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Anxiety Disorders and Rapid Cycling Data From a Cohort of 8129 Youths With Bipolar Disorder

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Abstract

Anxiety disorders (ADs) are common in youths with bipolar disorder (BD). We examine psychiatric comorbidity, hospitalization, and treatment in youths with versus without AD and rapid cycling (four or more cycles per year). Data from the Integrated Healthcare Information Services cohort were used and included 8129 youths (ages 1–18 years). Prevalence of AD, demographic, type of AD, hospitalization, and use of psychotropics were compared between rapid and nonrapid cycling. Overall, 51% of the youths met criteria for at least one comorbid AD; they were predominantly female and were between 12 and 17 years of age. The most common comorbid ADs were generalized ADs and separation ADs. In the patients with rapid cycling, 65.5% met criteria for comorbid AD. The BD youths with AD were more likely to have major depressive disorders and other comorbid ADs, to be given more psychotropics, and to be hospitalized for depression and medical conditions more often than were those without AD.

Keywords

Anxiety disorders; bipolar disorder; children and adolescents; comorbidity; rapid cycling

Despite the growing controversy about the presence of bipolar disorder (BD) among youths, the literature emphasizes that these patients are among the most psychosocially impaired because of the complexity of the clinical presentation and high comorbidities (Sala et al., 2012). Youths with BD have higher rates of mixed and rapid cycling presentations,

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DISCLOSURES

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substance abuse, suicidal behavior, and legal and social problems (Coryell et al., 2003; Geller et al., 2004). Some of the most common comorbid disorder conditions in youths with BD are anxiety disorder (AD), attention deficit hyperactivity disorders (ADHDs), disruptive behavior disorders, and pervasive developmental disorders. The presence of AD is frequently encountered. The association, however, of rapid cycling and mixed states remains insufficiently studied (Goldstein and Birmaher, 2012).

Prior research indicates that the presence of comorbid AD negatively affects course and treatment response in BD (DeBello et al., 2007). This comorbidity not only impairs the child's psychosocial development but also places him/her at risk for completed suicide, substance abuse, and legal problems (Axelson et al., 2006; Sala et al., 2009). There is a growing interest in studying rapid cycling in youths and in adults with comorbid AD (Findling et al., 2001). Rapid cycling has been identified as a common phenomenon among individuals with bipolar spectrum disorders who present with the symptoms before the age of 17 years (Coryell et al., 2003). As predicted by Geller et al. (2004), because of the high rate of switching from depression to bipolar spectrum in children, a complex presentation of rapid cycling episodes is expected. These episodes are usually accompanied by comorbidities such as ADHD, conduct disorder (CD), generalized AD (GAD), panic disorder (PD), and obsessive-compulsive disorder (OCD; Geller et al., 1998). There have been consistent reports that AD in youths with BD tend to persist over time and continue into adulthood (Dilsaver et al., 2008). A large study (>50,000 patients) found that the presence of rapid cycling has been associated with a younger age of onset, more depressive episodes, more unspecific hypomanic symptoms, considerable impairment, and increased prevalence of AD (Lee et al., 2010). Moreover, bipolarity is often presented in mixed depression, hypomanic symptoms, and dysphoria, those also encountered in patients with rapid-cycling forms of their mood disorder diathesis (Dilsaver and Akiskal, 2009; Staton et al., 2008).

Because of the complex clinical presentation of a rapid cycling phenomenon and its comorbidities among youths with BD, it is imperative to expand the existing literature in this area. Findling et al. (2001) reported 90 youths aged 5 to 17 years meeting full criteria for bipolar I disorder (BD-I). Among this sample, 50% had high rates of rapid cycling and close to 15% were diagnosed with at least one AD (Findling et al., 2001). The authors reported the importance of further study in the presentation of rapid cycling and comorbidities, especially AD, because this last condition seems to be associated with severe forms of mood lability.

The prevalence of AD in children and adults with BDs has been well identified; however, the prevalence of AD in patients with rapid cycling and mixed states remains insufficiently studied (Carballo et al., 2011). To our knowledge, this is the first epidemiological study to compare the association of AD in a cohort of youths with and without rapid cycles. On the basis of the abovementioned rationale, our objective was to demonstrate that youths with comorbid AD (BD/AD and BD rapid cycles/AD) will have a) more hospitalizations and readmissions, b) increased use of prescribed psychotropic medications, and c) higher rates of other disabling psychiatric disorders compared with youths without AD (BD/ without AD and BD rapid cycles/without AD).

