation may be misleading and may be accounted for by the child's cognitive, biological, or social development [2]

1.4. DSM versus Cardinal Symptoms versus Irritability

The overlap of manic symptoms with features of other psychiatric illnesses emphasizes the diagnostic importance of symptoms that tend to be more specific to mania. Some authors have advocated that two of these mania-specific symptoms, elated/elevated mood and grandiosity, are core features of the manic syndrome so that they should be considered cardinal symptoms [15, 16] [15]. These two symptoms are present in most manic youth, though there was considerable heterogeneity among studies in the rates of euphoria/elation, and one of the largest studies in the analysis required the presence of either elevated mood or grandiosity as an inclusion criterion for the BP subjects. However a subsequently published large study of BP-I youth that did not require either of these symptoms, also had high rates of elated/elevated mood (86%) and grandiosity (57%) [1]. Long-term longitudinal studies of youth meeting the *DSM-IV* criteria for mania with or without cardinal symptoms have not been completed.

Irritable mood may be a frequent presentation of manic mood disturbance, and irritability is generally accepted as one of the most impairing features of pediatric mania. Irritability can be a diagnostic feature of depression, generalized anxiety disorder (GAD), oppositional defiant disorder (ODD), post-traumatic stress disorder (PTSD), or intermittent explosive disorder, and it is a clinical feature frequently associated with conduct disorder, ADHD, Asperger's disorder, autism, and a variety of other conditions. Irritability provides a sensitive marker for pediatric BP, but it is not specific to any particular condition [6].

Some reports have prompted controversy by stating that chronic presentations of irritability alone, particularly when the irritability is severe and accompanied by aggression and volatility, is the primary mood disturbance in bipolar youth and that elevated or expansive mood is uncommon [9-11]. However the high prevalence of elated/expansive mood in most cross-sectional pediatric BP samples stands in contrast to these reports. Prospective evaluations of the phenomenology of new manic episodes in youth have not been published, so it is difficult to assess how frequently pediatric mania presents with only irritable mood.

Children with DBD or ADHD may also have irritability, mood lability, and episodes of anger, defined as "Severe Mood Dysregulation" (SMD) [17]. These children differ from youth with BP spectrum disorder in course, response to lithium, family history, and neuroimaging [18].

1.5. Subthreshold Presentations

Some children and adolescents present in clinical and research settings with what appears to be significant manic symptomatology, but they do not meet the *DSM-IV* criteria for BP-I or BP-II disorders. Reasons for this include: (1) the manic symptoms are not present for sufficient time to meet the *DSM-IV* duration criteria for a Manic, Hypomanic or Mixed Episode; (2) the mood disturbances and symptoms do not occur in distinct episodes; (3) the potential manic symptoms are not clearly temporally associated or do not intensify with the abnormal mood; or (4) it cannot be reliably determined whether the abnormal mood and symptoms are attributable to BP or better accounted for by another psychiatric diagnosis. The diagnosis and management of these children and adolescents is controversial, though many present for mental health treatment with significant impairment and are frequently assigned a diagnosis of Bipolar Disorder Not Otherwise Specified (BP-NOS) [2]. Empirical research in subthreshold presentations of bipolarity in youth is in its early stages.

A recent multicenter study, Course and Outcome of Bipolar Youth study (COBY), examined children and adolescents who presented with a history of clinically significant subthreshold manic symptoms. Specifically, BP-NOS patients had (a) elated mood plus two "B" mania symptoms, or irritable mood plus three "B" symptoms; (b) change in level of function associated with mood symptoms; (c) at least four hours of symptoms within 24 hours; and (d) at least four cumulative lifetime days meeting criteria Though the subjects could have been below the *DSM-IV* threshold for either the number

of manic symptoms or the duration of episode, the majority of these youth fulfilled the full mood and symptom criteria for mania and/or hypomania, but did not meet the 4-day duration criteria for a Hypomanic Episode or the 7-day duration criteria for a Manic/Mixed Episode [1]. These cases of BP-NOS uniformly presented with histories of significant impairment and nearly all had some form of psychiatric treatment prior to assessment. There were no significant differences among the BP-I and BP-NOS groups in age of onset, duration of illness, lifetime rate of comorbid diagnoses, suicidal ideation and major depression, family history, and the types of manic symptoms that were present during the most serious lifetime episode. Compared with youth with BP-NOS, subjects with BP-I had more severe manic symptoms, greater overall functional impairment, and higher rates of hospitalization, psychosis, and suicide attempts [1]. Elevated mood was present in 82% of subjects with BP-NOS and 92% of subjects with BP-I [1]. A significant proportion (36%) of these youth with BP-NOS has converted to BP-II or BP-I diagnoses over an average four year follow-up period [2].

Bipolar disorder is more likely to present with hypomania or subthreshold manic symptoms in community settings. A large community study of adolescents found that the lifetime prevalence of BP (primarily BP-II and cyclothymia) was approximately 1%. An additional 5.7% of the sample reported what would be categorized in the *DSM-IV* as BP-NOS [19]. Lifetime prevalence for subsyndromal BD was approximately 5%. Less than 1% of adolescents with MDD switched to BP by age 24. Adolescents with BP had an elevated incidence of BP from 19 to 23 years, while adolescents with subsyndromal BD exhibited elevated rates of MDD and anxiety disorders in young adulthood [20].

The diagnosis of BP-NOS was addressed in the recent American Academy of Child and Adolescent Psychiatry (AACAP) practice parameter guidelines [8]. These guidelines note that irritability and emotional reactivity are nonspecific symptoms found in multiple behavioral, affective, and developmental disorders and are therefore not diagnostic of mania [2]. The AACAP guidelines suggest that the BD-NOS diagnosis be given to youths with either (a) manic symptoms of insufficient duration (i.e., lasting less than four days) or (b) youths with "chronic manic-like symptoms which constitute baseline functioning" [8]. However, prominent differences between these two classifications may indicate that BP-NOS, as defined by the AACAP guidelines, are clinically heterogeneous [21].

1.6. Comorbid Disorders

Youth with BP are among the most impaired population, and the presence of comorbidity compounds disability, complicates treatment, and appears to worsen the prognosis in this population [4]. Comorbid disorders may have a significant impact on various indices of BP correlates. Knowledge of their comorbid presence with BP could be informative in determining course, prognosis, and functional and therapeutic outcomes. Early identification and appropriate management may lead to improved functioning, prevention of impending emergence of comorbid disorders such as anxiety, ODD, CD and SUD, and attenuation of the untreated course of BP [22, 23]. On the other hand, if comorbidity is not appropriately acknowledged, then misattribution of impairing

symptoms could lead to inappropriate therapeutic interventions, unnecessary exposure to neuroleptic agents, worsening of symptoms, delayed diagnosis, and misuse of mental health resources.

Recognition of comorbidity is important as it has therapeutic implications, such as (1) increased risk of mood destabilization, which is inherent to the therapeutic options for the comorbidity, as is the case with antianxiety, antidepressant, or anti-ADHD medications that have manicogenic potential, (2) atypical response (efficacy and tolerability) to psychotropics associated with certain disorders such as PDD, or (3) less than expected antimanic response to thymoleptic agents in the presence of certain comorbid disorders (for instance ADHD, obsessive compulsive disorder (OCD)). Comorbid disorders may be challenging to diagnose due to overlapping symptoms and developmentally sensitive, complicated patterns of symptom development [4].

Several methods have been applied to scientifically understand comorbidity. Structured diagnostic interviews (for instance, the Kiddie Schedule for Affective Disorders and Schizophrenia-Epidemiologic Fifth Version (K-SADS-E)) [24] are helpful in clinically parsing out comorbid conditions as they comprehensively assess the spectrum of psychopathologies described in the *DSM-IV*, including past and present severity of symptoms. Diagnoses are considered positive only if the diagnostic criteria are met to a degree that would be considered clinically meaningful. ‘‘Clinically meaningful’’ means that the data collected from the structured interview indicate that the diagnosis should be a clinical concern due to the nature of the symptoms, the associated impairment, and the

coherence of the clinical picture. For a given disorder, the overlapping nonspecific symptoms are considered for the diagnosis if the respective cardinal symptoms are present, and the disorder is cause for significant impairment. Furthermore, although *DSM-IV* criteria do not permit comorbid presence of certain disorders and assign diagnoses based on hierarchy, to fully characterize the clinical picture, a nonhierarchical diagnostic approach is taken to assess for comorbid disorders [4]. Thus, the approach taken by the structured interview objectively and comprehensively documents symptom presentation and minimizes diagnostic biases.

Perhaps the most compelling scientific method to examine comorbidity is familial risk analysis, which addresses uncertainties regarding complex phenotypes in probands by examining the transmission of comorbid disorders in families [25]. Therapeutic response has also provided evidence of the existence of separate conditions. For instance, in a review of clinical records in manic children, Biederman and colleagues [26] reported that whereas mood stabilizers significantly improved mania-like symptoms, antidepressants and stimulants did not, and, conversely, tricyclic antidepressants and not mood stabilizers were associated with improvement of ADHD symptoms. Finally, attributes of comorbidity can also be addressed by applying neurobiological probes to seek the existence of underlying changes commensurate with each comorbid disorder, either disorder or neither disorder indicating a unique subtype with distinct neurobiological attributes. The emerging proton magnetic resonance spectroscopic (1HMRS) imaging intervention research in youth with BP suggests a profile of cerebral metabolites in a specific region of the brain, which may facilitate the understanding of neurochemical

correlates of BP in the context of comorbidity. For instance, the 1HMRS profile of cerebral metabolites in the anterior cingulate cortex region of the brain in children with ADHD appears to have a significantly higher ratio of glutamate plus glutamine to myo-inositol-containing compounds than does the profile of children with comorbid BP and ADHD [27].

Present studies addressing comorbidity generally rely either on cross-sectional observations or on recall of disorders over the whole life course. Both of these approaches pose limitations. Longitudinal studies that offer the best possibility for observing the developmental progression of the emergence of comorbid conditions are required. Treatment guidelines for pediatric BP indicate that the treatment plan must include treatment for each comorbid disorder, which may become a complex process of trial and error to find the most effective combination of medications [28]. These guidelines further recommend that in the absence of treatment trials specifically studying a population of children with BP and specific comorbid disorders, clinicians should use psychopharmacologic and psychosocial treatments that are generally recommended for each comorbid disorder when that disorder occurs as the primary problem. Though certain comorbid disorders associated with BP respond to antimanic agents (DBD, PDD), there are frequently co-occurring disorders (ADHD, anxiety disorders, depression) with typical onset before the emergence of mania that require treatment with agents that have manicogenic potential. Available empiric evidence and clinical acumen dictate that treatment of comorbid conditions can be addressed only after the symptoms of BP are stabilized [29]. Decision to treat the comorbid disorders following stabilization of mania

should be guided by clinically determining the level of impairment associated with the disorder [4]. As a rule, medications with lower manicogenic potential are preferred in this population. Comorbid conditions frequently associated with pediatric-onset BP include ADHD, DBD, SUD, anxiety disorders, and PDD **(Figure 1).**

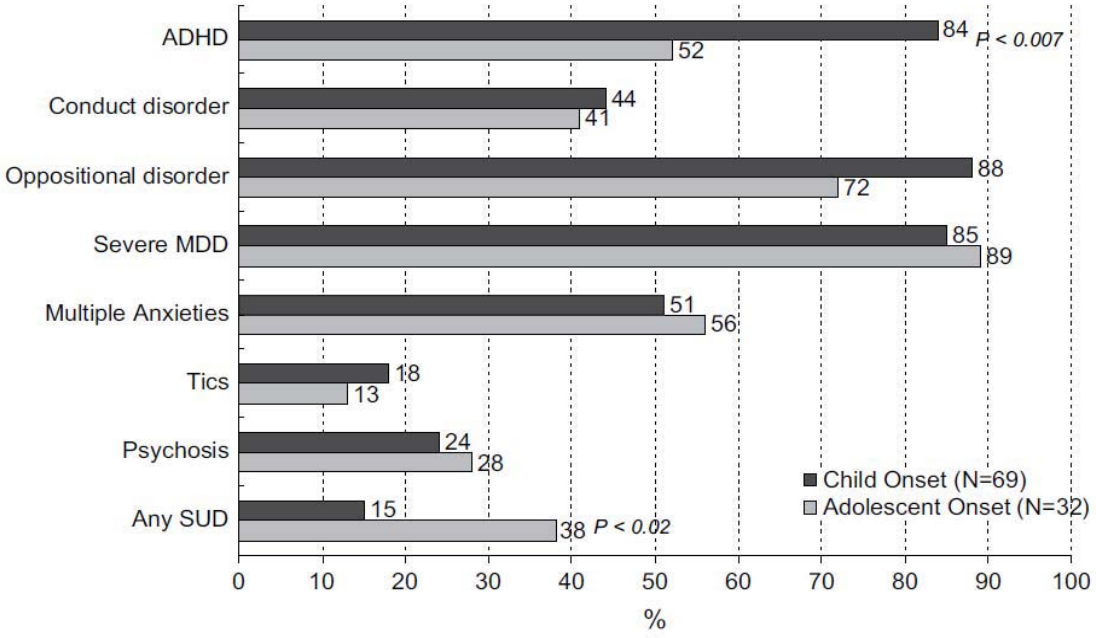

Figure 1. Rates of psychiatric comorbidity in bipolar youth stratified by age at onset of BP. (Adapted from Biederman J, Petty C, Faraone SV, et al. Moderating effects of major depression on patterns of comorbidity in referred adults with panic disorder: a controlled study. Psychiatry Res 2004

1.6.1. Anxiety Disorders

The presence of anxiety disorders in individuals who suffer from BP has been underrecognized and understudied. One reason for this lack of recognition could be the notion that it is counterintuitive to suggest that BP, which is characterized by high levels of disinhibition, could coexist with anxiety, which is characterized by fear and inhibition [4].

The few studies that have addressed this issue in small samples of youth with BP, have shown lifetime prevalence of comorbid anxiety disorders between 14% and 56%, with a weighted average of 27% [6, 30-34]. Furthermore, a recent detailed analysis of the comorbidity between pediatric BP and anxiety disorders in a clinically referred population revealed that 76% of youth with BP have one or more anxiety disorders comorbid with their BP [35]. In a community sample, Lewinsohn and colleagues [19] reported that a third of nonreferred BP adolescents had comorbid anxiety disorders, a significantly higher rate than that found in those without a history of BP. Moreover, family studies have consistently shown high rates of anxiety disorders in offspring of parents with BP [36-40]. Some clinical and epidemiologic studies in adult and pediatric populations have identified a wide range of anxiety disorders associated with BP, with rates ranging between 12.5% and 76% [19, 34, 35, 41-47]**(Figure 2)**.

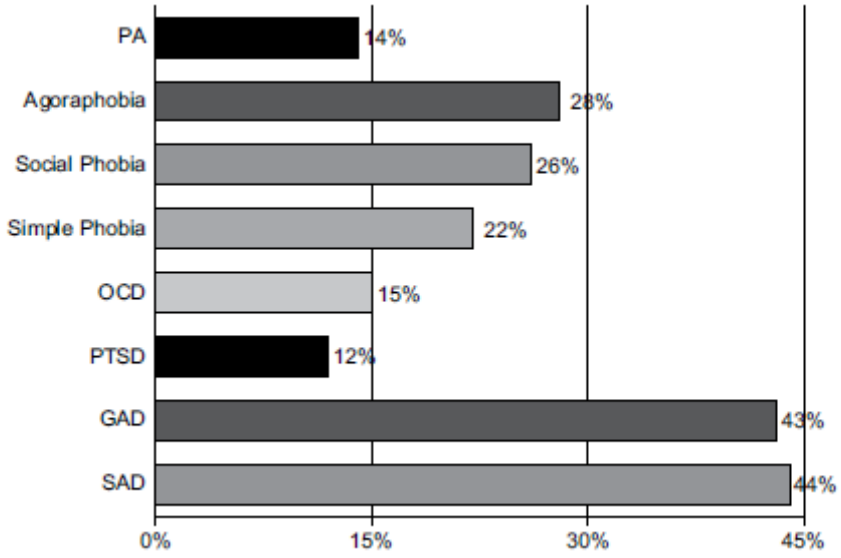

Figure 2. Anxiety disorders in clinically referred youth with BP. (Adapted from Harlpold T, Biederman J, Kwon A, et al., Examing the association between pediatric bipolar disorder and anxiety disorders in psychiatrically referred children and adoelscetns. Journal of Affective Disroders 2005; 88(1);19-26.

Among various anxiety disorders, a specific association of certain anxiety disorders more than others has been suggested in youth with BP [34, 48]. A number of investigators have suggested that a particular link exists between panic disorder and BP in adults [49, 50] and children [48]. Data from adult studies report a lifetime prevalence of panic disorder in 21% to 33% of individuals with BP [49-51] and conversely, lifetime BP in 6% to 23% of individuals with panic disorder [46, 52]. MacKinnon and colleagues [53, 54] use family genetic methodology in 57 families to argue that panic disorder with BP is a genetic subtype of BP. Savino and colleagues [55] systematically explored the intraepisodic and longitudinal comorbidity of 140 adults with panic disorder and reported comorbidity with BP in 13.5% of the patients with panic disorder. They also note that an additional 34.3% met features of ‘‘hyperthymic temperament’’, a possible bipolar spectrum

condition. Biederman and colleagues [32] reported high rates of panic disorder (52%) among youth with BP consistent with the observation by Birmaher and colleagues [48], suggesting that the association between BP and panic disorder in children and adolescents might be unique and specific. However, emerging literature indicates high prevalence of various anxiety disorders—including but not limited to panic disorder—in pediatric [35, 42, 44] and adult [45, 56, 57] populations with BP, which challenges the notion of a specific link between BP and panic disorder. Thus, more information is needed as to whether the association between BP and anxiety disorders in youth is limited to a single anxiety disorder or is more extensive and includes other anxiety disorders as well. In the presence of high levels of anxiety, adults with BP experience greater symptom severity, increased risk for suicide and alcohol abuse, higher frequency of a polypharmacy regimen, more severe adverse effects, poor treatment response, and higher rates of nonremission with poor course and functioning [41, 58-60].

Improving the understanding of the relationship between anxiety disorders and BP in youth has important treatment implications. Masi and colleagues [44] reported high rates of pharmacologic hypo/mania in youth with anxiety disorders, with the mean age at onset for anxiety disorders preceding that for BP. This finding suggests caution when considering antidepressant pharmacotherapy in a pediatric population with multiple anxiety disorders. Considering that treatments for BP with traditional mood stabilizers do not generally treat anxiety disorders and that treatment of anxiety disorders with selective serotonin reuptake inhibitors (SSRIs) can aggravate BP, the pharmacologic approach to bipolar children with comorbid anxiety disorders needs to be defined [4]. As BP and

anxiety disorders respond to different treatments, identification of the comorbid state is essential for proper treatment and for achieving optimal functioning. No systematic data are available that examine treatment of anxiety disorders in the context of bipolar comorbidity. Trials of pediatric anxiety disorders exclude children with BP by protocol design, and similarly, children with a BP diagnosis are typically excluded from the trials of treatment for both depression and anxiety. To-date, only one open-label trial has assessed response of co-occurring panic attacks and GAD in adults with BP, reporting significant decrease in or remission of anxiety symptoms with divalproex therapy [61]. Corroborative evidence for antianxiety effect of mood stabilizers comes from various open-label and controlled trials in adult population with anxiety disorders that suggest valproate to be effective in treating panic disorder and PTSD [62-65]. Antianxiety response of certain moodstabilizers could be specific to certain anxiety disorders. For instance, carbamazepine, though effective in treating certain symptoms of PTSD, is found to be ineffective in treating other anxiety disorders in adults, namely panic disorder and OCD [66-68].

The existent longitudinal studies of comorbid anxiety in youth [69, 70] and adults with BP [58, 59, 71, 72] have shown that anxiety disorders are associated with greater severity of BP. For example, Masi and colleagues (2007) [69] followed for at least 6 months a group of 224 children and adolescents with BP spectrum disorder. They reported that compared to BP youth without panic disorder, those with panic disorder showed less mood severity at baseline and less mood improvement during the follow-up. In addition, DelBello and colleagues (2007) [70] followed a group of 71 adolescents with BP-I one year after

discharge from the hospital. They found that adolescents with BP and comorbid anxiety disorder had more severe mood symptoms and lower rates of recovery than adolescents without anxiety.

Studies in adults with BP have also found that the presence of comorbid anxiety is associated with shorter euthymic periods, higher depression severity, rapid cycling, longer time to remission from the index episode, increased risk for recurrence, more time with depressive mood, suicidal behavior, substance abuse, lower quality of life, diminished role functioning, and poor response to treatment [41, 58, 59, 71-74].

The above-noted studies focused on the effect of anxiety on the course of BP, but to our knowledge there are no studies examining the course of anxiety disorders among in both youth and adults with BP. This is important because the early identification and management of anxiety disorders in youth with BP may improve the prognosis of BP.

1.7. Associated Features

Psychosis appears to be associated with pediatric BP. Most research groups have found that approximately one-fifth of youths meeting diagnostic criteria for BP I will also has hallucinations or delusions during the course of a mood episode [6]. The prevalence of psychotic features is lower in adolescent mania as compared with adult mania, with lower ratings on thought disorder and delusions. It is critical to pay attention to age-specific manifestation of the symptoms [3] .

Pediatric bipolar disorder significantly affects the normal psychosocial development of the child. Youth with bipolar disorder have a high risk for suicidal behaviors and completed suicide, substance abuse as well as for behavioral, academic social, legal problems, and health utilization [1, 3 75].

1.8. Differential Diagnosis

It can be difficult to diagnose pediatric BP because the variability in the clinical presentations, high comorbidity and overlap in symptom presentation with other psychiatric disorders. Depending on their level of cognitive development, children may have problems expressing or describing their symptoms. In addition, psychotropic medications used for treatment can potentially affect a child's mood and/or behavior [24]. Use of illicit drugs or alcohol can also complicate the diagnostic picture.

In daily practice, severe ODD and ADHD are the most frequent conditions that may be confused with BP. The *DSM-IV* diagnostic criteria for a Manic Episode overlap with that of ADHD (distractibility, motor hyperactivity, pressured speech) and ODD (irritability/anger). In addition, youth with ADHD frequently present with mood variability, difficulty falling asleep, and engage in risk-taking or thrill-seeking behavior that could be difficult to differentiate from BP. There are some symptoms that mainly occur in BP youth and may help to differentiate between BP and these disorders, such as clinically relevant euphoria, grandiosity, significant decreased need for sleep, hypersexuality (without history of sexual abuse or exposure to sex) and hallucinations [15].

Most depressed youth seen at psychiatric clinics are experiencing their first episode of depression [76]. Some of these subjects may develop BP, but so far it is almost impossible to know who will develop BP at the time of first assessment. Thus, a careful assessment for history of manic or hypomanic symptoms is indicated. Also, the presence of psychosis, family history of BP, and pharmacologically induced mania/hypomania may indicate an increased risk to develop BP [77-80]. Schizophrenia is rare in children and sometimes BP may manifest with psychosis and bizarre behavior. In older adolescents, the presence of mood-incongruent delusions and hallucinations and thought disorder can lead to the misdiagnosis of BP as schizophrenia in as may as 50% of cases [81, 82] . Therefore, mood disorders need to be ruled out in any child with psychosis. Youth with PDD-NOS or Asperger's disorder may have mood lability, aggression, and agitation and be misdiagnosed as having BP. Substance abuse may also induce severe mood changes that may be difficult to differentiate from BP.

The use of medications such as antidepressants, stimulants or steroids may unmask or trigger manic symptomatology in a susceptible individual [83]. However this does not necessarily mean the child has bipolar disorder. Family history, the severity, length, and quality of manic symptomatology as well as the temporal association to changes in medication may help to differentiate between BP and agitation induced by these or other medications [84].

1.9. Clinical Course

1.9.1. Recovery and Recurrence

There is a consensus for definitions used to characterize the longitudinal course of BP. Recovery is defined as eight consecutive weeks without meeting any of the *DSM-IV* criteria for mania, hypomania, depression, or mixed affective state. Remission is defined as 2–7 weeks without meeting for any of the *DSM-IV* criteria for affective episodes. Relapse is defined as two consecutive weeks of *DSM-IV* criteria for affective episodes with clinically significant impairment (Children's Global Assessment Scale score of <60). Chronicity is defined as failure to recover from an affective episode for a period of at least 2 years. Retrospective studies [82] and naturalistic longitudinal studies of children and adolescents with BP [19, 85-90] have reported that 40%–100% will recover in a period of 1–2 years. Of those patients who recovered, however, approximately 60%–70% showed recurrences in an average of 10–12 months [3].

Birmaher et al., (2006) [13] reported than overall 68% of subjects recovered from their index episode a median of 78 weeks after the onset of the episode. There were no significant differences in the rates of recovery among the BP-I, BP-II and BP-NOS, but subjects with BP-NOS had a significantly longer time to recovery than subjects with BP-I and BP-II (all comparisions, $p \leq .05$) **(Figure 3).** They reported also that overall 56% of subjects had at least 1 recurrence at a median of 61.0 weeks after recovery of the index episode. Subjects with BP-II had higher rates of recurrence than subjects with BP-NOS

and subjects with BP-NOS had significantly longer time to recurrence than those with BP-I and BP-II (all comparision, p≤ .05) **(Figure 4).** In summary, subjects with BP-I and BP-II recovered from their index episode and had recurrences more frequently than those with BP-NOS. In contrast, subjects with BP-NOS had a more protracted illness, but once they recovered from their index episode, they took a longer time to recur than those with BP-I and BP-II. On average, subjects had 1.5 syndromal recurrences per year, particularly depressive episodes.

