Correlates of Incident Bipolar Disorder in Children and Adolescents Diagnosed With Attention-Deficit/Hyperactivity Disorder

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ABSTRACT

Background: The greater severity and chronicity of illness in youths with co-occurring attention-deficit/hyperactivity disorder (ADHD) and bipolar disorder deserve further investigation as to the risk imparted by comorbid conditions and the pharmacotherapies employed.

Method: A retrospective cohort design was employed, using South Carolina's Medicaid claims dataset covering outpatient and inpatient medical and psychiatric service claims with *International Classification of Diseases, Ninth Revision, Clinical Modification* diagnoses and medication prescriptions between January 1996 and December 2006 for patients ≤ 17 years of age.

Results: The cohort included 22,797 cases diagnosed with ADHD at a mean age of 7.8 years; 1,604 (7.0%) were diagnosed with bipolar disorder at a mean age of 12.2 years. The bipolar disorder group developed conduct disorder (CD)/oppositional defiant disorder (ODD), anxiety disorder, and a substance use disorder later than the ADHD-only group. The odds of a child with ADHD developing bipolar disorder were significantly and positively associated with a comorbid diagnosis of CD/ODD (adjusted odds ratio [aOR] = 4.01), anxiety disorder (aOR = 2.39), or substance use disorder (aOR = 1.88); longer treatment with methylphenidate, mixed amphetamine salts, or atomoxetine (aOR = 1.01); not being African American (aOR = 1.61); and being treated with certain antidepressant medications, most notably fluoxetine (aOR = 2.00), sertraline (aOR = 2.29), bupropion (aOR = 2.22), trazodone (aOR = 2.15), or venlafaxine (aOR = 2.37) prior to the first diagnosis of mania.

Conclusions: Controlling for pharmacotherapy differences, incident bipolar disorder was more likely in individuals clustering specific patterns of comorbid psychiatric disorders, suggesting that there are different pathways to bipolarity and providing a clinical impetus for prioritizing prevention and preemptive strategies to reduce their hazardous influence.

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Over 60% of adults with bipolar I or II disorder have an age at onset during childhood or adolescence.[1–3] Moreover, 2.5% of youth meet epidemiologic criteria for lifetime bipolar disorder, with a 2-fold increase from ages 13–14 to 17–18 years. Pediatric bipolar disorder is complex and clinically challenging to assess and manage and is associated with higher rates of nonrecovery, recurrence, chronicity, and a progressive, accelerating course related to neurostructural changes, cognitive deterioration, and accumulating comorbidities.[4,5]

The most common phenomenological antecedents to overt bipolar disorder are externalizing behavioral disorders (eg, attention-deficit/hyperactivity disorder [ADHD], conduct disorder [CD]/oppositional defiant disorder [ODD], and substance use disorders) coupled with depressive/anxious symptoms/episodes.[6–11] Multiple psychotropic medications (eg, psychostimulants, antidepressants, and mood-stabilizing agents) are typically prescribed for these various "externalizing" or "complex" phenotypes.[12] Although the occurrences are rare, psychostimulant medications used to treat ADHD have been associated with psychotic or manic symptoms in approximately 0.1% of children or adolescents without a prior history of psychosis or mania, as well as with increased aggression and hostility.[13–17] Moreover, some antidepressants used to manage co-occurring depression have been associated with an increased risk of manic or hypomanic switch, suicidality, and rapid cycling.[17–21]

Co-occurrence of ADHD and bipolar disorder in children and adolescents, therefore, represents an important opportunity to identify a unique set of clinical factors associated with the complexity, severity, and chronicity of illness apparent in these youths. Few studies have characterized how these clinical characteristics and common treatment medications are systematically associated with incident bipolar disorder among those with ADHD. Given the substantially higher rates of long-term impairment, morbidity, cognitive deterioration, and increased risk of mortality (from suicide) associated with having co-occurring ADHD and bipolar disorder compared to having either disorder alone, this area of inquiry deserves further investigation.

