

# Toward an Understanding of Bipolar Disorder and Its Origin

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Bipolar disorder, a disease with significant morbidity and mortality, continues to present diagnostic and clinical challenges. Lifetime prevalence of bipolar I disorder has been estimated at 1.3%, with an equal distribution between males and females. Recognition of the illness may take years, but most patients are diagnosed before the age of 30. The role of genetic influences in bipolar disease is supported by family studies and high concordance rates among monozygotic twins. Current speculation proposes a likely interaction between genetic predisposition and environmental influences, including stressful life events. Diagnostic work-up should exclude mania secondary to drug use or general medical causes, particularly in patients whose symptoms begin after age 30 and in those with no family history of bipolar or unipolar disease. Patients with cyclothymia or thyroid dysfunction or postpartum women are at particular risk for bipolar disease. Substance abuse, which is extremely common among patients with bipolar disorder, interferes with diagnosis and can worsen the course of the disease. Alcohol dependence has been reported in approximately one third of those with bipolar I and one fifth of those with bipolar II disorder. To facilitate early diagnosis and effective management, clinicians should be aware of the risk factors, possible causes, and comorbidities of bipolar disease.

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Almost every aspect of bipolar disorder continues to be poorly understood. Scientists strive to identify molecular and biological factors in the pathogenesis of this illness, while clinicians struggle with diagnostic issues and appropriate management strategies. The following discussion will review current findings about the etiology of bipolar disorder, known risk factors, and common comorbidities that can complicate diagnosis and treatment.

## EPIDEMIOLOGY

It is particularly difficult to estimate the incidence of bipolar disorder because the disease generally becomes evident only over a period of years. It is not usually diagnosed at the time of a first episode.<sup>1</sup> Bipolar disorder can initially present with manic, depressive, or mixed symptoms. Mania is clearly the most reliable core feature of bipolar disorder, so it is not surprising that when patients first present with a major depressive episode, a possible diagnosis of bipolar disorder tends to be overlooked. These patients are

often diagnosed as having major depression until the first manic episode occurs, which might be years later.

For these reasons, incidence statistics on bipolar disorder must be based on retrospective data.<sup>1</sup> As a result, estimates of lifetime prevalence are often preferred over incidence rates for reporting frequency statistics.<sup>1</sup> Despite the difficulties in diagnosing bipolar disorder and the relative infrequency with which it occurs, reported prevalence figures appear to be fairly consistent.<sup>1</sup> Data gathered through the National Comorbidity Survey suggest a lifetime prevalence of manic episodes of 1.6%.<sup>2</sup> Estimates obtained from the Epidemiologic Catchment Area (ECA) surveys suggest an overall lifetime prevalence of bipolar disorder of 1.3%.<sup>1</sup> In a cross-national epidemiology study encompassing roughly 38,000 community subjects in 10 countries, lifetime rates of bipolar disorder (range, 0.3%–1.5%) were similar to those reported in U.S. surveys.<sup>3</sup> A more recent U.S. survey of 127,000 adults reports an overall prevalence of 3.7% for bipolar spectrum disorders.<sup>4</sup>

The overall occurrence rate of bipolar illness appears to be similar for men and women.<sup>3,5</sup> Some data suggest that women are more likely than men to be hospitalized during manic episodes and that rapid cycling occurs at a greater frequency in women than in men.<sup>5,6</sup> Bipolar disorder in female patients has also been associated with relatively predominant depressive, rather than manic, features.<sup>7</sup>

Although bipolar illness can develop at almost any age, the peak period of onset appears to be during adolescence, specifically between the ages of 15 and 19 years.<sup>1</sup> In the National Depressive and Manic-Depressive Association (DMDA) survey of members with bipolar disorder, 59% of respondents reported having experienced their first bipolar symptoms during childhood or adolescence.<sup>7</sup> Only 16% of