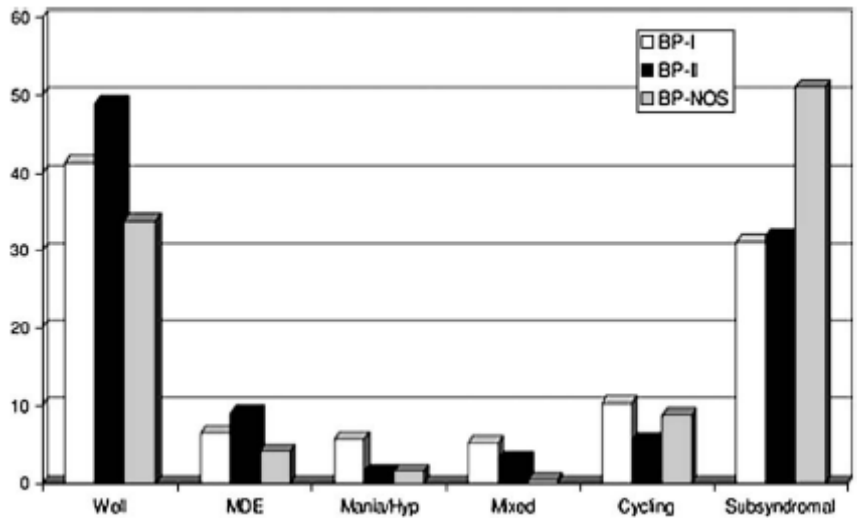

Figure 3. A comparison of the weekly symptomatic status of youth with bipolar I disorder, bipolar II disorder, and bipolar disorder not otherwise specified. The weekly symptoms status is the percentage of follow-up weeks that were asymptomatic or symptomatic in different mood categories. (From Birmaher B, Axelson D. Course and outcome of bipolar spectrum disorder in children and adolescents: a review of the existing literature. Dev Psychopathol 2006; 18(4):1023-35)

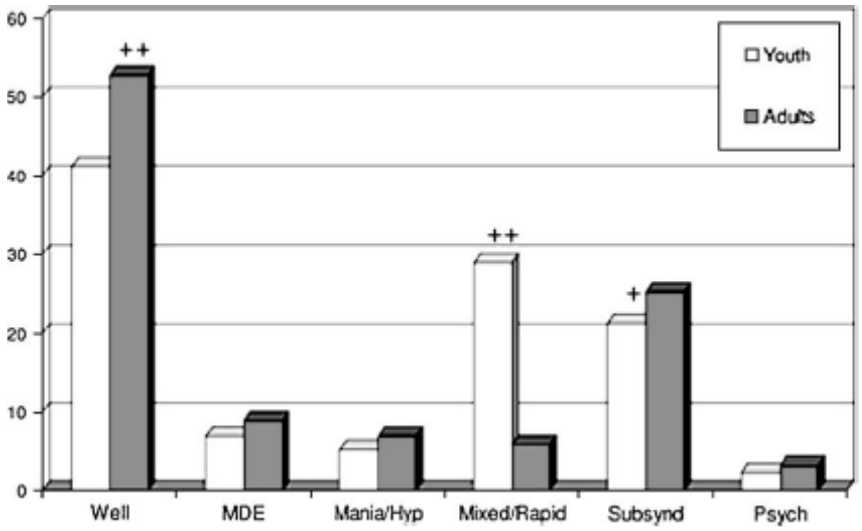

Figure 4. Weekly symptoms stauts. Comparision between youth with bipolar I disorder (BP-I) versus adults with BP-I. The weekly symptom status is the percentage of follow-up weeks ttaht were adysmptomatic or symptomatic in different mood categories; p=.05; p≤.001; +p=.05; ++p≤.001. (From Birmaher B, Axelson D. Course and outcome of bipolar spectrum disorder in children and adolescents: a review of the existing literature. Dev Psychopathol 2006; 18(4):1023-35

The results for BP-I subjects are similar to those of Geller et al. (2004) [85], who found that 70% to 100% of children and adolescents with bipolar disorder will eventually recover from their index episode over the 4-year follow-up, but of those who recover, up to 80% experience one or more recurrences in a period of 2 to 5 years. Del Bello et al. (2007) [70] showed that 85% had syndromic recovery in an average period of 27 weeks after the onset of their index episode when evaluated the 1-year outcome after discharge from an inpatient unit of BP I adolescents admitted for their first manic or mixed episode. However, of these subjects, about 52% had at least one syndromic recurrence 17 weeks on average after they recovered.

Several factors have been identified that may potentially affect the course and outcome of bipolar youth. DelBello et al. (2007) [70] reported that the comorbid presence of ADHD, anxiety disorders, low socioeconomic status, and poor adherence to pharmacological treatment was associated with longer time to recovery. Alcohol use disorder, lack of psychotherapy treatment and use of antidepressants were associated with shorter time to recurrence.

Preliminary analyses from the Course and Outcome of Bipolar Youth study showed that subjects with prepubertal-onset BP were approximately 2 times less likely than those with postpubertal-onset to recover [91]. In addition, subjects with prepubertal-onset BP had more chronic symptoms, defined as percentage of follow-up time with any mood symptoms, spent more follow-up time with any mood symptoms, and had more polarity changes per year than postpubertal-onset BP subjects. Preliminary analyses showed that mixed episodes, psychosis, low socioeconomic status, comorbid ADHD, conduct anxiety, substance abuse, and family psychopathology were associated with significantly more follow-up time with syndromal and subsyndromal symptoms [91].

Geller et al., (2004) [85] found that low scores on an assessment of maternal warmth was the factor with the strongest association with worse outcome and predicted faster relapse after recovery from mania. Psychosis predicted more weeks ill with mania or hypomania.

1.9.2. Week-to Week Mood Symptomatology

Recent studies have shown that bipolar disorder is not only manifest by punctuated recovery and recurrences, but also by ongoing fluctuating syndromal and subsyndromal symptoms [3, 12, 13, 85.] Birmaher et al., (2006) [91] analyses of weekly mood symptoms showed that subjects were symptomatic approximately 60% of the follow-up time, with about 22% of the time in full syndromal episodes (Manic, Hypomanic, Mixed or Major Depressive Episodes) and 38% of the time with subsyndromal symptoms of mania and/or depression. Subjects with BP I had more syndromal manic/hypomanic and mixed episodes than those with BP-NOS, and subjects with BP-II had more syndromal and subsyndromal depression that those with BP-I and BP-NOS. In contrast, subjects with BP-NOS showed more subsyndromal symptoms. During the follow-up, subjects with all types of BP, and particularly those with BP-NOS, with early onset or psychosis showed numerous changes in symptoms and shifts of polarity.

DelBello et al., (2007) [70] show that during 1 year follow-up after hospitalization, bipolar disorder adolescents spent 38% of their time meeting full syndromic criteria (mainly mixed episodes), 46% of the time with subsyndromal symptoms, and 16% without symptoms.

1.9.3. Developmental Differences in Course

There are developmental differences in the course of BP between children and adults [3, 9, 12, 85, 92, 93]. Youth with BP-I spent significantly more time symptomatic and had more mixed/cycling and subsyndromal episodes (see **Figure 4**; symptomatic periods and mixed $p<.001$; subsyndromal $p=.05$), than adults with BP-I. Moreover, BP-I youth showed significantly more polarity switches than adults with BP-I (**Figure 5**) (all comparisons $p<.001$). Thus, across the age span and especially in youth, BP usually follows an ongoing changeable course with patient having a wide spectrum of mood symptoms ranging from mild to severe depression, mania and/or hypomania [91].

Early-onset BP may be a particularly severe form of the illness. BP disrupts a child's developmental trajectory, limiting his or her ability to achieve critical developmental milestones that has a lasting impact on their functioning into adulthood. Bipolar adults with onset in childhood or adolescence have higher rates of manic and depressive episodes, comorbid psychiatric disorders and spend less time in a euthymic (normal) mood state as compared to those with adult-onset [94]. Children and adolescents with BD have phenotypic features that are associated with poor prognosis in adults with BD, including high rates of mixed depressive and manic symptomatology, psychosis and long periods of subsyndromal mood symptoms [91]. Given the severity of illness, identifying and treating bipolar disorder in children is extremely important, particularly since recent large studies indicate that between ⅓ – ½ of bipolar adults recall the onset of their symptoms during childhood or adolescence [94, 95].

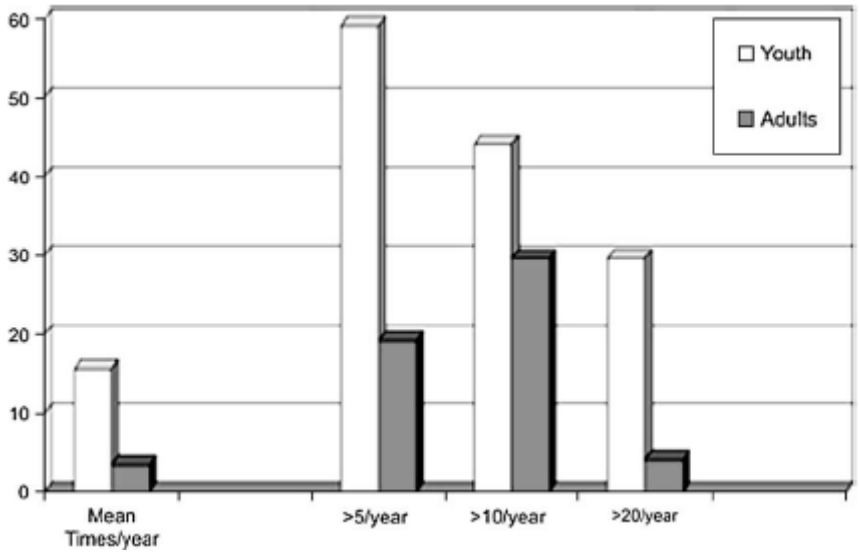

Figure 5. Change in polarity. Comparison between youth with bipolar I disorder (BP-I) versus adults with BP-I. The change in polarity is the switch between depression and mania/hypomania or vice versa with or without intervening weeks in asymptomatic status. All comparision are significant at p<.001. (From Birmaher B, Axelson D. Course and outcome of bipolar spectrum disorder in children and adolescents: a review of the existing literature. Dev Psychophatol 2006;18(4):1023-35.

1.10. Consequences

The enduring and rapid changeability of symptoms in children and adolescents with BP are occurring early in life and at crucial stages of their lives. This can deprive them of the opportunity for normal emotional, cognitive, and social development [3, 9, 12, 19, 20, 85, 88, 97-99]. The pediatric prospective naturalistic studies a well as retrospective reports [36, 48-53] have showed high rate of hospitalizations and health service utilization, psychosis,

suicide attempts and completions, switch from BP-NOS to BP-I or II and from BP-II to BP-I, substance abuse, unemployment, legal problems and poor psychosocial functioning. The ongoing BP symptoms also have negative impact in the family, marital, and sibling relationships as well as the family economics. The considerable impairment in psychosocial functioning reported in these studies is not only due to the fact that most of them were carried out in clinical samples, because similar findings have been reported BP adolescents never referred for treatment [19, 20].

1.10.1. Functional Impairment

Pediatric BP is associated with aggressive behavior, attention problems anxious and depressed symptoms delinquent behavior, social problems withdrawal, and thought problems [100-102]. Geller et al. (2002) [103] reported that more than half of youths diagnosed with BD had poor social skills, had no friends, and were teased by other children. They have poor relationships with siblings and conflictual relationship with their parents. Specifically, there was a high degree of hostility and low warmth in maternal-child relationships, poor agreement between parents on child-rearing practices, and minimal problem-solving skills. Parent and child reported elevated novelty-seeking traits in pediatric BD compared with those with ADHD and healthy controls [104.] Onset of bipolar illness in adolescence negatively impacts on the teenager's ability to function effectively in the school environment [105]. Additional studies are required to clarify whether social skill deficits are related to BP, comorbid disorders, family psychopathology, or demographic factors, and the interactions among these variables.

1.10.2. Suicidality

Longitudinal follow-up indicates that through age 18 years, 44% of cases with BP (excluding BP-NOS) attempted suicide, versus 22% of cases with MDD, 18% of BP-NOS cases, and only 1% of cases with no diagnosis [106]. BP was associate with the highest rates of suicidal ideation (72% of cases, versus 52% of major depressive disorder, 41% of core positive bipolar NOS, and 6% of participants with no diagnosis), as well as younger age at first attempt (mean of 13.3 years), higher rates of multiple attempts (88% of cases), and significantly greater medical lethality of attempts [106].

1.10.3. Substance Abuse and Behavior Problems

Comorbid SUD is common among adults with BP, and is associated with markedly increased burden of illness across multiple domains. Epidemiologic and clinical studies demonstrate that youth-onset BP confers even greater risk of SUD in comparison to adult-onset BP. Recent studies of youth with BP have not identified childhood SUD; however the prevalence escalates during adolescence, with estimates ranging from 16-39%. SUD among adolescence with BP is associated with suicide attempts, legal problems, pregnancy, and abortion [107]. Several studies suggest that substance use disorders are more common among youth with BP than among healthy and psychiatric controls. Wilens et al., (1999) [108] found that the prevalence of SUD was significantly higher among subjects with BP compared to those without BP. The increased prevalence of SUD among youth with BP remained significant after controlling for conduct disorder [108, 109].

2. APPROACH, OBJECTIVES AND HYPHOTHESES

2. OBJECTIVES AND HYPHOTESES

2.1. Study I: Comorbid Anxiety in Children and Adolescents with Bipolar Spectrum Disorders: Prevalence and Clinical Correlates

2.1.1. Objectives

Onset of bipolar disorder (BP) during childhood significantly affects an individual's psychosocial development. Moreover, youth with BP are at high risk for suicidal behaviors and completed suicide, substance abuse, and legal problems, and have particularly high rates of health services utilization. Some of the most common comorbid disorders among youth with BP are the anxiety disorders. Since anxiety disorders are also accompanied by significant impairment in the psychosocial functioning of the child, it is important to evaluate the prevalence and clinical correlates of the association between BP and anxiety in youth. Moreover, prior research indicates that the presence of comorbid anxiety disorders negatively affects course, outcome, and treatment response in BP.

The association between BP and comorbid anxiety disorders is of particular clinical significance since the pharmacological treatment for anxiety disorders with the most evidence of efficacy in both children and adults is SSRIs. Unfortunately, these medications have been shown to destabilize the symptoms of BP.

Given the clinical relevance of comorbid anxiety and BP and the existence of few studies with small samples, we aimed to investigate the prevalence, correlates, and familial risk associated with comorbid anxiety disorder in a large sample of children and adolescents with BP spectrum disorders.

2.1.2. Hypotheses

We hypothesized that as compared with youth with BP and no comorbid anxiety, those with BP and a comorbid anxiety disorder would have: (1) earlier BP onset and more severe lifetime BP symptoms, (2) higher rates of suicidal behavior and substance use disorders, (3) poorer overall functioning, and (4) higher rates of familial mood and anxiety disorders.

2.2. Study II: Factors Associated with the Persistence and the Onset of New Anxiety Disorders in Youth with Bipolar Spectrum Disorders

2.2.1. Objectives

Clinical and epidemiological studies have documented high rates of comorbid anxiety disorders in youth BP. The existent longitudinal studies of comorbid anxiety in youth and adults with BP have shown that anxiety disorders are associated with greater severity of BP. The above-noted studies focused on the effect of anxiety on the course of BP, but to our knowledge there are no studies examining the course of anxiety disorders in youth and adults with BP. This is important because the early identification and management of anxiety disorders in youth with BP may improve the prognosis of BP.

Since there are no other pediatric and adult longitudinal studies that have assessed the outcome of anxiety disorders in BP, the main goal of the current study was to evaluate the longitudinal course of the anxiety disorders of the BP youth who had anxiety disorders at intake. More specifically we sought to evaluate whether the anxiety disorders present during the follow-up were the same as those present at intake (homotypic continuity), and to identify the intake and follow-up factors associated with the persistence (>50% of the follow-up time) of anxiety disorders. In addition, we evaluated the factors at intake and follow-up that were associated with the development of new

anxiety disorders during the follow-up period in youth without any anxiety disorders at intake.

2.2.2. Hyphoteses

We hypothesized that: (1) most of the anxiety disorders during the follow-up will be the same type of those present at intake, (2) persistence of anxiety will be associated with multiple anxiety disorders, more depression, substance use, suicide behavior, less follow-up time in euthymia, and less psychopharmacologic treatment (3) new onset of anxiety will be associated with substance use, physical and/or sexual abuse, more follow-up time with manic or hypomanic symptoms, and less psychopharmacologic treatment.

3. METHODS

3. METHODS

3.1. Study I: Comorbid Anxiety in Children and Adolescents with Bipolar Spectrum Disorders: Prevalence and Clinical Correlates

3.1.1. Subjects

The sample consist in 446 youth, ages 7 to 17 years 11 months (mean = 12.7, SD = 3.2) who criteria for *DSM-IV* [110] BP-I (n=260), BP-II (n=32), and operationally defined BP-NOS (n=154) [31, 111, 112] were recruited primarily though clinical referrals from three academic medical centers: (University of Pittsburgh [Pittsburgh, Pennsylvania], Brown University [Providence, Rhode Island], and University of California at Los Angeles [Los Angeles, California]).

Study inclusion criteria were as follows: (1) aged 7 years 0 months to 17 years 11 months and (2) fulfilled the *DSM-IV* criteria for BP-I or BP-II or the COBY-established criteria for BP-NOS. Because the *DSM-IV* criteria for BP-NOS are vague, the COBY study investigators set the minimum inclusion threshold for the BP-NOS group as subjects who did not meet the *DSM-IV* criteria for BP-I or BP-II but had a distinct period of abnormally elevated, expansive, or irritable mood plus the following: (1) 2 *DSM-IV* manic symptoms (3 if the mood is irritability only) that were clearly associated with the onset of abnormal mood, (2) a clear change in functioning, (3) mood and symptom

duration of a minimum of 4 hours within a 24-hour period for a day to be considered meeting the diagnostic threshold, and (4) a minimum of 4 days (not necessarily consecutive) meeting the mood, symptom, duration, and functional change criteria over the subject's lifetime, which could be two 2-day episodes, four 1-day episodes, or another variation. Symptoms and mood changes that occurred during substance use or antidepressant treatment did not count toward a bipolar diagnosis. Study exclusion criteria were as follows: current or lifetime *DSM-IV* diagnosis of schizophrenia, mental retardation, autism, or severe autistic spectrum disorders or mood disorders due to substance abuse, due to a medical condition, or secondary to use of medications (eg, corticosteroids). Subjects determined to have the onset of BP before comorbid substance use disorder was included. Potential subjects with mild comorbid Asperger disorder or PDD-NOS were included if their mood symptomatology was clearly episodic and best accounted for by the bipolar diagnosis.

Subjects were recruited through clinical referrals from within the medical centers and the community and from advertisements. A telephone or brief face-to-face screening interview and discussion of the study protocol was administered to the parent or caregiver of a potential subject. Those with a history of likely manic symptoms and without an obvious exclusion criterion were scheduled for an in-person assessment at 1 of the 3 sites. Informed consent was obtained before initiation of the assessment from the subject's parent or guardian and from subjects 14 years or older. The study procedures were explained in age-appropriate language to younger subjects, 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 subject.

3.1.2 Procedures

Subjects were assessed by semistructured interviews of the child or adolescent and a parent or primary caregiver (about the subject) by a trained research clinician. Nonmood psychiatric disorders were assessed using the Schedule for Affective Disorders and Schizophrenia for School-age Children Present and Lifetime Version (K-SADS-PL) [112]. Mood symptoms were assessed by the mood disorder sections of the KSADS-P (Present Episode, fourth revision) plus additional items from the Kiddie Mania Rating Scale (K-MRS) [113].

The KSADS assessments begin with an unstructured interview that reviews lifetime treatment history and course of illness to construct a time line of mood and behavioral problems. Depression and manic symptom severity ratings were recorded on the KSADS-P mood disorder sections and the KSADS MRS for the most severe week in the month before the intake assessment; the 12-item KSADS depression rating was obtained from the KSADS-P. Per the KSADS instructions, mood symptoms that are also in common with other psychiatric disorders (such as motor hyperactivity or distractibility) are not rated as present in the mood sections unless they intensify with the onset of abnormal mood. Comorbid diagnoses were not assigned in the COBY study if they occurred exclusively during a mood episode. The onset of the first and most recent

episode of each type of *DSM-IV* major mood episode (manic, mixed, hypomanic, or major depressive episode) was recorded, as was the first time subjects met the criteria for BP-NOS. The age of onset for a subject's BP-spectrum illness was considered to be when the subject first met the *DSM-IV* criteria for a major mood episode or the COBY study criteria for BP-NOS. Given that the validity of *DSM-IV* diagnostic criteria for preschool-aged children has not been established, the minimum age of onset for BP-spectrum illness was set at 4 years.

Socioeconomic status was measured using the Hollingshead four-factor scale [114] and functional impairment was assessed using the Child Global Assessment Scale (CGAS) [115]. Pubertal status was reported by subjects 10 years and older using the Petersen Pubertal Developmental Scale (PDS) [116]. Parents assisted younger children with completing the Pubertal Developmental Scale.

The subject's primary caretaker was interviewed at intake about his or her personal psychiatric history using the Structured Clinical Interview (SCID-I) [117] for *DSM-IV*. The primary caretaker was interviewed about the psychiatric status of the subject's first- and second-degree relatives using the Family History Screen (FHS) [118] .

We considered a subject positive for the presence of any lifetime anxiety disorder if they met full threshold criteria for at least one of the following disorders: Separation Anxiety Disorder (SAD), Generalized Anxiety Disorder (GAD), Obsessive Compulsive Disorder (OCD), Post-traumatic Stress Disorder (PTSD), Social Phobia, Panic Disorder,

Anxiety Disorder Not Otherwise Specified (Anxiety NOS), or Agoraphobia. Twenty-nine youth with only specific phobia (i.e. fear to spider, dark, and insects) were excluded from the BP/anxiety group because simple phobias are ubiquitous. In addition, they are one of the least reliable anxiety diagnoses in children, perhaps due, in part, to imprecision in standards for distress and impairment since the threshold between a fear and a phobia is not always straightforward [119].

3.1.3. Statistical Analyses

Between-group comparisons in demographic factors were carried out using standard parametric and nonparametric univariate tests. Results were adjusted for BP subtype and any other significant between group demographic differences. Those variables with p-values≤0.25 were then entered into a multivariate logistic regression. Exploratory analyses were carried out examining the presence or absence of mood symptoms during the most severe lifetime episodes using the items from the K-MRS, and the Dep-12 plus the Hopelessness and Aches and Pains questions from the KSADS-P depression section, because these symptoms have been associated with more severe anxiety [120, 121]. All p-values are based on two-sided tests; when appropriate, we use Bonferroni corrections to keep the family-wise error rate at most alpha=0.05. Odds ratios (OR) and confidence intervals (CI) were computed.

3.2. Study II: Factors Associated with the Persistence and the Onset of New Anxiety Disorders in Youth with Bipolar Spectrum Disorders

3.2.1. Subjects

The sample included in this article consists of 413 youth, ages 7 to 17 years 11 months (12.6 ± 3.3 years old) who met criteria for *DSM-IV* BP-I (n=244), BP-II (n=28), and operationally defined BP-NOS (n=141) and who had at least one follow-up assessment. The sample was recruited primarily though clinical referrals from three academic medical centers (University of Pittsburgh [Pittsburgh, Pennsylvania], Brown University [Providence, Rhode Island], and University of California at Los Angeles [Los Angeles, California]). Institutional review board approval was obtained at each site prior to subject enrollment.

To date, subjects have been prospectively interviewed every 37.13±20.4 weeks for a mean of 261.7±94.1 weeks (approximately 5 years). At present, subject retention rate is 84.8%.

3.2.2. Procedures

Children and parents were interviewed for the presence of current and lifetime psychiatric disorders using K-SADS-PL [122], K-MRS [123], and the depression section of the KSADS-P.

Parents were interviewed at intake about their personal psychiatric history using SCID-I [117], and about their first- and second- degree psychiatric family history using a modified version of the FHS [124]. Socioeconomic status (SES) was measured using the Hollingshead four-factor scale (Hollingshead AB, 1975, unpublished). Functional impairment was assessed using CGAS [125], and the child and parent Screen for Child Anxiety Related Emotional Disorder (SCARED) [126] was used to evaluate severity of anxiety.

Longitudinal changes in psychiatric symptoms, functioning, and treatment exposure since the previous evaluation were assessed using the Longitudinal Interval Follow-up Evaluation (LIFE) [127, 128]. The LIFE evaluates the course of symptoms by identifying change points, frequently anchored by memorable dates for the subject (e.g., holidays, beginning of school). The severity of ongoing symptoms, onset of new symptoms, and episode polarity for BP since the last appointment are tracked using weekly LIFE Psychiatric Status Rating (PSR) scores. For *DSM-IV* mood disorders, the PSR scores range from 1 for no symptoms, to 2 to 4 for varying levels of subthreshold symptoms and impairment, to 5 or 6 for full criteria with different degrees of severity or impairment. Most of the anxiety disorders were also rated on a 6-point scale of 1 to 6, where 5 and 6 indicate presence of DSM threshold symptoms. Some anxiety disorders (Anxiety NOS and SAD), other comorbid disorders, and psychosis were assigned weekly scores on a 3-point scale of 1 to 3, where 3 indicate presence of DSM threshold symptoms. A past history of sub-syndromal anxiety was defined as youth with 75% of the *DSM-IV* criteria for any anxiety disorder and functional impairment and was

ascertained through K-SADS-PL completed at intake. Youth with only specific phobia (e.g., fear of the dark) were excluded because simple phobias are ubiquitous [129]. At intake, information about past and current pharmacological treatment was obtained. Information about pharmacological treatment during the follow-up was ascertained using the Psychotropic Treatment Record of the LIFE. Each specific type of treatment and dose was recorded on a weekly basis.