METHODS

The complete description of patients and methods has been published in detail elsewhere (Castilla-Puentes, 2008). For a brief description, the Integrated Healthcare Information Services (IHCIS) is a fully de-identified, Health Insurance Portability and Accountability Act-compliant database that includes complete medical history for more than 30 million managed care participants, with the mean follow-up time for these members being approximately 1.4 years. It includes data from more than 35 health plans covering eight census regions and complete patient demographics. In addition, this database has complete mental health data description of the participants. The use of claims databases has been documented as an alternative to expensive and labor-intensive randomized controlled trials as well as a valid information source (Blumentals et al., 2004; Gomez-Camirero et al., 2005; Motheral and Fairman, 1997). To identify disease diagnosis, the Thomson Medstat Disease Staging coding criteria were used (Thomson Medstat, 2003). The Thomson Medstat method is a proprietary coding criteria based on electronic screening and identification of a comprehensive map of ICD-9-CM diagnosis codes. This method is one of four systems selected for dissemination with the Healthcare Cost and Utilization Project Nationwide Inpatient Sample and has been widely used as a classification system for diagnostic categories (Thomson Medstat, 2003).

The study population consisted of patients from the IHCIS who met criteria for BD based on the ICD-9 (296.1, 296.4, 296.5, 296.6, 296.7, 296.8, 296.80, 296.81, 296.82, 296.89, 296.90, 296.90, 296.99, 301.1, 301.10, 301.11, and 301.13). The classification and description of subgroups according to the diagnosis and code are presented in Table 1. To be included in this study, the youths had to be 18 years or younger; have at least one BD diagnosis identified as being recorded during the period of June 30, 2000, to July 1, 2003; and be considered “active” in the IHCIS database for at least 6 months before and 2 years after their first diagnosis of BD. Patients diagnosed with schizophrenia or schizoaffective disorder were excluded for this study. In addition, only patients with full mental health and pharmacy benefits were included. For pharmacological treatments, pharmacy data were analyzed using the National Drug Codes. Considering that rapid cycling has been identified as a marker for BD recurrence, hospitalization, and resistance to conventional drug treatments (Calabrese et al., 2000; Romansky et al., 2003), we examined the number of hospital admissions with primary affective disorder (per year) as one of the outcome variables. The youths with four or more reports of inpatient treatment of any affective disorder per year were considered as rapid cyclers (defined as four or more cycles per year). The patients with three or fewer records of hospitalization for an affective disorder were included in the nonrapid cyclers group.

Comorbid AD was defined by the presence of at least one of the following diagnoses: separation AD (SAD), 309.21; GAD, 300.02; posttraumatic stress disorder (PTSD), 309.81; OCD, 300.30; social phobia (SP), 300.23; PD, 300.01; panic attack, 300.21; agoraphobia PD, 300.22; agoraphobia mention panic attacks; and AD not otherwise specified (NOS; 300.00; anxiety state unspecified, 300.09; anxiety states; Table 1). Prevalence of comorbid AD was evaluated in the cohort of youths with BD. In addition, demographic, type of AD, hospitalization history, and use of psychotropic medications were compared between the

rapid- and nonrapid-cycling youths diagnosed with BD. In this publication, and if NOS, the terms *youths*, *children*, and *adolescents* were used to describe subjects younger than 18 years, and rapid cycles are described in a 1-year period.

Statistical Analyses

For categorical variables, we used the chi-square or the Fisher's exact test for comparison between groups (BD/AD versus BD/without AD and BD rapid cycles/AD versus BD rapid cycles/without AD). For continuous variables with normal distribution, we used a two-sample *t*-test for comparison between groups. Where assumptions of normality were not adequately met, differences between groups were tested using the Mann-Whitney's *U*-test. Statistical significance was defined as a probability value of less than 0.05. Two stepwise logistic regression models were then used to identify factors associated with anxiety in BD and factors associated with anxiety in a subgroup of patients with rapid cycles. Those variables associated with AD on univariate analyses with a *p*-value of at least 0.2 or less were entered into the models as independent variables. Odds ratios (ORs) with 95% confidence intervals were used for observed associations. Analyses were conducted using the Statistical Package for the Social Sciences version 18.0.

