# A Cohort Study of the Prevalence and Impact of Comorbid Medical Conditions in Pediatric Bipolar Disorder

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***Objective:*** To identify the association between medical or psychiatric comorbidities, clinical characteristics, or course of illness/recovery in pediatric bipolar disorder (BD).

***Method:*** Data from the South Carolina Medicaid program covering all medical services and medication prescriptions between January 1996 and December 2005 were used to analyze the temporal onset of 12 comorbid medical or psychiatric conditions for 1,841 children and adolescents diagnosed with BD using *DSM-IV-TR* criteria and for a random sample of 4,500 children not treated for psychiatric disorders. The primary outcome measures were diagnostic codes and regression analyses of patterns of acute and outpatient treatment services for BD over time.

***Results:*** Ten conditions examined were significantly more prevalent in the BD cohort: obesity, type 2 diabetes mellitus, endocrine disorders, migraine headaches, central nervous system (CNS) disorders/epilepsy, organic brain disorders/mental retardation, cardiovascular disorders, attention-deficit/hyperactivity disorder (ADHD), asthma, and substance abuse ($P \leq .01$). For clinical characteristics within the BD cohort, an adolescent-onset diagnosis of BD (age ≥ 13 years) was significantly associated with the diagnosis of preexisting obesity, hypertension, migraine, mental retardation, endocrine disorders, and substance abuse ($P \leq .05$), whereas recurrent depressive episodes were associated with preexisting endocrine disorders and substance abuse. Preexisting ADHD, substance abuse, CNS disorders/epilepsy, cardiovascular disorders, obesity, and asthma were associated with higher overall medical and psychiatric outpatient and acute service use, but none of these comorbid disorders differentially impacted the course of illness or recovery for BD.

***Conclusions:*** Neuropsychiatric (ie, ADHD, substance abuse, CNS disorders/epilepsy) and medical (ie, obesity, asthma, cardiovascular disease) disorders temporally precede the diagnosis of early-onset BD in pediatric patients and are associated with discrete facets of illness presentation, but they do not substantially alter the clinical course of the BD over time.

*J Clin Psychiatry 2010;71(11):1518–1525*



***Submitted:*** *August 5, 2009; accepted December 1, 2009.*
***Online ahead of print:*** *June 15, 2010 (doi:10.4088/JCP.09m05585ora).*
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Adults with bipolar disorder (BD) are differentially affected by several comorbid medical and psychiatric disorders.[1] The pertinacity of comorbidity in BD is underscored by epidemiologic and clinical evidence indicating its adverse effect on BD presentation, course, outcome, and treatment response.[2,3] Pediatric BD is a relatively virulent phenotype associated with mixed mood states, rapid cycling, substance abuse, adverse psychosocial adjustment, childhood abuse, and high rates of suicide attempts.[4–7] Various reports have documented that over 60% of adults with BD had an age at onset during childhood or adolescence.[4,8,9] During the past decade, outpatient visits for pediatric-onset cases of BD have increased approximately 40-fold.[10]

Metabolic/endocrine disorders (eg, obesity, overweight, type 2 diabetes mellitus, dyslipidemia, and thyroid disorders) are more likely to co-occur in those with BD.[11–26] Moreover, abdominal obesity or overweight in individuals with BD has been associated with a multiepisode course, multiple psychiatric hospitalizations, suicidality, depression severity, decreased probability of symptomatic remission, substance abuse, and shorter time to episode recurrence.[27–30] Furthermore, the age-adjusted rate of cardiovascular disorders, including hypertension, in the adult BD population is also significantly higher than rates reported in the general population, with a younger mean age at onset.[18,19,22,26]

Disparate other comorbidities are also associated with BD: asthma,[18,22] neurologic disorders (ie, migraine headaches, seizures, multiple sclerosis, traumatic brain injury, and cerebrovascular accidents),[16,17,22,30,31] and substance-related disorders.[32,33] Alcohol and drug use disorders, in particular, are associated with high rates of treatment nonadherence, low rates of recovery, greater risk of aggression and violence, elevated rates of attempted and completed suicide, and less favorable response to conventional treatment.[33,34] Taken together, comorbid medical and psychiatric disorders are powerful predictors of total primary health care utilization[35] and may help define separate subpopulations of individuals with BD with differential course, outcome, and treatment response.[2,36,37]