3.2.3. Definition of Persistence of Anxiety Disorders

The mean and standard deviation of the distribution of time with anxiety disorders during the follow-up was 56.9±33 weeks with a median of 55.4 weeks. Based on this distribution, persistence of anxiety disorders over the follow-up period was defined as at least 50% of follow-up time meeting full-threshold *DSM-IV* anxiety disorders criteria.

3.2.4. Definition of Remission

Neither the *DSM-IV* nor the pediatric literature provides a definition of remission for anxiety disorders. Therefore, we used the criteria described in the adult literature of remission for anxiety disorders that is similar to the definition used for depression, namely at least 8 consecutive weeks with only 1 or 2 symptoms to a mild degree [130-132]. To avoid overlap with the anxiety disorders present at intake, new anxiety onsets were counted only if they started more than 8-weeks after intake.

3.2.5. Statistical Analyses

Analyses of the persistence of anxiety disorders included between-group comparisons using t-tests or chi-square tests as appropriate. As is customary [133], and given that this is the first study prospectively evaluating anxiety disorders in youth with BP, intake and follow-up variables with p-values < 0.1 associated with the persistence of anxiety disorder were entered into a stepwise logistic regression and controlled for between-group significant demographic variables.

Analyses of the factors associated with the onset of new anxiety disorders in BP youth were performed using the log-rank test or Cox proportional hazard regressions. A Cox proportional hazards regression with time-varying covariates was used to identify factors that occurred during prospective follow-up which were associated with onset of new anxiety disorders. Data for the time-varying covariates was ascertained with the LIFE. Weekly values on the PSR for individual diagnostic factors were aggregated over 8-week time intervals. A stepwise multivariate Cox regression analysis was performed including all variables with significance $p<0.1$ and controlled for any between-group significant demographic variables.

Odds ratios (OR) and confidence intervals (CI) were computed. All p-values are based on two-tailed tests with $\alpha = 0.05$.

4. RESULTS

4. RESULTS

4.1. Study I: Comorbid Anxiety in Children and Adolescents with Bipolar Spectrum Disorders: Prevalence and Clinical Correlates

4.1.1. Prevalence and Demographics

Forty-four percent (194/446) of subjects met lifetime criteria for at least one comorbid anxiety disorder. The most common comorbid anxiety disorders included SAD (n=108, 24%) and GAD (n=71, 16%), followed by OCD (n=29, 7%), PTSD (n=27, 6%), Social Phobia (n=26, 6%), Panic Disorder (n=25, 6%), Anxiety Disorder NOS (n=11, 3%) and Agoraphobia (n=10, 2%). Eighteen percent of subjects had more than one lifetime anxiety disorder, and 5% met criteria for three or more anxiety disorders. The proportion of subjects whose age onset of anxiety is less than age onset of BP was 78.7% (151 out of 192 subjects as two subjects were missing information of age onset of anxiety). The mean and standard deviation of age onset of anxiety and BP with this 192 subject was 6.3 ± 3.3 and 9.0 ± 3.7, respectively.

As shown in **Table 2**, compared to the BP/no-anxiety group, those with BP/anxiety had significantly lower socioeconomic status, although the actual difference is minimal (3.3 vs. 3.5), and a trend to be less likely to live with both natural parents. There were no other between-group demographic differences.

Table 2. Demographic Factors Associated with BP/anxiety vs. BP/non-anxiety in BP youth

	BP/anxiety (n=194)	BP/non-anxiety (n=252)	Statistics	p-value
Age	12.8 ± 3.3	12.6 ± 3.2	t=-0.62	0.5
Sex (Male) (%)	54.6	52.0	X^2=0.31	0.6
Race (White) (%)	81.4	81.4	X^2=0.0006	1.0
Socioeconomic Status	3.3 ± 1.2	3.5 ± 1.2	K-W=4.27	0.04
Living with both natural parents (%)	36.6	45.2	X^2=3.37	0.07
Pubertal Status (%)			X^2=2.46	0.3
I	21.4	28.8	X^2=2.44	0.1
II-III	29.9	27.8	X^2=0.19	0.7
IV-V	48.7	43.5	X^2=0.95	0.3

4.1.2. Clinical Characteristics of Bipolar Illness and Comorbidity

As shown in **Table 3**, the overall chi square comparing BP subtypes and presence of any lifetime anxiety disorder was significant (χ^2= 8.94, p-value = 0.01). However the differences were only accounted by the BP-II subtype.

Table 3. Frequencies of BP subtype vs. presence of any lifetime anxiety disorder

BP subtype	BP/anxiety	BP/non-anxiety
BP-I (%)	108/260 (41.5)	152/260 (58.5)
BP-II (%)	22/32 (68.8)	10/32 (31.3)
BP-NOS (%)	64/154 (41.6)	90/154 (58.4)

Overall test for independence: $\chi^2_{df=2}$ = 8.94, p-value = 0.01

After adjusting for BP subtype, SES, and living with both natural parents, the BP/anxiety group had significantly longer duration of mood symptoms, and higher depression scores for both current and most severe lifetime episodes compared with the BP/non-anxiety group. In addition, the BP/anxiety group was more likely to report that their most recent DSM mood episode was of the depressive subtype, and less likely to indicate that their index episode was of the manic subtype (all p-values ≤ 0.05). Lifetime history of suicidal ideation or attempts was not significantly different between groups. There were no other significant differences in comorbidity or functioning between groups **(Table 4).**

4.1.3. Family History

In comparison with the BP/no-anxiety group, those with BP/anxiety were more likely to endorse a positive first-or-second degree family history of depression, anxiety disorders (all p-values ≤ 0.001), and a trend of positive first-or-second degree family history of mania/hypomania (p-value =0.06) **(Table 4).**

Table 4. Factors associated with BP/anxiety vs. BP/non-anxiety in BP youth

	BP/anxiety (n=194)	BP/non-anxiety (n=252)	Wald chi-sq. statistic [a]	p-value
Characteristics of Bipolar Illness				
Age onset of mood Symptoms	7.9 ± 3.9	8.6 ± 4.1	2.54	0.1
Age onset BP episode*	9.0 ± 3.7	9.6 ± 4.0	1.99	0.2
Duration of mood symptoms **	5.0 ± 3.2	4.0 ± 2.6	9.04	0.003
MRS Current	22.8 ± 12.2	22.5 ± 12.1	0.0001	1.0
MRS Most Severe Lifetime	34.4 ± 8.5	33.4 ± 8.2	3.0964	0.08
Dep-12 -current	17.7 ± 10.1	12.4 ± 9.6	25.61	<.0001
Dep-12 -MSL	25.9 ± 10.2	20.4 ± 11.0	17.96	<.0001
CGAS -current	55.4 ± 10.8	54.3 ± 13.2	0.54	0.5
CGAS-MSL	37.0 ± 11.0	37.9 ± 9.9	1.67	0.2
Polarity of Index Episode (%)				
Depressed	20.6	10.3	8.30	0.004
Hypomanic	8.8	7.9	0.39	0.5
Manic	9.3	25.4	16.69	<.0001
Mixed	19.6	15.1	2.61	0.1
NOS	41.8	41.3	0.03	0.9
Lifetime History of Comorbid Disorders (%Yes)				
ADHD	60.8	59.5	0.0002	1.0
ODD	35.1	42.9	2.4019	0.1
Conduct Disorder	11.3	13.5	1.2377	0.3
PDD	0.5	0	0.0003	1.0
Substance abuse/dependence	7.2	8.7	0.4081	0.5
Alcohol abuse/dependence	3.1	5.6	1.7079	0.2
Lifetime Phenomenological Features and Treatment History (% Yes)				
Psychosis	23.7	19.4	1.4600	0.2
Suicide Ideation	78.9	73.0	1.0539	0.3
Suicide Attempts	33.5	27.4	1.5581	0.2
Psychiatric Hospitalization	54.1	49.8	1.0294	0.3
Psychiatric Family History (% of subjects with at least one 1st or 2nd degree relative)				
1st or 2nd degree with depression	94.5	80.9	13.91	0.0002
1st or 2nd degree with mania/hypomania	61.1	49.8	3.52	0.06
1st or 2nd degree with anxiety	77.7	61.6	10.96	0.0009

SES: socioeconomic status; BP: Bipolar Disorder; BP-I: Bipolar I Disorder; BP-II: Bipolar II Disorder; BP-NOS: Bipolar Not-Otherwise-Specified; MRS: Mania Rating Scale; CGAS: Child Global Assessment Scale; ADHD: Attention-Deficit/Hyperactivity Disorder; ODD: Oppositional Defiant Disorder; PDD: Pervasive Developmental Disorder (Pervasive Developmental Disorder NOS or Asperger Disorder); K-W: Kruskal-Wallis; FET: Fisher Exact Test.

* Age 4 is set as the minimum value. ** Since age of onset of any DSM mood episode.

[a] Logistic regression adjusting SES, living with both natural parents and BP subtype.

4.1.4. Multivariate Logistic Regression

The BP/anxiety group remained significantly associated with BP-II (OR=2.34, 95% CI 1.02-5.35), longer duration of mood symptoms (OR=1.11 95% CI 1.03-1.19), higher current depression scores in Dep-12 (OR=1.04, 95% CI 1.02-1.07), fewer manic episodes (OR=0.38, 95% CI 0.2-0.73), and higher rates of depression among first-or-second-degree relatives (OR 3.58, 95% CI 1.62-7.93) **(Table 5).**

Table 5. Logistic Regression of the Variables Associated with BP/anxiety vs. BP/no-anxiety in BP youth

Variable	OR	95%CI	Wald	p-value
SES	0.89	0.74-1.07	1.67	0.2
BP-II	2.34	1.02-5.35	4.03	0.04
Duration of mood symptoms	1.11	1.03-1.19	6.97	0.008
Dep-12 current	1.04	1.02-1.07	14.78	0.0001
Manic polarity	0.38	0.2-0.73	8.51	0.004
1st or 2nd degree with depression	3.58	1.62-7.93	9.91	0.002

SES: socioeconomic status; BP-II: Bipolar II Disorder.

4.1.5 Severity of Manic and Depressive Symptoms

To examine whether between-group differences exist in the severity of manic and depressive symptoms, exploratory analyses, adjusted for multiple comparisons, were conducted using ratings from the most severe lifetime manic/hypomanic (K-MRS) and

depressive episodes (Dep-12). Only symptoms rated at mild or higher (≥3) were analyzed. There were no between-group differences in manic/hypomanic symptoms. In contrast, youth with BP/anxiety depressive episodes had significantly more depressed mood, hopelessness, aches and pains, anhedonia, and fatigue after controlling for multiple comparisons using Bonferroni correction. Suicidal ideation was also significantly higher in the BP/anxiety group, but did not survive Bonferroni correction **(Table 6).**

In the multivariate analysis of Dep-12, hopelessness (OR=2.1, 95% CI 1.28-3.28) and aches and pains (OR=2.5, 95% CI 1.56-3.95) were the only two items that were significant during their worst lifetime depressive episode between both groups.

Table 6. Depressive Symptoms* during the Most Severe Lifetime in BP/anxiety vs. BP/non-anxiety in BP youth

	BP/anxiety (%) (n=194)	BP/non-anxiety (%) (n=252)	Statistics	p-value
Depressed mood	94.7	81	X^2=14.28	<0.001**
Excessive or inappropriate guilt	53.7	43.8	X^2=3.41	0.07
Hopelessness	69.5	49.5	X^2=14.43	<0.001**
Aches and pain	67.3	41.9	X^2=22.69	<0.001**
Anhedonia	80	63.2	X^2=11.84	0.001**
Fatigue	78.7	61.9	X^2=11.471	0.001**
Difficulty concentrating	79.5	68.6	X^2=5.31	0.02
Psychomotor agitation	51.3	49.5	X^2=0.115	0.7
Psychomotor retardation	55.3	46.7	X^2=2.63	0.1
Insomnia	74.1	61	X^2=6.31	0.01
Hypersomnia	49.3	38.6	X^2=4.13	0.04
Anorexia	38.5	33.3	X^2=1.01	0.3
Increased appetite	32.7	19.6	X^2=7.92	0.005
Suicidal ideation	65.8	54.8	X^2=4.33	0.04

* Items from Depression Rating Scale (Dep-12) plus hopelessness and aches and pain
** Remained significant after Bonferroni correction

4.2. Study II: Factors Associated with the Persistence and the Onset of New Anxiety Disorders in Youth with Bipolar Spectrum Disorders

Before analyzing the persistence of anxiety during the follow-up, analyses were done to ascertain for the presence of any anxiety at any time during the follow-up and whether the anxiety disorders during the follow-up were of the same type as those present at intake. At any time during the follow-up 80.6% (137/170) of the youth had an anxiety disorder (GAD: 49.6%, SAD: 44.5%, Social Phobia: 34.3%, OCD: 27.7 %, PD: 21.2%, PTSD: 15.3%, Anxiety NOS: 15.3%, and Agoraphobia: 11%). Fifty-three-percent of youth with any anxiety disorders had ≥2 anxiety disorders. Youth diagnosed with a given anxiety disorder at intake tended to have the same disorder over the follow-up (OCD: 90.5%, Social Phobia: 85.7%, GAD: 83.6%, Anxiety NOS: 80%, Agoraphobia: 77.8%, Panic Disorder: 73.7%, SAD: 69.7%, and PTSD: 57.9%).

Of the 137 youth who continued to have any anxiety disorder, 67 subjects spent ≤50% of the follow-up time with anxiety disorders, and 70 subjects spent more than 50% of the follow-up time with anxiety disorders.

4.2.1. Intake and Follow-up Factors Associated with the Persistence of Anxiety

For the intake factors, univariate analyses showed that BP youth with persistent anxiety were significantly more likely to have ≥2 comorbid anxiety disorders, GAD, and

less lifetime treatment with antimanic medications (**Table 7**; all p-values ≤ 0.05). In addition, analyses of medication used at intake showed less treatment with antimanic medications (80.6% vs. 62.9%; $\chi 2=5.3$; p=0.02) (data not included in the Table).

Table 7. Demographic and Clinical Characteristics at Intake Associated with the Persistence of Anxiety Disorders in BP youth

	≤50% time in Anxiety (n=67)	> 50% time in Anxiety (n=70)	stats	p-value
Demographics				
Age	12.8 ± 3.2	12.4 ± 3.5	|t| = 0.77	0.4
Sex (Female) (%)	40.3	54.3	$\chi^2 = 2.69$	0.1
Race (White) (%)	88.1	80	$\chi^2 = 1.65$	0.2
Socioeconomic Status	3.4 ± 1.1	3.1 ± 1.2	|t| = 1.5	0.1
Living with both natural parents (%)	40.3	35.7	$\chi^2 = 0.31$	0.6
Clinical Characteristics				
BP Subtype (%)				
BP-I	64.2	47.1	χ^2=4.03	0.1
BP-II	8.9	12.9		
BP-NOS	26.9	40.0		
Age Onset of Mood Symptoms *	7.9 ± 3.5	7.8 ± 4.2	|t| = 0.2	0.8
Duration of BP**	4.9 ± 3.1	4.7 ± 3.3	|t| = 0.43	0.7
Mania Rating Scale				
Current	22.5 ± 11.5	25.3 ± 12.7	|t| = 1.37	0.2
Most Severe Lifetime	35.6 ± 8.0	35.3 ± 8.2	|t| = 0.2	0.8
Depression Rating Scale				
Current	17.3 ± 9.6	18.6 ± 10.1	|t| = 0.75	0.5
Most Severe Lifetime	25.0 ± 10.0	25.1 ± 10.0	|t| = 0.02	1.0
Age of Onset of Anxiety Disorders	6.6 ± 3.1	5.8 ± 3.0	|t| = 1.6	0.1
Anxiety Disorders Subtype (%)				
SAD	50.8	60	χ^2=1.19	0.3
GAD	31.3	48.6	χ^2=4.23	0.04
OCD	11.9	18.6	χ^2=1.16	0.3
PTSD	14.9	12.9	χ^2=0.12	0.7
Social Phobia	11.9	18.6	χ^2=1.16	0.3
Panic Disorder	11.9	15.7	χ^2=0.41	0.5
Agoraphobia	3.0	10.0	F-E	0.2
Anxiety NOS	4.5	2.9	F-E	0.7
≥2 Anxiety Disorders (%)	34.3	58.6	χ^2=8.08	0.005
SCARED				
Child-Intake	30.2 ± 17.3	35.3 ± 18.4	|t| = 1.55	0.1
Parent-Intake	33.1 ± 16.3	36.3 ± 16.4	|t| = 1.13	0.3

ADHD (%)	58.2	61.4	χ^2=0.15	0.7
ODD (%)	35.8	34.3	χ^2=0.04	0.9
CD (%)	13.4	5.7	χ^2=2.38	0.1
SUD (%)	4.5	7.1	F-E	0.7
Suicide Attempt (%)	35.8	30.0	χ^2=0.53	0.5
History of Physical or Sexual Abuse (%)	26.9	25.7	χ^2=0.02	0.9
Psychotic Symptoms (%)	31.3	24.3	χ^2=0.85	0.4
CGAS				
Current	55.7 ± 11.3	55.4 ± 9.9	|t| = 0.16	0.9
Most Severe Lifetime	39.0 ± 10.9	35.5 ± 11.9	|t| = 1.75	0.08
Lifetime Pharmacological Treatment (% Yes)				
Any Psychotropics	97.0	95.7	F-E	1.0
Antimanics	89.6	75.7	χ^2=4.54	0.03
Antidepressants	62.7	68.6	χ^2=0.53	0.5
Stimulants	58.2	57.1	χ^2=0.02	0.9
Psychiatric Family History (% of subjects with at least one 1st or 2nd degree relative)				
Mania/Hypomania	49.3	60.0	χ^2=1.6	0.2
Depression	85.1	92.9	χ^2=2.13	0.1
ADHD	43.3	45.7	χ^2=0.08	0.7
CD	38.8	35.7	χ^2=0.14	0.7
Anxiety Disorder	71.6	78.6	χ^2=0.88	0.3
Schizophrenia	7.5	10.0	χ^2=0.28	0.6
Any Substance Use Disorder	68.7	71.4	χ^2=0.13	0.7
Suicide Attempt	40.3	45.7	χ^2=0.41	0.5

BP: Bipolar Disorder; BP-I: Bipolar I Disorder; BP-II: Bipolar II Disorder; BP-NOS: Bipolar Not-Otherwise-Specified; SAD: Separation Anxiety Disorder; GAD: Generalized Anxiety Disorder; OCD: Obsessive Compulsive Disorder; PTSD: Posttraumatic Stress Disorder; SCARED: Screen for Child Anxiety Related Emotional Disorder; ADHD: Attention-Deficit/Hyperactivity Disorder; ODD: Oppositional Defiant Disorder; CD: Conduct Disorder; SUD: Substance Use Disorder; CGAS: Child Global Assessment Scale;
* Age 4 is set as the minimum value. ** Since age of onset of any DSM mood episode.

For the follow-up factors, univariate analyses showed that BP youth with persistent anxiety had significantly less follow-up time in euthymia, more subthreshold and threshold mood symptoms, more full-threshold depression, and more follow-up time spent with any comorbid disorder (**Table 8**; all p-values ≤ 0.05).

Table 8. Follow-up Factors Associated with the Persistence of Anxiety Disorders in BP youth

	≤50% time in Anxiety (n=67)	> 50% time in Anxiety (n=70)	Stats (|t|)	p-value
% Weeks in Mood State				
Euthymia	41.5± 26.4	25.2 ± 22.3	3.91	<.001
Any Subthreshold Mood State (Depression or Mania/Hypomania)	41.8 ± 23.2	50.9 ± 25.2	2.20	0.03
Full threshold Depression	12.3 ± 14.0	18.0 ± 19.1	2.00	0.05
Full threshold of Mania/Hypomania	4.5 ± 9.2	5.9 ± 9.2	0.92	0.36
Any Full Threshold Mood State (Depression or Mania/Hypomania)	16.7 ± 18.1	23.9 ± 22.0	2.08	0.04
Comorbid Conditions (% weeks meeting full diagnostic criteria)				
Any Comorbid Disorder	53.0 ± 37.9	66.7 ± 40.8	2.03	0.05
ADHD	43.5 ± 38.1	56.8 ± 45.0	1.86	0.07
CD	6.8 ± 16.6	2.5 ± 12.0	1.72	0.09
ODD	20.3 ± 32.4	28.6 ± 37.8	1.38	0.2
SUD	5.1 ± 15.4	9.9 ± 21.5	1.51	0.2
Psychosis	3.9 ± 10.5	3.7 ± 13.3	0.10	0.9
% Weeks Receiving Psychopharmacologic Treatment				
Any Psychotropics	75.3 ± 31.3	74.2 ± 37.8	0.2	0.9
Antimanics	64.0 ± 37.4	61.6 ± 41.4	0.36	0.7
Antidepressants	34.5 ± 36.7	24.1 ± 33.4	1.74	0.08
Stimulants	26.3 ± 33.9	25.0 ± 39.3	0.20	0.8
% Weeks Receiving Other Services				
Any Psychosocial	43.8 ± 26.1	47.5 ± 28.0	0.79	0.4
Inpatient/Residential	4.8 ± 8.2	4.3 ± 10.7	0.32	0.7
Specialized Psychosocial	13.9 ± 18.8	17.4 ± 26.9	0.90	0.4
Outpatient	34.5± 23.5	32.0 ± 22.8	0.63	0.5

ADHD: Attention-Deficit/Hyperactivity Disorder; CD: Conduct Disorder; ODD: Oppositional Defiant Disorder; SUD: Substance Use Disorder.

Multivariate regression analyses for the intake and follow-up factors showed that persistent anxiety was associated with having ≥2 comorbid anxiety disorders (OR=2.14; 95% CI 1.03-4.47; p=0.04), less antimanic treatment at intake (OR=0.37; 95% CI 0.16-0.85; p=0.02), less follow-up time spent euthymic (OR=0.97; 95% CI 0.96-0.99; p=0.0004), less ongoing conduct disorder (CD) (OR=0.96; 95% CI 0.94-0.99; p=0.01),

and less follow-up time receiving antidepressant medications (OR=0.99 95% CI 0.98-1.00; p=0.04).

4.2.2. Prevalence of New Onset of Anxiety Disorders

Of the 243 youth who at intake did not have any lifetime *DSM-IV* anxiety disorders, 60 (24.7%) had new onsets including: GAD: 31.7%, Anxiety NOS: 28.3%, PTSD: 20%, Social Phobia: 18.3%, OCD: 15%, PD: 11.7%, SAD: 10%, and Agoraphobia: 3.3%. Eighteen- percent of subjects with any new anxiety disorder had new onset of ≥2 anxiety disorders.

4.2.3. Intake and Follow-up Factors Associated with New Onset of Anxiety Disorders

For the intake factors, univariate analyses showed that new onset anxiety disorders were significantly associated with lower SES, not living with both natural parents, and higher total scores on the child's and parent's SCARED. In addition, CD, SUD, history of physical or sexual abuse, history of sub-syndromal anxiety, and less lifetime antimanic medications were significantly associated with new onset of anxiety (**Table 9**; all p-values≤ 0.05). Additional analyses of medications used at the time of the intake showed that use of stimulants was associated with more new anxiety onsets (36.7 vs. 24.2; X^2=3.9; p=0.05) (data not included in the Table).

Table 9. Demographic and Clinical Characteristics at Intake Associated with the Onset of New Anxiety Disorders in BP youth

	BP with new onset anxiety (n=60)	BP-no anxiety (n=157)	Chi-sq	p-value
Demographics				
Age	12.5 ± 3.3	12.7 ± 3.2	0.58	0.4
Sex (Female) (%)	58.3	43.3	2.98	0.09
Race (White) (%)	75.0	83.4	2.78	0.1
Socioeconomic Status	3.3 ± 1.1	3.6 ± 1.2	5.13	0.02
Living with both natural parents (%)	35.0	49.0	3.83	0.05
Clinical Characteristics				
BP Subtype (%)				
BP-I	53.3	62.4	1.88	0.4
BP-II	8.3	3.8		
BP-NOS	38.3	33.7		
Age Onset of Mood Symptoms*	8.5 ± 3.8	9.0 ± 4.3	1.03	0.3
Duration of BP**	4.0 ± 2.6	3.7 ± 2.5	0.49	0.5
Mania Rating Scale				
Current	23.3 ± 10.4	22.2 ± 12.6	0.20	0.7
Most Severe Lifetime	33.1 ± 6.1	33.7 ± 9.0	0.10	0.8
Depression Rating Scale				
Current	14.1 ± 9.1	10.8 ± 9.5	3.69	0.06
Most Severe Lifetime	23.4 ± 10.3	19.4 ± 11.3	3.13	0.08
CGAS				
Current	56.1 ± 11.3	54.1 ± 13.8	0.84	0.4
Most Severe Lifetime	39.4 ± 12.1	37.4 ± 9.0	1.47	0.26
SCARED				
Child-Intake	23.2 ± 13.8	18.4 ± 17.5	3.92	0.05
Parent-Intake	23.0 ± 12.8	15.7 ± 12.2	13.70	<.001
ADHD (%)	63.3	55.4	1.91	0.2
ODD (%)	40.0	44.0	0.17	0.7
CD (%)	18.3	10.2	3.99	0.05
Subsyndromal Any Anxiety (%)	26.7	15.3	4.19	0.04
SUD (%)	16.7	5.7	6.43	0.01
Suicide Attempt (%)	35.0	21.7	3.20	0.07
History of Physical or SexualAbuse(%)	25.0	10.8	6.66	0.01
Psychotic Symptoms	21.7	19.8	0.001	0.9
Lifetime Pharmacological Treatment (% Yes)				

Any Psychotropics	91.7	96.2	1.29	0.3
Antimanics	68.3	84.7	7.37	0.007
Antidepressants	55.0	42.7	1.93	0.2
Stimulants	60.0	52.9	1.27	0.26
Psychiatric Family History (% of subjects with at least one 1st or 2nd degree relative)				
Mania/Hypomania	53.3	42.7	1.49	0.2
Depression	78.3	74.5	0.34	0.6
ADHD	40.0	35.7	0.49	0.5
CD	31.7	26.1	1.1	0.3
Anxiety Disorder	58.3	57.3	0.02	0.9
Schizophrenia	3.3	2.6	0.23	0.6
Any Substance Use Disorder	66.7	64.3	0.29	0.6
Suicide Attempt	33.3	38.2	0.15	0.7

SES: socioeconomic status; BP: Bipolar Disorder; BP-I: Bipolar I Disorder; BP-II: Bipolar II Disorder; BP-NOS: Bipolar Not-Otherwise-Specified; CGAS: Child Global Assessment Scale; SCARED: Screen for Child Anxiety Related Emotional Disorder; ADHD: Attention-Deficit/Hyperactivity Disorder; ODD: Oppositional Defiant Disorder; CD: Conduct Disorder; SUD; Substance Use Disorder.
* Age 4 is set as the minimum value. ** Since age of onset of any DSM mood episode.

