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Bipolar Disorder and Substance Abuse Comorbidities

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Introduction by Peter F. Buckley, MD

Introduction

Co-occurring medical conditions, including multiple psychiatric diagnoses, are common in patients with bipolar disorder. The majority of patients with bipolar illness have symptoms of at least 1 other underlying psychiatric state, often comprising various addictive behaviors, such as alcohol or drug abuse or dependence.[1] In fact, of all serious mental illnesses, patients with bipolar disorder experience the highest rates of co-occurring alcohol and drug use disorders, with estimates of lifetime prevalence exceeding 60%.[2]

A recent study that examined gender differences in the prevalence, risk, and clinical correlates of alcoholism in bipolar disorder found that more men than women with bipolar illness met criteria for lifetime alcoholism, but that the relative risk (that is, the risk compared to the general population) of having alcoholism is greater for women than men.[3] Additionally, in these bipolar subjects, alcoholism was associated with history of polysubstance abuse in women and with family history of alcoholism in men.

The specific reasons for elevated rates of substance use disorders in bipolar disorder are not known. One study of familial bipolar disorder found no significant differences between alcoholic and nonalcoholic bipolar patients in family history of alcoholism or affective disorders.[4] This study suggested that alcoholism in bipolar disorder is dissimilar to alcoholism as a primary disorder and is not simply a result of an increased genetic load of both conditions in these patients.

While other risk factors for and underlying mechanisms of comorbid alcohol and drug abuse in bipolar disorder are not well understood, it is known that the course of bipolar disorder worsens in the presence of substance abuse.[5] Substance abuse and dependence are associated with an earlier onset of bipolar disorder, more frequent episodes and hospitalizations, and more frequent mixed episodes, rapid cycling, and suicidality. Substance abuse/dependence is also associated with slower symptom remission and poor compliance with treatment regimens. Patients with bipolar disorder and comorbid substance use disorder commonly experience mood and/or anxiety symptoms, disruptive behaviors, and relationship problems. Consequently, optimal management of bipolar disorder must consider all related comorbidities, and may require combinations of psychotherapeutic interventions and pharmacotherapies targeting multiple disorders.

Course of Substance Use Disorders Co-occurring with Bipolar Disorder

A number of studies have examined the course of co-occurring syndromes in bipolar disorder in order to clarify the relationships between comorbid conditions. In 1995, Winokur and colleagues examined factors that underlie associations of alcoholism and bipolar disorder.[4] This study explored factors that might explain the high rates of alcoholism that are observed in bipolar disorder, using family study and outcome methods. One goal was to determine whether co-occurring bipolar disorder and alcoholism represented two distinct conditions; ie, a true comorbidity. The findings suggested that patients with primary bipolar illness (ie, in whom the symptoms of bipolar disorder preceded those of alcoholism) had an earlier onset of bipolar illness and

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more affective episodes after recovery while patients with primary alcoholism (ie, in whom alcoholism preceded the affective illness) had longer median times to first relapse and were more likely to achieve remittance of their alcoholism. The authors suggest that the relative order of onset of the two conditions impacts the subsequent course of illness and implies, potentially, different underlying causes.

To complement this work, a study of 77 patients diagnosed with bipolar disorder examined the syndromal course of co-occurring alcohol and drug use disorders as well as other psychiatric disorders, including posttraumatic stress disorder (PTSD), anxiety disorders, and obsessive-compulsive disorder (OCD) during 12 months after a first psychiatric hospitalization.[6] The study found that the rates of all syndromes, with the exception of 'other anxiety disorders,' were elevated. Alcohol and drug abuse syndromes were particularly common, were correlated with each other, and occurred with higher than expected prevalence.

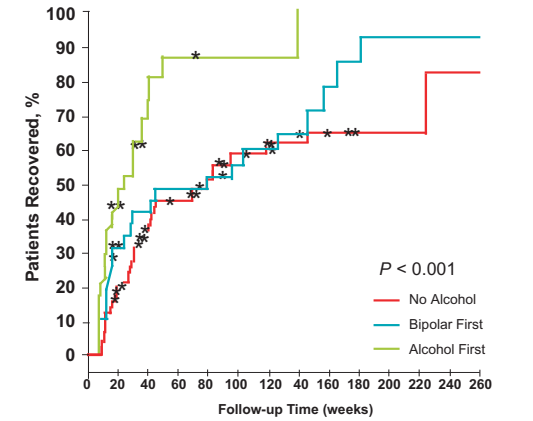
In over 70% of patients with both bipolar and substance use disorders, the onset of substance abuse predated the onset of bipolar disorder by more than 1 year, suggesting that antecedent substance use disorders may be prodromes of incipient bipolar illness.[6] Additionally, during the 12-month follow-up, 54% of patients with a history of alcohol abuse experienced affective episodes in the absence of alcohol abuse but when alcohol abuse occurred, it was always associated with concurrent affective syndromes, primarily depression. These results suggest that alcohol may initiate or perpetuate affective symptoms in some patients. In one-third of subjects, both substance use disorder and bipolar illness persisted throughout the follow-up period so that the relative effects of the conditions on each other could not be disentangled.

A more recent University of Cincinnati study sought to identify how the relative onsets of alcohol use and bipolar disorders affect the subsequent courses of illness in patients with both conditions.[7] This study tested 2 hypotheses: (1) the relative order of onset of bipolar disorder and alcoholism would affect the subsequent course of bipolar illness, such that patients whose alcohol use disorder preceded bipolar disorder would have a less severe course than those in whom bipolar disorder preceded alcoholism (consistent with the previously noted study by Winokur and colleagues), and (2) the relative order of onset of bipolar disorder and alcoholism would affect the subsequent course of alcoholism.