Hitherto, relatively few studies have evaluated the association between pediatric-onset BD and medical/psychiatric comorbidity with an emphasis on temporal onset and implications for both clinical characteristics and course of illness/recovery. The primary aim of this analysis is to evaluate the association between the onset of select medical and psychiatric conditions, more complex bipolar presentation, and course of illness/recovery. Our investigative focus is on age at onset, mixed mood state or rapid cycling, recurrent



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depressive episodes, suicidality, and illness severity using diagnostic codes and patterns of acute and outpatient treatment services for BD over time.[2,3]

## METHOD

Claims data for the South Carolina Medicaid program were obtained through the state's Office of Research and Statistics. Data from both medical and pharmacy claims were used, with encrypted patient demographics and identifiers to protect patient confidentiality. Each Medicaid medical claim identifies a service encounter and gives the date of service and the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (*DSM-IV-TR*) diagnosis codes related to that visit (296.4x to 296.8x). A separate data file regarding eligibility was used to summarize the demographics for each patient (person file). The databases are frequently updated prior to being made available for analysis. This study was approved by the University of South Carolina Institutional Review Board as exempt from human subject research guidelines under 45 Code of Federal Regulations, part 46.

Medical claims for the calendar years January 1, 1996, through December 31, 2005, were used to identify a cohort of child and adolescent individuals (aged 17 years and under) eligible for Medicaid for a minimum of 9 months in each calendar year included in this analysis who had a service encounter and who were diagnosed with BD on at least 1 service visit. The service visit records for the children and adolescents in this cohort were then analyzed. The dates of interest (ie, 1996–2005) were chosen as this epoch corresponded with a rising treatment rate for bipolar disorders in children and adolescents.[8,10]

Out of the same population and from the same time period, medical claims were also used to identify a randomly selected group of child and adolescent patients (aged 17 years and under) eligible for Medicaid 9 out of 12 months in all calendar years under study who had service encounters but *no* prescriptions in the database for *any* class of psychotropic medication (ie, antipsychotics, antidepressants, mood stabilizers, or psychostimulants) and no treatment visits for any psychiatric diagnosis. This process resulted in the identification of 40,660 patients who met the criteria. From this group, a random sample of 4,500 patients was selected to use as a representative control group.

### Coding of Medical or Psychiatric Conditions

The following categories of conditions and events were evaluated/coded: obesity and excessive weight gain (*International Classification of Diseases, Ninth Revision* [*ICD-9*] codes: 278, 278.00, 278.01, 783.1, 783.2), dyslipidemia (272xx), type 2 diabetes mellitus, (250, 250.00–251.92 with fifth digit = 0,2), hypertension (401xx–405xx), cardiovascular events (myocardial infarction 410xx–412xx; ischemic/pulmonary heart disease 413xx–416xx, 428xx–429xx; arrhythmias 426xx–427xx; and cardiomyopathy 425xx), cerebrovascular events (cerebrovascular disease 436xx–437xx, cerebrovascular accident 435xx, cerebrovascular hemorrhage 430xx–434xx, and peripheral vascular disease 440xx–448xx), substance-related disorders (304xx and 305xx), organic brain damage and moderate to profound mental retardation (310xx, 318xx), neurologic disorders (multiple sclerosis 340x, epilepsy 345x, and migraine 346x), and endocrine disorders (thyroid 240xx–246xx, pituitary including hyperprolactinemia 253xx, adrenal 255xx, ovarian including polycystic ovary syndrome 256xx, and testicular 257xx). History of physical or sexual abuse was coded from *DSM-IV-TR*: V15.41 or V15.42.[7] Death date and reason codes came from vital statistic records in the South Carolina Department of Health and Environmental Control.

Medical or psychiatric conditions that were detected prior to each patient's diagnosis of bipolar disorder (selection encounter date) were coded as "preexisting" for this study. If the patient developed a medical condition subsequent to the diagnosis of bipolar disorder, new variables were created for these "incident" conditions. Conditions diagnosed at the same time as the bipolar disorder were coded as "preexisting." In the control group, detection of *any* of the metabolic, neurologic, cardiovascular, or respiratory medical conditions in a service record during their coverage by Medicaid was coded for analysis.