For the follow-up factors, univariate analyses showed that onset of new anxiety disorders was significantly associated with less time euthymic, more time in depression and mania/hypomania, ADHD, CD, SUD, and less time receiving antimanic medications (**Table 10**; all p-values≤0.05).

Table 10. Follow-up Factors Associated with the Onset of New Anxiety Disorders in BP youth

	BP with new onset anxiety (n=60)		BP-no anxiety (n=157)	Chi-sq	p-value
	Time 1[†]	Time 2[‡]			
% Weeks in Mood State					
Euthymia	43.3 ± 38.7	39.5 ± 29.5	55.4 ± 31.0	3.80	0.05
Any Subthreshold Mood State (Depression or Mania/Hypomania)	36.7 ± 38.6	43.1 ± 28.7	34.6 ± 27.5	0.007	0.9
Full threshold Depression	10.4 ± 25.9	11.7 ± 21.7	5.7 ± 11.7	3.92	0.05
Full threshold of Mania/Hypomania	9.6 ± 23.6	5.6 ± 9.8	4.2 ± 10.9	6.92	0.009
Any Full Threshold Mood State (Depression or Mania/Hypomania)	20.0 ± 33.0	17.3 ± 21.9	9.9 ± 16.4	10.64	0.001
Comorbid Conditions (% weeks meeting full diagnostic criteria)					
Any Comorbid Disorder	75.4 ± 41.9	72.3 ± 38.9	52.2 ± 39.8	12.30	0.001
ADHD	59.6 ± 48.7	59.6 ± 45.3	45.0 ± 41.8	6.12	0.01
CD	11.5 ± 31.2	11.7 ± 27.3	6.3 ± 21.0	4.77	0.03
ODD	24.4 ± 40.2	26.5 ± 33.5	22.8 ± 33.7	0.27	0.6
Any Substance use	17.3 ± 36.6	13.0 ± 27.2	4.8 ± 13.8	12.48	<.001
Psychosis	3.3 ± 17.0	2.7 ± 10.9	1.1 ± 5.1	2.29	0.1
% Weeks Receiving Psychopharmacologic Treatment					
Any Psychotropics	64.8 ± 47.2	76.0 ± 34.1	73.7 ± 33.9	1.79	0.2
Antimanics	46.9 ± 49.3	61.0 ± 41.3	61.7 ± 38.8	4.36	0.04
Antidepressants	8.1 ± 27.2	11.7 ± 26.8	13.4 ± 26.5	1.38	0.2
Stimulants	24.6 ± 42.2	25.7 ± 39.4	22.6 ± 36.4	0.12	0.7
% Weeks Receiving Other Services					
Any Psychosocial	42.7 ± 41.4	42.9 ± 31.5	40.4 ± 30.2	0.82	0.4
Inpatient/Residential	4.2 ± 15.9	4.8 ± 12.1	4.5 ± 13.6	0.001	1.0
Specialized Psychosocial	17.5 ± 36.0	16.4 ± 27.5	11.5 ± 24.2	2.20	0.1
Outpatient	31.9 ± 33.1	32.6 ± 25.7	30.6 ± 25.0	0.49	0.5

ADHD: Attention-Deficit/Hyperactivity Disorder; CD: Conduct Disorder; ODD: Oppositional Defiant Disorder; HR: Hazard Ratio
[†]Time 1: 8 week prior to anxiety
[‡]Time 2: prior to Time 1

Multivariate regression analyses for the intake and follow-up factors showed that onset of new anxiety disorders was associated with being female (HR: 1.81; 95% CI 1.05-3.11; p=0.03), lower SES (HR: 0.8; 95% CI 0.65-0.99; p=0.05), stimulant treatment at intake (HR: 1.91; 95% CI 1.09-3.34; p=0.02), ongoing ADHD (HR: 1.01; 95% CI 1.002-1.01; p=0.01) and SUD (HR: 1.01; 95% CI 1.003-1.02; p=0.004), and more follow-up time with manic/hypomanic symptoms (HR: 1.01; 95% CI 1.001-1.02; p=0.04).

As noted above, use of stimulants was one of the intake factors associated with onset of new anxiety disorders. To disentangle the effects of stimulants and ADHD, both variables were entered into a regression. In this analysis, only ADHD was associated with new onset of anxiety disorders (p=0.05).

5. GENERAL DISCUSSION

5. GENERAL DISCUSSION

To our knowledge, this is the largest study to date examining prevalence, demographic and clinical correlates of comorbid anxiety disorder among youth with BP and the first study examining the long-term outcome of anxiety disorders and the factors that predict new onset of anxiety disorders among children and adolescents with BP.

Forty-four percent of BP youth in our sample met criteria for at least one lifetime anxiety disorder, most commonly SAD and GAD; 18% had two or more lifetime anxiety disorders. On average, the onset of anxiety predated the onset of BP. After adjusting for significant demographic factors and BP subtypes, youth with BP/anxiety, as compared with BP/no-anxiety, showed significantly higher rates of BP-II, longer duration of mood symptoms, higher current depression scores, lower likelihood of reporting an index episode of the manic subtype, higher rates of familial depression, and had a worst lifetime depressive episode characterized by greater severity of hopelessness, and aches and pains.

Present findings indicate that most anxiety disorders diagnosed at intake continued during the follow-up and were of the same type. Moreover, about 50% of the youth had persistent anxiety, particularly GAD. The persistence of anxiety disorders was associated with multiple anxiety disorders, less follow-up time euthymic, less comorbid CD, and less treatment with antimanic and antidepressant medications. Twenty-five percent of the sample who did not have an anxiety disorder at intake developed new anxiety disorders during follow-up, most commonly GAD. New onsets were significantly

associated with being female, lower SES, presence of ADHD and SUD, and more follow-up time with manic or hypomanic symptoms.

Our findings are consistent with those of previous studies in which anxiety disorders, particularly SAD and GAD, have been reported at high rates among youth and adults with BP [6, 19, 32-35, 44, 45, 71, 134-136]. Also similar to other studies in the child and adult literature, we found that BP subjects with comorbid anxiety disorders were more likely to have a diagnosis of BP-II [46, 56, 69, 134, 135, 137], longer duration of mood symptoms, and greater severity of depressive episodes [41, 58, 73, 138, 139]. Moreover, similar to the BP [33, 140] and unipolar depression [141, 142] literature we found that, on average, the anxiety disorders preceded the onset of the mood disorder. Contrary to our initial hypothesis [34, 42, 44, 74, 94], age onset of BP episode did not differ between the two groups.

Interestingly, we found that youth with BP/anxiety showed significantly more family history of depression. This finding is consistent with Wozniak et al. (2002) [47], who reported elevated risk for both BP and anxiety among relatives of BP/anxiety probands. As such, this group suggested that comorbid anxiety and BP may represent a genetic subtype of BP. Furthermore, a recent study by Birmaher and colleagues (2009) [36] found that offspring of parents with BP had higher rates of anxiety disorders than offspring of control parents suggesting that anxiety may be a precursor of BP among BP offspring. Thus, systematic evaluation of youth with anxiety disorder and family history of mood disorders is warranted because these youth may be at high risk to develop BP.

Contrary to our initial hypothesis [4, 57, 74, 107, 138, 143-145], we did not find significantly more suicidal behaviors [33], or substance use disorders in the BP with comorbid anxiety group as compared to those without. These discrepancies may be explained by the fact that most subjects in this study have not yet reached the age of highest risk for these conditions. Nonetheless, youth with BP and anxiety had significantly more suicidal ideation, as well as hopelessness during the most severe lifetime depressive episode than subjects without comorbid anxiety. Since hopelessness is highly associated with suicide attempts and suicide [146-148], careful evaluation and monitoring of suicide risk in youth with BP/anxiety is clearly indicated. Also contrary to our initial hypothesis [4, 57], we did not find poorer functioning in the BP group with comorbid anxiety as compared with those without. It is possible that the impact of BP on global functioning during childhood and adolescence is significantly profound such that any additional impairment associated with comorbid anxiety is relatively negligible.

Finally, after adjusting for multiple comparisons, youth with BP and comorbid anxiety reported more aches and pains than those without anxiety, as is the case in adults studies [149]. It has been well-documented that anxious youth experience somatic complaints and tend to consult primary care physicians or pediatricians before mental health clinicians [150]. Thus, it is important to educate such front-line providers about the possibility that anxious youth with a positive family history of mood disorder may also have BP.

Since there are no other pediatric and adult longitudinal studies that have assessed the outcome of anxiety disorders in BP, for comparison we used the existing literature on the course of anxiety disorders in youth **(Table 11)** and adults without BP.

Table 11. Literature of the Course of Anxiety Disorders in Children and Adolescent

Study (ref)	Sample	Age	Duration	Assessment	Results
Clinical studies					
Essau et al., 2002	1035(T1) 523(T2)	12-17	15 months	CIDI	23% showed chronic anxiety Factors associated with persistence included older age, somatoform and substance use disorder, and exposure to negative life events
Last et al., 1997	101	18-26	8 years	K-SADS-P	Anxious-depressed presented more psychosocial impairment, mental health services, and more psychological problems than both anxious and controls. The predictors of adjustment difficulty were male gender, presence of ≥1 anxiety disorder, early onset, severe impairment, and parental psychopathology
Last et al., 1996	84	5-18	3-to 4-year	K-SADS-P	82% recovered from their anxiety disorders, particularly SAD. 8% had recurrence
Keller et al., 1992	225	6-19	8 years	K-SADS-P	46% youth remained anxious, 34% recovered and 31% had recurrence
Cantwell and Baker, 1989	151	2-16	4 years	DICA	Speech impaired children showed ≥75% remission, particularly SAD, and 29% had recurrence. Overanxious anxiety disorder had the lowest recover rate

Epidemiological studies					
Pine et al., 1998	776(T1) 760(T2) 716(T3)	9-18	9 years	DISC	Presence of anxiety disorders predicted a 2-to 3-fold increased risk for anxiety in adulthood
Cohen et al., 1993	734	9-18	2.5 years	DISC	47% youth remained with overanxious disorder

CIDI: Composite International Diagnostic Interview; DISC: Diagnostic Interview Schedule for Children; K-SADS-P: Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present Episode; DICA: Diagnostic. Interview for Children and Adolescents; SAD: Separation Anxiety Disorder; T1: Time one (initial assessment); T2: Time two (follow-up assessment); T3: Time three (follow-up assessment).

Similar to our findings, longitudinal studies in youth with anxiety disorders have also shown that with the exception of SAD, most anxiety disorders and especially GAD [130, 131, 151, 152] tend to continue into adulthood [141, 152-154]. Also there is evidence for the homotypic continuation of the anxiety disorders [155, 156], and in concordance with our results, multiple anxiety disorders [157] predicted higher persistence of anxiety disorders. Perhaps due to the fact that other studies evaluating the association between CD and anxiety included primarily males [158 159] , in contrast to their findings, COBY found that persistence of anxiety was associated with less comorbid CD. The persistence of anxiety over time may explain in part the high association between anxiety disorders and BP and could be a unique factor that negatively influences BP severity and prognosis[59, 69, 70, 72] compared to other comorbid conditions such as ADHD and SUD. Furthermore, our results and those of one epidemiological study in youth [42] give evidence that the relationship between anxiety disorders and BP severity may be bi-directional, as ongoing

symptoms of mania or hypomania are associated with persistence and new onsets of anxiety disorders.

The results of our study together with the fact that pediatric anxiety disorders may continue into adulthood and that anxiety disorders worsen the course of BP [69, 70] indicate the need for early identification and treatment of these disorders in youth with BP. These findings are clinically relevant because currently the first line pharmacological treatments for anxiety disorders in youth are the selective serotonin reuptake inhibitors (SSRIs) [160, 161] and have been shown to trigger or destabilize BP symptoms [162]. Current evidence-based treatments for anxiety disorders show that cognitive behavior therapy (CBT) and the SSRIs, and in particular their combination, are efficacious for the acute treatment of anxiety in youth [163]. Although we know that CBT is efficacious for youth with anxiety disorders, youth with comorbid BP have been excluded from these trials, and thus we do not have data on its efficacy for this population. Moreover, even if the SSRIs are efficacious and well tolerated for youth with anxiety we do not know the efficacy and tolerability of these medications for youth with BP and anxiety. Thus, it is critically important to evaluate a child presenting with anxiety for the presence of manic or hypomanic symptoms, especially if depressive symptoms and a positive family history of mood disorders are also present. Although hypomanic symptoms can be difficult to ascertain in youth due to the unique developmental presentation [164] as well as symptom overlap with other conditions including depression and anxiety, recent studies clearly demonstrate that mania/hypomania in youth can be reliably diagnosed [1]. Additionally,

anxious children treated with antidepressants should be carefully monitored for the presence of manic/hypomanic symptoms [44].

Little is known about the most efficacious treatments for the treatment of comorbid anxiety in youth with BP. Since there are no randomized controlled trials comparing CBT, SSRIs or the combination of both treatments in youth (and adults) with anxiety and BP, we feel these studies are necessary. Such studies would inform clinical practice, and answer a very important question about the relative efficacy of CBT, SSRIs, and/or the combination, for youth with the common and impairing presentation of comorbid BP and anxiety. The risk/benefit ratio of the use of SSRIs in youth with BP who are on concurrent mood stabilizers also may be explored.

About one quarter of the sample developed new anxiety disorders during the follow-up. Similar to the pediatric and adult literature, female sex [5 165] and lower SES [5 166] increased the risk for new anxiety disorders, particularly GAD [5 167]. Our findings are also consistent with the epidemiological literature in which anxiety disorders are more prevalent in females, [141, 166] especially GAD in adolescent females [5, 168].

Epidemiologic as well as clinical studies have shown that youth [107 19 108, 109] and adults [169, 170] with BP are at high risk for SUD. Also, both BP and SUD are strongly associated with anxiety [145]. Similarly, our findings showed that BP youth with SUD or ADHD [171] were at high risk for onset of new anxiety disorders, suggesting that early

recognition and treatment of these disorders may prevent the development of new anxiety disorders.

These above-noted results need to be taken in the context of the limitations of this study. First, as most subjects were Caucasian and were recruited primarily from outpatient clinical settings, the generalizability of the findings remains uncertain. However, a community-based study of non-referred adolescents with BP reported similarly high rates of comorbid anxiety disorders [172]. Second, subjects were ascertained for bipolarity. Thus, results may not apply to subjects whose primary diagnosis is anxiety and then develop BP. Third, no psychiatric control group was included. Thus, we cannot conclude that anxiety disorders are more common in youth with BP than in youth with other childhood psychiatric disorders (e.g., major depressive disorder). However, other pediatric and adults studies have consistently shown that anxiety disorders are more common in BP than in other psychiatric disorders [57, 173]. Forth, the effects of treatment were not analyzed. Finally, since subjects were a referred sample, findings may not apply to other populations.

In summary**,** anxiety disorders usually predate the onset of BP and are very common in youth with BP, especially those with BP-II, longer duration of mood symptoms, more severe depressions, and family history of depression. Thus, most anxiety disorders persisted during the follow-up and a substantial group of subjects developed new anxiety disorders. Consistent with the literature for other disorders (e.g., major depressive disorder) [174], we found that different factors were associated with the

persistence and the new onset of anxiety disorders. Early identification and appropriate management of these risk factors may improve the course of BP youth. Randomized controlled trials are warranted to evaluate whether existing treatments known to be efficacious for anxiety disorders particularly psychosocial treatments, such as CBT, that are not associated with inducing mood instability, are equally efficacious and tolerable for youth with comorbid BP and anxiety disorders.

6. CONCLUSIONS

6. CONCLUSIONS

To our knowledge, this is the largest study to date examining prevalence, demographic and clinical correlates of comorbid anxiety disorder among children and adolescents with BP and the first study examining the long-term outcome of anxiety disorders and the factors that predict new onset of anxiety disorders among youth with BP.

The main conclusion of this thesis, derived from study I **(I, II, III)** and study II **(IV, V, VI, VII)** can be summarized as follow:

I: Anxiety disorders, particularly SAD and GAD, are very common in youth and usually predate the onset of BP.

II: BP youth with anxiety showed higher rates of BP-II, longer duration of mood symptoms, and more severe depressions. This association may be related to the fact that BP-II has a more chronic course and outcome, longer length of illness, shorter cycles, and greater number of episodes, more major and minor depressive episodes, shorter well intervals between episodes, and lower rates of recovery.

III: It is critically important to evaluate a child presenting with anxiety for the presence of manic or hypomanic symptoms, especially if depressive symptoms and a positive family history of mood disorders are also present.

IV: Most anxiety disorders persisted during the follow-up and could be a unique factor that negatively influences BP severity and prognosis compared to other comorbid conditions.

V: The relationship between anxiety disorders and BP severity may be bi-directional, as ongoing symptoms of mania or hypomania are associated with persistence and new onsets of anxiety disorders.

VI: BP youth with SUD or ADHD were at high risk for onset of new anxiety disorders, suggesting that early recognition and treatment of these disorders may prevent the development of new anxiety disorders.

VII: Randomized controlled trials are warranted to evaluate whether existing treatments known to be efficacious for anxiety disorders particularly psychosocial treatments, such as CBT, that are not associated with inducing mood instability, are equally efficacious and tolerable for youth with comorbid BP and anxiety disorders.

7. SUMMARY OF THE THESIS

RESUM DE LA TESI

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Prevalència, Correlacions Clíniques i Factors Associats amb el Curs i els Resultats dels Trastorns d'Ansietat en Joves amb Trastorn Bipolar

INTRODUCCIÓ

L'inici del trastorn bipolar (TB) durant la infància afecta significativament el desenvolupament psicosocial de l'individu. D'altra banda, els joves amb TB es troben en alt risc de conductes suïcides i suïcidis consumats, abús de substàncies i problemes legals amb taxes especialment elevades d'utilització de serveis sanitaris. Joves amb TB estan entre els malats psiquiàtrics amb més afectació psicosocial i la presència de comorbiditat dóna lloc a discapacitat, complica el tractament i sembla empitjorar el pronòstic del TB. Condicions de comorbiditat freqüentment associada amb el TB infantil són: el dèficit d'atenció amb hiperactivitat (TDAH), trastorns del comportament pertorbador, trastorns per ús de substàncies (TUS), trastorns d'ansietat i trastorns generalitzats del desenvolupament.

Alguns dels trastorns comòrbids més comuns entre els joves amb TB són els trastorns d'ansietat. No obstant això, la presència de trastorns d'ansietat en els pacients que pateixen de TB ha estat poc reconeguda i estudiada. Atès que els trastorns d'ansietat s'acompanyen també d'un deteriorament significatiu en el funcionament psicosocial dels

nens, és important avaluar la prevalença i les correlacions clíniques de l'associació entre TB i l'ansietat en la joventut. Els pocs estudis que han abordat aquesta qüestió en petites mostres de joves amb TB han demostrat que la prevalença de vida dels trastorns d'ansietat comòrbids està entre el 14% i el 56%, amb una mitjana ponderada del 27%. D'altra banda, els estudis familiars han demostrat altes taxes de trastorns d'ansietat en els fills de pares amb TB.

Els resultats ja esmentats són consistents amb la literatura d'estudis epidemiològics i clínics en adults. De fet, les dades retrospectives d'estudis en adults amb TB indiquen índexs de comorbiditat dels trastorns d'ansietat al llarg de la vida entre les persones amb una edat més primerenca d'inici del TB. En concret, en un estudi realitzat per Perlis i col.laboradors (2004), els adults amb l'aparició de TB abans dels 13 anys d'edat va demostrar una taxa del 70% d'ansietat comorbida al llarg de la vida, en comparació amb el 54% dels pacients amb inici del TB entre els 13 i 18 anys i el 38 % d'aquells amb inici de TB després dels 18 anys d'edat.

Els estudis longitudinals d'ansietat comòrbida en joves i adults amb TB han demostrat que els trastorns d'ansietat estan associats amb una major gravetat del TB. Per exemple, Masi i col.laboradors (2007) van fer un seguiment d'almenys 6 mesos a un grup de 224 nens i adolescents amb trastorn de l'espectre bipolar. Ells van trobar que en comparació amb els joves amb TB sense trastorn de pànic (TP), les persones amb TP van mostrar una menor gravetat de l'estat d'ànim en el moment basal i menys millorament de l'estat d'ànim durant el seguiment. A més, DelBello i col.laboradors (2007) van seguir a

un grup de 71 adolescents amb TB-I un any després de l'alta l'hospitalària. Ells van trobar que els adolescents amb TB i ansietat comórbida tenien símptomes més greus de l'estat d'ànim i menys taxes de recuperació que els adolescents sense ansietat.

Els estudis en adults amb TB també han trobat que la presència d'ansietat comòrbida s'associa amb períodes eutímics més curts, major severitat de la depressió, cicles ràpids, més temps per a la remissió, major risc de recurrència, més temps amb estat d'ànim depressiu, conducta suïcida, abús de substàncies, menor qualitat de vida, deteriorament funcional i mala resposta al tractament.

Els estudis ja esmentats es va centrar en l'efecte de l'ansietat en el curs del TB, però en el nostre coneixement no hi han estudis que hagin examinat el curs dels trastorns d'ansietat en joves i adults amb TB. Això és important perquè la identificació precoç i el tractament de trastorns d'ansietat en joves amb TB pot millorar el pronòstic del TB.

Per tant, l'associació entre el TB i els trastorns d'ansietat comòrbids és de particular importància clínica ja que el tractament farmacològic dels trastorns d'ansietat amb major evidència d'eficàcia en nens i adults son els inhibidors de la recaptació de serotonina (ISRS). Desafortunadament, aquests medicaments han demostrat desestabilització dels símptomes del TB.

OBJECTIUS

Donada la rellevància clínica de l'ansietat comòrbida i el TB i l'existència de pocs estudis amb mostres petites, el nostre objectiu ha estat investigar la prevalença, correlació i el risc familiar associat al trastorn d'ansietat comòrbida en una àmplia mostra de nens i adolescents amb trastorn de l'espectre bipolar en l'estudi I.

Atès que no hi ha altres estudis longitudinals que hagin avaluat el curs i resultants dels trastorns d'ansietat en nens i adults amb TB, el principal objectiu de l'estudi II va ser avaluar el curs longitudinal del trastorns d'ansietat en joves amb TB que tenien almenys un trastorn d'ansietat en el moment de començar l'estudi. Més concretament hem avaluat si els trastorns d'ansietat presents durant el seguiment van ser el mateixos que els presents en el moment del reclutament (continuïtat homotípica) i identificar els factors en l'admissió i el seguiment associats amb la persistència (> 50% del temps de seguiment) dels trastorns d'ansietat. A més, es van avaluar els factors en l'admissió i el seguiment associats amb el desenvolupament de nous trastorns d'ansietat durant el període de seguiment dels joves sense cap tipus de trastorn d'ansietat en el moment del reclutament.

MÈTODES

La mostra inclosa a l'estudi I va consistir en 446 joves d'entre 7 a 17 anys i 11 mesos (mitjana=12,7; SD=3,2) que complien els criteris del *Diagnostic and Statistical*

Manula of Mental Disorders (DSM-IV) per el TB-I (n=260), TB-II (n=32) i la definició operacionalitzada del TB-NOS (n = 154). La mostra inclosa a l'estudi II va consistir en 413 joves, d'entre 7 i 17 anys i 11 mesos (mitjana=12,6; SD=3,3) que complien els criteris del DSM-IV per el TB-I (n = 244), TB-II (n = 28) i TB-NOS (n = 141) i que tenien almenys una avaluació de seguiment. La mostra va ser reclutada fonamentalment a través de referències clíniques de tres centres mèdics acadèmics, com a part del *Course and Outcome of Bipolar Youth Study* (COBY). L'aprovació de la junta de revisió institucional es va obtenir en cada lloc abans d'iniciar l'estudi. Fins ara, els subjectes han estat entrevistats de forma prospectiva cada 37,13 ± 20,4 setmanes amb una mitjana de 261,7 ± 94,1 setmanes (aproximadament 5 anys). En l'actualitat, la taxa de retenció és del 84,8%.

Els criteris d'inclusió van ser els següents: (1) edad de 7 a 17 anys i 11 mesos i (2) complir amb els criteris DSM-IV per al TB-I o TB-II o els criteris establerts per COBY per el TP-NOS. Els símptomes i canvis d'humor que es van produir durant l'ús de substàncies o el tractament antidepressiu no van comptar per al diagnòstic del TB. Els criteris d'exclusió van ser els següents: diagnòstic basat amb els criteris del DSM-IV en el passat i en el moment actual d'esquizofrènia, retràs mental, autisme, greus trastorns de l'espectre autista o trastorns de l'estat d'ànim a causa de l'abús de substàncies, d'una condició mèdica o secundària a l'ús de medicaments.

