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**A COHORT STUDY OF THE PREVALENCE AND IMPACT OF COMORBID
MEDICAL CONDITIONS IN PEDIATRIC BIPOLAR DISORDER**

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Pediatric bipolar disorder (BP) is a relatively virulent phenotype that is associated with mixed mood states, rapid cycling, substance abuse, adverse psychosocial adjustment, childhood abuse, and high rates of attempted suicide. In the present study, the authors attempted to identify the association (if any) between medical or psychiatric comorbidities, clinical characteristics, and course of illness/recovery in pediatric BD.

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 in a cohort of 1,841 children and adolescents diagnosed with BD (according to DSM-IV-TR criteria) and in a random sample of 4,500 children not treated for any psychiatric disorder (control group). Primary outcome measures were diagnostic codes and regression analyses of patterns of acute and outpatient treatment services for BD over time. 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. In terms of clinical characteristics within the BD cohort, an adolescent-onset diagnosis of BD (age ≥ 13 years) was significantly associated with a diagnosis of preexisting obesity, hypertension, migraine, mental retardation, endocrine disorders, and substance abuse, 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 made an impact on the course of illness or recovery in the BD cohort.

According to the authors, the current data indicate that while some neuropsychiatric and medical disorders temporally precede the diagnosis of early-onset BD in pediatric patients and are associated with discrete facets of illness presentation, they do not substantially alter the clinical course of BD over time. (52 References)

EAF

**PSYCHIATRIC DISORDERS IN PRESCHOOL OFFSPRING OF
PARENTS WITH BIPOLAR DISORDER: THE PITTSBURGH
BIPOLAR OFFSPRING STUDY (BIOS)**

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AM J PSYCHIATRY, 167:321-30, March 2010**

The single largest risk factor for the development of bipolar disorder is a positive family history of the illness. Several risk studies of pediatric bipolar disorder have shown that offspring between the ages of 6 and 18 years whose parents are bipolar have an elevated risk of developing early-onset bipolar disorder as well as other psychiatric illnesses. In the present report, the authors evaluated the lifetime prevalence and specificity of DSM-IV psychiatric disorders and the severity of depressive and manic symptoms at intake in preschool offspring of parents with bipolar I and II disorders.

A total of 121 offspring (age range, 2 to 5 years) of 83 parents with bipolar disorder and 102 offspring of 65 demographically matched comparison parents (29 with non-bipolar psychiatric disorders and 36 without any lifetime psychopathology) were recruited for the study. The parents with bipolar disorder were recruited through advertisements and adult outpatient clinics; comparison parents were selected randomly from the community. The participants were evaluated by means of standardized instruments, and staff were blind to parental diagnoses. After adjusting for within-family correlations and both biological parents' non-bipolar psychopathology, the researchers found that offspring of parents with bipolar disorder (particularly those older than age 4) showed an eight-fold greater lifetime prevalence of attention deficit hyperactivity disorder (ADHD) and significantly higher rates of having two or more psychiatric disorders relative to the offspring of the comparison parents. Only three offspring of bipolar parents had mood disorders. However, the offspring of parents with bipolar disorder (especially those with ADHD and oppositional defiant disorder) had significantly more severe current manic and depressive symptoms than the offspring of comparison parents.

According to the authors, the present findings indicate that preschool offspring of parents with bipolar disorder have an elevated risk for ADHD and have higher levels of subthreshold manic and depressive symptoms than offspring of parents with non-bipolar psychiatric disorders or without any lifetime psychopathology. (71 References) EAF

**LONGITUDINAL COURSE OF BIPOLAR I DISORDER
Duration of Mood Episodes**

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ARCH GEN PSYCHIATRY, 67:339-47, April 2010**

Bipolar I disorder is usually characterized by recurrent mood episodes, with the risk of having additional episodes remaining relatively high for at least 40 years after illness onset. Because the phenomenology of bipolar I disorder affects treatment and prognosis, the authors of the present investigation attempted to describe the duration of bipolar I mood episodes and factors associated with recovery from these episodes by prospectively following 219 subjects with bipolar I disorder (97 males, 122 females) for up to 25 years.

