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DOES THE COURSE OF MANIC SYMPTOMS IN PEDIATRIC BIPOLAR DISORDER IMPACT THE COURSE OF CONDUCT DISORDER? FINDINGS FROM FOUR PROSPECTIVE DATASETS

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Abstract

Background—To assess whether the course of pediatric bipolar-I (BP-I) disorder impacts the course of conduct disorder (CD)/antisocial personality disorder (ASPD). We hypothesized that remission of manic symptoms in BP-I youth will be associated with remission of CD/ASPD.

Methods—We used data from four longitudinal datasets of carefully characterized and comprehensively assessed youth with structured diagnostic interview based diagnoses of BP-I disorder and CD/ASPD assessed at baseline in childhood and at follow-up onto adolescent years. The baseline sample consisted of 240 subjects with full BP-I disorder. The average follow-up time was 6.6 ± 2.4 years.

Results—Subjects with remitting BP-I disorder in adolescent years had a significantly lower one-year prevalence of CD or ASPD compared to those with persistent BP-I disorder ($\chi^2=10.35$, $p=0.001$).

Limitations—Our inferences were derived from the examination of naturalistic longitudinal follow-up data and not results of a clinical trial.

Conclusions—Results indicate that remission of manic symptoms at the adolescent follow up in youth with BP-I disorder were associated with a significant decrease in rates of CD/ASPD. These results suggest that targeting manic symptoms in youth with BP-I disorder could mitigate the

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course of CD/ASPD in youth. Considering the high morbidity and disability associated CD/ASPD in youth and the limited treatment options available to address it, if replicated, these findings would have very important clinical and public health significance.

Keywords

mania; bipolar disorder; conduct disorder; children

INTRODUCTION

A body of literature documents a high and bidirectional overlap between bipolar-I (BP-I) disorder and conduct disorder (CD)/antisocial personality disorder (ASPD) in both clinical (Biederman et al., 1996b; Faraone et al., 1998; Geller et al., 1994; Kovacs and Pollock, 1995; Kutcher et al., 1989; Wozniak et al., 1995a; Wozniak et al., 1995b) and epidemiological samples (Lewinsohn et al., 1995).

Our own studies documented a high and bidirectional comorbidity between BP-I disorder and CD within and without the context of ADHD (Biederman et al., 1999). Examination of symptoms of mania and patterns of familial aggregation in youth with BP-I disorder and CD indicated that the presence of one disorder did not alter the symptomatic picture or familiarity of the other. In other words, the symptom profile of BP-I disorder and CD were the same irrespective of the comorbidity with the other disorder. Likewise, both BP-I disorder and CD bred true in families irrespective of the presence of the other disorder. We also found significant evidence of cosegregation between CD and BP-I disorder among relatives of probands with comorbid CD+BP-I disorder supporting the hypothesis the CD +BP-I disorder may represent a distinct subgroup of either BP-I disorder or CD (Wozniak et al., 2001). More recently, Masi et al. (2008) examined the co-occurrence of CD and BP-I disorder in a sample of 307 youth using structured clinical interviews and found that youth with comorbid CD plus BP-I disorder had higher rates of aggression when compared with those with CD alone and had the highest risk for substance abuse. Likewise, Olvera et al. (2014) reported that subjects with the co-occurrence of CD and BP-I disorder had poorer lifetime functioning, more mood and attentional dysfunction, and more medication exposure than subjects with CD who were not bipolar.

Furthermore, Mallett et al. (2009) using data from a random sample of youth before the juvenile courts in two Northeast Ohio counties in the USA (n = 555) over a 4-year time frame, identified a lifetime diagnosis of depression and/or bipolar disorder to be predictive of later youth delinquency adjudication. Webb et al. (2014) compared risks for suicidality and criminality in a national cohort of people diagnosed with bipolar disorder using data from the Swedish national registers. Findings revealed that 22.2% of bipolar disorder cohort members engaged in suicidal or criminal acts after diagnosis. They were at greatly elevated risk for completed suicide (risk ratio = 18.8; 95% CI, 16.0–22.2), attempted suicide (risk ratio = 14.3; 95% CI, 13.5–15.2), violent crime (risk ratio = 5.0; 95% CI, 4.6–5.4), and nonviolent crime (risk ratio = 2.9; 95% CI, 2.8–3.1) compared with the general population.