METHOD

Data for this study were obtained retrospectively from the South Carolina (SC) Medicaid database (SC Department of Health and Human Services and the SC Office of Research and Statistics) during an 11-year period from January 1, 1996, through December 31, 2006. Medical claims were used to identify a service encounter, date of service, and the *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) diagnosis related to that visit. Selection criteria were age ≤ 17 years, continuous enrollment in Medicaid for a minimum of 9 months in each calendar year, and at least 1 initial service encounter with an *ICD-9-CM* diagnosis of 314.00 or 314.01 (attention-deficit/hyperactivity disorder). *ICD-9-CM* codes indicating hyperkinesis

Clinical Points

- A fundamental and ongoing clinical challenge is the lack of a clear consensus regarding diagnostic criteria for pediatric bipolar disorder. Prevalence is inextricably linked to diagnostic clarity.
- Neurobiological, neuropsychological, and genetic connections among attention-deficit/hyperactivity disorder (ADHD), conduct disorder (CD)/oppositional defiant disorder (ODD), anxiety disorder, and bipolar disorder need to be more precisely determined during the early period of rapid development of the comorbid disorders (6–12 years) in order to advance clinical assessment and treatment decision making for syndromal bipolar disorder.
- Delayed onset of comorbid CD/ODD and anxiety disorders in those with ADHD may signal a heightened risk of incident bipolar disorder and provide a "window of opportunity" for intervening to preempt or prevent progression to syndromal bipolar disorder.

not associated with attention deficit disorder were omitted from this study. Pharmacy file claims for these cases were then extracted for the same time periods.

Within this ADHD cohort, the following conditions were investigated: bipolar disorder (*ICD-9-CM* codes for the first mania/mixed episode: 296.0, 296.1, 296.4, 296.5, 296.6, 296.7, 296.8x), CD/ODD, anxiety, or a substance use disorder. Cases with *ICD-9-CM* codes for only depressive disorders were excluded from this investigation. These data sets are routinely checked and cleaned prior to being made available for statistical analysis. Furthermore, the diagnoses and pharmacotherapies contained in the Medicaid billing system have been compared with information available in the clinical records of 300–400 children with each primary diagnosis (ADHD, CD/ODD, and bipolar disorder) to provide validation of the secondary source data.[22,23] The methods involved in this study were approved by the University of South Carolina Institutional Review Board as exempt from human subject research guidelines (45 Code of Federal Regulations part 46).

Descriptive statistical analyses were performed to determine the prevalence/incidence of each condition and any bivariate associations between the predictor variables of interest. To address our primary research questions regarding the factors that are significantly associated with the odds of a child with ADHD being diagnosed with syndromal bipolar disorder, a multiple variable logistic regression equation was constructed using individual risk factors (dichotomously coded sex and ethnicity; continuously coded age at ADHD diagnosis), the independently diagnosed psychiatric disorders (CD/ODD, anxiety disorder, and substance use disorder), and prescribed psychostimulant medication or atomoxetine (coded as the number of months the child was taking/exposed to the medication), or antidepressants prescribed prior to a mania diagnosis (dichotomously coded yes/no) as predictor variables. The full regression model was then reduced to reflect only the statistically significant variables through a stepwise procedure that identified the variables contributing most significantly to explaining the differences in those diagnosed and not diagnosed with bipolar disorder, using a preset significance level of $P = .05$. The measure of association reported for these results is the adjusted odds ratio (aOR) with a corresponding 95% confidence interval.

Table 1. Descriptive Analysis of the Cohort of 22,797 Youths Diagnosed With ADHD

Indicator	Value
Gender, male, n (%)	15,864 (69.6)
Race, n (%)	
Non–African American	11,891 (52.2)
African American	10,906 (47.8)
Age at ADHD diagnosis, mean (SD), y	7.8 (2.9)
Diagnosed with bipolar disorder, n (%)	1,604 (7.0)
Age at bipolar disorder diagnosis, mean (SD), y	12.2 (3.9)
Diagnosed with CD/ODD, n (%)	9,146 (40.1)
Age at CD/ODD diagnosis, mean (SD), y	10.3 (3.9)
Diagnosed with anxiety disorder, n (%)	3,428 (15.0)
Age at anxiety diagnosis, mean (SD), y	11.7 (4.1)
Diagnosed with substance use disorder, n (%)	1,300 (5.7)
Age at substance use diagnosis, mean (SD), y	15.9 (3.7)

Abbreviations: ADHD = attention-deficit/hyperactivity disorder, CD = conduct disorder, ODD = oppositional defiant disorder.

RESULTS

The ADHD cohort consisted of 22,797 child and adolescent cases. Descriptive results regarding this cohort indicate that the cohort was predominantly male and non–African American, with a mean age of 7.8 years at diagnosis of ADHD. Bipolar disorder was diagnosed in 7.0% of the cohort at a mean age of 12.2 years (Table 1). Forty percent of the ADHD cohort was diagnosed with CD/ODD at a mean age of 10.3 years, 15% with anxiety disorder (predominantly generalized anxiety disorder [GAD]) at 11.7 years, and 5.7% with a substance use disorder at 15.9 years of age (Table 1). An episode of mixed mania and depression was first diagnosed in 772 children (48.1%). Those developing bipolar disorder developed their comorbid disorders later than the ADHD-only cohort: CD/ODD (present in 80.2% of the bipolar disorder group) at 11.9 years, anxiety disorder at 13.0 years, and a substance use disorder at 16.4 years of age.