### Statistical Analyses

To address research questions regarding differences in the prevalence of these metabolic, neurologic, cardiovascular, and respiratory conditions in the BD versus control groups, conditional logistic regression, matched on age, race, and sex (PROC LOGISTIC with Strata [SAS Institute Inc, Cary, North Carolina]), was used to evaluate the association of metabolic conditions among cases and controls. Twelve cardio-metabolic and neuropsychiatric conditions were used as predictor variables. Collinearity was assessed by preliminary analyses for the association between predictor metabolic conditions, such as type 2 diabetes and other endocrine disorders. However, no collinearity was noted in our cohort. With an aim of identifying which metabolic, neuropsychiatric, and cardiovascular conditions in the cohort of pediatric patients diagnosed with BD were associated with illness severity variables, several multiple logistic regression equations were constructed to assess the relative odds associated with being diagnosed with "mixed mood state" diagnosis (*DSM-IV-TR* codes: 296.6x, 296.7x), "severity," or "rapid cycling" (using the fifth digit of the diagnostic code, eg, as "3" or "4"), or "adolescent age" at onset (≥ 13 years), using the metabolic, neuropsychiatric, or cardiovascular conditions as the main covariates, controlling for dichotomously coded individual risk factors (ie, sex and ethnicity).

To examine the influence of these comorbid conditions on the course of illness/recovery (a severity/acuity indicator) for a BD diagnosis or "recurrent depressive episodes" (296.5x), 3 additional regression analyses were performed representing changes over time in outpatient (maintenance) and acute

(inpatient and emergency) treatment services. Since the dependent utilization variables involved overdispersed count data with a mean less than the variance, a negative binomial regression model (PROC GENMOD facility in SAS version 9.1; SAS Institute Inc, Cary, North Carolina) was employed to calculate a ratio of the log rate of service utilization per 6-month period or the number of depressive episodes while the patient was covered in the Medicaid data set. In order to assess the association of outpatient visits with the comorbid conditions over time, the visits count data were clustered into 6-month periods, with 4 periods before and 5 periods after the BD diagnoses, in order to avoid the zero-inflated data. The acute service utilization data were clustered into 12-month periods, 2 before and 3 after the BD diagnosis.

A generalized estimating equation was used to account for the covariance due to repeated measures over the time periods for the outpatient and acute services use for BD regressions. Various covariance structures were explored before choosing compound symmetry as it gave the least deviance and goodness of fit parameters. Individual risk factors, ie, race (African American/non–African American), sex (male/female), age (12 years and under/13 years and over), and whether the child had a documented history of prior physical or sexual abuse (yes/no) were used as control variables, since service utilization in pediatric patients with mental illness has been shown to differ according to these demographics.[38–40] In order to achieve a more parsimonious model, interactions and potential confounders were explored one by one, depending on their statistical significance and assessing if the removal causes more than 10% change in the main association of interest. In addition, likelihood ratio testing was used to compare the models.

Finally, to evaluate the influence of these comorbid conditions on total health care visits (medical and psychiatric, outpatient and acute services), a negative binomial regression analysis of the ratio of total service utilization per total time in the Medicaid system was performed using each of the 12 preexisting medical conditions and individual risk factors, ie, race, sex, and age, as independent variables in the equation. Total time served under continuous Medicaid coverage was used as the denominator for rate of service in this regression, so that all subjects and all time periods were included in this analysis.

## RESULTS

The cohort of pediatric patients diagnosed with BD consisted of 1,841 children (n = 979) and adolescents (n = 862); 62.5% were male; 27.2% were African American; and 58.9% were white. The mean age of the BD cohort was 11.9 years (SD = 3.7) at the time of diagnosis. The random sample control group was more predominantly female and African American, with a lower mean age of 7.3 years (SD = 3.5). Although clients in the bipolar disorder cohort were about 4.5 years older at enrollment into the cohort than those in the control sample, data were compiled on the BD cohort for at least 2 years prior to their selection date for analysis of the preexisting conditions, making their mean age at start date in this data set more comparable to the control group (9.9 years). The prevalence rates of the comorbid medical conditions in the BD cohort and the control sample are presented in Table 1. The most prevalent cardiovascular conditions were arrhythmias (n = 132), congestive heart failure (n = 34), and ischemic/pulmonary heart disease (n = 14); some children had 2 or more of these conditions diagnosed during the study period. A cumulative frequency of the total number of comorbid conditions indicated that 28.4% of the BD cohort had 2 or more comorbid conditions. As only a small number (n = 14) of the cases had a history of physical or sexual abuse noted prior to the diagnosis of BD, this variable was not included in any of the final-model multivariate analyses.