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patients reported an onset of bipolar symptoms at the age of 30 years or beyond.<sup>7</sup> It is possible, however, for bipolar disorder to manifest itself for the first time in later years. Yassa et al. reported new onset of mania in 9.3% of patients over the age of 60 with affective disorders.<sup>8</sup>

Bipolar disorder appears to have a similar clinical presentation regardless of age at onset, but etiology seems to be less genetically influenced in patients with later onset since positive family histories of bipolar illness are uncommon in these older patients.<sup>1</sup> Some research suggests a sex-related difference in the degree of genetic influence in older patients. In a study by Shulman and Post,<sup>9</sup> women diagnosed with bipolar disorder after the age of 50 were no more likely than younger patients to have a second medical diagnosis upon work-up. However, in new-onset bipolar cases in men of the same age, an underlying medical etiology was often present.

Prevalence of bipolar disorder appears similar across ethnicities, although the disorder may be underdiagnosed in African American and Hispanic populations. Patients in these ethnic groups who have bipolar disorder are at a significantly higher risk than Caucasians for an initial, incorrect diagnosis of schizophrenia, particularly if they are young and experience auditory hallucinations during the mood episodes.<sup>10,11</sup>

Bipolar disorder is associated with significant morbidity and mortality. The lifetime risk of death by suicide among patients with bipolar illness has been estimated to be approximately 19%, a rate comparable to the mortality rates for many types of heart disease and cancer.<sup>12</sup> Bipolar illness is well known to have negative ramifications on the patient's employment status and personal relationships.<sup>12</sup> Begley et al.<sup>13</sup> developed an economic model of lifetime cost of bipolar disorder in the United States for cases with an onset in 1998. The model estimated an average lifetime cost per case ranging from \$11,720 for patients with a single manic episode to \$624,785 in patients with non-responsive/chronic episodes. Cost calculations included direct medical expenditures, costs related to comorbidity treatment, and indirect costs related to reduced earnings and substance abuse.<sup>13</sup>

## ETIOLOGY

### Genetics

Family studies have confirmed that the presence of bipolar disorder is higher among relatives of bipolar probands than among relatives of individuals with no psychiatric illness.<sup>14</sup> While family studies are helpful in establishing a pattern of aggregation, the underlying association is still not necessarily genetic.

Twin studies provide valuable information regarding genetic versus nongenetic disease associations. Concordance rates for bipolar disorder have been estimated to be 57% for monozygotic twins and 14% for dizygotic twins, thereby

suggesting a significant genetic component to this disease.<sup>15</sup> The genetic theory is supported further by the finding that concordance rates for bipolar disorder among identical twins are similar regardless of whether the twins are raised together or separately.<sup>14</sup>

Data such as these confirm the importance of genetic factors in the expression of bipolar illness, but the less-than-100% concordance rate observed among monozygotic twins implies additional etiologic factors.<sup>14</sup> Many questions remain about the role of genetics in the development and transmission of bipolar disorder. As discussed elsewhere in this supplement,<sup>16</sup> some degree of genetic linkage has been found between bipolar disorder and schizophrenia. Cardno et al.<sup>17</sup> have observed a set of monozygotic triplets in which one had a chronic schizophrenic illness, one had a schizoaffective disorder, and one had bipolar disease. Findings such as this lend credence to a theory of susceptibility genes common to these diagnoses. Predisposing genetic vulnerability may set the stage for an individual to be pushed one way or another into expressing a particular psychiatric disorder.