The subjects (drawn from five academic medical centers (1) met Research Diagnostic Criteria for a major mood episode at the time of study enrollment, (2) were diagnosed at study intake or during follow-up as having either bipolar I disorder or schizoaffective disorder (mainly affective subtype), (3) recovered from the mood episode that was present at study intake, and (4) eventually had at least one recurrent mood episode. Level of psychopathology was assessed with the Longitudinal Interval Follow-up Evaluation every six months for the first five years of follow-up and annually thereafter. The probability of recovery over time from multiple successive mood episodes was examined by means of survival analytic techniques, including a mixed-effects grouped-time survival model. Of the 219 subjects, 196 (90%) were followed up for at least five years, 169 (77%) for at least 10 years, 144 (66%) for at least 15 years, and 122 (56%) for at least 20 years. A total of 1,208 mood episodes were observed during follow-up. The mean number of episodes per subject was 5.5. The probability of recovery was significantly less for those subjects whose mood episode had a severe onset (psychosis or severe psychosocial impairment in week 1 of the episode) and for subjects with greater cumulative morbidity (total number of years spent ill with any mood episode). Compared with the probability of recovery from a major depressive episode, there was a significantly greater probability of recovery from an episode of mania, hypomania, or minor depression, and conversely, a significantly reduced probability of recovery from a cycling episode (switching from one pole to the other without an intervening period of recovery).

The authors found that more than 75% of the subjects recovered from their mood episodes within one year of onset, with the median duration of bipolar I mood episodes being 13 weeks. (*42 References*)

EAF

ASSOCIATION OF SEASONALITY AND PREMENSTRUAL SYMPTOMS IN BIPOLAR I AND BIPOLAR II DISORDERS

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J AFFECT DISORD, 129:313-6, March 2011**

Seasonal affective disorder (SAD) and premenstrual syndrome (PMS) are cyclic forms of clinical conditions in which characteristic mood symptoms recur and remit in a rhythmic pattern. Although SAD and PMS are frequently seen in patients with mood disorders (including bipolar disorder), it is not known whether general traits for seasonality and premenstrual distress are related to bipolar disorder independently of its affective episodes. In the present study, the authors attempted to identify the prevalence of seasonality and PMS, independently of mood episodes, in female patients with bipolar disorder and to clarify whether an association exists between these two conditions.

The sample was composed of 61 female patients who met DSM-IV diagnostic criteria for bipolar I (N=30) or bipolar II (N=31) disorder and 122 age-matched healthy women with no history of psychiatric illness (controls). Lifetime histories of seasonality and premenstrual distress were assessed by means of the following self-report rating scales: the Seasonal Pattern Assessment Questionnaire (SPAQ) and the Premenstrual Symptoms Screening Tool (PSST). The sum of individual item scores (5-point scale) on the SPAQ yielded a global seasonality score. All items were measured retrospectively on the basis of premorbid traits, regardless of the disease state. The data indicated that the bipolar patients showed higher global seasonality scores on the SPAQ than the normal controls. Furthermore, this patient-control difference was more prominent in patients with bipolar II disorder than in those with bipolar I disorder. Results from the PSST revealed that the prevalence of moderate to severe PMS was significantly greater in the patients with bipolar II disorder (51.6%) than in the healthy controls (19.7%). A significant association between seasonality and PMS was observed in both patient and control groups.

According to the authors, the findings of the current investigation suggest that female patients with bipolar disorder experience seasonal and premenstrual changes in mood and behavior that are independent of their affective episodes. The data also indicate that traits of seasonality and PMS are associated with each other. A biological mechanism held in common by these two cyclic conditions may be involved in the development of the cyclic nature of bipolar disorder. (30 References)

EAF

RACIAL/ETHNIC GROUP DIFFERENCES IN BIPOLAR SYMPTOMATOLOGY IN A COMMUNITY SAMPLE OF PERSONS WITH BIPOLAR I DISORDER

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J NERV MENT DIS, 198:16-21, January 2010**