Els nens i els pares van ser entrevistats per determinar la presència de trastorns psiquiàtrics en el passat i en el moment actual utilitzant el *Schedule of Affective Disorders*

and Schizophrenia for School-age Children Present and Lifetime Version (K-SADS-PL), *Kiddie Mania Rating Scale* (K-MRS) i la secció de depressió del KSADS-P (Dep-12). Els pares van ser entrevistats a l'inici de l'estudi sobre la història personal psiquiàtrica utilitzant el *Structured Clinical Interview for DSM-IV* (SCID) i sobre els antecedents familiars psiquiàtrics de primer i segon grau utilitzant una versió modificada del *Family History Screen*. El nivell socioeconòmic es va mesurar utilitzant el *Hollingshead four-factor scale*. El deteriorament funcional es va avaluar mitjançant el *Child Global Assessment Scale* i el *Screen for Child Anxiety Related Emotional Disorders* (SCARED) per als nens i als pares es va utilitzar per avaluar la severitat de l'ansietat.

Els canvis longitudinals en els símptomes psiquiàtrics, el funcionament i l'exposició al tractament des de l'avaluació anterior es van avaluar utilitzant el *Longitudinal Interval Follow-up Evaluation* (LIFE). El LIFE avalua el curs dels símptomes mitjançant la identificació de punts de canvi sovint ancorats en les dates memorables pel subjecte. Un seguiment setmanal des de l'última cita es va realitzar utilitzant el LIFE *Psychiatric Status Rating* (PSR) per tal d'avaluar la gravetat dels símptomes en curs, l'aparició de nous símptomes i la polaritat dels episodis del TB. En l'admissió, es va obtenir informació sobre el tractament farmacològic en el passat i actual. La informació sobre el tractament farmacològic durant el seguiment es va determinar utilitzant el *Psychotropic Treatment Record* per el LIFE. Cada tipus específic de tractament i la dosi es va registrar de forma setmanal.

Es va considerar un subjecte positiu per la presència de qualsevol trastorn

d'ansietat en algun moment de la seva vida si complien almenys un dels criteris pels següents trastorns: trastorn d'ansietat per separació (TAS), trastorn d'ansietat generalitzada (TAG), trastorn obsessiu compulsiu (TOC), trastorn per estrès posttraumàtic, fòbia social, trastorn de pànic (TP), trastorn d'ansietat no especificada (Ansietat-NOS) o agorafòbia.

La mitjana i desviació estàndard de la distribució del temps amb trastorns d'ansietat durant el seguiment va ser de 56,9 ± 33 setmanes amb una mitjana de 55,4 setmanes. Amb base a aquesta distribució, la persistència dels trastorns d'ansietat en el període de seguiment va ser definida com un mínim del 50% del temps de seguiment amb compliment dels criteris del DSM-IV pels trastorns d'ansietat.
Ni el DSM-IV, ni la literatura pediàtrica, ofereix una definició de la remissió dels trastorns d'ansietat. Per tant, es van utilitzar els criteris descrits a la literatura per a adults sobre la remissió dels trastorns d'ansietat que és similar a la utilitzada per a la depressió, és a dir, com a mínim 8 setmanes consecutives amb només un o dos símptomes de grau lleu. Per evitar la superposició amb els trastorns d'ansietat presents en el reclutament, l'inici d'un nou transtorn d'ansietat es van comptabilitzar només si es va iniciar després de 8 setmanes del començament de l'estudi.

En l'estudi I, les comparacions entre grups dels factors demogràfics es van dur a terme utilitzant test estàndards univariables paramètrics i no paramètrics. Els resultats van ser ajustats pel subtipus de TB i qualsevol altre diferència demogràfica significativa. Les variables amb valors de $p \leq 0,25$ van ser introduïdes en una regressió logística

multivariant. Els anàlisis exploratòris es van dur a terme examinant la presència o absència de símptomes afectius durant els episodis més greus de la vida utilitzant els ítems del K-MRS i del Dep-12 incloent a més les preguntes de desesperança i molèsties i dolor de la secció de depressió del KSADS-P, ja que aquests símptomes s'han associat amb ansietat més severa.

En l'estudi II, per l'anàlisis de la persistència dels trastorns d'ansietat es van utilitzar comparacions entre els grups utilitzant la t d'student o el chi-quadrat test segons correspongués. Les variables en el reclutament i en el seguiment associades amb la persistència del trastorn d'ansietat amb valors de $p < 0,1$ es van introduir en una regressió logística i van ser controlades per variables demogràfiques significatives entre els grups. Els anàlisis dels factors associats amb l'aparició de nous trastorns d'ansietat en la joventut amb TB es van realitzar mitjançant el test de *log-rank* o el model de riscos proporcionals de la regressió de Cox. El model de riscos proporcionals de la regressió de Cox amb covariables temps dependent es va utilitzar per identificar els factors que es van produir durant el seguiment prospectiu associat amb l'aparició de nous trastorns d'ansietat. Les dades utilitzades per les covariables temps dependent van ser obtingudes amb el LIFE. Els valors setmanals en el PSR pels factors diagnòstics individuals es van agrupar en intervals de temps de 8 setmanes. El model multivariable de regressió de Cox utilitzant l'*stepwise* es va realitzar incloent totes les variables amb significació $p < 0,1$ i controlant per qualsevol variable demogràfica significativa entre els grups.

Tots els p-valors es van basar en test de dos cues; si s'escau, vam utilitzar

correccions de Bonferroni per mantenir la taxa d'error tipus I alfa = 0,05. Els Odds ratio (OR) i els intervals de confiança (IC) es van també calcular.

RESULTATS

Estudi I. Ansietat Comòrbida en Nens i Adolescents amb Trastorns de l'Espectre Bipolar: Prevalença i Correlacions Clíniques

Quaranta-quatre per cent (194/446) dels subjectes van complir com a mínim els criteris per un trastorn d'ansietat comòrbid al llarg de la vida. Els trastorns comòrbids més comuns eren TAS (n = 108, 24%) i TAG (n = 71, el 16%), seguit pel TOC (n = 29, 7%), trastorn per estrès posttraumàtic (n = 27, 6%), fòbia social (n = 26, 6%), TP (n = 25, 6%), ansietat-NOS (n = 11, 3%) i agorafòbia (n = 10, 2%). Divuit per cent dels subjectes tenien més d'un trastorn d'ansietat al llarg de la vida i el 5% complien els criteris per a tres o més trastorns d'ansietat. La proporció de subjectes amb una edat d'inici d'ansietat menor que l'edat d'inici del TB va ser del 78,7% (151 dels 192 subjectes ja que dos subjectes tenien falta d'informació de l'edat d'inici de l'ansietat). La mitjana i desviació estàndard de l'edat d'inici de l'ansietat i del TB dels 192 subjectes va ser de 6,3 ± 3,3 i 9,0 ± 3,7, respectivament.

El grup amb ansietat i TB es va mantenir significativament associat amb TB-II (OR=2,34; IC 95% 1,02-5,35), major durada dels símptomes de l'estat d'ànim (OR=1.11;

IC 95% 1,03-1,19), augment de les puntuacions de depressió actual en el Dep-12 (OR=1,04; IC 95% 1,02-1,07), menys episodis de mania (OR=0,38; IC 95%: 0,2-0,73) i majors taxes de depressió entre els familiars de primer o de segon grau (OR=3.58; IC 95% 1,62-7,93). D'altra banda, en l'anàlisi multivariable del Dep-12, la desesperança (OR=2,1; IC 95% 1.28-3.28) i les molèsties i els dolors (OR=2,5; IC 95% 1,56-3,95) van ser els dos únics elements que van ser significatius durant el pitjor episodi depressiu al llarg de la vida entre ambdós grups.

Estudi II. Factors Associats amb la Persistència i l'Aparició de Nous Trastorns d'Ansietat en els Joves amb Trastorns de l'Espectre Bipolar

En qualsevol moment durant el seguiment, el 80,6% (137/170) dels joves va tenir un trastorn d'ansietat (TAG: 49,6%, TAS: 44,5%, fòbia social: 34,3%, TOC: 27,7%, TP: el 21,2%, trastorn d'estrès posttraumàtic: 15,3%, ansietat-NOS: 15,3% i agorafòbia: 11%). Cinquanta-tres per cent dels joves amb trastorns d'ansietat tenien ≥ 2 trastorns d'ansietat. Joves diagnosticats amb un trastorn d'ansietat en el reclutament tendeixen a mantenir el mateix trastorn durant el seguiment (TOC: 90,5%, fòbia social: 85,7%, TAG: 83,6%, ansietat-NOS: 80%, agorafòbia: 77,8%, TP: 73,7%, TAS: 69,7% i trastorn d'estrès posttraumàtic:57,9%).

Dels 137 joves que van continuar amb qualsevol trastorn d'ansietat, 67 subjectes van passar ≤ 50% del temps de seguiment amb trastorn d'ansietat i 70 subjectes van passar més de 50% del temps de seguiment amb trastorns d'ansietat.

El model de regressió multivariable pels factors de reclutament i de seguiment va mostrar que la persistència d'ansietat s'associa amb tenir ≥ 2 trastorns d'ansietat comòrbids (OR=2,14; IC 95% 1.03-4.47; p=0,04), menys medicació antimaníaca en el reclutament (OR=0,37; IC 95% 0,16-0,85; p=0,02), menor temps de seguiment en eutímia (OR=0,97; IC 95% 0,96-0,99; p=0,0004), menys comorbilitat amb els trastorns de conducta (OR=0,96, IC 95% 0,94 -0,99;p = 0,01) i menor temps de seguiment reben medicació antidepressiva (OR=0,99; IC 95% 0.98-1.00; p=0,04).

Dels 243 joves que en el reclutament no havien tingut mai cap criteri del DSM-IV per als trastorns d'ansietat, 60 (24,7%) van tenir nous inicis, entre ells: TAG: 31,7%, ansietat-NOS: 28,3%, trastorn d'estrès posttraumàtic: 20%, fòbia social: 18,3%, TOC: 15%, PD: 11,7%, TAS: 10% i agorafòbia: 3,3%. Divuit per cent dels subjectes amb qualsevol trastorn d'ansietat nou van tenir ≥ 2 nous trastorns d'ansietat.

El model de regressió multivariable pels factors de reclutament i de seguiment van mostrar que l'aparició de nous trastorns d'ansietat està associat amb el sexe femení (HR: 1.81; IC 95% 1.05-3.11; p = 0,03), menor estatus socioeconòmic (HR: 0,8; 95% IC 0,65-0,99; p = 0,05), més medicació estimulant en el reclutament (HR: 1.91; IC 95% 1.09-3.34; p = 0,02), TDAH (HR: 1.01; IC 95% 1.002-1.01; p = 0,01) i TUS (HR: 1.01; IC 95% 1.003-1.02; p = 0,004) i més temps de seguiment amb símptomes maníacs o hipomaníacs (HR: 1.01; IC 95% 1.001-1.02; p=0,04).

Com s'ha assenyalat anteriorment, l'ús d'estimulants va ser un dels factors del

reclutament associat amb l'aparició de nous trastorns d'ansietat. Per separar els efectes dels estimulants i el TDHA, ambdues variables es van introduir en una regressió. En aquest anàlisis, només el TDHA es va associar amb la nova aparició de trastorns d'ansietat (p=0,05).

DISCUSSIÓ

Pel que nosaltres sabem, aquest és el major estudi fins a la data que examina la prevalença, correlacions demogràfiques i clíniques dels trastorns d'ansietat comòrbids entre els joves amb TB i el primer estudi en examinar els resultats a llarg termini dels trastorns d'ansietat i els factors que prediuen l'aparició de nous trastorns d'ansietat entre els nens i adolescents amb TB.

Quaranta-quatre per cent dels joves amb TB en la nostra mostra complien els criteris de tenir almenys un trastorn d'ansietat al llarg de la vida, més freqüentment TAS i TAG. El 18% tenia dos o més trastorns d'ansietat al llarg de la vida. De mitjana, l'aparició de l'ansietat és anterior a l'aparició del TB. Després d'ajustar per factors demogràfics i subtipus de TB, els joves amb BP i ansietat, en comparació amb aquells que no tenien ansietat, van mostrar taxes significativament més altes de TB-II, major durada dels símptomes de l'estat d'ànim, augment de les puntuacions de depressió actual, menys episodis de mania, majors taxes de depressió familiar i tenir el pitjor episodi de depressió al llarg de la vida caracteritzada amb una major severitat de desesperança i de molèsties i

dolors.

Els resultants presents indiquen que la majoria dels trastorns d'ansietat que han estat diagnosticats en el reclutament van continuar durant el seguiment i van ser del mateix tipus. D'altra banda, al voltant del 50% dels joves es va observar persistència d'ansietat, particularment de TAG. La persistència dels trastorns d'ansietat s'associa amb trastorns d'ansietat múltiples, menys temps de seguiment amb eutímia, menys comorbilitat amb els trastorns de conducta i menys medicació antidepressiva i antimaníaca. El vint-i-cinc per cent de la mostra sense cap trastorn d'ansietat en el reclutament van desenvolupar nous trastorns d'ansietat durant el seguiment, en general TAG. Els nous inicis es van associar significativament amb el sexe femení, menor estatus socioeconòmic, presència de TDHA i TUS i més temps de seguiment amb símptomes maníacs/hipomaníacs.

Els nostres resultats són consistents amb els anteriors estudis en els quals s'han trobat altes taxes de trastorns d'ansietat, en particular TAS i TAG, entre els joves i adults amb TB. També similar a la literatura en nens i adults, s'ha trobat que els subjectes amb TB i trastorns d'ansietat comòrbida tenen més probabilitats d'aconseguir un diagnòstic de TB-II, major durada dels símptomes de l'estat d'ànim i una major severitat dels episodis depressius. D'altra banda, similar al TB i a la depressió unipolar, trobem a la literatura que de mitjana, els trastorns d'ansietat precedeixen a l'aparició dels trastorns de l'humor. Contràriament a la nostra hipòtesi inicial, no hi va haver diferències entre els dos grups en l'edat d'inici del TB.

El més interessant és que hem trobat que els joves amb TB i ansietat van mostrar significativament més història familiar de depressió. Aquesta troballa és consistent amb Wozniak i els seus col·laboradors (2002), que va trobar un risc elevat tant per el TB com per l'ansietat entre els familiars dels examinats amb TB i ansietat. Com a conseqüència, aquest grup suggereix que l'ansietat comòrbida al TB pot representar un subtipus genètic del TB. D'altra banda, un estudi recent de Birmaher i col.laboradors (2009) va trobar que els fills de pares amb TB tenien taxes més altes de trastorns d'ansietat que els fills dels pares controls, suggerint que l'ansietat pot ser un precursor del TB entre els descendents amb TB. Per tant, l'avaluació sistemàtica dels joves amb trastorn d'ansietat i antecedents d'història familiar de trastorns de l'ànim es justifica pel fet que aquests joves poden estar en alt risc de desenvolupar un TB.

Contràriament a la nostra hipòtesi inicial, no hem trobat significativament més comportaments suïcides o abús de substàncies en el grup de TB i ansietat comòrbida en comparació amb els que no tenen ansietat. Aquestes discrepàncies poden explicar-se pel fet que la majoria dels subjectes d'aquest estudi encara no han assolit l'edat de major risc per a aquestes condicions. No obstant això, els joves amb TB i ansietat van tenir més ideació suïcida, així com desesperació durant l'episodi depressiu més sever al llarg de la seva vida en comparació amb els subjectes sense ansietat comòrbida. Atès que la desesperança està altament associada amb intents de suïcidi i el suïcidi consumat, una acurada avaluació i seguiment del risc de suïcidi entre els joves amb TB i ansietat està clarament indicada. També contrari a la nostra hipòtesi inicial, no hem trobat un pitjor funcionament en el grup de TB amb ansietat comòrbida en comparació amb els que no

tenien ansietat. És possible que l'impacta del TB en el funcionament global de la infància i adolescència és significativament tant profunda que qualsevol deteriorament addicional associat amb l'ansietat comòrbida és relativament insignificant.

Finalment, després d'ajustar per a comparacions múltiples, els joves amb TB i ansietat comòrbida van reportar més molèsties i dolors que aquells sense ansietat, com és el cas d'estudis en adults. Ha estat ben documentat que la joventut ansiosa experimenta queixes somàtiques i tendeixen a consultar a metges d'atenció primària o pediatres abans que els metges de salut mental. Per tant, és important educar a aquests proveïdors de primera línia sobre la possibilitat que els joves ansiosos amb una història familiar positiva de trastorn de l'estat d'ànim també poden tenir un TB.

Atès que no hi ha altres estudis longitudinals en nens i adults que han avaluat el resultat dels trastorns d'ansietat en el TB, es va utilitzar la bibliografia existent sobre el curs dels trastorns d'ansietat en els joves i adults sense TB per poder comparar-ne els resultants.

Similar als nostres resultats, els estudis longitudinals en joves amb trastorns d'ansietat també han demostrat que amb l'excepció del TAS, la majoria dels trastorns d'ansietat i en especial el TAG tendeixen a continuar en l'edat adulta. També hi ha evidència de la continuació homotípica dels trastorns d'ansietat i en concordança amb els nostres resultats, els trastorns d'ansietat múltiples tenen una probabilitat més alta de persistència dels trastorns d'ansietat. Potser a causa del fet que altres estudis que avaluen

l'associació entre el trastorn de conducte i els trastorns d'ansietat es componen principalment per homes i en contrast amb els seus resultats, COBY ha trobat que la persistència de l'ansietat s'associa amb menys comorbilitat amb els tratorns de conducte. La persistència de l'ansietat a través del temps es pot explicar en part per l'alta associació entre els trastorns d'ansietat i el TB i podria ser un factor únic que influeix negativament en la gravetat del TB i el prognòstic, en comparació amb altres trastorns comòrbids com el TDAH i el TUS. A més, els nostres resultats i els d'un estudi epidemiològic en la joventut posen en evidència que la relació entre els trastorns d'ansietat i la gravetat del TB pot ser bidireccional, ja que és la manifestació de símptomes de mania o hipomania que s'associen amb la persistència i els inicis de nous trastorns d'ansietat.

Els resultats del nostre estudi, juntament amb el fet que els trastorns d'ansietat pediàtrics poden continuar en l'edat adulta i que els trastorns d'ansietat empitjoren el curs del TB, indiquen la necessitat de la identificació precoç i el tractament d'aquests trastorns en els joves amb TB. Aquestes troballes són clínicament rellevants perquè en l'actualitat els tractaments farmacològics de primera línia per als trastorns d'ansietat en els joves són els ISRS i s'ha demostrat que poden activar o desestabilitzar símptomes del TB. Els tractaments basats en l'evidència per als trastorns d'ansietat mostren que la teràpia cognitiva-conductual (TCC) i els ISRS i en particular la seva combinació, són eficaços per al tractament agut de l'ansietat en la joventut. Encara que sabem que la TCC és eficaç per als joves amb trastorns d'ansietat, els joves amb TB han estat exclosos d'aquests assajos i per tant no tenim dades sobre la seva eficàcia per a aquesta població. A més, tot i que els ISRS són eficaços i ben tolerats per als joves amb ansietat, no sabem l'eficàcia i

tolerabilitat d'aquests medicaments per als joves amb TB i ansietat. Per tant, és molt important avaluar la presència de símptomes maníacs o hipomaníacs en un nen que es presenta amb ansietat, especialment si els símptomes depressius i una història familiar positiva dels trastorns de l'humor estan també presents. Encara que els símptomes hipomaníacs poden ser difícils de determinar en els joves a causa de la presentació única del desenvolupament, així com la superposició de símptomes amb altres malalties com la depressió i l'ansietat, els estudis recents demostren clarament que la manía/hipomanía en la joventut pot ser diagnosticada amb fiabilitat. A més, els nens ansiosos tractats amb antidepressius han de ser acuradament monitoritzats per detectar la presència de símptomes de mania o hipomania.

Poc se sap sobre els tractaments més eficaços per al tractament de l'ansietat comòrbida en els joves amb TB. Atès que no hi ha estudis randomitzats que hagin comparar el TCC, els ISRS o la combinació d'ambdós tractaments en els joves (i adults) amb ansietat i TB, creiem que aquests estudis són necessaris. Aquests estudis podrien informar a la pràctica clínica i respondre a una pregunta molt important sobre l'eficàcia relativa del TCC, els ISRS, i/o la seva combinació, per als joves amb la presentació comú i discapacitant de la comorbilitat de l'ansietat i el TB. La relació risc/benefici de l'ús dels ISRS en els joves amb TB que estan en tractament amb estabilitzadors de l'ànim també haurien de ser explorats.

Al voltant d'una quarta part de la mostra va desenvolupar nous trastorns d'ansietat durant el seguiment. Igual que en la literatura pediàtrica i en adults, el sexe femení i un

menor estatus socioeconòmic augmenta el risc de nous trastorns d'ansietat, especialment TAG. Els nostres resultats també són consistents amb els estudis epidemiològics en què els trastorns d'ansietat són més freqüents en les dones, especialment en dones adolescents amb TAG.

Estudis epidemiològics i clínics han demostrat que els joves i adults amb TB es troben en alt risc de TUS. D'altra banda, tant el TB com el TUS estan fortament associats amb l'ansietat. De la mateixa manera, els nostres resultants mostren que els joves amb TB i TUS o ADHD estan en alt risc per l'aparició de nous trastorns d'ansietat, suggerint que el reconeixement precoç i el tractament d'aquests trastorns poden prevenir el desenvolupament de nous trastorns d'ansietat.

CONCLUSIONS

La conclusions d'aquesta tesi derivades de l'estudi I **(I, II, III)** i l'estudi II **(IV, V, VI, VII)** es poden resumir de la manera següent:

I: Els trastorns d'ansietat, en particular TAS i TAG, són molt comuns en la joventut i en general són anteriors a l'aparició del TB.

II: Els joves amb TB i ansietat van mostrar majors taxes de TB-II, major durada dels símptomes de l'estat d'ànim i depressions més severes. Aquesta associació pot estar

relacionada amb el fet que el TB-II té un curs més crònic, major durada de la malaltia, cicles més curts, un major nombre d'episodis principalment depressius, intervals més curts de millora entre els episodis i menors taxes de recuperació.

III: És molt important avaluar un nen que té ansietat amb la presència de símptomes maníacs o hipomaníacs, especialment si també estan presents símptomes depressius i una història familiar positiva dels trastorns de l'humor.

IV: La majoria dels trastorns d'ansietat es va mantenir durant el seguiment i podria ser un factor únic que influeix negativament en la gravetat del TB i el pronòstic en comparació amb altres trastorns comòrbids.

V: La relació entre els trastorns d'ansietat i la gravetat del TB pot ser bidireccional, ja que la manifestació de símptomes de mania o hipomania s'associen amb la persistència i els inicis de nous trastorns d'ansietat.

VI: Joves amb TB i TDAH o TUS tenen un alt risc per l'aparició de nous trastorns d'ansietat, el que suggereix que el reconeixement i el tractament precoç d'aquests trastorns podem prevenir el desenvolupament de nous trastorns d'ansietat.

VII: Els estudis randomitzats són necessaris per avaluar si els tractaments existents per als trastorns d'ansietat, particularment els psicosocials com ara el TCC, son

iguals d'eficaços i tolerables i no tenen relació amb la inducció de la inestabilitat de l'estat d'ànim per als joves amb TB i trastorns d'ansietat.

8. REFERENCES

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1. Axelson D, Birmaher B, Strober M, et al. Phenomenology of children and adolescents with bipolar spectrum disorders. Arch Gen Psychiatry 2006 Oct;63(10):1139-1148.

2. Sala R, Axelson D, Birmaher B. Phenomenology, longitudinal course, and outcome of children and adolescents with bipolar spectrum disorders. Child Adolesc Psychiatr Clin N Am 2009 Apr;18(2):273-289, vii.

3. Pavuluri MN, Birmaher B, Naylor MW. Pediatric bipolar disorder: a review of the past 10 years. J Am Acad Child Adolesc Psychiatry 2005 Sep;44(9):846-871.

4. Joshi G, Wilens T. Comorbidity in pediatric bipolar disorder. Child Adolesc Psychiatr Clin N Am 2009 Apr;18(2):291-319, vii-viii.

5. Beesdo K, Knappe S, Pine DS. Anxiety and anxiety disorders in children and adolescents: developmental issues and implications for DSM-V. Psychiatr Clin North Am 2009 Sep;32(3):483-524.

6. Kowatch RA, Youngstrom EA, Danielyan A, Findling RL. Review and meta-analysis of the phenomenology and clinical characteristics of mania in children and adolescents. Bipolar Disord 2005 Dec;7(6):483-496.

7. Soutullo CA, Chang KD, Diez-Suarez A, et al. Bipolar disorder in children and adolescents: international perspective on epidemiology and phenomenology. Bipolar Disord 2005 Dec;7(6):497-506.

8. McClellan J, Kowatch R, Findling RL. Practice parameter for the assessment and treatment of children and adolescents with bipolar disorder. J Am Acad Child Adolesc Psychiatry 2007 Jan;46(1):107-125.

9. Biederman J, Faraone SV, Wozniak J, Mick E, Kwon A, Aleardi M. Further evidence of unique developmental phenotypic correlates of pediatric bipolar disorder: findings from a large sample of clinically referred preadolescent children assessed over the last 7 years. J Affect Disord 2004 Oct;82 Suppl 1:S45-58.

10. Mick E, Spencer T, Wozniak J, Biederman J. Heterogeneity of irritability in attention-deficit/hyperactivity disorder subjects with and without mood disorders. Biol Psychiatry 2005 Oct 1;58(7):576-582.

11. Wozniak J, Biederman J, Kiely K, et al. Mania-like symptoms suggestive of childhood-onset bipolar disorder in clinically referred children. J Am Acad Child Adolesc Psychiatry 1995 Jul;34(7):867-876.