Work by our group and others showed that both predatory and non-predatory types of aggression occur in youth with BP-I disorder (Biederman et al., 1999; Eichenman, 1987;

Eichelman, 1992). Such aggressive behaviors can lead to arrest and incarceration. For example, Plizka et al. (2000) found that 20% of adolescents admitted to a juvenile detention center met criteria for mania and those with mania had much higher rates of substance use disorders than those with bipolar disorder. In our studies (Biederman et al., 1996a; Biederman et al., 1999), the rate of psychiatric hospitalization in children with CD in the absence of BP-I disorder was very low and indistinguishable from that of youth with ADHD. In contrast, it was very high in those with comorbid CD with BP-I disorder, suggesting that the presence of BP-I disorder drives the need for psychiatric hospitalization in children with CD.

While pharmacological treatments can successfully treat pediatric BP-I disorder (Liu et al., 2011), pharmacological approaches are less certain in the management of CD youth (Thomas, 2016). A series of small early controlled clinical trials (Campbell et al., 1995; Campbell et al., 1984; Cueva et al., 1996; Malone et al., 2000; Rifkin et al., 1997) in hospitalized aggressive children with CD suggested that mood stabilizers (lithium carbonate and carbamazepine) (Steiner et al., 2003) may be effective in the treatment of aggressive symptoms in CD children. Similar findings were reported in more recent small studies of risperidone in youths with conduct disorder and aggressivity (Findling et al., 2000) and in a sample of children with subnormal intelligence, aggression and disruptive behavior disorders (Aman et al., 2002), as well as a study of olanzapine in the treatment of adolescents with severe conduct disorder with marked aggressive symptoms (Masi et al., 2006).

While none of these studies addressed the question of whether these children may have had comorbidity with bipolar disorder, in all these studies, the investigators targeted aggression in the context of CD with antimanic agents. These findings suggest that the therapeutic benefits observed in aggressive children with CD with anti-manic treatments could have been due to their anti-manic effects of the medications used targeting manic symptoms. However, to the best of our knowledge, no study to date directly assessed whether treating manic symptoms in youth with BP- I disorder improves symptoms of CD.

In the absence of clinical trial data, one approach to indirectly probe this important issue is to examine whether the naturalistic longitudinal course of manic symptoms in BP-I youth impacts the course of CD overtime. Specifically, prospective data can provide important insight as to whether remission of manic symptoms in youth with BP-I disorder is associated with remission of CD symptoms. Since improvement of manic symptoms can be achieved in the short-term with appropriate antimanic armamentarium (Liu et al., 2011), this information would support the conduct of clinical trials targeting manic symptoms in youth with CD and comorbid BP-I disorder with antimanic agents.

Whether the course of manic symptoms in youth with BP-I disorder impacts the course of CD has important implications. Clinically, such information will encourage clinicians to consider the diagnosis of BP-I disorder in mood dysregulated youth with CD and address the BP-I disorder component of the clinical picture with appropriate antimanic treatment. Considering the morbidity and poor prognosis associated with CD, the ability to address manic symptoms in CD youth with comorbid BP-I disorder may allow these very high-risk

youths to attain clinical stability and avoid institutionalization and incarceration, an issue of high societal and public health relevance.

The main aim of the present study was to assess whether the course of pediatric BP-I disorder impacts the course of CD/ASPD. To this end we used data from four longitudinal datasets of carefully characterized and comprehensively assessed youth with structured diagnostic interview based diagnoses of BP-I disorder and CD assessed at baseline in childhood and at follow-up during adolescent years. We hypothesized that remission of manic symptoms in BP-I youth will be associated with remission of CD.