A range of ADHD medications was prescribed to this cohort: 62.6% were taking methylphenidate for a mean of 17.1 months, 56.3% were taking mixed amphetamine salts/dextroamphetamine for a mean of 15.8 months, 1.4% were taking pemoline for a mean of 8.0 months, and 22.6% were taking atomoxetine for a mean of 7.8 months (Table 2). Of the 17 antidepressants examined, only citalopram, escitalopram, fluoxetine, paroxetine, sertraline, bupropion, mirtazapine, trazodone, and venlafaxine were prescribed to these children prior to a diagnosis of mania in sufficient numbers to analyze further.

In the logistic regression modeling the predictors of incident bipolar disorder in the ADHD cohort, controlling for ADHD pharmacotherapies coded as length of exposure/duration of prescription to the ADHD medications (Table 3),

Table 2. Prescribed Medications in ADHD Cohort

	Value
Current medication use	
Methylphenidate, n (%)	14,268 (62.6)
Length of methylphenidate use, mean (SD), mo	17.1 (18.1)
Mixed amphetamine salts/dextroamphetamine, n (%)	12,831 (56.3)
Length of mixed amphetamine salts/dextroamphetamine use, mean (SD), mo	15.8 (17.5)
Pemoline, n (%)	329 (1.4)
Length of pemoline use, mean (SD), mo	8.0 (12.8)
Atomoxetine, n (%)	5,143 (22.6)
Length of atomoxetine use, mean (SD), mo	7.8 (8.9)
Medication use prior to bipolar disorder diagnosis, n (%)	
Citalopram	52 (3.2)
Escitalopram	144 (9.0)
Fluoxetine	167 (10.4)
Paroxetine	104 (6.5)
Sertraline	253 (15.8)
Bupropion	214 (13.3)
Mirtazapine	222 (13.8)
Trazodone	204 (12.7)
Venlafaxine	72 (4.5)

Abbreviation: ADHD = attention-deficit/hyperactivity disorder.

Table 3. Adjusted Odds Ratios for Incident Bipolar Disorder Related to Comorbid Conditions, Prescribed Medications, and Individual Risk Factors (stepwise regression model)

Variable	Adjusted Odds Ratio	95% Confidence Interval
Ethnicity (not African American)	1.61**	1.42–1.82
Conduct disorder/oppositional defiant disorder diagnosis	4.01**	3.49–4.60
Anxiety diagnosis	2.39**	2.11–2.72
Substance abuse diagnosis	1.88**	1.58–2.23
Length of mixed amphetamine salts/dextroamphetamine treatment (mo)	1.01**	1.00–1.01
Length of methylphenidate treatment (mo)	1.01*	1.00–1.01
Length of atomoxetine treatment (mo)	1.01*	1.01–1.02
Medications used prior to bipolar disorder diagnosis		
Citalopram	1.69**	1.30–2.20
Escitalopram	1.84**	1.49–2.28
Fluoxetine	2.00**	1.70–2.08
Paroxetine	1.75**	1.48–2.08
Sertraline	2.29**	1.99–2.63
Bupropion	2.22**	1.90–2.59
Mirtazapine	1.69**	1.45–1.97
Trazodone	2.15**	1.82–2.54
Venlafaxine	2.37**	1.81–3.11

*Significant at $P \leq .01$.
**Significant at $P \leq .0001$.

16 predictor variables were significantly associated with the higher odds of a child being diagnosed with bipolar disorder: being diagnosed with comorbid CD/ODD (aOR = 4.01), anxiety disorder (aOR = 2.39), or substance use disorder (aOR = 1.88); longer treatment with methylphenidate, mixed amphetamine salts/dextroamphetamine, or atomoxetine (aOR = 1.01); not being African American (aOR = 1.61); and being treated with citalopram (aOR = 1.69), escitalopram (aOR = 1.84), fluoxetine (aOR = 2.00), paroxetine (aOR = 1.75), sertraline (aOR = 2.29), bupropion (aOR = 2.22), mirtazapine (aOR = 1.69), trazodone (aOR = 2.15), or venlafaxine (aOR = 2.37) prior to the diagnosis of mania. The longer a child was exposed to one of the 3 ADHD pharmacotherapies, the greater his/her chances of being diagnosed with bipolar disorder, increasing about 1% per month of treatment.