### Perinatal Insult

Perinatal insult has been studied as a possible etiologic factor in the development of psychiatric disease, particularly schizophrenia. In fact, several studies have consistently implicated obstetric complications as a risk factor for schizophrenia, and such complications appear to be significantly more frequent in patients with schizophrenia than those with bipolar disorder.<sup>18,19</sup> Perinatal insult as a risk factor in bipolar disorder has been investigated to a far lesser extent.<sup>20</sup> Four studies<sup>18,21-23</sup> comparing bipolar cases with normal controls have assessed the association between prenatal and perinatal complications and bipolar disorder. Three of these studies indicated a positive association between prenatal and perinatal complications and adult bipolar disorder.<sup>21-23</sup> Schwarzkopf et al.<sup>18</sup> found a significantly higher frequency of perinatal insult in patients with bipolar disorder (8/10) who displayed considerable psychotic features than in those patients who did not. These data raise the question of whether perinatal insult is more linked to psychotic features than to affective features. This issue warrants further study.

### Genetic-Environmental Interaction

In the 1980s, a single gene responsible for the expression of bipolar disorder was thought to exist. This theory made it possible to consider the existence of a completely genetic variant of bipolar disease in some patients and a totally environmentally induced variant in other patients. Current opinion holds to the likelihood that bipolar disease is triggered by an interaction of genetics and environmental factors. There may be several susceptibility genes, leading to a gradient of liability.<sup>24-26</sup> Thus, even in late-onset cases, a minor genetic component may still play a role. Early-on-

set cases may simply have a heavier degree of genetic loading with a significantly lower threshold for environmental triggering. If this hypothesis holds true, individuals with a strong family history of bipolar disorder who sustain head trauma should be considered at higher risk of developing post-trauma bipolar disorder than a person with no family history, although not all studies support this.<sup>27,28</sup> Conversely, until complete genetic information on this disease is available, it remains unclear whether an environmental insult alone could induce expression of bipolar disorder in a patient with no apparent predisposing genetic susceptibility.

### Medical/Physiologic Factors

In some situations, an existing medical condition or intervention, or other physiologic factors, can trigger the expression of bipolar disorder. For example, in women the postpartum period is a time of particular risk for depression and other mood changes, including mania. Other reproductive system events, such as puberty, menstruation, pregnancy, or menopause, have not been well studied.<sup>6</sup> Mood changes should be carefully assessed during the postpartum period, especially in women with past personal or family histories of bipolar or other mood disorders.

## RISK FACTORS

### Medical

Disturbances in thyroid function have repeatedly been shown to be linked with bipolar disorder. Patients with bipolar disorder have been documented as having higher rates of positive anti-thyroid antibody titers compared with patients without this disease.<sup>29</sup> Studies have also found hypothyroidism to be a risk factor for rapid cycling.<sup>30,31</sup>

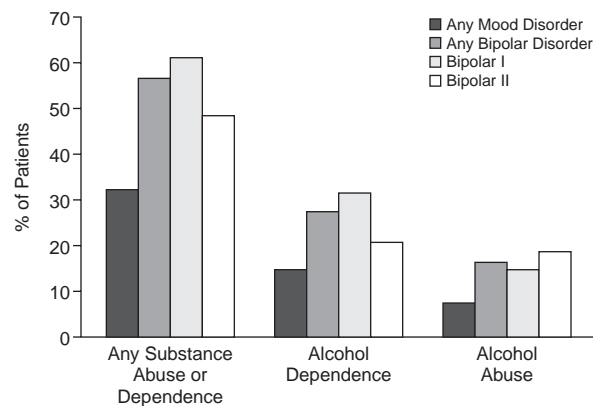
### Psychiatric

Cyclothymia is characterized by symptom patterns similar, but less severe, to those seen in full-blown bipolar disorder. A history of cyclothymic mood swings is reported in most patients with a bipolar diagnosis, and cyclothymia is commonly considered to be a precursor of bipolar I or II disorder. In a prospective study of cyclothymic patients, 35% developed full hypomanic, manic, or depressive episodes during a drug-free follow-up period of up to 3 years.<sup>32</sup> Cyclothymic patients should be monitored carefully for the emergence of these symptoms.

