Comorbidity in Bipolar Disorder

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The central tenet of clinical comorbidity, the occurrence of 2 syndromes in the same patient, presupposes that they are distinct categorical entities.

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The central tenet of clinical comorbidity, the occurrence of 2 syndromes in the same patient, presupposes that they are distinct categorical entities. By this definition, 2 or more coexisting syndromes do not negate one another, nor paradoxically does this coexistence negate the potential for one to influence the course, outcome, and treatment response of the other. Isolating a syndrome by characterizing it through a unique pathogenic process allows for diagnostic fidelity even while acknowledging overlapping phenotypes.

Bipolar disorder (BPD) is highly prevalent and heterogeneous. Its increasing complexity is often caused by the presence of comorbid conditions, which have become the rule rather than the exception. Lifetime prevalence of psychiatric comorbidity has been reported in community and clinical studies. Most (95%) of the respondents with BPD in the National Comorbidity Survey met criteria for 3 or more lifetime psychiatric disorders.\(^1\) In a Stanley Foundation Bipolar Treatment Outcome Network study of almost 300 patients, 65% met DSM-IV criteria for at least 1 comorbid Axis I disorder.\(^2\)

Analogous to models in medicine (eg, cardiovascular disease), BPD incorporates psychiatric and medical comorbidities (Table) whose simultaneous treatment is equally pressing to the core mood disturbance.\(^3\) Checks and balances must be used to address the distressing comorbid condition (eg, anxiety) whose treatment with an SSRI or serotonin norepinephrine reuptake inhibitor (SNRI) may catalyze a round of mood cycling in an otherwise stable patient; a greater degree of protection via mood stabilizers may be warranted in such an individual to reduce this possibility.
Overall, the presence of comorbidities in BPD has negative prognostic implications for psychological health and for medical well-being and longevity. The most common comorbid conditions are reviewed below to help guide the clinician through this diagnostic maze and associated treatment considerations.

**Anxiety**

The well-established relationship between anxiety symptoms and major depressive disorder usually forges a more complicated course, something that is equally, if not more, characteristic of bipolar depression. Recent studies suggest that rates of anxiety in bipolar depression tend to exceed those in the general population. In the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD), lifetime prevalence for a comorbid anxiety disorder reached 51.2% while rates for a current anxiety disorder reached 30.5%; comorbid anxiety tended to be more common in patients with bipolar I disorder compared with bipolar II.  

Anxiety may be interwoven into the fabric of syndromic bipolarity, may occur alongside it as a comorbid condition, and may occur in subsyndromal bipolar states as well. Patients with BPD are at higher risk for many other anxiety subtypes, including generalized anxiety disorder, simple phobia, social phobia, obsessive-compulsive disorder, posttraumatic stress disorder, and panic disorder. Of these, panic disorder appears to have the highest risk of comorbidity. Panic disorder also tends to cosegregate with BPD in families with high rates of BPD. Panic disorder and anxiety tend to be particularly manifest in bipolar mixed states, which echoes Emil Kraepelin’s description of mixed states as “anxious mania” or “excited depression” whereby the “mood is anxiously despairing.” Mixed states tend to have an early onset and are associated with other risks including suicide and substance abuse.  

In general, anxiety tends to predict an earlier age at onset of BPD and results in a more complicated and severe disease course. Aside from an early onset, the parallels to bipolar mixed states include an increased incidence of suicide, psychotic features, substance abuse, panic comorbidity, and poor response to lithium. Anxiety and substance abuse are the most frequent lifetime comorbid disorders in BPD and the presence of comorbid anxiety further increases the likelihood of substance abuse. Rates of alcohol dependency can be up to 2-fold higher in patients with anxiety. The risk of suicide is increased in patients with bipolar depression and comorbid anxiety and/or substance abuse. Overall, the presence of anxiety in patients with BPD tends to amplify or intensify core bipolar symptoms or to aggravate other comorbid conditions. The course of the illness and response to treatment are also adversely affected.

**Treatment approaches**

There are relatively few studies and no randomized controlled trials that isolate pharmacological treatment strategies in bipolar patients with comorbid anxiety. Traditional bipolar treatments (such as lithium) tend to be less effective when anxiety coexists: combination therapy is often necessary in this setting. Anticonvulsants, including valproate, carbamazepine, lamotrigine, topiramate, gabapentin, and pregabalin, have been studied in anxiety conditions; there is limited controlled evidence to support the use of these agents in comorbid anxiety.  

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**CHECK POINTS**

- Patients with bipolar disorder (BPD) are at higher risk for many anxiety subtypes, including generalized anxiety disorder, simple phobia, social phobia, obsessive-compulsive disorder, posttraumatic stress disorder, and panic disorder.
- As with other comorbidities, substance use may start before presentation of actual bipolar symptoms, subsequently obscuring the mood diagnosis.
- One study showed that attention-deficit/hyperactivity disorder (ADHD) occurred in up to 85% of children with BPD, and that BPD occurred in up to 22% of children with ADHD.
- Attempts at diagnostic and therapeutic clarity are essential to offset the high cost of elevated rates of suicide, interpersonal and legal difficulties, and repeated hospitalizations.