DISCUSSION

Bipolar disorder was diagnosed in 7.0% of this population-based ADHD cohort at a mean age of 12.2 years, which is lower than the rates of 11%–29% reported previously in children with an ADHD diagnosis referred for specialized psychiatric care and diagnosed with bipolar disorder.[24,25] The discrepancies could be due to methodological differences, as the earlier cohorts were ascertained in highly specialized care clinics, whereas our cohort was composed of cases referred by primary care physicians to public mental health treatment. However, during the epoch examined, early-onset bipolar disorder was, and continues to be, an underrecognized and underdiagnosed condition among children and adolescents by both primary and specialty care providers. A fundamental and abiding clinical challenge is that a clear consensus regarding the diagnostic criteria for bipolar disorder in children is lacking, although this disorder is widely acknowledged as being associated with considerable morbidity and mortality.[26] Questions regarding the prevalence of early-onset bipolar disorder are inextricably linked to the clarity of its diagnostic criteria.

Moreover, comorbid psychiatric disorders of CD/ODD and anxiety disorders, primarily GAD, not only were significantly prevalent in this ADHD/bipolar disorder cohort, confirming findings of other clinical and neuroscience investigators,[7,27,28] but also were the most significant factors predicting a heightened risk of being diagnosed with syndromal bipolar disorder in those with ADHD. This association suggests a need to further explore the neurobiological connections among these comorbid disorders more precisely during this particular period of rapid development, because neuroimaging findings have identified overlapping neural substrates representing common pathophysiologies not only for major depressive disorder and GAD, but also in the frontal lobe structures that regulate attention, behavior selection, and emotion for the comorbidities of ADHD, CD/ODD, and bipolar disorder.[29–32]

Since previous studies have demonstrated a low or nonsignificant genetic risk factor correlation for ADHD and bipolar disorder,[33,34] it might be productive to refocus on the genetic relationship between CD/ODD and bipolar disorder. CD/ODD predominated in our incident bipolar disorder prediction equation, and a similar cluster of symptoms has been identified by pediatric researchers,[26] suggesting that children with these externalizing/impulsive/aggressive features might represent a third broad pattern of comorbidity or phenotype of bipolarity, besides comorbid ADHD or anxiety disorders.[35] Longitudinal studies are needed, especially in early-onset bipolar disorder cases, that combine neurobiological, neuropsychological, and genetic methodologies to clarify trajectories of change as these constellations of new symptoms rapidly develop.[36]

While a substance use disorder was statistically associated with incident bipolar disorder in this cohort, comporting with previous clinical studies,[6–8] it consistently developed after the bipolar disorder and in a small subset of adolescents. Therefore, it may represent a secondary condition, perhaps developing due to inadequate control of the multiple symptom constellations present in these complex cases. That African Americans were less likely to develop bipolar disorder may indicate the clinical bias among practitioners during the epoch examined, wherein African Americans were less likely, in general, to be diagnosed with affective disorders, or that African Americans exhibit higher rates of cognitive/psychotic symptoms even after controlling for serious affective disorders.[37–39]

When the association of incident bipolar disorder and duration of exposure to the ADHD pharmacotherapies was explored in this analysis, the pharmacotherapies appear to contribute relatively little as predictors of incident bipolar disorder. For example, whereas the presence of comorbid CD/ODD was associated with a 301% increase in the likelihood of developing bipolar disorder, the ADHD pharmacotherapies were associated with only a 1% increase for every month of exposure, so their observable clinical impact may be minimal. In certain susceptible individuals, exposure to certain ADHD medications may be associated with amplification of affective symptomatology, but the ADHD medications per se do not attenuate or accentuate the overarching influence of other risk factors on incident bipolar disorder.

Moreover, although a few previous investigators have suggested that antidepressants may unmask manic symptoms, there has been no systematic, compelling evidence that any single antidepressant or class of antidepressants is immune from the hazard of unmasking bipolar disorder, and no relative estimate of these risks in children and adolescents has previously been reported.[13–18,40] Our results concerning the antidepressants being prescribed to adolescents in this clinical cohort indicate that the potential for unmasking manic symptoms in those already diagnosed with ADHD and depression was quite similar across the individual agents and the 2 classes of antidepressants represented. Furthermore, although we identified a heightened relative difference in the risk of developing syndromal bipolar disorder associated with some antidepressants, especially fluoxetine, sertraline, bupropion, trazodone, and venlafaxine, these associations should be interpreted cautiously as potential clinical "warning signals" for individual patients because we do not have access to any specific clinical data regarding why one antidepressant was prescribed versus another, so other clinical factors could explain these differences, and because no direct causal effects have been demonstrated herein.