### Environmental/Social

Studies of the socioeconomic status of individuals with bipolar disorder and other mental illnesses often raise as many questions as they answer. Much uncertainty exists regarding causal relationships linking mental illness and social class. Several studies have suggested a higher rate of bipolar illness among individuals and/or families of relatively higher degrees of social advantage or achieve-

Figure 1. Rates of Substance Abuse and Dependence Among U.S. Patients With Any Mood Disorder or Bipolar Disorder<sup>a</sup>



<sup>a</sup>Data from Epidemiologic Catchment Area (ECA) Program Survey.<sup>42</sup>

ment.<sup>33-35</sup> However, the ECA community surveys found a general trend suggesting bipolar disorder to be more common in non-white-collar groups and in those having less education or lower incomes.<sup>1</sup> Data from the ECA studies also found bipolar disorder to be more prevalent in urban versus rural settings.<sup>1</sup>

Social environment and major life stressors have been repeatedly implicated as having a negative effect on the course of bipolar disease. Stressful life events have been shown to increase recurrence rates significantly<sup>36,37</sup> and also prolong time to recovery from bipolar episodes. Time to recovery among patients with bipolar illness experiencing severely negative life events was found to be more than 3 times as long as that among patients not experiencing such events.<sup>38</sup> Manic symptoms were found to increase in patients with bipolar disease during a 2-month period following life events that involved goal attainment.<sup>39</sup> A low level of social support has been shown to increase recovery time and increase depressive symptomatology.<sup>40</sup>

## COMORBIDITIES

### Psychiatric

Psychiatric comorbidity in bipolar disorder has not been well studied, although the available data suggest a higher-than-expected frequency of certain psychiatric conditions in patients with this illness. Specific disorders that seem to occur frequently with bipolar disorder include obsessive-compulsive disorder, panic disorder, bulimia nervosa, impulse control disorders, and certain personality disorders.<sup>41</sup>

### Substance Abuse

Substance abuse is a particularly common and problematic condition among individuals with affective disorders, including bipolar disease. According to the ECA study data, bipolar disorder is the most likely of all Axis I diagnoses to be associated with alcohol or drug abuse, with an odds ratio

**Table 1. Possible Causes of Secondary Mania<sup>a</sup>**

Substance abuse	Toxic metabolic states
Amphetamines	Hyperthyroidism
Caffeine	Electrolyte abnormalities
Cocaine	Central nervous system disorders
Methylphenidate	Multiple sclerosis
Drug withdrawal states	Brain tumor
Ethanol	Sleep deprivation
Monoamine oxidase inhibitors	Structural damage to right (nondominant) hemisphere
Sympathomimetic agents	Temporal lobe (complex partial) seizures
Tricyclic antidepressants	
Therapeutic agents	Infections
Isoniazid	Encephalitis
Levodopa	Syphilis of the central nervous system
Monoamine oxidase inhibitors	Sepsis
Steroids	
Tricyclic antidepressants	

<sup>a</sup>Reprinted with permission from Krauthammer and Klerman.<sup>55</sup>

of 6.6 relative to a non-bipolar subject.<sup>42</sup> Alcohol and stimulants, such as amphetamines or cocaine, are commonly abused by persons with bipolar disorder. More than 60% of bipolar I and approximately 50% of bipolar II patients have a history of substance abuse (Figure 1).<sup>42</sup> Among all patients with bipolar disorder, the frequency of substance abuse was reported to be 56.1%.<sup>43</sup> Substance abuse rates tend to be higher among men than women with bipolar disorder, which mimics patterns seen among the general population.<sup>44</sup>

The cause-and-effect relationship between bipolar disorder and substance abuse is not clear and may not be the same in all patients. It is possible that preexisting psychopathology renders patients prone to addictive behaviors, with substance abuse emerging against the backdrop of bipolar illness. Conversely, in some patients bipolar symptoms may surface during chronic periods of drug or alcohol intoxication.<sup>43</sup> In some cases, substance abuse may occur as an attempt by patients to manage their symptoms. For example, cocaine may be used to precipitate hypomania during depressive phases, whereas alcohol or sedatives may be used in an attempt to quiet racing thought patterns.<sup>45</sup> It is also possible that certain patients possess a particular risk factor that is common to both bipolar disorder and substance abuse.<sup>46</sup>

