Bipolar disorder in adults: Epidemiology and pathogenesis

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INTRODUCTION

Bipolar disorder is common and disabling [1]. The hallmark of the disorder is mood elevation (mania or hypomania) [2]. Patients with bipolar I disorder have episodes of mania and nearly always experience major depressive episodes. Patients with bipolar II disorder suffer both hypomanic episodes and major depressive episodes.

This topic addresses the epidemiology and pathogenesis of bipolar disorder. The clinical features, diagnosis, and treatment of bipolar disorder in adults are discussed separately:

- (See "Bipolar disorder in adults: Clinical features".)
- (See "Bipolar disorder in adults: Assessment and diagnosis".)
- (See "Bipolar mania and hypomania in adults: Choosing pharmacotherapy".)
- (See "Bipolar major depression in adults: Choosing treatment".)
- (See "Bipolar disorder in adults: Choosing maintenance treatment".)

DEFINITION OF BIPOLAR DISORDER

Bipolar disorder is a mood disorder that is characterized by episodes of mania (table 1), hypomania (table 2), and major depression (table 3) [2]. The subtypes of bipolar disorder include bipolar I and bipolar II. Patients with bipolar I disorder experience manic episodes and

nearly always experience major depressive and hypomanic episodes (table 4). Bipolar II disorder is marked by at least one hypomanic episode, at least one major depressive episode, and the absence of manic episodes. Additional information about the clinical features and diagnosis of bipolar disorder is discussed separately. (See "Bipolar disorder in adults: Clinical features" and "Bipolar disorder in adults: Assessment and diagnosis".)

EPIDEMIOLOGY

The prevalence of bipolar disorder in adults depends upon the population and setting that is studied.

The epidemiology of bipolar disorder in pediatric and geriatric populations is discussed separately. (See "Pediatric bipolar disorder: Epidemiology and pathogenesis", section on 'Epidemiology' and "Geriatric bipolar disorder: Epidemiology, clinical features, assessment, and diagnosis", section on 'Epidemiology'.)

General population

Global — Depending upon the study, the estimated lifetime prevalence of bipolar disorder among adults worldwide is 1 to 3 percent [3]:

- Community surveys in 14 countries found that the lifetime prevalence of bipolar I and bipolar II disorder was 2.8 percent [4].
- Another set of community surveys in 11 countries found that the lifetime prevalence of bipolar I disorder was 0.6 percent and bipolar II disorder 0.4 percent [1].

The mean age of onset for bipolar I disorder is 18 years and for bipolar II disorder 20 years [1]. The ratio of males to females who develop bipolar disorder is approximately 1:1 [5].

The World Health Organization estimated that bipolar disorder was the 46th greatest cause of disability and mortality in the world among 291 diseases and causes of injuries, which placed bipolar disorder ahead of breast cancer as well as Alzheimer's disease and other dementias [6]. Many bipolar patients never receive treatment [1].

United States — In a nationally representative sample of adults in the United States, the estimated lifetime prevalence of bipolar I disorder was 1 percent, and bipolar II disorder 1.1 percent [1]. The mean age of onset for bipolar I and bipolar II disorder was 18 and 20 years [7].

Bipolar disorder is the 18th leading cause of disability in the United States [8]. Among individuals who suffer manic or hypomanic episodes, psychosocial functioning is severely impaired in approximately 70 percent; during episodes of major depression, functioning is severely impaired in approximately 90 percent of affected individuals [7].

Clinical settings — Bipolar patients often present at primary care clinics. A systematic review of 10 studies found that in primary care patients (n >14,000) who underwent structured psychiatric interviews, the prevalence of bipolar disorder ranged from 1 to 4 percent [9].

PATHOGENESIS

The pathogenesis of bipolar disorder is not known. The etiology may involve biologic, psychologic, and social factors.

Genetics — Family, twin, and adoption studies demonstrate that inherited factors are involved in the pathogenesis of bipolar disorder [10-13]:

- The lifetime risk of bipolar disorder for the first degree relative of a bipolar proband is 5 to 10 percent [10]. In a national registry study of 2 million nuclear families in Sweden, the risk for bipolar disorder increased if bipolar disorder was present in a parent (relative risk 6.4, 95% CI 5.9-7.1) or sibling (relative risk 7.9, 7.1-8.8) [14].