Returning to potential explanations for the high rate of ADHD/bipolar disorder co-occurrence previously advanced by Singh et al,[24] our evidence suggests that ADHD may be one of the prodromal manifestations of pediatric onset bipolar disorder, that its treatment factors are somewhat associated with the onset of bipolar disorder, and that ADHD, bipolar disorder, and their associated psychiatric (especially CD/ODD) may share an underlying biological etiology that requires further investigation. The consistent and significant association of these comorbid disorders over time, that is, heterotypic continuity, should be recognized and addressed as an important component in an early period of rapid development of pediatric bipolar disorder, perhaps a more broadly defined "prodrome phase," affecting the progression of symptoms from a preclinical illness to fully syndromal bipolar disorder.[41,42] Moreover, a major challenge for improving outcomes is the large lag time between symptom onset, first correct diagnosis, and appropriate treatment.[41] More accurately characterizing this broadly defined "prodromal" period as several years prior to the first diagnosis of a mania/mixed episode could facilitate earlier identification and intervention in a significantly larger proportion of bipolar disorder patients. Finally, and again considering the complexity of this more broadly conceptualized "prodromal" period, the potential interventions initially used for these cases may need to focus on preventive/preemptive strategies.

The perspective provided by this longitudinal data set has several strengths. The cohort represents a large, heterogeneous group of children and adolescents being treated for diagnosed ADHD who have varying periods of exposure to the ADHD medications examined. Generally, there is sufficient power in the treated cohort to detect low-incidence comorbid psychiatric conditions. Previous studies have found that although observational (Medicaid) databases provide much less detailed clinical information on individuals and the care received, the physician diagnoses and utilization data are more reliable than patient or family self-reports.[43,44] The cohort is also representative of pediatric patients in routine care settings in the southeastern US states and in small states with predominantly small-city and rural populations in terms of age, sex, racial demographics, and Medicaid eligibility, but these results may not be generalizable to other patient groups.[45–47]

However, the results should also be interpreted with several limitations in mind. Identification of psychiatric conditions was based on spontaneous reporting to or observation by a primary care physician or psychiatrist and that physician's designation of each diagnosis in the Medicaid billing system. Consequently, the prevalence/incidence of these conditions may be an underestimate, which we cannot quantify. No structured research and clinical interviews were employed to confirm any of the assigned clinical diagnoses. Children and adolescents who dropped out of treatment or who were periodically ineligible for Medicaid are not represented in this data set. Moreover, the methods employed in this study focus exclusively on diagnosed/treated cases, not on the prevalence of bipolar disorder in a community sample of cases that may include those not seeking or receiving treatment. Data regarding key risk factors such as family history of related psychiatric disorders are not modeled in these analyses. Furthermore, these results report associations, and, as a result, directions of causality cannot be inferred. Finally,

although many significant covariates have been controlled for, other unmeasured differences in patients may explain the findings.

CONCLUSIONS

The results of our analysis provide empirical support for the emerging conceptualization of bipolar disorder as a neurodevelopmental disorder with an unfolding trajectory that is subject to heterotypic continuity/comorbidity preceding its adult declaration. A widely replicated observation is that the presence of comorbidity in both pediatric and adult bipolar disorder is associated with a more complex presentation, lower probability of recovery, and diminished treatment responsiveness. The evidence from our community-based, treated cohort further suggests that 3 comorbidities, ADHD, CD/ODD, and anxiety disorder, are most influential in the 6–12 year age range with regard to the emergence of syndromal bipolar disorder relative to other risk factors. The heightened effect of these comorbidities on bipolar disorder outcome provides an impetus for prioritizing prevention and preemptive strategies to reduce their hazardous influence on the onset and progression of bipolar disorder. However, it remains a testable hypothesis that successful achievement of this therapeutic objective would reduce the progressivity of early-onset bipolar disorder.

Drug names: atomoxetine (Strattera), bupropion (Wellbutrin, Aplenzin, and others), citalopram (Celexa and others), escitalopram (Lexapro and others), fluoxetine (Prozac and others), methylphenidate (Focalin, Daytrana, and others), mirtazapine (Remeron and others), paroxetine (Paxil, Pexeva, and others), sertraline (Zoloft and others), trazodone (Oleptro and others), venlafaxine (Effexor and others).

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Editor's Note: We encourage authors to submit papers for consideration as a part of our Focus on Childhood and Adolescent Mental Health section. Please contact Karen D. Wagner, MD, PhD, at kwagner@psychiatrist.com.