Table 2 presents statistical comparisons of the BD cohort and control sample, controlling for their individual risk factor (ie, age, sex, and ethnic) differences, using the conditional case-control matching process. Most medical conditions examined in the conditional logistic regression

**Table 1. Overall Prevalence and Incidence Rates for Pediatric Patients With Bipolar Disorder and the Control Group**

| Condition | Control Group Prevalence Rate (n = 4,500), n (%) | Preexisting Prevalence Rate (n = 1,841), n (%) | Incidence Rate, n (%) |
|---|---|---|---|
| Obesity, weight gain | 388 (8.6) | 196 (10.7) | 159 (8.6) |
| Type 2 diabetes mellitus | 85 (1.9) | 42 (2.3) | 64 (3.5) |
| Dyslipidemia | 486 (10.8) | 49 (2.7) | 53 (2.9) |
| Endocrine disorder | 103 (2.3) | 96 (5.2) | 118 (6.4) |
| Reproductive disorder | 55 (1.2) | 121 (6.6) | 177 (9.6) |
| Hypertension | 171 (3.8) | 72 (3.9) | 73 (4.0) |
| Cardiovascular disorder | 151 (3.4) | 118 (6.4) | 91 (4.9) |
| Cerebrovascular disorder | 64 (1.4) | 14 (0.8) | 7 (0.4) |
| Organic brain disorders/ mental retardation | 162 (3.6) | 274 (14.9) | 129 (7.0) |
| Migraine | 140 (3.1) | 114 (6.2) | 78 (4.2) |
| Epilepsy | 91 (2.0) | 160 (8.7) | 76 (4.1) |
| Multiple sclerosis | 3 (0.07) | 3 (0.2) | 0 (0) |
| Asthma | 1,023 (22.7) | 473 (25.7) | 88 (4.8) |
| Substance abuse | 116 (2.6) | 202 (11.0) | 226 (12.3) |
| Attention-deficit/ hyperactivity disorder | 0 (0) | 1,413 (76.8) | 123 (6.7) |

**Table 2. Comparison of Prevalence of Medical Conditions in the Bipolar Cohort and Untreated Control Sample, Controlling for Individual Risk Factors**

| Dependent Variable | Bipolar Cohort, OR (95% CI)[a] |
|---|---|
| Obesity, weight gain | 1.92 (1.53–2.40) |
| Type 2 diabetes mellitus | 1.59 (1.08–2.35) |
| Dyslipidemia | NS |
| Endocrine disorder | 2.06 (1.49–2.85) |
| Organic brain disorder/mental retardation | 1.81 (1.47–2.23) |
| Migraine headache | 1.84 (1.37–2.48) |
| Epilepsy | 3.38 (2.48–4.59) |
| Cardiovascular | 1.38 (1.06–1.79) |
| Hypertension | NS |
| Asthma | 1.43 (1.21–1.68) |
| Substance abuse | 4.80 (3.70–6.23) |

[a]All reported ORs and CIs are significant at $P \leq .01$.
Abbreviation: NS = nonsignificant.