- The lifetime risk of bipolar disorder for a monozygotic co-twin is 40 to 70 percent [10]. As an example, a study of 30 monozygotic and 37 dizygotic twins, in which one twin from each pair had bipolar disorder, found that the concordance rate for bipolar disorder in the co-twin was eight times greater for monozygotic twins than dizygotic twins (40 versus 5 percent of the twin pairs) [15]. By contrast, the estimated lifetime prevalence rate of bipolar disorder in the general population of the United States is 2 percent [7], and the cross-national rate is 1 to 3 percent [1,4]. (See 'General population' above.)

However, the risk of developing bipolar disorder appears to involve environmental factors as well, as indicated by the finding in monozygotic twins that the concordance rate of bipolar disorder is not 100 percent.

Candidate genes — Candidate genes involved in bipolar disorder have been studied extensively, but no single gene has been identified [10]. Genetic susceptibility appears to involve the interaction of many genes with small effects rather than a single gene with a major effect [16,17].

Genome wide association studies have found that several genetic variants are associated with bipolar disorder [10]. One consistent susceptibility locus is CACNA1C, which codes for a subunit of a calcium channel and is involved in channel gating [18]. A meta-analysis of genetic studies suggests that other biologic pathways are also involved in bipolar disorder, including cardiac β-adrenergic signaling, cardiac hypertrophy signaling, corticotropin releasing hormone signaling, endothelin 1 signaling, glutamate signaling, and phospholipase C signaling [17].

In addition, genes involved in the pathogenesis of bipolar disorder may have pleiotropic effects and confer risk for other types of psychopathology [14]. As an example, a meta-analysis of genome-wide association studies (33,332 patients with bipolar disorder, unipolar major depression, schizophrenia, autism spectrum disorders, or attention deficit-hyperactivity disorder, and 27,888 controls) identified three single-nucleotide polymorphisms on chromosomes 3 and 10 that were associated with all five disorders [19]. One of the polymorphisms was located on a brain expressed gene that encodes calcium channel subunits; calcium signaling regulates neuronal growth and development [20].

Gene expression — Ribonucleic acid sequencing of postmortem tissue from patients with bipolar disorder and healthy controls indicates that gene expression is altered in bipolar disorder. One study of tissue from the dorsolateral prefrontal cortex of patients with bipolar disorder found that four genes were downregulated, including two genes that are thought to be involved in neuroplasticity [21]. A second study of tissue from the anterior cingulate gyrus found that 10 genes were downregulated [22], including genes thought to encode neurotransmitter and hormone receptors that are targets of psychotropic drugs [23].

Epigenetics — Epigenetics refers to changes in chromosomes that do not alter the nucleotide base sequence, but nevertheless change gene expression and thus possibly contribute to bipolar mood episodes [24]. Epigenetic phenomena may involve environmental factors such as toxins (eg, metals and air pollutants) and early life experiences or chronic stress, which induce changes such as methylation of deoxyribonucleic acid and histone acetylation.

In addition, epigenetic changes may involve heritable (across cell division for an individual or from an individual to offspring) modifications of the genome that change gene expression without altering any DNA sequence. Evidence that implicates epigenetic factors in the pathophysiology of bipolar disorder includes a study of postmortem hippocampus tissue from patients with bipolar disorder (n = 8) and matched healthy controls (n = 8) that found bipolar disorder was associated with specific methylation changes of glutamic acid decarboxylase 67 genes [25].

Neurobiology — Multiple lines of evidence demonstrate that brain structure and function are altered in bipolar disorder. However, it is not clear whether the observed changes represent etiologic causes, sequelae, neither, or both [26].

Neuroimaging — Based primarily upon functional magnetic resonance imaging and diffusion tensor imaging, one model of the functional neuroanatomy of bipolar I disorder hypothesizes that early developmental processes (eg, establishing white matter connections and pruning the prefrontal cortex) within brain networks that modulate emotional behavior are disrupted; this leads to decreased connections among prefrontal networks and limbic structures, especially the amygdala [27].

In addition, neuroimaging suggests that bipolar disorder may be a neuroprogressive disorder. A brain magnetic resonance imaging study of bipolar patients (n = 54, mean lifetime duration of illness of 24 years) found that after controlling for age, a longer duration of illness and a longer exposure to antipsychotic medication were each associated with smaller total gray matter volumes [28].

Inflammation — Serum markers of inflammation are increased in bipolar disorder and suggest that the disorder is associated with immune system dysregulation. One such biomarker is a group of signaling molecules called cytokines, which mediate both central and peripheral inflammation. Separate meta-analyses have each found that cytokines (eg, interleukin-4 and tumor necrosis factor-alpha) and cytokine receptors are elevated in patients with bipolar disorder, compared with healthy controls [29,30].