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The efficacy of antidepressant agents, including the SSRIs and SNRIs, has been extensively demonstrated in anxiety conditions. These agents are often used to manage anxiety conditions when comorbid with BPD. Although controversial, the use of these agents is widespread in bipolar depression and its associated comorbidities; rapid switching of moods may be more prominent in the face of early-onset bipolarity, anxiety comorbidity, and antidepressant activation. Therefore, the challenge in treating BPD comorbidities is to avoid exacerbating other elements within the comorbid symptom complex—especially the core mood disturbance. Second-generation antipsychotic agents, including olanzapine, risperidone, and quetiapine, have shown direct or adjunctive benefits in the treatment of anxiety conditions; their additional role as mood stabilizers, with a relatively protective effect against bipolar mood switching, may be advantageous for the patient with comorbidities. The clinician’s task is to treat the comorbid anxiety condition (along with its heightened attendant risks) while first insulating the patient against further destabilization of the primary mood disorder.

**Substance use disorder**

As noted, the added burden of substance use disorder (SUD) to comorbid anxiety in BPD substantially raises the risk profile of the disorder while complicating treatment options. Comorbid SUD was found to exist in 61% of patients with bipolar I disorder and in 48% of bipolar II patients in the Epidemiologic Catchment Area. These rates are much higher than the rate of 10% to 20%, respectively, in patients without the SUD comorbidity and the highest rate within any psychiatric disorder. Reflecting findings from other studies, the most common SUD appears to be alcohol abuse and dependence. Research from the Stanley Foundation Bipolar Network found that the lifetime prevalence rate of alcohol abuse or dependence was 49% for bipolar men and 29% for bipolar women. Women with BPD seemed to be at higher risk for alcoholism than women in the general population. Whereas alcoholism in bipolar men may have more of a genetic influence, in women the risk may be more of an acquired burden related to depressive illness. Depressive symptoms are especially common in female bipolar patients with comorbid alcohol abuse.

The phenomenological and treatment course of bipolar illness is significantly affected by comorbid SUD. As with other comorbidities, substance use may start before presentation of actual bipolar symptoms, and may obscure the mood diagnosis. The temporal onset of substance abuse and bipolar disorder may also reflect different clinical courses. In general, higher rates of mood lability, rapid cycling, mixed episodes, suicidality, and other medical conditions complicate BPD and affect recovery times as well as rates of remission during hospitalization. There is also the risk of violent behavior with comorbid substance abuse. Impulsivity is an overlapping and overarching feature of bipolar and substance use disorders, and it further complicates the course of the illness. Comorbid substance abuse is also a significant contributor to treatment nonadherence in patients with bipolar disorder. Its presence confounds attempts at symptomatic and functional recovery.

**Treatment approaches.** Unfortunately, there are few controlled data on the pharmacotherapeutic management of comorbid SUD and BPD. Response to lithium is generally poor in patients with BPD comorbid with alcohol abuse, although it is not clear whether this relates to nonadherence or the association with mixed states. Anticonvulsants (e.g., valproate, topiramate, carbamazepine, and lamotrigine) have shown a favorable effect in decreasing use of alcohol and cocaine. In another study, treatment with valproate or carbamazepine was more likely to induce remission in hospitalized bipolar patients with histories of substance abuse other than lithium. A major concern with these agents, however, is balancing the treatment effects with the potential for hepatic, hematological, and other adverse effects, especially in this susceptible patient population. Second-generation antipsychotic agents, including quetiapine and aripiprazole, reduced drug use and craving in small open-label studies.

Treatment of comorbid BPD and SUD invariably requires an integrated approach that focuses on both disorders simultaneously, and incorporates both psychotherapy and pharmacotherapy. This dual-disorder approach incorporates case management, vocational rehabilitation, individual and family counselling, housing, and medications.

**Attention-deficit/hyperactivity disorder**

Kraepelin’s insight into the onset and atypical phenomenology of BPD in childhood/adolescence was not fully acknowledged until recently. Despite the lack of a formal nosology in this age group, a 2001 NIMH consensus conference affirmed the existence and potential diagnosis of BPD in prepubertal children. This atypical mixed-state phenotype seems to overlap with symptoms of...
attention-deficit/hyperactivity disorder (ADHD), which include irritability, impulsivity, distractibility, overactivity, rapid speech, and emotional lability. The overlap generates the need for diagnostic precision or the determination of a separate comorbid condition. The lack of diagnostic tools and the overlap of these disorders with conduct disorder and oppositional defiant disorder adds to the diagnostic confusion. Irritability, for example, cuts across all diagnostic categories and is a poor differentiator.