Regardless of causality, concurrent substance abuse complicates both the diagnosis and the management of bipolar disorder. Chronic substance abuse can mimic almost any psychiatric disorder, thereby further complicating the already difficult diagnosis of bipolar disorder. Stimulant abuse, in particular, can produce symptoms that cannot be clinically differentiated from mania or hypomania. Furthermore, stimulant withdrawal results in significant depressive symptomatology.<sup>47</sup> Bipolar illness can actually become more severe as a result of substance abuse, and the complications associated with substance abuse appear to worsen the course of the disease. In either event, bipolar disorder patients who concurrently abuse alcohol or drugs have a more intractable course of illness, as evidenced by higher

rates of rapid cycling ( $\geq 4$  episodes within a year) and longer recovery times from mood episodes.<sup>48</sup> Substance abuse is also associated with increased resistance to treatment, more frequent episodes of irritability and dysphoria, and a greater need for hospitalization in patients with bipolar disease.<sup>43</sup> Drug abuse has been associated with earlier onset of bipolar disorder.<sup>49</sup>

Alcohol abuse is particularly common among individuals with bipolar disorder. Almost one third of patients with bipolar I and one fifth of those with bipolar II disorder are alcohol dependent.<sup>42</sup> Alcohol abuse is most likely a comorbid condition in bipolar disorder, as opposed to a causal factor.<sup>50</sup> Nevertheless, in a setting of heavy alcohol use, bipolar disease becomes extremely difficult to diagnose accurately. Early mood changes are often blamed on the effects of drinking, and a correct diagnosis may not occur until 9 or 10 years after the illness has surfaced.<sup>51</sup> Comorbid alcohol abuse, as with other substance abuse, can have a significant negative effect on the course of bipolar illness. The results of one study suggested an approximate doubling of the lifetime attempted suicide rate in alcoholic patients with bipolar disease compared with nonalcoholic patients with this illness (38.4% vs. 21.7%).<sup>52</sup> Familial clustering of bipolar disorder and alcoholism has been observed in some studies, suggesting a shared heritability for these conditions.<sup>53,54</sup>

## SECONDARY MANIA

It is now evident that manic symptoms can present in some patients who do not have bipolar disorder. In 1978, Krauthammer and Klerman<sup>55</sup> first proposed the concept of secondary mania, or mania precipitated by an underlying medical disorder or drug use. Table 1 summarizes many of the substances and clinical scenarios that have been reported to cause secondary mania.

Secondary mania can be difficult to differentiate from episodes in manic bipolar disorders. However, Krauthammer and Klerman found that cases of secondary mania were generally characterized by later onset (median age at onset = 41 years) and a negative family history for bipolar disorder, both of which contrast with patterns seen in bipolar disorder.<sup>55</sup> It is important to distinguish between secondary mania and bipolar disorder to tailor treatment most effectively. Possible causes of secondary mania should be investigated in patients with no family history of affective disorders and in those with a poor response to standard treatments for bipolar disorder.<sup>32</sup>

## SUMMARY

Much remains unknown about the pathogenesis of bipolar disorder and other psychiatric illnesses. It is apparent that bipolar disorder arises out of a complex interaction of genetic, medical, environmental, and social factors. Unfortunately, the continued ambiguity concerning the origin of

the disease prohibits effective prevention strategies. It is critical for clinicians to familiarize themselves with the known risk factors and comorbidities of bipolar disorder to aid in the recognition and proper management of affected patients. Careful consideration of family and personal psychiatric histories, including history of prior hypomanic episodes, can provide valuable diagnostic information.

*Drug names:* isoniazid (Rifamate and others), methylphenidate (Ritalin, Concerta, and others).

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