Proinflammatory cytokines induce acute phase proteins such as C reactive protein. A meta-analysis of 11 observational studies (n = 730 patients with bipolar disorder and 888 healthy controls) found that levels of C reactive protein were higher in patients than controls, and the difference was small to moderate [31].

Overlap with other disorders — Some studies suggest that the neurobiology of bipolar disorder overlaps with that of other mental illnesses, such as schizophrenia. As an example:

- A study of postmortem brains from patients with bipolar disorder (n = 9), schizophrenia (n = 14), and unaffected controls (n = 19) examined basilar dendrites of pyramidal cells from the dorsolateral prefrontal cortex. The mean number of spines per dendrite and the mean dendrite length were both reduced in bipolar disorder and schizophrenia, compared with controls [32].

- The volume of central nervous system gray matter structures is often decreased in bipolar disorder as well as other mental illnesses. A meta-analysis of 193 magnetic resonance

imaging studies compared the volume of gray matter structures in psychiatric patients (n >7000 patients with bipolar disorder, schizophrenia, unipolar major depression, obsessive-compulsive disorder, substance use disorders, or anxiety disorders) with healthy controls (n >8000) [33]. The amount of gray matter in many brain structures (eg, hippocampus, insula, and anterior cingulate cortex) was less in patients than controls. By contrast, gray matter volumes were generally comparable across diagnoses.

Psychosocial factors — Advancing paternal age, which is associated with increased genetic mutations during spermatogenesis, can increase the risk of bipolar disorder in one's offspring [34]. As an example, a national registry study (n >6800 individuals with bipolar disorder) evaluated the association of paternal age at childbearing and bipolar disorder, after adjusting for several potential confounding factors (eg, parental education, income, and history of psychiatric hospitalization, and maternal age) [35]. Compared to offspring born to fathers 20 to 24 years old, the risk of bipolar disorder in offspring of fathers 45 years and older was approximately six times greater.

Stressful life events such as childhood maltreatment may be associated with onset of bipolar disorder and a more severe course of illness [36], but the results across studies are not entirely consistent:

- A nationally representative sample of the United States adult population found that bipolar disorder was more common among individuals who reported a history of childhood physical abuse, compared to individuals without this history, after adjusting for sociodemographic characteristics, other childhood adversities, and comorbid psychiatric disorders (odds ratio 1.5) [37]. A second study using the same dataset found comparable results [38].

- A study of 587 patients with bipolar disorder found that emotional abuse and sexual abuse each predicted a lower age at onset and a lifetime history of suicide attempt [39]. In addition, sexual abuse was also associated with a history of rapid cycling.

- One study used prospectively collected records of involvement with a child protection agency for possible abuse or neglect as a proxy for childhood maltreatment [40]. Among adolescents and young adults aged 16 to 27 years, the lifetime prevalence bipolar disorder was comparable for individuals with a history of childhood maltreatment (n = 221) and individuals with no such history (n = 1923), after adjusting for sociodemographic characteristics.

Obstetric complications and bipolar disorder in offspring — Obstetrical complications do not appear to play a role in the pathogenesis of bipolar disorder. (See "Bipolar disorder in

women: Contraception and preconception assessment and counseling", section on 'Obstetric complications and bipolar disorder in offspring'.)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, “The Basics” and “Beyond the Basics.” The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on “patient info” and the keyword(s) of interest.)

- Basics topics (see "Patient education: Bipolar disorder (The Basics)")
- Beyond the Basics topics (see "Patient education: Bipolar disorder (Beyond the Basics)")

SUMMARY

- Bipolar disorder is characterized by periods of mood elevation; patients with bipolar I disorder have episodes of mania and nearly always experience major depressive episodes. Patients with bipolar II disorder suffer both hypomanic episodes and major depressive episodes. (See 'Introduction' above and "Bipolar disorder in adults: Assessment and diagnosis", section on 'Bipolar disorders'.)
- The lifetime prevalence of bipolar disorder among adults worldwide is approximately 1 to 3 percent, depending upon the survey. Bipolar disorder affects males and females equally, and the mean age of onset is approximately 19 years. (See 'Global' above.)
- The pathogenesis of bipolar disorder is not known. However, family, twin, and adoption studies demonstrate that genetic factors are involved. In addition, altered brain structure and function are present in bipolar disorder; it is not clear whether these changes precede onset of bipolar disorder or represent its consequences. (See 'Pathogenesis' above.)

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