Research has found systematic racial and ethnic variations in the expression of psychopathology. For example, compared with whites, African Americans with bipolar disorder tend to present with more severe psychotic symptoms, particularly auditory hallucinations, persecutory delusions, and delusions of inference. To date, few studies have examined the extent to which symptoms differ between racial groups or whether racial/ethnic bias in diagnosis may be explained by differential presentation of bipolar disorder symptoms. To better understand the problems associated with the diagnosis of bipolar disorder, especially those related to race and ethnicity, the present authors compared whites, African Americans, and Latinos with bipolar I disorder in terms of the presentation of manic symptoms, depressive episodes, functional impairments (as measured by the 12-item Short-Form Health Survey [SF-12]), and self-reports of a schizophrenia diagnosis.

Data for the study were derived from the 2001-2002 National Epidemiologic Survey on Alcohol and Related Disorders, which included a community-based representative sample of over 43,000 adults in the United States. Approximately 3.6% of those surveyed met lifetime criteria for bipolar I disorder, with rates being comparable across racial/ethnic groups. Compared with whites, African Americans and Latinos expressed similar rates in the presentation of 14 out of 16 manic symptoms, with the exception of grandiosity/self-esteem, a symptom that they were more likely to exhibit than were whites. Higher rates of depressive episodes were observed among whites, and these episodes occurred significantly earlier than they did in African Americans and Latinos. Latinos had slightly higher vitality scores on the SF-12 measures after adjustments were made for sociodemographic and clinical factors, but no other differences across the groups were found.

According to the authors, the results gleaned from the current community-based sample indicate that the expressions and functional impairments of bipolar I disorder appear to be very similar across different racial/ethnic groups. These findings also suggest that provider biases are more likely to explain problems in misdiagnosis than are fundamental differences in the presentation of bipolar disorder across racial/ethnic groups. (32 References) EAF

**GENDER AND DEPRESSIVE SYMPTOMS IN 711 PATIENTS WITH
BIPOLAR DISORDER EVALUATED PROSPECTIVELY IN THE
STANLEY FOUNDATION BIPOLAR TREATMENT OUTCOME NETWORK**

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AM J PSYCHIATRY, 167:708-15, June 2010**

While men and women are equally likely to develop bipolar disorder over the course of their lifetime, gender differences have been identified in certain aspects of the illness, including risk for rapid cycling, mixed states, and age at onset. However, few reports have systematically and prospectively followed patients with bipolar disorder to evaluate time spent in episodes of depression, mania, or euthymia as a function of gender. In the present study, the authors assessed gender differences in terms of the proportion of clinical visits spent depressed, manic, or euthymic in patients with bipolar disorder.

Data were gathered from 711 patients (406 women, 305 men) who met criteria for bipolar I (N=572) or bipolar II (N=139) disorder and who made visits during which they were not actively participating in a clinical trial. They were followed prospectively over a period of seven years (13,191 visits). The main outcome measures were the presence of symptoms of depression or of mania or hypomania. Assessment tools were the Inventory of Depressive Symptomatology and the Young Mania Rating Scale. In approximately half of the visits, the patients had depressive, manic or hypomanic symptoms. The likelihood of having depressive symptoms was significantly greater in women than in men. This could be accounted for by the women's having higher rates of rapid cycling and anxiety disorders, each of which was associated with increased rates of depression. In the overall cohort, no gender differences were observed with regard to time spent in mania or hypomania. However, among patients with bipolar II disorder, men were significantly more likely than women to be hypomanic at any given visit. On average, the longer patients participated in the study, the less likely they were to be ill at a visit.