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Table 3. Predictors of Adolescent-Onset BD and Recurrent Depressive Episodes

| Predictor | Adolescent-Onset BD, OR (95% CI)[a] | Recurrent Depressive Episodes, Rate Ratio (95% CI) |
|---|---|---|
| Female | 2.13 (1.70–2.66) | NS |
| African American | 1.41 (1.12–1.78) | 0.68 (0.50–0.91) |
| Obesity | 1.58 (1.10–2.27) | NS |
| Type 2 diabetes mellitus | NS | NS |
| Dyslipidemia | NS | NS |
| Endocrine disorder | 4.81 (3.11–7.42) | 1.50 (1.04–2.17) |
| Organic brain disorder/ mental retardation | 1.50 (1.12–2.02) | NS |
| Migraine headache | 2.24 (1.41–3.55) | NS |
| Epilepsy | NS | NS |
| Cardiovascular disorder | NS | NS |
| Hypertension | 2.93 (1.56–5.51) | NS |
| Asthma | NS | NS |
| ADHD | 0.50 (0.38–0.64) | NS |
| Substance abuse | 14.35 (8.39–24.54) | 1.37 (1.02–1.84) |

[a]All reported ORs and CIs are significant at $P \leq .05$.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, NS = nonsignificant.

were significantly more prevalent in the BD cohort: obesity (OR = 1.92), type 2 diabetes mellitus (OR = 1.59), endocrine disorders (OR = 2.06), migraine headaches (OR = 1.84), epilepsy (OR = 3.38), organic brain disorders/mental retardation (OR = 1.81), cardiovascular disorders (OR = 1.38), asthma (OR = 1.43), and substance abuse (OR = 4.80).

Within the treated BD cohort, sex by medical or psychiatric condition interactions indicated that females were more likely to be diagnosed with obesity and substance abuse, whereas males were more likely to be diagnosed with organic brain disorders/mental retardation and attention-deficit/hyperactivity disorder (ADHD).

### Age at Onset

The odds of having an adolescent onset of bipolar disorder (age ≥ 13 years) were significantly higher for those patients with preexisting obesity (OR = 1.58), hypertension (OR = 2.93), migraine headaches (OR = 2.24), endocrine disorders (OR = 4.81), and substance abuse (OR = 14.35) (Table 3), as well as females and African Americans. Comorbid ADHD was more likely to be diagnosed in children 12 years and under (OR = 0.50). Further analysis of the least square mean differences indicated that most of the BD cases with these comorbid conditions were diagnosed at 15 to 17 years of age, on average, so the comorbid conditions may have been diagnosed at the same time or earlier in adolescence.

### Mixed Mood State, Rapid Cycling, Recurrent Depressive Episodes, and Severity

The odds of having a "mixed mood state" diagnostic code were lower for those patients with preexisting asthma (OR = 0.68). Preliminary descriptive analyses indicated that the number of cases with the fifth digit of the diagnostic code identifying "severe" or "rapid cycling" clinical features was too small (n = 12; n = 0, respectively) to use in further multivariate analyses. Recurrent depressive episodes were more likely for those with preexisting endocrine disorders (rate ratio [RR] = 1.50) and substance abuse (RR = 1.37) (Table 3).

### Outpatient Service Use/Time to Recovery for BD

Results of the negative binomial regression predicting the log-transformed ratio of rate of total outpatient service utilization/6-month period for 24 months (four 6-month periods) prior to the BD diagnosis and 30 months (five 6-month periods) after the BD diagnosis demonstrate that preexisting mental retardation, ADHD, hypertension, substance abuse, epilepsy, cardiovascular disorders, obesity, and asthma are associated with higher rates of outpatient service use in the BD patients with these disorders than in those without the disorders. However, none of these conditions increased service use over time or time to recovery for BD (Table 4, negative estimate values in the third column). Figure 1 provides a visual representation of this trend over time for patients with the most prevalent comorbid medical conditions (asthma, obesity, organic brain disorders/mental retardation, and substance abuse). Prior to the diagnosis and treatment of BD (time period "4" in Figure 1), rates of outpatient service use are uniformly higher than in the years after treatment was initiated, when rates of service use for BD are decreasing by about half, regardless of the comorbid medical conditions.

### Acute Service Use for BD/Unstable Periods of Illness

Results of the negative binomial regression predicting the log-transformed ratio of rate of total acute service utilization per 12-month period for 2 years prior to and 3 years after the BD diagnosis demonstrate significant reductions in acute service use after BD was diagnosed, controlling for higher rates of service use for females and African American youth. Furthermore, significant interactions were present for preexisting substance abuse, ADHD, asthma, dyslipidemia, and obesity by time, but none of these conditions changed the overall course of reductions in acute service use for BD over time (Table 4).