RESULTS

Overall, 51% (4158/8129) of the youths met criteria for at least one comorbid AD, and 54.6% were females. The mean $\pm$ SD age was 14.8 ± 3.1 years, ranging from 6 to 18 years, and more than 80% of the youths with BD were between 12 and 18 years of age. The most common comorbid ADs were GAD and SAD, followed by OCD, SP, PTSD, PD with and without agoraphobia, and AD NOS. Twenty-two percent of the subjects (915/4158) had more than one AD, and 3.5% ($n = 146$) met criteria for three or more ADs.

As shown in Table 2, the BD/AD youths compared with the BD/without AD youths had significantly higher comorbid major depressive disorder (MDD), greater psychosis, higher comorbid CD/oppositional defiant disorder (ODD), and greater ADHD (all *p*'s < 0.0001). Having OCD did not show any significant difference between BD/AD and BD/without AD. In addition, compared with those with BD/without AD, those with BD/AD also had a significantly higher rate of hospital admission for BD, hospitalization of any nature; depression; and other psychiatric and medical conditions (all at a significance level of *p* < 0.0001). Moreover, the BD/AD patients were more likely than the BD/without AD patients to be prescribed mood stabilizers, antidepressants, and antipsychotics (all *p*'s = 0.005). However, the use of stimulants did not differ between the two groups (Table 2).

Logistic regression analysis was used to identify predictors of AD comorbidity in the BD youths. Hospitalizations, mainly for depression, were highly associated with the presence of AD in those with BD. AD in those with BD was also positively related to use of antidepressants, mood stabilizers, and antipsychotics and the presence of MDD, CD/ODD, and ADHD after controlling for demographic variables age and sex, with ORs in the range of 1.16 to 26.93 (all *p*'s $\leq$ 0.0004; Table 3).

As shown in Table 4, comparing the BD subtypes and the presence of any AD was significant ($\chi^2 = 10.051$, $p = 0.0015$) for all subtypes of BD. The main differences were by the bipolar II disorder (BD-II) subtype. Likewise, in the youths with rapid cycling, 65.5% met criteria for at least one comorbid AD. The most common comorbid AD in this subgroup included GAD and SAD, followed by OCD, PTSD, SP, PD, and AD NOS (Table 5). Thirty percent of the youths had more than one AD, and 10% met criteria for three or more ADs. In comparison with the BD rapid cycles/without AD group, those with BD rapid cycles/AD were more likely to be prescribed mood stabilizers, antidepressants, and antipsychotics (all p 's < 0.0001). As in the BD without rapid cycles, the use of stimulants did not differ between the two groups. Compared with those without AD, the BD rapid cycles/AD youths also had a higher rate of hospital admission for BD, hospitalization of any nature, depression, and other psychiatric and medical conditions (all p 's < 0.0001 ; Table 5).

In the logistic regression analysis of the youths with rapid cycles, comorbid AD was positively related to persistence of MDD, GAD, PD, and SAD. Similarly, AD was associated with at least one hospitalization for depression and for any medical conditions (ORs in the range 2.25–49.2; all p 's < 0.001 ; Table 6).

DISCUSSION

Our results add an important contribution to the growing literature on how frequently comorbid AD is found in youths with BD. To our knowledge, this is the first epidemiological study looking at comorbid AD among rapid-cycling youths with BD. The numerous patients under study enabled even relatively rare conditions to be detected with statistical significance. On the basis of our results, youths with comorbid AD (BD/AD) tend to have other psychiatric comorbidities, and close to 50% were hospitalized for other associated psychiatric conditions, and close to 25% were hospitalized for a comorbid medical condition. Our findings are consistent with those of other reports in which female patients have a higher rate of comorbid AD and bipolar spectrum disorders (Cosoff and Hafner, 1998; Frank et al., 2002).

These results also add to the existing literature the importance of closely evaluating youths presenting with ADs and mood lability in nonpsychiatric settings. Clinicians seeing these patients in busy practices in community settings are left with the dilemma of which psychotropics are appropriate to address the constellation of disabling mood and anxiety symptoms. As shown in our results, close to 80% of the youths with comorbid AD and rapid-cycling BD were prescribed an antidepressant. Issues of antidepressant-induced mania or associated dysphoria are important factors to consider when choosing a pharmacological treatment for these patients. This is an important consideration because antidepressants are the treatment of choice for AD. Moreover, studies have shown that close to 25% of patients with BD will develop more than one AD throughout the course of their condition (Sala et al., 2012).