According to the authors, the current findings provide support for the notion that bipolar women spend a greater proportion of their time ill struggling with various degrees of depressive symptoms, whether they are in the depressive or manic phase of the disorder. The reasons for this, which may be biological (hormonal), psychosocial, or cultural, remain to be determined, the researchers conclude. (51 References)

EAF

**CHARACTERISTICS OF PATIENTS WITH BIPOLAR DISORDER
MANAGED IN VA PRIMARY CARE OR SPECIALTY
MENTAL HEALTH CARE SETTINGS**

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PSYCHIATR SERV, 61:500-7, May 2010**

Bipolar disorders (types I and II) are chronic illnesses that are associated with substantial functional impairment and economic loss. In the Department of Veterans Affairs (VA), over 60,000 individuals were diagnosed with bipolar disorder in fiscal year (FY) 2000; by FY 2006 that number had increased by 25%. Little is known about the extent to which patients with bipolar disorder rely on general medical (primary) care as opposed to mental health care. In the present study, the authors compared clinical characteristics, use of guideline-concordant pharmacotherapy, and outcomes in two groups of patients with bipolar disorder: those who were seen exclusively in VA primary care settings and those who received any VA mental health services.

Data from the 1999 Large Health Survey of Veterans were linked with VA data from the National Psychosis Registry to identify patients diagnosed as having bipolar disorder (N=14,643). Multivariate analyses adjusted for sociodemographic characteristics and clinical and severity factors and determined whether exclusive primary care use versus any mental health care use was associated with poor clinical and services outcomes. Of the 14,643 individuals diagnosed with bipolar disorder, 7.6% (N=1,120) used primary care (general medical) services exclusively. Compared with persons who used specialty mental health care services (N=13,523), those who used primary care exclusively were more likely to be diagnosed with cardiovascular disease or hypertension, less likely to receive guideline-concordant pharmacotherapy, more likely to have an inpatient medical visit, and less likely to have an inpatient psychiatric visit. Results of the 36-Item Short-Form Health Survey indicated that individuals who received primary care exclusively were more likely to have poorer physical health and better mental health.

The findings of the current investigation showed that among patients with bipolar disorder, those who were treated in primary care settings were more likely to have comorbid general medical disorders than those who received some care in a mental health specialty setting. Optimal treatment settings for patients with bipolar disorder may require strategies that address gaps in both general medical and psychiatric care. (39 References)

EAF

**TREATMENT DELAY AND EXCESSIVE SUBSTANCE USE
IN BIPOLAR DISORDER**

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J NERV MENT DIS, 198:628-33, September 2010**

Bipolar disorder (BD) is a severe mental illness that involves both significant personal suffering and functional loss. Despite this severity, however, a substantial proportion of persons with BD do not receive psychiatric treatment and of those who do, many experience long delays between illness onset and/or initiation of adequate treatment. There are some indications that the presence of substance abuse in BD patients may be associated with both shorter and longer treatment delays than in BD patients without a history of substance abuse. In the current study, the authors explored the ways in which differences in temporal sequencing of BD and substance abuse onsets may be related to delays in beginning adequate pharmacological treatment.

A total of 151 bipolar patients (91 with BD I and 60 with BD II) were recruited from inpatient and outpatient psychiatric units; 117 were categorized as having primary BD (no excessive substance use preceding the first affective episode) and 34, as having secondary BD (onset of first affective episode occurring after onset of excessive substance use). Logistic regression analyses were used to evaluate predictors of treatment delay in all patients as well as predictors of subsequent excessive substance use in patients with primary BD. The median treatment delay was two years; 79 patients had a short treatment delay (two years or less), and 72 had a long treatment delay (longer than two years). The risk of long treatment delays was increased in patients with BD II, in those with no lifetime history of psychosis, in those who were older at the time of first contact with specialized psychiatric services, in those with primary BD, and in those with excessive substance use. Among patients with primary BD, the risk of developing excessive substance use was increased in males, in those with lower levels of education, and in those with longer treatment delays. Patients with antecedent excessive substance use had a reduced risk for long treatment delays. The risk of developing excessive substance use after the onset of BD was found to increase with longer treatment delays.