### Total Service Utilization Over Time for All Comorbid Medical and Psychiatric Conditions

Results of the negative binomial regression predicting the log-transformed ratio of rate of total outpatient service utilization/time in this Medicaid data set (Table 5) indicate that pediatric clients with BD with preexisting organic brain disorders/mental retardation (RR = 1.55), epilepsy (RR = 1.31), and cardiovascular disorders (RR = 1.23) had a significantly higher rate/time of services utilization during their time in the Medicaid data set, as did African Americans, than those without these conditions.

### Suicidality

The mortality rate in the BD cohort was 0.3% (n = 6) compared to that of 0.8% (n = 38) in the control group. None of these deaths was directly attributed to suicide on the death certificates. Therefore, no further analyses were performed for this clinical indicator.

Table 4. Negative Binomial Regressions Predicting Recovery Rate (services used) for Bipolar Diagnosis (N = 1,841)[a]

| Source | Outpatient Services Used for BD Diagnosis, Rate Ratio (95% CI) | Outpatient Services Used for BD Diagnosis × Time, Estimate (SE) | Acute Services Used for BD Diagnosis, Rate Ratio (95% CI) | Acute Services Used for BD Diagnosis × Time, Estimate (SE) |
|---|---|---|---|---|
| Female | 1.11 (1.02–1.20) | NA | 1.20 (1.06–1.35) | NA |
| African American | 1.35 (1.13–1.62) | NA | 1.24 (1.09–1.40) | NA |
| Aged 12 years or under | 1.20 (1.00–1.30) | NA | NS | NA |
| History of abuse | NS | NA | 1.88 (1.45–2.45) | NA |
| Obesity | NS | −0.05 (0.02)* | 1.43 (1.09–1.88) | −0.11 (0.05)* |
| Type 2 diabetes mellitus | 2.36 (2.02–2.75) | NS | NS | NS |
| Dyslipidemia | NS | NS | 3.72 (2.13–6.49) | −0.40 (0.11)* |
| Endocrine disorder | NS | NS | NS | NS |
| Organic brain disorder/ mental retardation | 1.21 (1.03–1.41) | −0.10 (0.02)** | NS | NS |
| ADHD | 1.68 (1.31–2.16) | −0.07 (0.01)** | 1.32 (1.05–1.66) | −0.13 (0.04)* |
| CNS disorder | 1.19 (1.05–1.35) | −0.08 (0.03)* | 1.49 (1.11–1.99) | NS |
| Cardiovascular disorder | 1.87 (1.62–2.15) | −0.04 (0.02) | 1.24 (1.03–1.50) | NS |
| Hypertension | 1.68 (1.34–2.10) | −0.07 (0.01)* | NS | NS |
| Asthma | NS | −0.05 (0.01)** | NS | −0.11 (0.04)* |
| Substance abuse | NS | −0.12 (0.06)** | 2.28 (1.77–2.94) | −0.21 (0.04)* |

[a]Outpatient services goodness of fit: deviance/*df* = 1.20; acute services goodness of fit: deviance/*df* = 0.72.
*Significant at *P* = .05. **Significant at *P* < .0001.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, CNS = central nervous system, NA = not applicable, NS = nonsignificant.

Figure 1. Estimated Rate of Outpatient Service Use Over Time

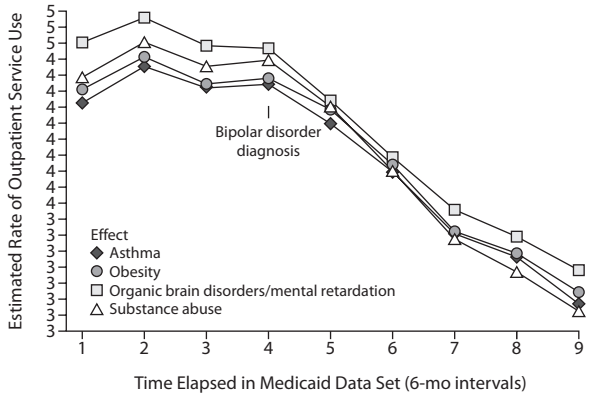


Table 5. Negative Binomial Regression Predicting Rate of Total Service Utilization to Total Time in Medicaid (N = 1,841)[a]