Another important factor is the high prevalence of associated hospitalizations for other medical conditions encountered in our sample. After adjusting for multiple comparisons, the youths with BD and comorbid AD had more hospitalizations for medical conditions than of

those without AD, which is the case in adult studies (Goldstein et al., 2009). It has been well established that anxious youths experience somatic complaints and tend to consult primary care physicians or pediatricians before mental health clinicians (Bell-Dolan, 1993; Sareen et al., 2005). Therefore, it is important to educate these providers about the possibility that BD youths may also have AD. Mood and ADs are known risk factors of the development of metabolic conditions and cardiovascular disease (Vnitr Lek, 2009). In addition, patients with bipolar spectrum disorders tend to be obese and at risk for developing diabetes and other metabolic disorders (Regenold et al., 2002). In addition, patients with comorbid mood and AD are prone to develop more severe medical conditions (Ball et al., 2002). Our results provide an indirect evidence for the hypothesis suggesting that anxiety and depressive disorders are linked to higher cardiometabolic risk, higher incidence of acute cardiovascular events, and poorer prognosis for cardiac patients, and they are comorbid to a range of other chronic internal diseases. The association between cardiovascular disease, diabetes, and BD is bilateral, that is, patients with anxiety and BD experience cardiovascular events more frequently, and patients with type 2 diabetes and cardiometabolic diseases more frequently experience AD. In clinical practice, we should search for patients with AD. At present, the patients with comorbid AD should be considered in the primary disease prevention as patients at high risk for atherosclerotic vascular diseases as well as metabolic disorders and type 2 diabetes. Treatment of these diseases as part of secondary prevention in patients with anxiety and BD must be more rigorous and intensive than in patients without these psychiatric disorders (Pistorio et al., 2011).

Interestingly, we have found that youths with BD/AD did not show significantly more use of stimulants. Although to our knowledge, there are no previous studies evaluating the effect of AD among youths with rapid cycling, this finding is consistent with Levin (2005), who reported that treating children and adolescents who have both BD and ADHD with a mood stabilizer first, then adding a stimulant, proved safe and effective. As such, this study also added insight into the nature and the diagnosis of these illnesses when these are comorbid. Thus, systematic evaluation of youths with BD/AD and stimulant use is warranted because these youths may be at high risk to develop rapid cycles.

Our study has some limitations, and the results have to be interpreted with caution. Although the prospective cohort design has unique advantages, the use of a large administrative database does have some limitations. One limitation would be that the IHCIS database represents patients who have sought treatment of BD, and this often includes more severe cases. Although patients with a diagnosis of schizophrenia were excluded from this study, there may have been patients with undetected comorbidities or underlying disease. However, we are not aware of any evidence that can confirm this occurrence. Because of the fact that claims were used to define the diagnosis and treatments, the potential for misclassification bias exists, and compliance with the drug treatment cannot be established. However, misclassifications or flawed diagnoses are randomly distributed among the two groups and, in this way, do not give rise to differential bias. This is a secondary analysis of a claims database. Although a major strength is the sample size, the results might not be generalized to other populations. Ethnic and socioeconomic differences should be taken into account because the presentation of these disorders could vary among groups. Despite the limitations, the results of this study add an important contribution to the literature on how

common, disabling, and difficult to treat BD with comorbid mood and AD is, especially in youths.

More studies are needed to include mood and AD seen within a dimensional approach to examine the adequate treatment approach, level of disability, and existing comorbid medical conditions. With the new version of the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*, the dimensional approach will be highly useful to early identify youths with mood lability, rapid cycling, and comorbid AD (American Psychiatric Association, 2012; First, 2002).

CONCLUSIONS

In summary, in youths with BD with and without rapid cycles, comorbid ADs are very common. Conditions such as AD and other medical comorbidities often occur along with BD, making management of the illness more difficult. Given the treatment implications of these findings, early identification and accurate diagnosis for these youths are very important. Taking into account that a) the presence of AD in patients with BD tends to amplify or intensify core bipolar symptoms or to aggravate other comorbid conditions and b) that the course of the illness and response to treatment are also adversely affected, early identification of comorbid AD and mood diathesis in youths could help to improve the course of this disorder into adulthood.