Notwithstanding this ambiguity and the lack of large epidemiological studies, there is general agreement regarding the co-occurrence of BPD and ADHD. In a recent review, Singh and colleagues found a bidirectional relationship between the 2: ADHD occurred in up to 85% of children with BPD, and BPD occurred in up to 22% of children with ADHD. The authors further explored 4 hypotheses:

- BPD symptoms lead to overdiagnosis of ADHD in youth.
- ADHD is a prodromal or early manifestation of childhood BPD.
- ADHD is treated with psychostimulants that trigger the onset of childhood BPD.
- ADHD and BPD share an underlying biological mechanism (ie, common familial, genetic, or neurophysiological).

Despite limitations, current literature best supports the second hypothesis—that ADHD may be a marker of the development of early-onset BPD. Ultimately, longitudinal controlled studies are needed to help us diagnose this disorder more precisely and to manage it rationally. Pharmacological studies may offer insights into the efficacy of mood stabilizers and/or the failure of psychostimulants; conversely, the induction of bipolar symptoms with psychostimulants or antidepressants may also be instructive.

**Personality disorders**

As with the comorbid conditions discussed earlier, the presence of a comorbid personality disorder complicates diagnostic interpretation and treatment decisions. Marked personality disorder–related symptoms may also negatively influence the outcome of the bipolar illness. The severity of residual mood symptoms in bipolar patients with personality disorders differs from that in bipolar patients without personality disorders—even during periods of remission. Features of a personality disorder may overlap with a bipolar mood episode. It may therefore be too challenging to diagnose a personality disorder until the mood episode has been successfully treated. A careful personal and collateral history may be most instructive in establishing the presence of personality traits that predate the onset of a discreet mood disturbance. Conversely, personality features that endure after the resolution of a mood episode may reveal the comorbid condition. A positive family history of a mood disorder and antidepressant-induced mood elevation also serve as important clues.

A recent study found that cluster B (borderline, narcissistic, antisocial, histrionic) personality disorder features were evident in about one-third of bipolar patients, with possible associations to childhood emotional and/or physical abuse. An independent, elevated lifetime risk of suicide was attributed to cluster B comorbidity. Recent literature advocates a more careful approach to diagnosing borderline personality disorder in the face of the mood-cycling pattern seen in bipolar II disorder; a cyclothymic temperament has been proposed as the underlying feature of this atypical mood, anxiety, impulsivity continuum.

Clearly, treatment of this comorbid subtype requires a greater degree of finesse in the integration of psychotherapeutic and psychopharmacological modalities—especially in restoring functionality and ensuring compliance. Again, mood stabilization with lithium appears less effective than anticonvulsants, such as valproate or lamotrigine, in this comorbid population. Second generation antipsychotics (olanzapine, risperidone) have also played a role in improving symptoms and regulating affective lability.

**Medical comorbidities**

Cardiovascular disease, type 2 diabetes mellitus, and other endocrine disorders tend to occur more often in patients with BPD than in the general population. According to population-based studies, cardiovascular mortality is almost twice as high in patients with BPD, which may be related to higher rates of obesity. Mechanisms hypothesized to explain this finding include smoking, diet, sedentary lifestyle, and unrecognized risk factors (insulin resistance, inflammation, hypercortisolemia).

Comorbid neurological disorders, including migraine headache, have also been reported at higher rates in patients with BPD, especially bipolar II disorder. The latter may represent a subtype of the disease.

**Conclusion**
Given the substantial overlap between symptoms of BPD and other psychiatric conditions, an accurate cross-sectional assessment is inherently difficult to achieve. A careful longitudinal assessment that establishes a chronology of onset of different conditions, a symptom and functional profile between mood episodes, the course of illness, and response to treatment are essential for a more robust diagnosis. Furthermore, the inherent challenge in obtaining an accurate history from a bipolar patient—especially one with comorbidities—requires corroboration from family members. Although clinical guidelines for BPD acknowledge the complexity of treating the illness, most have limited recommendations specific to the patient with comorbidities. This may reflect the limited nature of the clinical evidence in this field. The cost of diagnostic and therapeutic uncertainty, however, is calculated through the high cost of chronicity, with elevated rates of suicide, legal and interpersonal difficulties, and repeated hospitalizations.

As the field of neurobiology of bipolar and affective disorders advances, we hope to begin to refine our view of the comorbid interface. Forging the pathophysiological links between specific medical illnesses and BPD, including the use of clinical biomarkers to help refine the understanding of bipolar subtypes, may help clarify the pathophysiology of BPD itself. This will ultimately suggest new measures for secondary prevention and long-term treatments.

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References:

Drugs Mentioned in This Article

Aripiprazole (Abilify)
Carbamazepine (Carbatrol, Tegretol, others)
Gabapentin (Neurontin)
Lamotrigine (Lamictal)
Lithium (Eskalith, Lithane, Lithobid)
Olanzapine (Zyprexa)
Pregabalin (Lyrica)
Quetiapine (Seroquel)
Risperidone (Risperdal)
Topiramate (Topamax)
Valproate/valproic acid (Depakote, others)

References

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