Methods

Sample

The sample was derived from four independent studies using identical assessment methodology: Two were prospective controlled family studies of boys and girls 6 to 17 years of age with and without ADHD (Boys Study: N=140 ADHD and N=120 Controls; Girls Study: N=140 ADHD and N=122 Controls) (Biederman et al., 1996a; Biederman et al., 2006); The third one was a prospective controlled family study of youth 10 to 18 years of age with (N=105) and without (N=98) DSM-IV pediatric BP-I disorder (Wilens et al., 2008); and the fourth one was a prospective family study of youth 6 to 17 years of age of both sexes with active symptoms of DSM-IV BP-I disorder (N=105) (Wozniak et al., 2011). The ADHD studies recruited subjects from pediatric and psychiatric clinics. The BP-I disorder studies recruited subjects from referrals to the Clinical and Research Programs in Pediatric Psychopharmacology at the Massachusetts General Hospital and through advertisements in the community. All studies excluded adopted subjects, subjects where the nuclear family was not available, subjects with major sensorimotor handicaps, autism, inadequate command of the English language, or Full Scale IQ < 70 (< 80 for ADHD studies). Potential subjects were also excluded from the ADHD studies if they had psychosis and from the BP-I disorder studies if their BP-I disorder was due solely to a medication reaction. For all four studies parents provided written informed consent to participate. Children and adolescents provided written assent to participate. The Partners Human Research Committee approved these studies.

Assessment Procedures

In all four studies, psychiatric assessments of subjects were made with the Kiddie Schedule for Affective Disorders – Epidemiologic Version (KSADS-E). (Orvaschel and Puig-Antich, 1987) Diagnoses were based on independent interviews with parents and direct interviews with children older than 12 years of age. Data were combined such that endorsement of a diagnosis by either reporter resulted in a positive diagnosis.

Extensively trained and supervised psychometricians with undergraduate degrees in psychology conducted all interviews. For the ADHD studies and the controlled BP disorder study, raters were blind to the ascertainment status of the families. For the BP disorder family study, raters were blind to the study assignment and whether the subject was a proband or sibling.

To assess the reliability of our overall diagnostic procedures, we computed kappa coefficients of agreement by having experienced, blinded, board-certified child and adult psychiatrists and licensed experienced clinical psychologists diagnose subjects from audiotaped interviews made by the assessment staff. Based on 500 assessments from interviews of children and adults, the median kappa coefficient was 0.98 for the ADHD studies and the controlled BP disorder study, and 0.99 for the BPD Family study. Socioeconomic status (SES) was measured using the 5-point Hollingshead scale based on education and occupation (Hollingshead, 1975). A higher score indicates being of lower socioeconomic status.

Statistical Analysis

We first compared demographic characteristics between those who returned for follow-up and those who were lost to follow-up using Student's t-test for continuous variables, Wilcoxon rank-sum tests for ordinal variables, and Pearson's chi-square or Fisher's exact tests for binary variables. Next, we examined lifetime rates of BP-I disorder and CD/ASPD at baseline and one- year prevalence at follow-up to determine persistence or remission of the disorders. We defined persistence of BP-I and CD as meeting full (or subthreshold for BP-I) DSM-IV criteria for the disorder in the year prior to the follow-up and remission as not meeting full (or subthreshold for BP-I) DSM-IV criteria for the disorder in the year prior to follow-up. We used Pearson's chi- square test to compare the one-year prevalence of CD/ ASPD at follow-up between subjects with remitting BP-I disorder and subjects with persistent (subthreshold or full) BP-I disorder.

Results

Demographic Characteristics of the Sample

Our baseline sample consisted of 240 subjects with full BP-I disorder. There were no significant differences between the studies in the baseline rate of CD/ASPD (Boys ADHD: 53% vs. Girls ADHD: 33% vs. BP Family: 54% vs. BP Controlled: 55%; $\chi^2=2.60$, $p=0.45$). Subjects at baseline were an average age of 11.8 ± 3.5 years, had an average socioeconomic status (SES) of 1.9 ± 1.0 , and were predominantly male (72%) and Caucasian (95%). At baseline, 44% of patients were both taking medication and receiving counseling, 34% were hospitalized, 8% were receiving counseling only, 6% were taking medication only, and 8% were not receiving any treatment. At follow-up, 36% of patients with persistent BP-I disorder were both taking medication and receiving counseling, 24% were hospitalized, 13% were taking medication only, 8% were receiving counseling only, and 18% were not receiving any treatment. Of the 240 subjects with BP-I disorder at baseline, 185 (77%) returned for follow-up (93% (14/15) of subjects from the boys ADHD study, 100% (15/15) of subjects from the girls ADHD study, 84% (88/105) of subjects from the BP family study, and 65% (68/105) of subjects from the BP controlled study). The average follow-up time among all subjects was 6.6 ± 2.4 years (Boys ADHD: 10.1 ± 2.8 years; Girls ADHD: 9.5 ± 3.1 years; BP Family: 5.8 ± 1.8 years; BP Controlled: 6.1 ± 1.7 years). There were significant differences in baseline SES and sex between those who returned for follow-up and those who were lost to follow-up (Table 1). Those who returned for follow-up were of higher SES and had a lower proportion of males compared to those who were lost to follow-

up. There were no significant differences between the two groups in baseline age, race, or rate of baseline CD/ASPD. There were 9 subjects who were missing information needed to determine persistence or remission of BP-I disorder or CD/ASPD at follow-up and were excluded from subsequent follow-up analyses. Thus, the final sample at follow-up included 176 subjects.