12. Findling RL, Gracious BL, McNamara NK, et al. Rapid, continuous cycling and psychiatric co-morbidity in pediatric bipolar I disorder. Bipolar Disord 2001 Aug;3(4):202-210.

13. Birmaher B, Axelson D, Strober M, et al. Clinical course of children and adolescents with bipolar spectrum disorders. Arch Gen Psychiatry 2006 Feb;63(2):175-183.

14. Carlson GA. Who are the children with severe mood dysregulation, a.k.a. "rages"? Am J Psychiatry 2007 Aug;164(8):1140-1142.

15. Geller B, Zimerman B, Williams M, et al. DSM-IV mania symptoms in a prepubertal and early adolescent bipolar disorder phenotype compared to attention-deficit

hyperactive and normal controls. J Child Adolesc Psychopharmacol 2002 Spring;12(1):11-25.

16. Geller B, Zimerman B, Williams M, Delbello MP, Frazier J, Beringer L. Phenomenology of prepubertal and early adolescent bipolar disorder: examples of elated mood, grandiose behaviors, decreased need for sleep, racing thoughts and hypersexuality. J Child Adolesc Psychopharmacol 2002 Spring;12(1):3-9.

17. Leibenluft E. Severe mood dysregulation, irritability, and the diagnostic boundaries of bipolar disorder in youths. Am J Psychiatry Feb;168(2):129-142.

18. Leibenluft E, Charney DS, Towbin KE, Bhangoo RK, Pine DS. Defining clinical phenotypes of juvenile mania. Am J Psychiatry 2003 Mar;160(3):430-437.

19. Lewinsohn PM, Klein DN, Seeley JR. Bipolar disorders in a community sample of older adolescents: prevalence, phenomenology, comorbidity, and course. J Am Acad Child Adolesc Psychiatry 1995 Apr;34(4):454-463.

20. Lewinsohn PM, Klein DN, Seeley JR. Bipolar disorder during adolescence and young adulthood in a community sample. Bipolar Disord 2000 Sep;2(3 Pt 2):281-293.

21. Leibenluft E, Rich BA. Pediatric bipolar disorder. Annu Rev Clin Psychol 2008;4:163-187.

22. Campbell M, Cueva JE. Psychopharmacology in child and adolescent psychiatry: a review of the past seven years. Part II. J Am Acad Child Adolesc Psychiatry 1995 Oct;34(10):1262-1272.

23. Tarter RE. Evaluation and treatment of adolescent substance abuse: a decision tree method. Am J Drug Alcohol Abuse 1990;16(1-2):1-46.

24. Ambrosini PJ. Historical development and present status of the schedule for affective disorders and schizophrenia for school-age children (K-SADS). J Am Acad Child Adolesc Psychiatry 2000 Jan;39(1):49-58.

25. Faraone SV TM, Tsuang D. Genetics and mental disorders: a guide for students, clinicians, and researchers. New York: The Guilford Press. 1999.

26. Biederman J, Mick E, Bostic JQ, et al. The naturalistic course of pharmacologic treatment of children with maniclike symptoms: a systematic chart review. J Clin Psychiatry 1998 Nov;59(11):628-637; quiz 638.

27. Moore CM, Biederman J, Wozniak J, et al. Differences in brain chemistry in children and adolescents with attention deficit hyperactivity disorder with and without comorbid bipolar disorder: a proton magnetic resonance spectroscopy study. Am J Psychiatry 2006 Feb;163(2):316-318.

28. Kowatch RA, Fristad M, Birmaher B, Wagner KD, Findling RL, Hellander M. Treatment guidelines for children and adolescents with bipolar disorder. J Am Acad Child Adolesc Psychiatry 2005 Mar;44(3):213-235.

29. Wozniak J, Biederman J. A pharmacological approach to the quagmire of comorbidity in juvenile mania. J Am Acad Child Adolesc Psychiatry 1996 Jun;35(6):826-828.

30. DelBello MP, Hanseman D, Adler CM, Fleck DE, Strakowski SM. Twelve-month outcome of adolescents with bipolar disorder following first hospitalization for a manic or mixed episode.[see comment]. American Journal of Psychiatry 2007;164(4):582-590.

31. Axelson D, Birmaher B, Strober M, et al. Phenomenology of children and adolescents with bipolar spectrum disorders. Archives of General Psychiatry 2006 Oct;63(10):1139-1148.

32. Biederman J, Faraone SV, Marrs A, et al. Panic disorder and agoraphobia in consecutively referred children and adolescents. J Am Acad Child Adolesc Psychiatry 1997 Feb;36(2):214-223.

33. Dickstein DP, Rich BA, Binstock AB, et al. Comorbid anxiety in phenotypes of pediatric bipolar disorder. J Child Adolesc Psychopharmacol 2005 Aug;15(4):534-548.

34. Tillman R, Geller B, Bolhofner K, Craney JL, Williams M, Zimerman B. Ages of onset and rates of syndromal and subsyndromal comorbid DSM-IV diagnoses in a prepubertal and early adolescent bipolar disorder phenotype. J Am Acad Child Adolesc Psychiatry 2003 Dec;42(12):1486-1493.

35. Harpold TL, Wozniak J, Kwon A, et al. Examining the association between pediatric bipolar disorder and anxiety disorders in psychiatrically referred children and adolescents. J Affect Disord 2005 Sep;88(1):19-26.

36. Birmaher B, Axelson D, Monk K, et al. Lifetime psychiatric disorders in school-aged offspring of parents with bipolar disorder: the Pittsburgh Bipolar Offspring study. Arch Gen Psychiatry 2009 Mar;66(3):287-296.

37. Simeonova DI, Jackson V, Attalla A, et al. Subcortical volumetric correlates of anxiety in familial pediatric bipolar disorder: A preliminary investigation. Psychiatry Res 2009 Aug 30;173(2):113-120.

38. Henin A, Biederman J, Mick E, et al. Psychopathology in the offspring of parents with bipolar disorder: a controlled study. Biological Psychiatry 2005 Oct 1;58(7):554-561.

39. Grigoroiu-Serbanescu M, Christodorescu D, Jipescu I, Totoescu A, Marinescu E, Ardelean V. Psychopathology in children aged 10-17 of bipolar parents: psychopathology rate and correlates of the severity of the psychopathology. J Affect Disord 1989 Mar-Jun;16(2-3):167-179.

40. Hammen C, Burge D, Burney E, Adrian C. Longitudinal study of diagnoses in children of women with unipolar and bipolar affective disorder. Archives of General Psychiatry 1990;47(12):1112-1117.

41. Feske U, Frank E, Mallinger AG, et al. Anxiety as a correlate of response to the acute treatment of bipolar I disorder. Am J Psychiatry 2000 Jun;157(6):956-962.

42. Johnson JG, Cohen P, Brook JS. Associations between bipolar disorder and other psychiatric disorders during adolescence and early adulthood: a community-based longitudinal investigation. Am J Psychiatry 2000 Oct;157(10):1679-1681.

43. Masi G, Perugi G, Toni C, et al. Obsessive-compulsive bipolar comorbidity: focus on children and adolescents. J Affect Disord 2004 Mar;78(3):175-183.

44. Masi G, Toni C, Perugi G, Mucci M, Millepiedi S, Akiskal HS. Anxiety disorders in children and adolescents with bipolar disorder: a neglected comorbidity. Can J Psychiatry 2001 Nov;46(9):797-802.

45. McElroy SL, Altshuler LL, Suppes T, et al. Axis I psychiatric comorbidity and its relationship to historical illness variables in 288 patients with bipolar disorder. Am J Psychiatry 2001 Mar;158(3):420-426.

46. Perugi G, Akiskal HS, Ramacciotti S, et al. Depressive comorbidity of panic, social phobic, and obsessive-compulsive disorders re-examined: is there a bipolar II connection? J Psychiatr Res 1999 Jan-Feb;33(1):53-61.

47. Wozniak J, Biederman J, Monuteaux MC, Richards J, Faraone SV. Parsing the comorbidity between bipolar disorder and anxiety disorders: a familial risk analysis. J Child Adolesc Psychopharmacol 2002 Summer;12(2):101-111.

48. Birmaher B, Kennah A, Brent D, Ehmann M, Bridge J, Axelson D. Is bipolar disorder specifically associated with panic disorder in youths? J Clin Psychiatry 2002 May;63(5):414-419.

49. Chen YW, Dilsaver SC. Comorbidity of panic disorder in bipolar illness: evidence from the Epidemiologic Catchment Area Survey. Am J Psychiatry 1995 Feb;152(2):280-282.

50. Goodwin RD, Hoven CW. Bipolar-panic comorbidity in the general population: prevalence and associated morbidity. J Affect Disord 2002 Jun;70(1):27-33.

51. Kessler RC, Stang PE, Wittchen HU, Ustun TB, Roy-Burne PP, Walters EE. Lifetime panic-depression comorbidity in the National Comorbidity Survey. Arch Gen Psychiatry 1998 Sep;55(9):801-808.

52. Bowen R, South M, Hawkes J. Mood swings in patients with panic disorder. Can J Psychiatry 1994 Mar;39(2):91-94.

53. MacKinnon DF, Xu J, McMahon FJ, et al. Bipolar disorder and panic disorder in families: an analysis of chromosome 18 data. Am J Psychiatry 1998 Jun;155(6):829-831.

54. MacKinnon DF, Zandi PP, Cooper J, et al. Comorbid bipolar disorder and panic disorder in families with a high prevalence of bipolar disorder. Am J Psychiatry 2002 Jan;159(1):30-35.

55. Savino M, Perugi G, Simonini E, Soriani A, Cassano GB, Akiskal HS. Affective comorbidity in panic disorder: is there a bipolar connection? J Affect Disord 1993 Jul;28(3):155-163.

56. Cassano GB, Pini S, Saettoni M, Dell'Osso L. Multiple anxiety disorder comorbidity in patients with mood spectrum disorders with psychotic features. Am J Psychiatry 1999 Mar;156(3):474-476.

57. Freeman MP, Freeman SA, McElroy SL. The comorbidity of bipolar and anxiety disorders: prevalence, psychobiology, and treatment issues. J Affect Disord 2002 Feb;68(1):1-23.

58. Gaudiano BA, Miller IW. Anxiety disorder comobidity in Bipolar I Disorder: relationship to depression severity and treatment outcome. Depress Anxiety 2005;21(2):71-77.

59. Otto MW, Simon NM, Wisniewski SR, et al. Prospective 12-month course of bipolar disorder in out-patients with and without comorbid anxiety disorders. Br J Psychiatry 2006 Jul;189:20-25.

60. Young LT, Cooke RG, Robb JC, Levitt AJ, Joffe RT. Anxious and non-anxious bipolar disorder. J Affect Disord 1993 Sep;29(1):49-52.

61. Calabrese JR, Delucchi GA. Spectrum of efficacy of valproate in 55 patients with rapid-cycling bipolar disorder. Am J Psychiatry 1990 Apr;147(4):431-434.

62. Baetz M, Bowen RC. Efficacy of divalproex sodium in patients with panic disorder and mood instability who have not responded to conventional therapy. Can J Psychiatry 1998 Feb;43(1):73-77.

63. Clark RD, Canive JM, Calais LA, Qualls CR, Tuason VB. Divalproex in posttraumatic stress disorder: an open-label clinical trial. J Trauma Stress 1999 Apr;12(2):395-401.

64. Fesler FA. Valproate in combat-related posttraumatic stress disorder. J Clin Psychiatry 1991 Sep;52(9):361-364.

65. McElroy SL, Keck PE, Jr., Lawrence JM. Treatment of panic disorder and benzodiazepine withdrawal with valproate. J Neuropsychiatry Clin Neurosci 1991 Spring;3(2):232-233.

66. Looff D, Grimley P, Kuller F, Martin A, Shonfield L. Carbamazepine for PTSD. J Am Acad Child Adolesc Psychiatry 1995 Jun;34(6):703-704.

67. Stewart JT, Bartucci RJ. Posttraumatic stress disorder and partial complex seizures. Am J Psychiatry 1986 Jan;143(1):113-114.

68. Tondo L, Burrai C, Scamonatti L, et al. Carbamazepine in panic disorder. Am J Psychiatry 1989 Apr;146(4):558-559.

69. Masi G, Perugi G, Millepiedi S, et al. Clinical and research implications of panic-bipolar comorbidity in children and adolescents. Psychiatry Res 2007 Sep 30;153(1):47-54.

70. DelBello MP, Hanseman D, Adler CM, Fleck DE, Strakowski SM. Twelve-month outcome of adolescents with bipolar disorder following first hospitalization for a manic or mixed episode. Am J Psychiatry 2007 Apr;164(4):582-590.

71. Boylan KR, Bieling PJ, Marriott M, Begin H, Young LT, MacQueen GM. Impact of comorbid anxiety disorders on outcome in a cohort of patients with bipolar disorder. J Clin Psychiatry 2004 Aug;65(8):1106-1113.

72. Coryell W, Solomon DA, Fiedorowicz JG, Endicott J, Schettler PJ, Judd LL. Anxiety and outcome in bipolar disorder. Am J Psychiatry 2009 Nov;166(11):1238-1243.

73. Frank E, Cyranowski JM, Rucci P, et al. Clinical significance of lifetime panic spectrum symptoms in the treatment of patients with bipolar I disorder. Arch Gen Psychiatry 2002 Oct;59(10):905-911.

74. Simon NM, Otto MW, Wisniewski SR, et al. Anxiety disorder comorbidity in bipolar disorder patients: data from the first 500 participants in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). Am J Psychiatry 2004 Dec;161(12):2222-2229.

75. Birmaher B AD, Pavuluri MN. Pediatric bipolar disorder. In: Martin A, Volkmar FR, editors. Lewis' child and adolescent psychiatry: a comprehensive textbook. 4th edition. Baltimore (MD): Lippincott Williams & Wilkins. 2007; 513-28. 2007.

76. Birmaher B, Ryan ND, Williamson DE, et al. Childhood and adolescent depression: a review of the past 10 years. Part I. J Am Acad Child Adolesc Psychiatry 1996 Nov;35(11):1427-1439.

77. Geller B, Zimerman B, Williams M, Bolhofner K, Craney JL. Bipolar disorder at prospective follow-up of adults who had prepubertal major depressive disorder. Am J Psychiatry 2001 Jan;158(1):125-127.

78. Kovacs M. Presentation and course of major depressive disorder during childhood and later years of the life span. J Am Acad Child Adolesc Psychiatry 1996 Jun;35(6):705-715.

79. Strober M, Carlson G. Bipolar illness in adolescents with major depression: clinical, genetic, and psychopharmacologic predictors in a three- to four-year prospective follow-up investigation. Arch Gen Psychiatry 1982 May;39(5):549-555.

80. Weissman MM, Wolk S, Wickramaratne P, et al. Children with prepubertal-onset major depressive disorder and anxiety grown up. Arch Gen Psychiatry 1999 Sep;56(9):794-801.

81. Carlson GA. Child and adolescent mania--diagnostic considerations. J Child Psychol Psychiatry 1990 Mar;31(3):331-341.

82. Werry JS, McClellan JM, Chard L. Childhood and adolescent schizophrenic, bipolar, and schizoaffective disorders: a clinical and outcome study. J Am Acad Child Adolesc Psychiatry 1991 May;30(3):457-465.

83. Martin A, Young C, Leckman JF, Mukonoweshuro C, Rosenheck R, Leslie D. Age effects on antidepressant-induced manic conversion. Arch Pediatr Adolesc Med 2004 Aug;158(8):773-780.

84. Wilens TE, Wyatt D, Spencer TJ. Disentangling disinhibition. J Am Acad Child Adolesc Psychiatry 1998 Nov;37(11):1225-1227.

85. Geller B, Tillman R, Craney JL, Bolhofner K. Four-year prospective outcome and natural history of mania in children with a prepubertal and early adolescent bipolar disorder phenotype. Arch Gen Psychiatry 2004 May;61(5):459-467.

86. Birmaher B, Williamson DE, Dahl RE, et al. Clinical presentation and course of depression in youth: does onset in childhood differ from onset in adolescence? J Am Acad Child Adolesc Psychiatry 2004 Jan;43(1):63-70.

87. Carlson GA, Bromet EJ, Sievers S. Phenomenology and outcome of subjects with early- and adult-onset psychotic mania. Am J Psychiatry 2000 Feb;157(2):213-219.

88. Carlson GA, Bromet EJ, Driessens C, Mojtabai R, Schwartz JE. Age at onset, childhood psychopathology, and 2-year outcome in psychotic bipolar disorder. Am J Psychiatry 2002 Feb;159(2):307-309.

89. Jairam R, Srinath S, Girimaji SC, Seshadri SP. A prospective 4-5 year follow-up of juvenile onset bipolar disorder. Bipolar Disord 2004 Oct;6(5):386-394.

90. Strober M, Schmidt-Lackner S, Freeman R, Bower S, Lampert C, DeAntonio M. Recovery and relapse in adolescents with bipolar affective illness: a five-year naturalistic, prospective follow-up. J Am Acad Child Adolesc Psychiatry 1995 Jun;34(6):724-731.

91. Birmaher B, Axelson D. Course and outcome of bipolar spectrum disorder in children and adolescents: a review of the existing literature. Dev Psychopathol 2006 Fall;18(4):1023-1035.

92. Post RM, Denicoff KD, Leverich GS, et al. Morbidity in 258 bipolar outpatients followed for 1 year with daily prospective ratings on the NIMH life chart method. J Clin Psychiatry 2003 Jun;64(6):680-690; quiz 738-689.

93. Schneck CD, Miklowitz DJ, Calabrese JR, et al. Phenomenology of rapid-cycling bipolar disorder: data from the first 500 participants in the Systematic Treatment Enhancement Program. Am J Psychiatry 2004 Oct;161(10):1902-1908.

94. Perlis RH, Miyahara S, Marangell LB, et al. Long-term implications of early onset in bipolar disorder: data from the first 1000 participants in the systematic treatment enhancement program for bipolar disorder (STEP-BD). Biol Psychiatry 2004 May 1;55(9):875-881.

95. Chengappa KN, Kupfer DJ, Frank E, et al. Relationship of birth cohort and early age at onset of illness in a bipolar disorder case registry. Am J Psychiatry 2003 Sep;160(9):1636-1642.

96. Coryell W, Endicott J, Maser JD, Keller MB, Leon AC, Akiskal HS. Long-term stability of polarity distinctions in the affective disorders. Am J Psychiatry 1995 Mar;152(3):385-390.

97. Weller RA, Weller EB, Tucker SG, Fristad MA. Mania in prepubertal children: has it been underdiagnosed? J Affect Disord 1986 Sep-Oct;11(2):151-154.

98. Brent DA, Perper JA, Moritz G, et al. Psychiatric risk factors for adolescent suicide: a case-control study. J Am Acad Child Adolesc Psychiatry 1993 May;32(3):521-529.

99. Geller B, Bolhofner K, Craney JL, Williams M, DelBello MP, Gundersen K. Psychosocial functioning in a prepubertal and early adolescent bipolar disorder phenotype. J Am Acad Child Adolesc Psychiatry 2000 Dec;39(12):1543-1548.

100. Youngstrom E, Youngstrom JK, Starr M. Bipolar diagnoses in community mental health: Achenbach Child Behavior Checklist profiles and patterns of comorbidity. Biol Psychiatry 2005 Oct 1;58(7):569-575.

101. Kahana SY, Youngstrom EA, Findling RL, Calabrese JR. Employing parent, teacher, and youth self-report checklists in identifying pediatric bipolar spectrum

disorders: an examination of diagnostic accuracy and clinical utility. J Child Adolesc Psychopharmacol 2003 Winter;13(4):471-488.

102. Mick E, Biederman J, Pandina G, Faraone SV. A preliminary meta-analysis of the child behavior checklist in pediatric bipolar disorder. Biol Psychiatry 2003 Jun 1;53(11):1021-1027.

103. Geller B, Craney JL, Bolhofner K, Nickelsburg MJ, Williams M, Zimerman B. Two-year prospective follow-up of children with a prepubertal and early adolescent bipolar disorder phenotype. Am J Psychiatry 2002 Jun;159(6):927-933.

104. Tillman R, Geller B, Craney JL, et al. Temperament and character factors in a prepubertal and early adolescent bipolar disorder phenotype compared to attention deficit hyperactive and normal controls. J Child Adolesc Psychopharmacol 2003 Winter;13(4):531-543.

105. Quackenbush D, Kutcher S, Robertson HA, Boulos C, Chaban P. Premorbid and postmorbid school functioning in bipolar adolescents: description and suggested academic interventions. Can J Psychiatry 1996 Feb;41(1):16-22.

106. Lewinsohn PM SJ, Klein DN. . Bipolar disorder in adolescents: epidemiology and suicidal behavior. In: Geller B, DelBello MP, editors. Bipolar disorder in childhood and early adolescence. New York: Guilford. 2003: 7-24. 2003.

107. Goldstein BI, Strober MA, Birmaher B, et al. Substance use disorders among adolescents with bipolar spectrum disorders. Bipolar Disord 2008 Jun;10(4):469-478.

108. Wilens TE, Biederman J, Millstein RB, Wozniak J, Hahesy AL, Spencer TJ. Risk for substance use disorders in youths with child- and adolescent-onset bipolar disorder. J Am Acad Child Adolesc Psychiatry 1999 Jun;38(6):680-685.

109. Wilens TE, Biederman J, Kwon A, et al. Risk of substance use disorders in adolescents with bipolar disorder. J Am Acad Child Adolesc Psychiatry 2004 Nov;43(11):1380-1386.

110. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorder: 4th ed. Washington, DC: American Psychiatric Association; 1994.

111. Birmaher B, Axelson D, Strober M, et al. Clinical course of children and adolescents with bipolar spectrum disorders. Archives of General Psychiatry 2006;63:175-183.

112. Kaufman J, Birmaher B, Brent D, et al. Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL): initial reliability and validity data.[see comment]. Journal of the American Academy of Child & Adolescent Psychiatry 1997 Jul;36(7):980-988.

113. Axelson D, Birmaher BJ, Brent D, et al. A preliminary study of the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children mania rating scale for children and adolescents. Journal of Child & Adolescent Psychopharmacology 2003;13:463-470.

114. Hollingshead AB. Index of Social Status: Mangen, D. J., & Peterson, W. A. (Eds.). (1982). Research instruments in social gerontology: Vol. 2. Social roles and social participation. Minneapolis, MN: University of Minnesota Press. .

115. Shaffer D, Gould MS, Brasic J, et al. A children's global assessment scale (CGAS). Arch Gen Psychiatry 1983 Nov;40(11):1228-1231.

116. Petersen AC, Crockett, L., Richards, M., & Boxer, A. A self-report measure of pubertal status: Reliability, validity, and initial norms. : Journal of Youth and Adolescence; 1988.

117. First MB SR, Williams JBW, Gibbon M. . *Structured Clinical Interview for* DSM-IV *(SCID)*. Washington, DC: American Psychiatric Association; 1995.

118. Weissman MM, Wickramaratne P, Adams P, Wolk S, Verdeli H, Olfson M. Brief screening for family psychiatric history: the family history screen. Archives of General Psychiatry 2000 Jul;57(7):675-682.

119. Klein RG. Anxiety disorders. J Child Psychol Psychiatry 2009 Jan;50(1-2):153-162.

120. Valtonen HM, Suominen K, Haukka J, et al. Hopelessness across phases of bipolar I or II disorder: a prospective study. J Affect Disord 2009 May;115(1-2):11-17.

121. Carleton RN, Abrams MP, Asmundson GJ, Antony MM, McCabe RE. Pain-related anxiety and anxiety sensitivity across anxiety and depressive disorders. J Anxiety Disord 2009 Aug;23(6):791-798.

122. Kaufman J, Birmaher B, Brent D, et al. Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL): initial reliability and validity data. J Am Acad Child Adolesc Psychiatry 1997 Jul;36(7):980-988.

123. Axelson D, Birmaher BJ, Brent D, et al. A preliminary study of the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children mania rating scale for children and adolescents. J Child Adolesc Psychopharmacol 2003 Winter;13(4):463-470.

124. Weissman MM, Wickramaratne P, Adams P, Wolk S, Verdeli H, Olfson M. Brief screening for family psychiatric history: the family history screen. Arch Gen Psychiatry 2000 Jul;57(7):675-682.

125. Shaffer D, Gould MS, Brasic J, et al. A children's global assessment scale (CGAS). Archives of General Psychiatry 1983 Nov;40(11):1228-1231.

126. Birmaher B, Khetarpal S, Brent D, et al. The Screen for Child Anxiety Related Emotional Disorders (SCARED): scale construction and psychometric characteristics. J Am Acad Child Adolesc Psychiatry 1997 Apr;36(4):545-553.

127. Keller MB, Lavori PW, Friedman B, et al. The Longitudinal Interval Follow-up Evaluation. A comprehensive method for assessing outcome in prospective longitudinal studies. Arch Gen Psychiatry 1987 Jun;44(6):540-548.

128. Warshaw MG, Dyck I, Allsworth J, Stout RL, Keller MB. Maintaining reliability in a long-term psychiatric study: an ongoing inter-rater reliability monitoring program using the longitudinal interval follow-up evaluation. J Psychiatr Res 2001 Sep-Oct;35(5):297-305.

129. Sala R, Axelson DA, Castro-Fornieles J, et al. Comorbid anxiety in children and adolescents with bipolar spectrum disorders: prevalence and clinical correlates. J Clin Psychiatry Sep 7.

130. Bruce SE, Yonkers KA, Otto MW, et al. Influence of psychiatric comorbidity on recovery and recurrence in generalized anxiety disorder, social phobia, and panic disorder: a 12-year prospective study. Am J Psychiatry 2005 Jun;162(6):1179-1187.

131. Yonkers KA, Dyck IR, Warshaw M, Keller MB. Factors predicting the clinical course of generalised anxiety disorder. Br J Psychiatry 2000 Jun;176:544-549.