| Source | Rate Ratio | 95% CI |
|---|---|---|
| Female | NS | NA |
| African American | 1.22** | 1.13–1.32 |
| Obesity | NS | NA |
| Type 2 diabetes mellitus | NS | NA |
| Dyslipidemia | NS | NA |
| Endocrine disorder | NS | NA |
| Organic brain disorder/mental retardation | 1.55** | 1.41–1.71 |
| Migraine headache | NS | NA |
| Epilepsy | 1.31** | 1.14–1.50 |
| Cardiovascular disorder | 1.23* | 1.05–1.44 |
| Hypertension | NS | NA |
| Asthma | NS | NA |
| Substance abuse | NS | NA |

[a]Goodness of fit: deviance/*df* = 1.10.
*Significant at *P* = .05. **Significant at *P* < .0001.
Abbreviations: NA = not applicable, NS = nonsignificant.

## DISCUSSION

The results of our study expand on extant research by documenting a high rate of medical and psychiatric comorbidity in pediatric individuals with BD compared to a general Medicaid population, control sample. Many of the metabolic/endocrine, cardiovascular, neurologic, respiratory, and substance use disorders, which are more likely to co-occur in those with adult BD,[11,12,14–22,26,30–33] were evident in this pediatric BD cohort during adolescence. However, only ADHD was significantly associated with the childhood onset of BD (age ≤ 12 years), as found by other investigators.[41,42] Our finding that 28.4% of youth with BD have 2 or more chronic health conditions is generally consistent with other recent results underscoring the extensive somatic burden in pediatric BD.[43]

Moreover, in this study, preexisting mental retardation, ADHD, hypertension, substance abuse, epilepsy, cardiovascular disorders, obesity, and asthma were associated with higher rates of outpatient service use than in BD patients without these disorders, as would be expected if the comorbid conditions were being adequately treated in the primary care system.[35] However, the presence of any one of these comorbid conditions was not associated with a more severe course for BD, as evidenced by service use for BD over time, or a longer time in treatment for these BD patients. These findings may differ from the results of previous clinical trial investigations or smaller observational clinical studies[27,28,33] because children and adolescents with comorbid conditions are often excluded from the clinical populations investigated in randomized clinical trials.

Several sex differences in this study were noteworthy. Females were more likely to be diagnosed with preexisting obesity and substance abuse, whereas males were more likely to be diagnosed with organic brain disorders/mental retardation and ADHD. These results are consistent with previous clinical findings from medical record reviews in this state mental health system.[41,42] If the temporal onset of

comorbid medical or psychiatric conditions in BD is used to define separate subpopulations of the disorder with differential course, outcome, and treatment response,[2,36,37] these early sex differences need to be carefully considered. It might be conjectured that females are more likely to have depressive symptoms, a history of physical or sexual abuse, and substance abuse[39–41] and are more likely to develop metabolic or endocrine sequelae, perhaps related to early-onset obesity,[44] when exposed to psychotropic medications that exacerbate the preexisting conditions.[45] Males, on the other hand, are more likely to have early neurologic conditions (organic brain disorders/mental retardation) and/or ADHD and to receive early treatment with stimulant medications[41] and are more likely to develop cardiovascular conditions, including hypertension,[44] and neurologic adverse events when exposed to additional psychotropic medications that exacerbate the preexisting conditions.[44] The question of whether early psychotropic medication use predicts the onset and/or exacerbation of these cardio-metabolic conditions would be interesting to examine.

Furthermore, our finding that recurrent depressive episodes were more likely for those with preexisting endocrine disorders and substance abuse is generally consistent with previous investigations which found that metabolic/endocrine disorders (eg, obesity, overweight, type 2 diabetes mellitus, dyslipidemia, and thyroid disorders) are more likely to co-occur in those with BD[11–26] and to be associated with a multiepisode course, depression severity, and substance abuse.[27–30]

Finally, various investigators have hypothesized that the neurobiology of BD most likely overlaps with the causative factors for some medical comorbidities.[2] More specifically, alterations in interacting metabolic, inflammatory, and oxidative systems appear likely to contribute to the cumulative "organ damage," eg, allostatic load, observed in adult patients with BD.[46–48] Hypothalamic-pituitary-adrenal signaling disturbance with resultant chronic hypercortisolemia is a critical mediator of the allostatic load reported in mood disorders.[2,45–47] Although we cannot confirm associations between the early development of specific medical conditions and a more severe course of early-onset BD, we can speculate that for almost half of these children (45.9%), being treated for 2 or more chronic medical conditions in addition to BD and the adverse events associated with early treatment with a range of psychotropic agents as adolescents contribute to their cumulative allostatic load and potential for further organ damage in adulthood.