According to the authors, the current data indicate that in BD, comorbid substance use is an important factor with regard to both diagnostic work and outcome prediction. (53 References) EAF

**COMPLEXITY OF PHARMACOLOGIC TREATMENT REQUIRED FOR
SUSTAINED IMPROVEMENT IN OUTPATIENTS WITH BIPOLAR DISORDER**

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J CLIN PSYCHIATRY, 71:1176-86, September 2010**

Several recent studies have pointed out the need for complex pharmacologic regimens in a large proportion of inpatients and outpatients with bipolar illness; however, the details of which drugs and combinations are successful (or not) in achieving relative long-term stability in a prospectively followed cohort have rarely been delineated. In the present investigation, conducted from 1996 to 2002, the authors evaluated the types and clinical correlates of naturalistic treatments associated with sustained improvement/remission for at least six months in a cohort of outpatients with bipolar disorder.

The sample was composed of 525 outpatients with bipolar disorder. All gave informed consent, recorded all medications taken, and had their mood rated daily by means of the National Institute of Mental Health Life Chart Method for at least one year. Demographics and clinical characteristics of patients with a “sustained response” (ratings of “improved” or “very much improved” on the Clinical Global Impressions-Bipolar Version for at least six months) were compared with those of treatment nonresponders. Of the 525 patients, 96 were minimally impaired or essentially well at study entry and remained so for at least six months. Of the remaining 429 patients who were ill at study entry, 195 (45.5%) showed a sustained response, and 234 (54.5%) showed either an insufficient response or no response. A mean of 2.98 drugs was given at the time of improvement (beginning of sustained response), which occurred after a mean of 18 months of study participation. Lithium and valproate were the drugs most frequently prescribed at the time of improvement and were among those with the highest overall success rates. Equally complex drug regimens were employed in the nonresponders who did, however, have a more adverse clinical course prior to study entry. The nonresponders ultimately were exposed to more antidepressants and antipsychotics than the sustained responders.

The authors conclude that during naturalistic treatment of outpatients with bipolar disorder, a mean duration of one and a half years and, at times, highly complex medication regimens were required to achieve a sustained response for at least six months. (*44 References*)

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EFFICACY AND SAFETY OF LONG-TERM FLUOXETINE VERSUS LITHIUM MONOTHERAPY OF BIPOLAR II DISORDER: A RANDOMIZED, DOUBLE-BLIND, PLACEBO-SUBSTITUTION STUDY

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The long-term use of antidepressant therapy for individuals with bipolar disorder has received relatively little attention. Although some practice guidelines have recommended the cautious use of antidepressants in bipolar depression, these guidelines differ widely with regard to the optimum duration of antidepressant therapy. The authors of the present investigation examined the safety and efficacy of long-term fluoxetine monotherapy, lithium monotherapy, and placebo therapy in preventing the relapse and recurrence of bipolar type II major depressive episodes. They hypothesized that fluoxetine monotherapy would be superior to lithium monotherapy and would have a similar hypomanic mood conversion rate.

Patients who met DSM-IV-TR criteria for bipolar II disorder, who were at least 18 years of age, and who had recovered from a major depressive episode during and initial course of open-label fluoxetine monotherapy were randomly assigned to receive 50 weeks of double-blind monotherapy with fluoxetine (10-40 mg/day), lithium (300-1200 mg/day), or placebo. The primary outcome measure was time to relapse or recurrence. Secondary outcome measures included the proportion of patients who remained well and the frequency of hypomanic symptoms. There were no significant differences in clinical or demographic characteristics among the fluoxetine (N=28), lithium (N=26), and placebo (N=27) groups. The mean time to relapse was 249.9 days for the fluoxetine group, 156.4 days for the lithium group, and 186.9 days for the placebo group. The Cox proportional hazards ratio for relapse was significantly lower with fluoxetine than with lithium, and the estimated hazard of relapse with lithium was 2.5 times greater than with fluoxetine. There were no statistically significant or clinically meaningful differences in hypomanic symptoms among the treatment groups over time. One patient taking fluoxetine and one patient taking placebo discontinued treatment because of hypomania.

According to the authors, the findings of the current study suggest that, in patients who have recovered from a bipolar II major depressive episode, fluoxetine monotherapy may provide superior relapse-prevention benefits relative to lithium monotherapy and may do so without an increase in hypomanic mood conversion episodes. (40 References) EAF