132. Yonkers KA, Bruce SE, Dyck IR, Keller MB. Chronicity, relapse, and illness--course of panic disorder, social phobia, and generalized anxiety disorder: findings in men and women from 8 years of follow-up. Depress Anxiety 2003;17(3):173-179.

133. Hoaglin D, Mosteller, F, & Rukey, JW. Understanding Robust and Exploratory Data Analysis. John Wiley & Sons. New York, NY. 1983.

134. Pini S, Cassano GB, Simonini E, Savino M, Russo A, Montgomery SA. Prevalence of anxiety disorders comorbidity in bipolar depression, unipolar depression and dysthymia. J Affect Disord 1997 Feb;42(2-3):145-153.

135. Henry C, Van den Bulke D, Bellivier F, Etain B, Rouillon F, Leboyer M. Anxiety disorders in 318 bipolar patients: prevalence and impact on illness severity and response to mood stabilizer. J Clin Psychiatry 2003 Mar;64(3):331-335.

136. Kessler RC, Rubinow DR, Holmes C, Abelson JM, Zhao S. The epidemiology of DSM-III-R bipolar I disorder in a general population survey. Psychol Med 1997 Sep;27(5):1079-1089.

137. Doughty CJ, Wells JE, Joyce PR, Olds RJ, Walsh AE. Bipolar-panic disorder comorbidity within bipolar disorder families: a study of siblings. Bipolar Disord 2004 Jun;6(3):245-252.

138. Lee JH, Dunner DL. The effect of anxiety disorder comorbidity on treatment resistant bipolar disorders. Depress Anxiety 2008;25(2):91-97.

139. Bauer MS, Altshuler L, Evans DR, Beresford T, Williford WO, Hauger R. Prevalence and distinct correlates of anxiety, substance, and combined comorbidity in a multi-site public sector sample with bipolar disorder. J Affect Disord 2005 Apr;85(3):301-315.

140. Henin A, Biederman J, Mick E, et al. Childhood antecedent disorders to bipolar disorder in adults: a controlled study. J Affect Disord 2007 Apr;99(1-3):51-57.

141. Pine DS, Cohen P, Gurley D, Brook J, Ma Y. The risk for early-adulthood anxiety and depressive disorders in adolescents with anxiety and depressive disorders. Arch Gen Psychiatry 1998 Jan;55(1):56-64.

142. Merikangas KR, Zhang H, Avenevoli S, Acharyya S, Neuenschwander M, Angst J. Longitudinal trajectories of depression and anxiety in a prospective community study: the Zurich Cohort Study. Arch Gen Psychiatry 2003 Oct;60(10):993-1000.

143. Goldstein TR, Birmaher B, Axelson D, et al. History of suicide attempts in pediatric bipolar disorder: factors associated with increased risk. Bipolar Disord 2005 Dec;7(6):525-535.

144. Steinbuchel PH, Wilens TE, Adamson JJ, Sgambati S. Posttraumatic stress disorder and substance use disorder in adolescent bipolar disorder. Bipolar Disord 2009 Mar;11(2):198-204.

145. Goldstein BI, Levitt AJ. The specific burden of comorbid anxiety disorders and of substance use disorders in bipolar I disorder. Bipolar Disord 2008 Feb;10(1):67-78.

146. Beck AT, Brown GK, Steer RA, Dahlsgaard KK, Grisham JR. Suicide ideation at its worst point: a predictor of eventual suicide in psychiatric outpatients. Suicide Life Threat Behav 1999 Spring;29(1):1-9.

147. Brown GK, Beck AT, Steer RA, Grisham JR. Risk factors for suicide in psychiatric outpatients: a 20-year prospective study. J Consult Clin Psychol 2000 Jun;68(3):371-377.

148. Fawcett J, Scheftner WA, Fogg L, et al. Time-related predictors of suicide in major affective disorder. Am J Psychiatry 1990 Sep;147(9):1189-1194.

149. Goldstein BI, Houck PR, Karp JF. Factors associated with pain interference in an epidemiologic sample of adults with bipolar I disorder. J Affect Disord 2009 Oct;117(3):151-156.

150. Bell-Dolan DB, T.J. Separation anxiety disorder, overanxious disorder, and school refusal. Child Adolesc Psychiatr Clin N Am 1993:2:563-580.

151. Cantwell DP, Baker L. Stability and natural history of DSM-III childhood diagnoses. J Am Acad Child Adolesc Psychiatry 1989 Sep;28(5):691-700.

152. Cohen P, Cohen J, Brook J. An epidemiological study of disorders in late childhood and adolescence--II. Persistence of disorders. J Child Psychol Psychiatry 1993 Sep;34(6):869-877.

153. Essau CA, Conradt J, Petermann F. Course and outcome of anxiety disorders in adolescents. J Anxiety Disord 2002;16(1):67-81.

154. Keller MB, Lavori PW, Wunder J, Beardslee WR, Schwartz CE, Roth J. Chronic course of anxiety disorders in children and adolescents. J Am Acad Child Adolesc Psychiatry 1992 Jul;31(4):595-599.

155. Costello EJ, Mustillo S, Erkanli A, Keeler G, Angold A. Prevalence and development of psychiatric disorders in childhood and adolescence. Arch Gen Psychiatry 2003 Aug;60(8):837-844.

156. Gregory AM, Caspi A, Moffitt TE, Koenen K, Eley TC, Poulton R. Juvenile mental health histories of adults with anxiety disorders. Am J Psychiatry 2007 Feb;164(2):301-308.

157. Last CG, Hansen C, Franco N. Anxious children in adulthood: a prospective study of adjustment. J Am Acad Child Adolesc Psychiatry 1997 May;36(5):645-652.

158. Lahey BB, Loeber R, Burke J, Rathouz PJ, McBurnett K. Waxing and waning in concert: dynamic comorbidity of conduct disorder with other disruptive and emotional problems over 7 years among clinic-referred boys. J Abnorm Psychol 2002 Nov;111(4):556-567.

159. Nock MK, Kazdin AE, Hiripi E, Kessler RC. Prevalence, subtypes, and correlates of DSM-IV conduct disorder in the National Comorbidity Survey Replication. Psychol Med 2006 May;36(5):699-710.

160. Birmaher B, Axelson DA, Monk K, et al. Fluoxetine for the treatment of childhood anxiety disorders. J Am Acad Child Adolesc Psychiatry 2003 Apr;42(4):415-423.

161. Allgulander C, Dahl AA, Austin C, et al. Efficacy of sertraline in a 12-week trial for generalized anxiety disorder. Am J Psychiatry 2004 Sep;161(9):1642-1649.

162. Ghaemi SN, Hsu DJ, Soldani F, Goodwin FK. Antidepressants in bipolar disorder: the case for caution. Bipolar Disord 2003 Dec;5(6):421-433.

163. Walkup JT, Albano AM, Piacentini J, et al. Cognitive behavioral therapy, sertraline, or a combination in childhood anxiety. N Engl J Med 2008 Dec 25;359(26):2753-2766.

164. Birmaher B AD, Pavuluri MN. Pediatric Bipolar Disorder, in Lewis' Child and Adolescent Psychiatric. A Comprehensive Textbook, 4th Edition. : Edited by A. Martin and F.R. Volkmar. Baltimore, Lippincott Williams 7 Wilkins; 2007.

165. Merikangas KR. Vulnerability factors for anxiety disorders in children and adolescents. Child Adolesc Psychiatr Clin N Am 2005 Oct;14(4):649-679, vii.

166. Wittchen HU, Nelson CB, Lachner G. Prevalence of mental disorders and psychosocial impairments in adolescents and young adults. Psychol Med 1998 Jan;28(1):109-126.

167. Blazer D, Hughes D, George LK. Stressful life events and the onset of a generalized anxiety syndrome. Am J Psychiatry 1987 Sep;144(9):1178-1183.

168. Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry 2005 Jun;62(6):593-602.

169. Chengappa KN, Levine J, Gershon S, Kupfer DJ. Lifetime prevalence of substance or alcohol abuse and dependence among subjects with bipolar I and II disorders in a voluntary registry. Bipolar Disord 2000 Sep;2(3 Pt 1):191-195.

170. Grant BF, Stinson FS, Dawson DA, et al. Prevalence and co-occurrence of substance use disorders and independent mood and anxiety disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions. Arch Gen Psychiatry 2004 Aug;61(8):807-816.

171. Kim-Cohen J, Caspi A, Moffitt TE, Harrington H, Milne BJ, Poulton R. Prior juvenile diagnoses in adults with mental disorder: developmental follow-back of a prospective-longitudinal cohort. Arch Gen Psychiatry 2003 Jul;60(7):709-717.

172. Lewinsohn PM, Klein DN, Seeley JR. Bipolar disorder during adolescence and young adulthood in a community sample. Bipolar Disorders 2000;2:281-293.

173. Jolin EM, Weller EB, Weller RA. Anxiety symptoms and syndromes in bipolar children and adolescents. Curr Psychiatry Rep 2008 Apr;10(2):123-129.

174. Lewinsohn PM, Rohde P, Seeley JR. Major depressive disorder in older adolescents: prevalence, risk factors, and clinical implications. Clin Psychol Rev 1998 Nov;18(7):765-794.

9. PUBLICATIONS

Comorbid Anxiety in Children and Adolescents With Bipolar Spectrum Disorders: Prevalence and Clinical Correlates

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Objective: Anxiety disorders are among the most common comorbid conditions in youth with bipolar disorder. We aimed to examine the prevalence and correlates of comorbid anxiety disorders among youth with bipolar disorder.

Method: As part of the Course and Outcome of Bipolar Youth study, 446 youth, ages 7 to 17 years, who met *DSM-IV* criteria for bipolar I disorder (n = 260) or bipolar II disorder (n = 32) or met operationalized criteria for bipolar disorder not otherwise specified (n = 154) were included. Subjects were evaluated for current and lifetime Axis I psychiatric disorders at intake using the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Aged Children–Present and Lifetime version, and standardized instruments were used to assess functioning and family history.

Results: Forty-four percent (n = 194) of the sample met *DSM-IV* criteria for at least 1 lifetime anxiety disorder, most commonly separation anxiety (24%) and generalized anxiety disorders (16%). Nearly 20% met criteria for 2 or more anxiety disorders. Overall, anxiety disorders predated the onset of bipolar disorder. Subjects with bipolar II disorder were more likely than subjects with bipolar I disorder or bipolar disorder not otherwise specified to have a comorbid anxiety disorder. After adjusting for confounding factors, youth with bipolar disorder with anxiety were more likely to have bipolar II disorder; longer duration of mood symptoms; more severe ratings of depression; and family history of depression, hopelessness, and somatic complaints during their worst lifetime depressive episode than those without anxiety.

Conclusions: Comorbid anxiety disorders are common in youth with bipolar disorder, and they most often predate bipolar disorder onset. Bipolar II disorder, a family history of depression, and more severe lifetime depressive episodes distinguish youth with bipolar disorder with comorbid anxiety disorders from those without. Careful consideration should be given to the assessment of comorbid anxiety in youth with bipolar disorder.

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Onset of bipolar disorder during childhood significantly affects an individual's psychosocial development. Moreover, youth with bipolar disorder are at high risk for suicidal behaviors and completed suicide, substance abuse, and legal problems, and they have particularly high rates of health services utilization.[1–3]

Some of the most common comorbid disorders among youth with bipolar disorder are the anxiety disorders.[4] Since anxiety disorders are also accompanied by significant impairment in the psychosocial functioning of the child,[5] it is important to evaluate the prevalence and clinical correlates of the association between bipolar disorder and anxiety in youth. The few studies that have addressed this issue in small samples of youth with bipolar disorder have shown lifetime prevalence of comorbid anxiety disorders between 14% and 56%, with a weighted average of 27%.[3,6–10] Moreover, family studies have consistently shown high rates of anxiety disorders in offspring of parents with bipolar disorder.[11–15]

The above-noted findings are consistent with the adult epidemiologic[16–18] and clinical literature.[19,20] In fact, retrospective data from studies of adults with bipolar disorder indicate higher rates of comorbid lifetime anxiety disorders among those with earlier age at bipolar disorder onset. Specifically, in 1 study by Perlis and colleagues,[21] adults who reported bipolar disorder onset before age 13 years demonstrated a 70% rate of comorbid lifetime anxiety disorder as compared with 54% of those with bipolar disorder onset between 13 and 18 years and 38% of those with bipolar disorder onset after age 18 years.

Prior research indicates that the presence of comorbid anxiety disorders negatively affects course, outcome, and treatment response in bipolar disorder. In a study by Masi and colleagues,[22] youth with bipolar disorder with panic disorder, as compared to those without panic, demonstrated less bipolar disorder severity at baseline but had poorer response to treatment. Furthermore, DelBello and colleagues[7] found that adolescents with bipolar disorder and comorbid anxiety had more severe mood symptoms and lower rates of recovery 1 year after index hospitalization than adolescents without comorbid anxiety. Similarly, studies among adults with bipolar disorder consistently find that the presence of comorbid anxiety is associated with worse course and outcomes, including higher rates of rapid cycling, more severe depression, substance abuse, and suicide attempts, as well as lower rates of treatment response and recovery. Furthermore,

adult patients with bipolar disorder and comorbid anxiety report poorer psychosocial functioning and lower overall quality of life.[19,20]

The association between bipolar disorder and comorbid anxiety disorders is of particular clinical significance, since the pharmacologic treatment for anxiety disorders with the most evidence of efficacy in both children and adults is the use of selective serotonin reuptake inhibitors (SSRIs).[23–25] Unfortunately, these medications have been shown to destabilize the symptoms of bipolar disorder.[26,27]

Given the clinical relevance of comorbid anxiety and bipolar disorder and the existence of few studies with small samples, we aimed to investigate the prevalence, correlates, and familial risk associated with comorbid anxiety disorder in a large sample of children and adolescents with bipolar disorder spectrum disorders. We hypothesized that, as compared with youth with bipolar disorder and no comorbid anxiety (BP/no anxiety), those with bipolar disorder and a comorbid anxiety disorder (BP/anxiety) would have (1) earlier bipolar disorder onset and more severe lifetime bipolar disorder symptoms, (2) higher rates of suicidal behavior and substance use disorders, (3) poorer overall functioning, and (4) higher rates of familial mood and anxiety disorders.

METHOD

Subjects and Procedures

The methods for the Course and Outcome of Bipolar Youth (COBY) study have been described in detail elsewhere.[3,28] Briefly, 446 youth, ages 7 to 17 years 11 months (mean = 12.7 years, SD = 3.2 years), who met criteria for *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (*DSM-IV*)[29] bipolar I disorder (n = 260), bipolar II disorder (n = 32), and operationally defined bipolar disorder not otherwise specified (NOS; n = 154)[3,28,30] were recruited primarily though clinical referrals from 3 academic medical centers (University of Pittsburgh [Pittsburgh, Pennsylvania], Brown University [Providence, Rhode Island], and University of California at Los Angeles [Los Angeles, California]). Institutional review board approval was obtained at each site prior to subject enrollment.

Because the *DSM-IV* criteria for bipolar disorder NOS are vague, the COBY study investigators set the minimum inclusion threshold for the bipolar disorder NOS group as subjects who did not meet the *DSM-IV* criteria for bipolar I disorder or bipolar II disorder but had a distinct period of abnormally elevated, expansive, or irritable mood plus the following: (1) 2 *DSM-IV* manic symptoms (3 if the mood is irritability only) that were clearly associated with the onset of abnormal mood; (2) a clear change in functioning; (3) mood and symptom duration of a minimum of 4 hours within a 24-hour period for a day to be considered meeting the diagnostic threshold; and (4) a minimum of 4 days (not necessarily consecutive) meeting the mood, symptom, duration, and functional change criteria over the subject's lifetime, which could be two 2-day episodes, four 1-day episodes, or another variation.

Children and parents were directly interviewed for the presence of current and lifetime psychiatric disorders using the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Aged Children–Present and Lifetime version (K-SADS-PL),[30] the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Aged Children Mania Rating Scale (K-SADS-MRS),[31] and the depression section of the K-SADS-P (from which the Dep-12 depression rating scale was extracted). The K-SADS-PL utilized in COBY did not include the new pervasive developmental disorder (PDD) module. For PDD, we used a *DSM-IV* checklist.

Parents were interviewed at intake about their personal psychiatric history using the Structured Clinical Interview for *DSM-IV* (SCID),[32] and about their first- and second-degree psychiatric family history using the Family History Screen (FHS).[33] The Petersen Pubertal Developmental Scale (PDS)[34] was used to evaluate and categorize pubertal stages. Socioeconomic status was measured using the Hollingshead 4-factor scale (Hollingshead AB, 1975, unpublished), and functional impairment was assessed using the Children's Global Assessment Scale (CGAS).[35]

Research interviewers were trained to high reliability in administration of the K-SADS, the SCID, and the FHS before interviewing any subjects or parents. The results of each interview were reviewed by a child psychiatrist or psychologist. Diagnostic reliability was measured by having research interviewers from all sites rate 13 audiotapes of actual COBY study interviews. There was high reliability for differentiating subjects with bipolar disorder from non–bipolar disorder subjects ($\kappa = 0.90$) and for the bipolar disorder diagnostic subtypes ($\kappa = 0.79$). For the non–mood disorders, κ values were 0.80 or higher. The intraclass correlation coefficient was 0.96 for the K-SADS-MRS and 0.98 for the K-SADS depression scale.

We considered subjects positive for the presence of any lifetime anxiety disorder if they met full threshold criteria for at least 1 of the following disorders: separation anxiety disorder, generalized anxiety disorder (GAD), obsessive-compulsive disorder (OCD), posttraumatic stress disorder (PTSD), social phobia, panic disorder, anxiety disorder NOS, or agoraphobia. Obsessive-compulsive disorder and PTSD have often been classified as distinct from other anxiety disorders for the complexity of the clinical description and diagnosis. Obsessive-compulsive disorder is characterized by the presence of either obsessions or compulsions, and PTSD refers to a characteristic set of psychological and physiologic symptoms following exposure to a stressor event. The majority of subjects with OCD or PTSD also met criteria for a different anxiety disorder (11.9%), and that is the reason that we decided to include them in the BP/anxiety group—because both cause marked distress and significant impairment similar to the other anxiety disorders. Twenty-nine youth with only specific phobia (eg, fear of spider, dark, or insects) were excluded from the BP/anxiety group because simple phobias are ubiquitous. In addition, they are one of the least reliable anxiety diagnoses in children, perhaps due, in part, to imprecision in standards for distress and

Table 1. Demographic Factors Associated With BP/Anxiety Versus BP/No Anxiety in Children and Adolescents With Bipolar Spectrum Disorders

Demographic Factor	BP/ Anxiety (n = 194)	BP/No Anxiety (n = 252)	Statistic	*P* Value
Age, mean ± SD, y	12.8 ± 3.3	12.6 ± 3.2	$t = -0.62$	.5
Sex, male, %	54.6	52.0	$\chi^2 = 0.31$	.6
Race, white, %	81.4	81.4	$\chi^2 = 0.0006$	1.0[a]
Socioeconomic status, mean ± SD	3.3 ± 1.2	3.5 ± 1.2	Kruskal-Wallis = 4.27	.04
Living with both natural parents, %	36.6	45.2	$\chi^2 = 3.37$	.07
Pubertal status, %			$\chi^2 = 2.46$	.3
I	21.4	28.8	$\chi^2 = 2.44$	.1
II–III	29.9	27.8	$\chi^2 = 0.19$	.7
IV–V	48.7	43.5	$\chi^2 = 0.95$	.3

[a]Fisher exact test.
Abbreviations: BP/Anxiety = bipolar disorder and a comorbid anxiety disorder, BP/No Anxiety = bipolar disorder and no comorbid anxiety.

impairment, since the threshold between a fear and a phobia is not always straightforward.[36]

Youth with autism were not included because it is very difficult to obtain information about their mood status, and about 70% have low IQ. Subjects with IQ less than 70 were excluded from the grant. In contrast, youth with Asperger's disorder or PDD NOS were recruited. In COBY, only 2% of the subjects fulfilled criteria for these disorders.

Statistical Analyses

Between-group comparisons in demographic factors were carried out using standard parametric and nonparametric univariate tests. Results were adjusted for bipolar disorder subtype and any other significant between-group demographic differences. Those variables with *P* values ≤ .25 were then entered into a multivariate logistic regression. Exploratory analyses were carried out examining the presence or absence of mood symptoms during the most severe lifetime episodes using the items from the K-SADS-MRS and the Dep-12 plus the hopelessness and aches and pains questions from the K-SADS-P depression section, because these symptoms have been associated with more severe anxiety.[37,38] All *P* values were based on 2-sided tests, and, when appropriate, we used Bonferroni corrections to keep the family-wise error rate at α = .05, at most. Odds ratios (ORs) and confidence intervals (CIs) were computed.

RESULTS

Prevalence and Demographics

Forty-four percent (194/446) of subjects met lifetime criteria for at least 1 comorbid anxiety disorder. The most common comorbid anxiety disorders included separation anxiety disorder (n = 108, 24%) and GAD (n = 71, 16%), followed by OCD (n = 29, 7%), PTSD (n = 27, 6%), social phobia (n = 26, 6%), panic disorder (n = 25, 6%), anxiety disorder NOS (n = 11, 3%), and agoraphobia (n = 10, 2%). Eighteen percent of subjects had more than 1 lifetime anxiety disorder, and 5% met criteria for 3 or more anxiety disorders. The

Table 2. Frequencies of Bipolar Disorder Subtype Versus Presence of Any Lifetime Anxiety Disorder[a]

Subtype	Anxiety, n (%)	No Anxiety, n (%)
Bipolar I disorder	108/260 (41.5)	152/260 (58.5)
Bipolar II disorder	22/32 (68.8)	10/32 (31.3)
Bipolar disorder not otherwise specified	64/154 (41.6)	90/154 (58.4)

[a]Overall test for independence: $\chi^2_2 = 8.94$, *P* value = .01.

proportion of subjects whose age at onset of anxiety was less than age at onset of bipolar disorder was 78.7% (151 out of 192 subjects, as 2 subjects were missing information on age at onset of anxiety). The means and standard deviations of age at onset of anxiety and bipolar disorder for these 192 subjects were 6.3 ± 3.3 years and 9.0 ± 3.7 years, respectively.

As shown in Table 1, compared to the BP/no anxiety group, those with BP/anxiety had significantly lower socioeconomic status, although the actual difference is minimal (3.3 vs 3.5), and a trend to be less likely to live with both natural parents. There were no other between-group demographic differences.

Clinical Characteristics of Bipolar Illness and Comorbidity

As shown in Table 2, the overall χ^2 comparing bipolar disorder subtypes and presence of any lifetime anxiety disorder was significant ($\chi^2_2 = 8.94$, *P* value = .01). However, the differences were only accounted by the bipolar II disorder subtype.

After adjusting for bipolar disorder subtype, socioeconomic status, and living with both natural parents, the BP/anxiety group had significantly longer duration of mood symptoms and higher depression scores for both current and most severe lifetime episodes compared with the BP/no anxiety group. In addition, the BP/anxiety group was more likely to report that their most recent *DSM* mood episode was of the depressive subtype and less likely to indicate that their index episode was of the manic subtype (all *P* values ≤ .05). Lifetime history of suicidal ideation or attempts was not significantly different between groups. There were no other significant differences in comorbidity or functioning between groups (Table 3).

Family History

In comparison with the BP/no anxiety group, those with BP/anxiety were more likely to endorse a positive first- or second-degree family history of depression and anxiety disorders (all *P* values ≤ .001), and a trend of positive first- or second-degree family history of mania or hypomania (*P* value = .06) (Table 3).

Multivariate Logistic Regression

The BP/anxiety group remained significantly associated with bipolar II disorder (OR = 2.34; 95% CI, 1.02–5.35), longer duration of mood symptoms (OR = 1.11; 95% CI, 1.03–1.19), higher current depression scores in Dep-12 (OR = 1.04; 95% CI, 1.02–1.07), fewer manic episodes

Table 3. Factors Associated With BP/Anxiety Versus BP/No Anxiety in Children and Adolescents With Bipolar Spectrum Disorders

Factor	BP/Anxiety (n = 194)	BP/No Anxiety (n = 252)	Wald χ^2 Statistic[a]	*P* Value
Characteristic of bipolar illness, mean ± SD				
Age at onset of mood symptoms, y	7.9 ± 3.9	8.6 ± 4.1	2.54	.1
Age at onset of bipolar disorder episode,[b] y	9.0 ± 3.7	9.6 ± 4.0	1.99	.2
Duration of mood symptoms,[c] y	5.0 ± 3.2	4.0 ± 2.6	9.04	.003
K-SADS-MRS current	22.8 ± 12.2	22.5 ± 12.1	0.0001	1.0[d]
K-SADS-MRS most severe lifetime	34.4 ± 8.5	33.4 ± 8.2	3.0964	.08
Dep-12 current	17.7 ± 10.1	12.4 ± 9.6	25.61	<.0001
Dep-12 most severe lifetime	25.9 ± 10.2	20.4 ± 11.0	17.96	<.0001
CGAS current	55.4 ± 10.8	54.3 ± 13.2	0.54	.5
CGAS most severe lifetime	37.0 ± 11.0	37.9 ± 9.9	1.67	.2
Polarity of index episode, %				
Depressed	20.6	10.3	8.30	.004
Hypomanic	8.8	7.9	0.39	.5
Manic	9.3	25.4	16.69	<.0001
Mixed	19.6	15.1	2.61	.1
Not otherwise specified	41.8	41.3	0.03	.9
Lifetime history of comorbid disorders, % yes				
ADHD	60.8	59.5	0.0002	1.0[d]
ODD	35.1	42.9	2.4019	.1
Conduct disorder	11.3	13.5	1.2377	.3
PDD	0.5	0.0	0.0003	1.0[d]
Substance abuse or dependence	7.2	8.7	0.4081	.5
Alcohol abuse or dependence	3.1	5.6	1.7079	.2
Lifetime phenomenological features and treatment history, % yes				
Psychosis	23.7	19.4	1.4600	.2
Suicide ideation	78.9	73.0	1.0539	.3
Suicide attempts	33.5	27.4	1.5581	.2
Psychiatric hospitalization	54.1	49.8	1.0294	.3
First- or second-degree family history, % subjects				
With depression	94.5	80.9	13.91	.0002
With mania or hypomania	61.1	49.8	3.52	.06
With anxiety	77.7	61.6	10.96	.0009

[a]Logistic regression adjusting for socioeconomic status, living with both natural parents, and bipolar disorder subtype. [b]Age 4 years is set as the minimum value. [c]Since age at onset of any *Diagnostic and Statistical Manual of Mental Disorders* mood episode. [d]Fisher exact test.