The perspective provided by this longitudinal database has several strengths: (1) the BD cohort and the control sample represent a large, heterogeneous group of children and adolescents; (2) the long-term observational study of a large pediatric bipolar cohort provides additional information regarding important clinical correlates and their impact on pediatric patients with BD; (3) there is sufficient power in the treated cohort and control sample sizes to detect somewhat low-incidence medical conditions; and (4) previous studies have found that although Medicaid databases provide much less detailed information on individuals than a structured research interview, the physician diagnoses and utilization data are more reliable than client or family self-reports, and the administrative data correspond to clinical medical records reviews in 75%–95% of the cases examined.[48–51] However, these results also need to be interpreted with several limitations in mind: (1) the data were not gathered using a prospective, controlled design; (2) structured research and clinical interviews were not employed to confirm any of the assigned medical disorders or clinical features; (3) important clinical features as determined using the diagnostic codes (ie, mixed mood states, rapid cycling, and severity) were not available in the administrative data set for further analysis or should be considered highly tenuous indicators; (4) these results report associations and, as a result, directions of causality cannot be inferred; (5) key risk factors such as family history of obesity, metabolic disorders, and cardiovascular disorders were not available in the database and are not modeled in these analyses; (6) there is no way to estimate how representative this Medicaid cohort is in relation to those in other states and service systems; and (7) children and adolescents who dropped out of treatment or were periodically ineligible for Medicaid coverage are not represented in this data set, and their outcomes may differ from those patients who remained over time.

Comorbid obesity, hypertension, migraine, mental retardation, asthma, endocrine disorders, or substance abuse present during early adolescence does not appear to worsen the severity of BD or its course of illness/recovery over time, using the indicators available in this data set. Furthermore, these results suggest separate subpopulations of the disorder, eg, using the sex differences apparent in the early development of comorbid obesity, endocrine, and neuropsychiatric disorders, which might lead to the further development of related metabolic or cardiovascular problems/adverse events when exposed to psychotropic medications during treatment. Prospective, controlled clinical trials or large-scale observational studies[52] encompassing a more heterogeneous patient population with BD and comorbid medical conditions are needed to elaborate on these findings. Nevertheless, we hypothesize that these comorbid conditions probably increase the "allostatic load" and potential for continued organ damage experienced by these individuals as they mature, inviting the need for their treatment providers to carefully screen and provide opportunistic surveillance for comorbidity, especially medical comorbidity, in the BD population.

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***Potential conflicts of interest:*** **Dr McIntyre** has received research/funding support from Stanley Medical Research Institute, National Alliance for Research on Schizophrenia and Depression, Eli Lilly, Merck, Servier, and Wyeth; is on the speakers/advisory boards for AstraZeneca, Bristol-Myers

Squibb, France Foundation, GlaxoSmithKline, Ortho-McNeil-Janssen, Solvay/Wyeth, Eli Lilly, Organon, Lundbeck, Biovail, Pfizer, Shire, Oryx, and Prestwick; and has participated in CME activities for AstraZeneca, Bristol-Myers Squibb, France Foundation, I3CME, Solvay/Wyeth, and Physicians Postgraduate Press. **Drs Jerrell** and **Tripathi** have no personal affiliations or financial relationships with any commercial interest to disclose relative to the article.

***Funding/support:*** Data analysis was supported by a State Mental Health Data Infrastructure Grant (SAMHSA SM54192) and the Department of Medicine, University of South Carolina School of Medicine.

***Disclaimer:*** The views expressed do not necessarily represent those of the funding agency or official findings of the South Carolina Department of Health and Human Services (Medicaid).

***Previous presentation:*** This research was presented in poster form at the 8th International Conference on Bipolar Disorder; June 25–27, 2009; Pittsburgh, Pennsylvania.

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