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TABLE 1

BD and ADs Classification According to ICD-9 Code and Description

Condition	Code	ICD 9 Description
BDs	296.00, 296.01, 296.02	BD-I, single manic episode (unspecified, mild, moderate)
	296.03, 296.04	BD-I, single manic episode, severe (without mention of psychotic behavior, specified as with psychotic behavior)
	296.05, 296.06	BD-I, single manic episode (in partial or unspecified remission, in full remission)
	296.10, 296.11, 296.12, 296.13, 296.14, 296.15, 296.16	Manic affective disorder recurrent episode (unspecified, mild, moderate, severe without psychotic behavior, severe specified as with psychotic behavior, in partial or unspecified remission, in full remission)
	296.40, 296.41, 296.42, 296.43, 296.44, 296.45, 296.46, 296.50, 296.51, 296.52, 296.53, 296.54, 296.55, 296.56, 296.60, 296.61, 296.62, 296.63, 296.64, 296.65, 296.66, 296.70	BD-I, most recent episode (or current) manic, unspecified, mild, moderate, severe, without mention of psychotic behavior, severe, specified as with psychotic behavior, in partial or unspecified remission, in full remission, depressed, unspecified, depressed mild, depressed, moderate, depressed, severe, without mention of psychotic behavior, depressed, severe, specified as with psychotic behavior, depressed, in partial or unspecified remission, depressed, in full remission, mixed, unspecified, mixed, mild, mixed, moderate, mixed, severe, without mention of psychotic behavior, mixed, severe, specified as with psychotic behavior, mixed, in partial or unspecified remission, mixed, in full remission, BD, unspecified
	296.80	BD, unspecified
	296.81	Atypical manic disorder
	296.89	Other and unspecified BDs, other
	300.00	Anxiety state, unspecified ^a
	300.09	Anxiety states ^a
	300.01	Panic disorder, no agoraphobia ^b
	300.02	GAD
	300.20	Phobic disorders
ADs	300.21	Agoraphobia with PD ^b
	300.22	Agoraphobia with panic attacks ^b
	300.23	SP
	300.30	OCD
	309.20	SAD
	309.81	PTSD

^aCodes for anxiety NOS.^bCodes for PD.

TABLE 2

Demographic Factors, Psychotropic Use, Hospitalizations, and Psychiatric Comorbidity Associated With Anxiety Versus Nonanxiety in the youths With BD

	BD/AD (<i>n</i> = 4158), 51.2%	BD/without AD (<i>n</i> = 3971), 48.8%	Statistics^a	<i>p</i>
Demographics				
Sex (female), %	54.6	52.3	4.22	0.0398
Age, %, yrs				
0–11	16.9	30.4	205.19	<0.0001
12–17	65.9	57.4	61.77	<0.0001
18	17.2	12.2	39.97	<0.0001
Psychotropic of all Rx, %				
Mood stabilizers	71.4	40.3	796.86	<0.0001
Antidepressants	59.3	39.2	327.47	<0.0001
Antipsychotics	49.7	45.8	12.22	0.0005
Stimulants	44.1	43.0	0.955	0.3283
Hospitalizations, ^b %				
BD	25.3	19.2	41.89	<0.0001
Any nature ^c	54.2	30.7	457.44	<0.0001
Depression	32.9	1.8	1346.04	<0.0001
Medical conditions	12.3	3.9	189.34	<0.0001
Other psychiatric conditions	32.2	11.2	521.77	<0.0001
Psychiatry comorbidity, %				
MDD	53.3	32.9	343.40	<0.0001
Psychosis	44.4	25.3	311.94	<0.0001
CD/ODD	25.2	17.6	69.09	<0.0001
OCD	11.4	11.1	0.15	0.6945
ADHD	60.9	49.4	108.19	<0.0001

^a Chi-square or Fisher's exact test.

^b At least one hospitalization for each category.

^c Hospitalization for either medical or psychiatric conditions.