Abbreviations: ADHD = attention-deficit/hyperactivity disorder, BP/Anxiety = bipolar disorder and a comorbid anxiety disorder, BP/No Anxiety = bipolar disorder and no comorbid anxiety, CGAS = Children's Global Assessment Scale, DEP-12 = depression rating scale extracted from the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Aged Children–Present version, K-SADS-MRS = Kiddie Schedule for Affective Disorders and Schizophrenia for School-Aged Children Mania Rating Scale, ODD = oppositional defiant disorder, PDD = pervasive developmental disorder (pervasive developmental disorder NOS or Asperger's disorder).

(OR = 0.38; 95% CI, 0.2–0.73), and higher rates of depression among first- or second-degree relatives (OR = 3.58; 95% CI, 1.62–7.93) (Table 4).

Severity of Manic and Depressive Symptoms

We examined whether there were differences between the BP/anxiety and BP/no anxiety groups in the severity of manic and depressive symptoms. Exploratory analyses, adjusted for multiple comparisons, were conducted using ratings from the most severe lifetime manic or hypomanic (K-SADS-MRS) and depressive episodes (Dep-12). Only symptoms rated at mild or higher (≥ 3) were analyzed. There were no between-group differences in manic or hypomanic symptoms. In contrast, youth with BP/anxiety depressive episodes had significantly more depressed mood, hopelessness, aches and pains, anhedonia, and fatigue after controlling for multiple comparisons using Bonferroni correction. Suicidal ideation was also significantly higher in the BP/anxiety group but did not survive Bonferroni correction (Table 5).

In the multivariate analysis of Dep-12, hopelessness (OR = 2.1; 95% CI, 1.28–3.28) and aches and pains (OR = 2.5; 95% CI, 1.56–3.95) were the only 2 items that were significant in the BP/anxiety group during their worst lifetime depressive episode.

DISCUSSION

To our knowledge, this is the largest study to date examining prevalence and demographic and clinical correlates of comorbid anxiety disorder among children and adolescents with bipolar disorder.

Forty-four percent of youth with bipolar disorder in our sample met criteria for at least 1 lifetime anxiety disorder, most commonly separation anxiety disorder and GAD; 18% had 2 or more lifetime anxiety disorders. On average, the onset of anxiety predated the onset of bipolar disorder. After adjusting for significant demographic factors and bipolar disorder subtypes, youth with BP/anxiety, as compared with BP/no anxiety, showed significantly higher rates of bipolar II disorder, longer duration of mood symptoms, higher current depression scores, lower likelihood of reporting an index episode of the manic subtype, and higher rates of familial depression, and they had a worst lifetime depressive episode characterized by greater severity of hopelessness and aches and pains.

Our findings are consistent with those of previous studies in which anxiety disorders, particularly separation anxiety disorder and GAD, have been reported at high rates among youth and adults with bipolar disorder.[6,8–10,18,39–45] Also similar to other studies in the child and adult literature, we found that subjects with bipolar disorder with comorbid anxiety disorders were more likely to have a diagnosis of bipolar II disorder,[22,42,44,46–48] longer duration of mood symptoms, and greater severity of depressive episodes.[49–53] This association may be related to the fact that bipolar II disorder has a more chronic course and outcome, longer length of illness, shorter cycles, greater number of episodes, more major and minor depressive episodes, shorter well intervals between episodes, and lower rates of recovery.[54,55] Moreover, we found, similar to the bipolar disorder[9,56] and unipolar depression[57,58] literature, that, on average, the anxiety disorders preceded the onset of the mood disorder. Contrary to our initial hypothesis,[10,40,59–60] age at onset of bipolar disorder episode did not differ between the 2 groups.

Table 4. Logistic Regression of the Variables Associated With BP/Anxiety Versus BP/No Anxiety in Children and Adolescents With Bipolar Spectrum Disorders

Variable	OR	95% CI	Wald χ^2 Statistic	*P* Value
Socioeconomic status	0.89	0.74–1.07	1.67	.2
Bipolar II disorder	2.34	1.02–5.35	4.03	.04
Duration of mood symptoms	1.11	1.03–1.19	6.97	.008
Dep-12 current	1.04	1.02–1.07	14.78	.0001
Manic polarity	0.38	0.2–0.73	8.51	.004
First- or second-degree relative with depression	3.58	1.62–7.93	9.91	.002

Abbreviations: BP/Anxiety = bipolar disorder and a comorbid anxiety disorder, BP/No Anxiety = bipolar disorder and no comorbid anxiety, DEP-12 = depression rating scale extracted from the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Aged Children–Present version.

Table 5. Depressive Symptoms[a] During the Most Severe Lifetime in BP/Anxiety Versus BP/No Anxiety in Children and Adolescents With Bipolar Spectrum Disorders

Symptom	BP/Anxiety (n = 194), %	BP/No Anxiety (n = 252), %	Wald χ^2 Statistic	*P* Value
Depressed mood	94.7	81.0	14.28	<.001*
Excessive or inappropriate guilt	53.7	43.8	3.41	.07
Hopelessness	69.5	49.5	14.43	<.001*
Aches and pain	67.3	41.9	22.69	<.001*
Anhedonia	80.0	63.2	11.84	.001*
Fatigue	78.7	61.9	11.471	.001*
Difficulty concentrating	79.5	68.6	5.31	.02
Psychomotor agitation	51.3	49.5	0.115	.7
Psychomotor retardation	55.3	46.7	2.63	.1
Insomnia	74.1	61.0	6.31	.01
Hypersomnia	49.3	38.6	4.13	.04
Anorexia	38.5	33.3	1.01	.3
Increased appetite	32.7	19.6	7.92	.005
Suicidal ideation	65.8	54.8	4.33	.04

[a]Items from the depression rating scale extracted from the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Aged Children–Present version (Dep-12) plus hopelessness and aches and pain.
*Remained significant after Bonferroni correction.
Abbreviations: BP/Anxiety = bipolar disorder and a comorbid anxiety disorder, BP/No Anxiety = bipolar disorder and no comorbid anxiety.

These findings are clinically relevant because, currently, the first-line pharmacologic treatments for anxiety disorders in youth are the SSRIs.[24,25] Selective serotonin reuptake inhibitors have been shown to trigger or destabilize bipolar disorder symptoms.[26] Thus, it is critically important to evaluate a child presenting with anxiety for the presence of manic or hypomanic symptoms, especially if depressive symptoms and a positive family history of mood disorders are also present. Although hypomanic symptoms can be difficult to ascertain in youth due to the unique developmental presentation[61] as well as symptom overlap with other conditions including depression and anxiety, recent studies clearly demonstrate that mania or hypomania in youth can be reliably diagnosed.[3] Additionally, anxious children treated with antidepressants should be carefully monitored for the presence of manic or hypomanic symptoms.[40]

Little is known about the most efficacious treatments for the treatment of comorbid anxiety in youth with bipolar disorder. Future studies may evaluate the efficacy of psychotherapy approaches with empirical support for the treatment of anxious youth, such as cognitive-behavioral therapy.[23] The risk/benefit ratio of the use of SSRIs in youth with bipolar disorder who are taking concurrent mood stabilizers may also be explored.

Interestingly, we found that youth with BP/anxiety showed significantly more family history of depression. This finding is consistent with Wozniak et al,[62] who reported elevated risk for both bipolar disorder and anxiety among relatives of BP/anxiety probands. As such, this group suggested that comorbid anxiety and bipolar disorder may represent a genetic subtype of bipolar disorder. Furthermore, a recent study by Birmaher and colleagues[11] found that offspring of parents with bipolar disorder had higher rates of anxiety disorders than offspring of control parents, suggesting that anxiety may be a precursor of bipolar disorder among bipolar disorder offspring. Thus, systematic evaluation of youth with anxiety disorder and family history of mood disorders is warranted because these youth may be at high risk to develop bipolar disorder.

Contrary to our initial hypothesis,[4,20,49,59,63–66] we did not find significantly more suicidal behaviors[9] or substance use disorders in the bipolar disorder with comorbid anxiety group as compared to those without. These discrepancies may be explained by the fact that most subjects in this study have not yet reached the age of highest risk for these conditions. Nonetheless, youth with bipolar disorder and anxiety had significantly more suicidal ideation as well as hopelessness during the most severe lifetime depressive episode than subjects without comorbid anxiety. Since hopelessness is highly associated with suicide attempts and suicide,[67–69] careful evaluation and monitoring of suicide risk in youth with BP/anxiety are clearly indicated. Also contrary to our initial hypothesis,[4,20] we did not find poorer functioning in the bipolar disorder group with comorbid anxiety as compared with those without. It is possible that the impact of bipolar disorder on global functioning during childhood and adolescence is significantly profound, such that any additional impairment associated with comorbid anxiety is relatively negligible.

Finally, after adjusting for multiple comparisons, youth with bipolar disorder and comorbid anxiety reported more aches and pains than those without anxiety, as is the case in adult studies.[70] It has been well documented that anxious youth experience somatic complaints and tend to consult primary care physicians or pediatricians before mental health clinicians.[71] Thus, it is important to educate such front-line providers about the possibility that anxious youth with a positive family history of mood disorder may also have bipolar disorder.

It is important to note the limitations of this study. First, as most subjects were white and were recruited primarily from outpatient clinical settings, the generalizability of the findings remains uncertain. However, a community-based

study of nonreferred adolescents with bipolar disorder reported similarly high rates of comorbid anxiety disorders.[72] Second, subjects were ascertained for bipolarity. Thus, results may not apply to subjects whose primary diagnosis is anxiety and then develop bipolar disorder. Third, this study is cross-sectional, and data were ascertained retrospectively. We are currently following these subjects longitudinally, and we will thus be able to further examine the associations over follow-up. Finally, no psychiatric control group was included. Thus, using the current sample, we cannot conclude that lifetime anxiety disorders are more common in youth with bipolar disorder than in youth with other childhood psychiatric disorders (eg, major depressive disorder).

In summary, anxiety disorders usually predate the onset of bipolar disorder and are very common in youth with bipolar disorder, especially those with bipolar II disorder, longer duration of mood symptoms, more severe depressions, and family history of depression. Given the clinical and treatment implications of these findings, early identification and accurate diagnosis for these youth is very important. Randomized trials to evaluate treatments for anxiety in youth with bipolar disorder are needed. Finally, longitudinal studies to determine the impact of comorbid anxiety disorder on the course and outcome of pediatric bipolar disorder spectrum disorders are warranted.

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REFERENCES

1. Sala R, Axelson D, Birmaher B. Phenomenology, longitudinal course, and outcome of children and adolescents with bipolar spectrum disorders. *Child Adolesc Psychiatr Clin N Am.* 2009;18(2):273–289, vii.
2. Pavuluri MN, Birmaher B, Naylor MW. Pediatric bipolar disorder: a review of the past 10 years. *J Am Acad Child Adolesc Psychiatry.* 2005;44(9):846–871.
3. Axelson D, Birmaher B, Strober M, et al. Phenomenology of children and adolescents with bipolar spectrum disorders. *Arch Gen Psychiatry.* 2006; 63(10):1139–1148.
4. Joshi G, Wilens T. Comorbidity in pediatric bipolar disorder. *Child Adolesc Psychiatr Clin North Am.* 2009;18(2):291–319, vii–viii.
5. Beesdo K, Knappe S, Pine DS. Anxiety and anxiety disorders in children and adolescents: developmental issues and implications for *DSM-V*. *Psychiatr Clin North Am.* 2009;32(3):483–524.
6. Kowatch RA, Youngstrom EA, Danielyan A, et al. Review and meta-analysis of the phenomenology and clinical characteristics of mania in children and adolescents. *Bipolar Disord.* 2005;7(6):483–496.
7. DelBello MP, Hanseman D, Adler CM, et al. Twelve-month outcome of adolescents with bipolar disorder following first hospitalization for a manic or mixed episode. *Am J Psychiatry.* 2007;164(4):582–590.
8. Biederman J, Faraone SV, Marrs A, et al. Panic disorder and agoraphobia in consecutively referred children and adolescents. *J Am Acad Child Adolesc Psychiatry.* 1997;36(2):214–223.
9. Dickstein DP, Rich BA, Binstock AB, et al. Comorbid anxiety in phenotypes of pediatric bipolar disorder. *J Child Adolesc Psychopharmacol.* 2005;15(4):534–548.
10. Tillman R, Geller B, Bolhofner K, et al. Ages of onset and rates of syndromal and subsyndromal comorbid *DSM-IV* diagnoses in a prepubertal and early adolescent bipolar disorder phenotype. *J Am Acad Child Adolesc Psychiatry.* 2003;42(12):1486–1493.
11. Birmaher B, Axelson D, Monk K, et al. Lifetime psychiatric disorders in school-aged offspring of parents with bipolar disorder: the Pittsburgh Bipolar Offspring study. *Arch Gen Psychiatry.* 2009;66(3):287–296.
12. Simeonova DI, Jackson V, Attalla A, et al. Subcortical volumetric correlates of anxiety in familial pediatric bipolar disorder: a preliminary investigation. *Psychiatry Res.* 2009;173(2):113–120.
13. Henin A, Biederman J, Mick E, et al. Psychopathology in the offspring of parents with bipolar disorder: a controlled study. *Biol Psychiatry.* 2005; 58(7):554–561.
14. Grigorotu-Serbănescu M, Christodorescu D, Ilpescu I, et al. Psychopathology in children aged 10–17 of bipolar parents: psychopathology rate and correlates of the severity of the psychopathology. *J Affect Disord.* 1989;16(2–3):167–179.
15. Hammen C, Burge D, Burney E, et al. Longitudinal study of diagnoses in children of women with unipolar and bipolar affective disorder. *Arch Gen Psychiatry.* 1990;47(12):1112–1117.
16. Chen YW, Dilsaver SC. Comorbidity of panic disorder in bipolar illness: evidence from the Epidemiologic Catchment Area Survey. *Am J Psychiatry.* 1995;152(2):280–282.
17. Chen YW, Dilsaver SC. Comorbidity for obsessive-compulsive disorder in bipolar and unipolar disorders. *Psychiatry Res.* 1995;59(1–2):57–64.
18. Kessler RC, Rubinow DR, Holmes C, et al. The epidemiology of *DSM-III-R* bipolar I disorder in a general population survey. *Psychol Med.* 1997;27(5):1079–1089.
19. Keller MB. Prevalence and impact of comorbid anxiety and bipolar disorder. *J Clin Psychiatry.* 2006;67(suppl 1):5–7.
20. Freeman MP, Freeman SA, McElroy SL. The comorbidity of bipolar and anxiety disorders: prevalence, psychobiology, and treatment issues. *J Affect Disord.* 2002;68(1):1–23.
21. Perlis RH, Miyahara S, Marangell LB, et al. STEP-BD Investigators. Long-term implications of early onset in bipolar disorder: data from the first 1000 participants in the systematic treatment enhancement program for bipolar disorder (STEP-BD). *Biol Psychiatry.* 2004;55(9):875–881.
22. Masi G, Perugi G, Millepiedi S, et al. Clinical and research implications of panic-bipolar comorbidity in children and adolescents. *Psychiatry Res.* 2007;153(1):47–54.
23. Walkup JT, Albano AM, Piacentini J, et al. Cognitive behavioral therapy, sertraline, or a combination in childhood anxiety. *N Engl J Med.* 2008; 359(26):2753–2766.
24. Birmaher B, Axelson DA, Monk K, et al. Fluoxetine for the treatment of childhood anxiety disorders. *J Am Acad Child Adolesc Psychiatry.* 2003;42(4):415–423.
25. Allgulander C, Dahl AA, Austin C, et al. Efficacy of sertraline in

a 12-week trial for generalized anxiety disorder. *Am J Psychiatry*. 2004;161(9):1642–1649.
26. Ghaemi SN, Hsu DJ, Soldani F, et al. Antidepressants in bipolar disorder: the case for caution. *Bipolar Disord*. 2003;5(6):421–433.
27. Goldberg JF, Nassir Ghaemi S. Benefits and limitations of antidepressants and traditional mood stabilizers for treatment of bipolar depression. *Bipolar Disord*. 2005;7(suppl 5):3–12.
28. Birmaher B, Axelson D, Strober M, et al. Clinical course of children and adolescents with bipolar spectrum disorders. *Arch Gen Psychiatry*. 2006; 63(2):175–183.
29. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition. Washington, DC: American Psychiatric Association; 1994.
30. Kaufman J, Birmaher B, Brent D, et al. Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime version (K-SADS-PL): initial reliability and validity data. *J Am Acad Child Adolesc Psychiatry*. 1997;36(7):980–988.
31. Axelson D, Birmaher BJ, Brent D, et al. A preliminary study of the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children Mania Rating Scale for children and adolescents. *J Child Adolesc Psychopharmacol*. 2003;13(4):463–470.
32. First MB Sr, Williams JBW, Gibbon M. *Structured Clinical Interview for DSM-IV (SCID)*. Washington, DC: American Psychiatric Association; 1995.
33. Weissman MM, Wickramaratne P, Adams P, et al. Brief screening for family psychiatric history: the Family History Screen. *Arch Gen Psychiatry*. 2000;57(7):675–682.
34. Petersen AC, Crockett L, Richards M, et al. A self-report measure of pubertal status: reliability, validity, and initial norms. *J Youth Adolesc*. 1988;17(2):117–133.
35. Shaffer D, Gould MS, Brasic J, et al. A Children's Global Assessment Scale (CGAS). *Arch Gen Psychiatry*. 1983;40(11):1228–1231.
36. Klein RG. Anxiety disorders. *J Child Psychol Psychiatry*. 2009; 50(1–2):153–162.
37. Valtonen HM, Suominen K, Haukka J, et al. Hopelessness across phases of bipolar I or II disorder: a prospective study. *J Affect Disord*. 2009; 115(1–2):11–17.
38. Carleton RN, Abrams MP, Asmundson GJ, et al. Pain-related anxiety and anxiety sensitivity across anxiety and depressive disorders. *J Anxiety Disord*. 2009;23(6):791–798.
39. Harpold TL, Wozniak J, Kwon A, et al. Examining the association between pediatric bipolar disorder and anxiety disorders in psychiatrically referred children and adolescents. *J Affect Disord*. 2005;88(1):19–26.
40. Masi G, Toni C, Perugi G, et al. Anxiety disorders in children and adolescents with bipolar disorder: a neglected comorbidity. *Can J Psychiatry*. 2001;46(9):797–802.
41. McElroy SL, Altshuler LL, Suppes T, et al. Axis I psychiatric comorbidity and its relationship to historical illness variables in 288 patients with bipolar disorder. *Am J Psychiatry*. 2001;158(3):420–426.
42. Pini S, Cassano GB, Simonini E, et al. Prevalence of anxiety disorders comorbidity in bipolar depression, unipolar depression and dysthymia. *J Affect Disord*. 1997;42(2–3):145–153.
43. Boylan KR, Bieling PJ, Marriott M, et al. Impact of comorbid anxiety disorders on outcome in a cohort of patients with bipolar disorder. *J Clin Psychiatry*. 2004;65(8):1106–1113.
44. Henry C, Van den Bulke D, Bellivier F, et al. Anxiety disorders in 318 bipolar patients: prevalence and impact on illness severity and response to mood stabilizer. *J Clin Psychiatry*. 2003;64(3):331–335.
45. Lewinsohn PM, Klein DN, Seeley JR. Bipolar disorders in a community sample of older adolescents: prevalence, phenomenology, comorbidity, and course. *J Am Acad Child Adolesc Psychiatry*. 1995;34(4):454–463.
46. Perugi G, Akiskal HS, Ramacciotti S, et al. Depressive comorbidity of panic, social phobic, and obsessive-compulsive disorders re-examined: is there a bipolar II connection? *J Psychiatr Res*. 1999;33(1):53–61.
47. Cassano GB, Pini S, Saettoni M, et al. Multiple anxiety disorder comorbidity in patients with mood spectrum disorders with psychotic features. *Am J Psychiatry*. 1999;156(3):474–476.
48. Doughty CJ, Wells JE, Joyce PR, et al. Bipolar-panic disorder comorbidity within bipolar disorder families: a study of siblings. *Bipolar Disord*. 2004;6(3):245–252.
49. Lee JH, Dunner DL. The effect of anxiety disorder comorbidity on treatment resistant bipolar disorders. *Depress Anxiety*. 2008;25(2):91–97.
50. Bauer MS, Altshuler L, Evans DR, et al. VA Cooperative Study No 430 Team. Prevalence and distinct correlates of anxiety, substance, and combined comorbidity in a multi-site public sector sample with bipolar disorder. *J Affect Disord*. 2005;85(3):301–315.
51. Feske U, Frank E, Mallinger AG, et al. Anxiety as a correlate of response to the acute treatment of bipolar I disorder. *Am J Psychiatry*. 2000;157(6): 956–962.
52. Frank E, Cyranowski JM, Rucci P, et al. Clinical significance of lifetime panic spectrum symptoms in the treatment of patients with bipolar I disorder. *Arch Gen Psychiatry*. 2002;59(10):905–911.
53. Gaudiano BA, Miller IW. Anxiety disorder comorbidity in bipolar I disorder: relationship to depression severity and treatment outcome. *Depress Anxiety*. 2005;21(2):71–77.
54. Judd LL, Akiskal HS, Schettler PJ, et al. Psychosocial disability in the course of bipolar I and II disorders: a prospective, comparative, longitudinal study. *Arch Gen Psychiatry*. 2005;62(12):1322–1330.
55. Angst J. The course of affective disorders. *Psychopathology*. 1986; 19(suppl 2):47–52.
56. Henin A, Biederman J, Mick E, et al. Childhood antecedent disorders to bipolar disorder in adults: a controlled study. *J Affect Disord*. 2007; 99(1–3):51–57.
57. Pine DS, Cohen P, Gurley D, et al. The risk for early-adulthood anxiety and depressive disorders in adolescents with anxiety and depressive disorders. *Arch Gen Psychiatry*. 1998;55(1):56–64.
58. Merikangas KR, Zhang H, Avenevoli S, et al. Zurich Cohort Study. Longitudinal trajectories of depression and anxiety in a prospective community study: the Zurich Cohort Study. *Arch Gen Psychiatry*. 2003; 60(10):993–1000.
59. Simon NM, Otto MW, Wisniewski SR, et al. Anxiety disorder comorbidity in bipolar disorder patients: data from the first 500 participants in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). *Am J Psychiatry*. 2004;161(12):2222–2229.
60. Johnson JG, Cohen P, Brook JS. Associations between bipolar disorder and other psychiatric disorders during adolescence and early adulthood: a community-based longitudinal investigation. *Am J Psychiatry*. 2000; 157(10):1679–1681.
61. Birmaher BAD, Pavuluri MN. In: Martin A, Volkmar FR, eds. *Pediatric Bipolar Disorder, in Lewis' Child and Adolescent Psychiatric. A Comprehensive Textbook*, 4th ed. Baltimore, MD: Lippincott Williams and Wilkins; 2007.
62. Wozniak J, Biederman J, Monuteaux MC, et al. Parsing the comorbidity between bipolar disorder and anxiety disorders: a familial risk analysis. *J Child Adolesc Psychopharmacol*. 2002;12(2):101–111.
63. Goldstein TR, Birmaher B, Axelson D, et al. History of suicide attempts in pediatric bipolar disorder: factors associated with increased risk. *Bipolar Disord*. 2005;7(6):525–535.
64. Goldstein BI, Strober MA, Birmaher B, et al. Substance use disorders among adolescents with bipolar spectrum disorders. *Bipolar Disord*. 2008;10(4):469–478.
65. Steinbuchel PH, Wilens TE, Adamson JJ, et al. Posttraumatic stress disorder and substance use disorder in adolescent bipolar disorder. *Bipolar Disord*. 2009;11(2):198–204.
66. Goldstein BI, Levitt AJ. The specific burden of comorbid anxiety disorders and of substance use disorders in bipolar I disorder. *Bipolar Disord*. 2008;10(1):67–78.
67. Beck AT, Brown GK, Steer RA, et al. Suicide ideation at its worst point: a predictor of eventual suicide in psychiatric outpatients. *Suicide Life Threat Behav*. 1999;29(1):1–9.
68. Brown GK, Beck AT, Steer RA, et al. Risk factors for suicide in psychiatric outpatients: a 20-year prospective study. *J Consult Clin Psychol*. 2000;68(3):371–377.
69. Fawcett J, Scheftner WA, Fogg L, et al. Time-related predictors of suicide in major affective disorder. *Am J Psychiatry*. 1990;147(9): 1189–1194.
70. Goldstein BI, Houck PR, Karp JF. Factors associated with pain interference in an epidemiologic sample of adults with bipolar I disorder. *J Affect Disord*. 2009;117(3):151–156.
71. Bell-Dolan DB. Separation anxiety disorder, overanxious disorder, and school refusal. *Child Adolesc Psychiatr Clin N Am*. 1993;2:563–580.
72. Lewinsohn PM, Klein DN, Seeley JR. Bipolar disorder during adolescence and young adulthood in a community sample. *Bipolar Disord*. 2000;2(3 pt 2):281–293.

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