Prevalence of Bipolar Disorder & Conduct Disorder/Antisocial Personality Disorder

We first examined the rates of BP-I disorder and CD/ASPD at baseline and follow-up. As shown in Table 2, the rate of BP-I disorder dropped to from 100% at baseline to 52% (40% full BP-I disorder and 12% subthreshold BP-I disorder) at follow-up, i.e., 52% of subjects had persistent BP-I disorder at follow-up. Similarly, the rate of CD/ASPD dropped from 53% at baseline to 19% at follow-up (Table 2), i.e., 19% of subjects had persistent CD/ASPD at follow-up.

We then stratified the sample by those with remitting BP-I disorder (N=85) and those with persistent BP-I disorder (N=91). Although the baseline rate of CD/ASPD did not significantly differ between those with remitting and persistent BP-I disorder (Table 3), those with remitting BP-I disorder had a significantly lower one-year prevalence of CD/ASPD at follow-up compared to those with persistent BP-I disorder (Table 3).

Discussion

Using data from four naturalistic longitudinal datasets of youth of both sexes with and without BP-I disorder and ADHD, we examined whether the course of pediatric BP-I disorder affects the course of CD/ASPD. Results indicate that remission of manic symptoms in youth with BP-I disorder was associated with a significant decrease in rates of CD/ASPD. If replicated, these results suggest that targeting symptoms of mania in youth with CD with comorbid BP-I disorder could indirectly mitigate the course of CD/ASPD.

Previous research showed that children with both CD and BP-I disorder shared striking similarities in the phenotypic features of both disorders irrespective of the comorbidity with the other disorder. CD symptoms were nearly identical in CD children irrespective of the comorbidity with BP-I disorder, and the same was true for manic symptoms in youth with BP-I disorder. Familial risk analyses supported the same conclusion: CD and BP-I disorder bred true in families irrespective of the comorbidity with the other disorder (Biederman et al., 2003). This research also documented that CD comorbid with BP-I disorder puts children at risk for a highly compromised outcome including psychiatric hospitalization and addictions (Biederman et al., 2003; Wilens et al., 2016).

As recently shown by Olvera et al. (2014), the comorbidity between CD and BP may also have unique neurobiological underpinnings. These investigators conducted an optimized voxel based morphometry study of adolescent juvenile offenders in a residential treatment facility for repeat offenders. Subjects were stratified based on the presence or absence a diagnosis of CD with and without a comorbid diagnosis of bipolar disorder. Adolescents with CD comorbid with bipolar disorder not only had poorer lifetime functioning, more mood and attentional dysfunction, and more medication exposure than subjects with CD

who were not comorbid with bipolar disorder but also had unique neurobiological underpinnings. Neuroimaging findings revealed that adolescents with CD plus bipolar disorder had decreased volume relative to controls at the voxel level in the right medial prefrontal cortex as well as significantly decreased volumes of the right medial prefrontal cortex and portions of the superior and inferior frontal gyrus, anterior cingulate and temporal gyrus. In contrast, CD subjects without comorbid bipolar disorder did not have differences in brain volume compared to controls.

However, in contrast to uncertainties on pharmacological approaches to treat CD, safe and effective treatments are available in the treatment of pediatric BP-I disorder (Liu et al., 2011) affording the opportunity to indirectly target CD by treating manic symptoms in CD youth with comorbid BP-I disorder. Considering the poor prognosis of CD, its remission has important clinical and public health relevance. Clearly, confirmation of these findings in the context of a randomized clinical trial is needed.