TABLE 3

Logistic Regression of the Variables Associated With BD/Anxiety Versus BD/No Anxiety in the Youths With BD

Variable	OR	95% CI	Wald	<i>p</i>
Hospitalization for depression	26.93	21.11–34.35	26.51	<0.0001
Hospitalization for other psychiatric conditions	3.76	3.34–4.23	21.99	<0.0001
At least one hospitalization for medical conditions	3.44	2.86–4.15	13.09	<0.0001
At least one hospitalization of any nature	2.67	2.44–2.92	21.18	<0.0001
Use of antidepressants	2.26	2.06–2.47	18.00	<0.0001
Use of mood stabilizers	2.21	2.03–2.40	18.26	<0.0001
Psychosis	2.35	2.14–2.59	17.85	<0.0001
MDD	2.32	2.12–2.54	18.40	<0.0001
CD/ODD	1.58	1.41–1.76	8.30	<0.0001
ADHD	1.59	1.46–1.74	10.40	<0.0001
Hospitalization for BD	1.43	1.28–1.58	6.59	<0.0001
Use of antipsychotics	1.16	1.07–1.27	3.55	0.0004

CI indicates confidence interval.

TABLE 4

Frequencies of BD Subtype, Comorbid With AD, in the Patients With and Without Rapid Cycles

BD Subtype	BD Rapid Cycles (<i>n</i> = 58)		BD Without Rapid Cycling (<i>n</i> = 8071)	
	AD (<i>n</i> = 38), 65.5%	Without AD (<i>n</i> = 20), 34.5%	AD (<i>n</i> = 4120), 51.0%	Without AD (<i>n</i> = 3951), 49%
BD-I, <i>n</i> (%)	22/34 (64.7)	14/34 (41.2)	1921/4681 (41.0)	2758/4681 (58.9)
BD-II, <i>n</i> (%)	3/4 (75.0)	1/4 (25.0)	447/646 (69.2)	199/646 (30.1)
BD-NOS, <i>n</i> (%)	13/20 (65.0)	5/20 (25.0)	1752/2744 (63.8)	994/2744 (36.3)

Overall test for independence: $\chi^2(df = 1) = 10.051, p = 0.0015$.

NOS indicates nos.

TABLE 5

Prevalence of Psychiatry Comorbidity and Hospitalizations in the Bipolar Youths With Versus Without Rapid Cycles

	ADs (<i>n</i> = 4158)			
	BD Rapid Cycles/AD (<i>n</i> = 38)	BD Rapid Cycles/Without AD (<i>n</i> = 4120)	Wald's χ^2 Statistic	<i>p</i>
Psychiatry comorbidity, %				
MDD	53.3%	32.9%	343.40	<0.0001
Psychosis	44.4%	25.3%	311.94	<0.0001
CD/ODD	25.2%	17.6%	69.09	<0.0001
ADHD	60.9%	49.4%	108.19	<0.0001
GAD	54.6%	23.3%	18.76	<0.0001
SAD	44.5%	14.8%	23.67	<0.0001
OCD	11.4%	11.1%	0.15	<i>p</i> = 0.6945
PTSD	9.0%	6.2%	0.14	<i>p</i> = 0.7085
PD	8.8%	2.0%	5.58	<i>p</i> = 0.0181
SP	8.5%	2.1%	4.58	<i>p</i> = 0.0322
AD NOS	6.8%	1.5%	3.89	<i>p</i> = 0.0484
Hospitalizations, ^{<i>a</i>} %				
BD	100% ^{<i>a</i>}	22.2%	124.671	<0.0001
Any nature	100% ^{<i>a</i>}	30.7%	80.855	<0.0001
Depression	48.1%	1.8%	350.332	<0.0001
Medical conditions	32.4%	3.9 %	69.720	<0.0001
Other psychiatric conditions	22.3%	8.2%	8.045	<i>p</i> = 0.0046

^a Inclusion criteria for rapid cycling.

TABLE 6

Logistic Regression of the Variables Associated With Rapid Cycles/Anxiety Versus Nonrapid Cycles/Anxiety in Children and Adolescents

Variable	OR	95% CI	Wald	<i>p</i>
Hospitalization for depression	49.20	25.00–96.84	11.2	<0.0001
Hospitalization for medical conditions	11.42	5.66–23.05	6.80	<0.0001
ADs NOS	5.61	1.68–18.72	2.80	0.0050
GAD	4.65	2.44–8.88	4.67	<0.0001
PD	4.22	1.27–14.00	2.35	0.0185
SAD	4.06	2.13–7.73	4.27	<0.0001
Use of mood stabilizers	3.69	3.35–4.05	7.72	<0.0001
MDD	2.26	1.19–4.29	2.50	0.0123
Use of antidepressants	2.25	2.06–2.46	7.98	<0.0001

CI indicates confidence interval.