Our findings need to be viewed considering some methodological limitations. Our inferences were derived from the examination of naturalistic longitudinal follow-up data and not results of a clinical trial. Although manic and hypomanic states can be associated with behavioral disinhibition and accentuate antisocial behavior, we carefully assessed with structured diagnostic interviews the presence of BP-I disorder and CD suggesting that both disorders were present. Our finding of significant differences in baseline SES and sex between those who did and did not return for follow-up further limits generalization. Because none of the original studies were conducted with the explicit intention of examining conduct disorder, uncertainties remain as to whether similar results would have been obtained using samples with the explicit intention of examining conduct disorder. Because our sample consisted largely of referred Caucasian children they may not generalize to non-referred samples or other ethnic groups.

Despite these considerations, results from these naturalistic longitudinal datasets of youth of both sexes with and without BP-I disorder and CD indicate that remission of manic symptoms in youth with BP-I disorder are associated with a significant decrease in rates of CD. Although we cannot assert causality or medication effects based on these naturalistic results, they suggest that reducing manic symptoms in youth with BP-I disorder via appropriate treatment strategies might have important benefits in mitigating the course of CD in youth with both disorders. Considering that pediatric BP-I disorder can be successfully treated with antimanic agents and the high morbidity and disability associated with CD, if replicated these findings would have important clinical and public health significance.

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Abbreviations

ASPD	antisocial personality disorder
ADHD	attention-deficit/hyperactivity disorder
BP-I	bipolar-I
CD	conduct disorder
KSADS-E	Kiddie Schedule for Affective Disorders – Epidemiologic Version
SES	socioeconomic status

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HIGHLIGHTS

- Conduct disorder and bipolar disorder are prevalent and highly morbid psychiatric conditions
- There is a high and bidirectional overlap between conduct disorder and bipolar disorder
- Youth with both disorders are at extremely high risk for very adverse outcomes, including psychiatric hospitalization, suicidal risk, and addictions
- While bipolar disorder can be treated pharmacologically, conduct disorder cannot. Using longitudinal, naturalistic data, this study tested the hypothesis that reduction of symptoms of mania will lead to reduction of symptoms of conduct disorder. The findings support this hypothesis

Table 1

Baseline demographic characteristics of subjects with pediatric bipolar-I (BP-I) disorder who were lost to follow-up and who returned for follow-up.

	Lost to Follow-up N=55	Returned for Follow-up N=185	Test Statistic	P-Value
	Mean $\pm$ SD	Mean $\pm$ SD		
Age	12.5 $\pm$ 3.1	11.5 $\pm$ 3.6	$t_{238}=-1.72$	0.09
Socioeconomic Status [†]	2.5 $\pm$ 1.1	1.8 $\pm$ 0.9	$z=-3.31$	<0.001
	N (%)	N (%)		
Male	48 (87)	124 (67)	$\chi^2=8.56$	0.003
Caucasian [†]	48 (91)	176 (96)	Fisher's exact	0.15
Conduct Disorder/ASPD [‡]	29 (53)	99 (54)	$\chi^2=0.01$	0.92

[†] Smaller sample sizes. SES: Lost to Follow-up: N=42, Returned for Follow-up: N=170; Caucasian: Lost to Follow-up: N=53, Returned for Follow-up: N=183

[‡] ASPD=Antisocial personality disorder

Table 2

Rates of bipolar-I (BP-I) disorder and conduct disorder (CD)/antisocial personality disorder (ASPD) at baseline (N=240) and follow-up (N=176) in subjects who had bipolar disorder at baseline. The average follow-up time was 6.6 ± 2.4 years.

	N (%)
Bipolar-I Disorder	
Baseline ^[N=240]	240 (100)
Follow-up ^[N=176]	
Persistent BP-I	91 (52)
Remitting BP-I	85 (48)
Conduct/ASPD Disorder	
Baseline ^[N=240]	128 (53)
Follow-up ^[N=176]	
Persistent CD/ASPD	34 (19)
Remitting CD/ASPD	142 (81)

Table 3

Baseline prevalence and one-year prevalence at follow-up of conduct disorder (CD)/antisocial personality disorder (ASPD) in subjects with remitting and persistent subthreshold or full bipolar-I (BP-I) disorder.

	Remitting BP-I Disorder N=85	Persistent BP-I Disorder N=91	Test Statistic	P-Value
	N (%)	N (%)		
CD/ASPD at Baseline	38 (45)	53 (58)	$\chi^2 = 3.22$	0.07
Persistent CD/ASPD at Follow-up	8 (9)	26 (29)	$\chi^2 = 10.35$	p=0.001