The study enrolled 144 patients who were followed for up to 5 years and included 27 subjects in whom the onset of alcohol abuse preceded the onset of bipolar disorder (alcohol first), 33 in whom bipolar disorder preceded or was concurrent with alcohol abuse (bipolar first), and 83 subjects with bipolar disorder only. The main outcome measures were symptomatic recovery and recurrence of both conditions and percentage of follow-up with affective episodes and affective and alcohol use disorder symptoms.

Significant differences among groups in affective symptomatic recovery were observed **(Figure 1)**.[7]

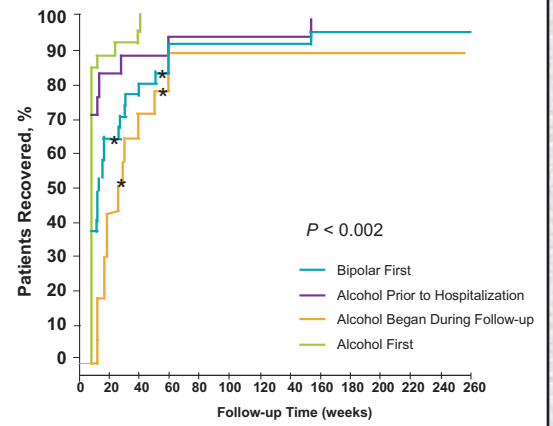
Figure 1. Affective Symptomatic Recovery



* Asterisk indicates censored data (subjects dropped out of the study prior to recovery).

The Alcohol First group was older, had a later age at onset of bipolar disorder, and showed greater and more rapid recovery than did the other two groups. Symptomatic recurrences of affective episodes were common and did not differ significantly among the groups. The two comorbid groups showed significant differences in recovery time; patients in the Bipolar First group in whom alcohol use disorder began after hospitalization demonstrated slower recovery than patients in whom alcohol use began prior to hospitalization **(Figure 2)**.[7]

Figure 2. Alcohol-Use Disorder Recovery



* Asterisk indicates censored data (subjects dropped out of the study prior to recovery).

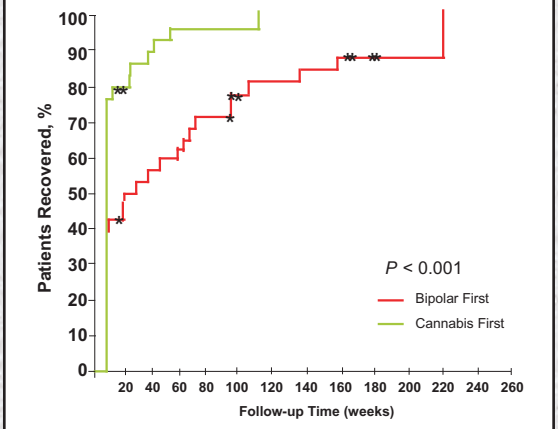
Patients in whom alcohol use began prior to hospitalization, regardless of whether the bipolar or alcohol use disorder was antecedent, were more likely to recover than those in whom alcohol use began during follow-up. This finding may be related to hospitalization, since 75% of patients who used alcohol prior to hospitalization did not resume alcohol use for at least 8 weeks following discharge. The post-hospitalization recovery from alcohol use suggests that this period may provide 'a window of opportunity' to treat alcohol abuse in the course of bipolar disorder.[7]

These study results support the hypothesis that the course of bipolar illness is affected by the relative age of onset of alcohol use and bipolar disorder in patients with both conditions. Antecedent alcohol use was associated with later age at bipolar onset, more rapid symptomatic recovery, and less time spent in affective episodes. The findings suggest that

a subgroup of bipolar patients may require several years of alcohol use before bipolar disorder is expressed.

A recent study examined the co-occurrence of cannabis use disorders in bipolar disorder to determine how the sequence of the onsets of both disorders is associated with their subsequent outcomes.[8] The study included the same sample in whom alcohol effects were examined, as previously discussed. In a 5-year follow-up period, 33 patients had onset of cannabis use disorder prior to the onset of bipolar disorder (Cannabis First), 36 had onset of bipolar disorder prior to the onset of cannabis use disorder (Bipolar First), and 75 had bipolar disorder only (Bipolar Only).

Figure 3. Cannabis-Use Disorder Recovery



* Asterisk indicates censored data (subjects dropped out of the study prior to recovery).

The results showed that among the 69 patients with a co-occurring cannabis use disorder, the Cannabis First group had a later age of onset of bipolar disorder than the Bipolar First group and exhibited higher rates of other drug disorders than the Bipolar First or Bipolar Only groups. When evaluated by simple survival analysis, the Cannabis First group showed higher rates of and more rapid recovery than did the 2 other groups; recovery rates in the other two groups did not differ. However, when adjusted for potential mediator variables (eg, age at onset, gender), these differences did not persist. The results also showed that the Bipolar First group spent significantly greater follow-up in an affective episode than did Cannabis First or Bipolar Only groups. Both comorbid groups showed more rapid cycling during follow-up than did the Bipolar Only group. Significant differences in recovery were observed, in that recovery was more common in the Cannabis First group than in the Bipolar First group **(Figure 3)**.[8]

Analysis of the interactions between courses of bipolar and cannabis use disorders showed that the percentage of weeks during follow-up in a depressive episode was significantly associated with the percentage of weeks of cannabis abuse symptoms, while the percentage of time in remission was inversely associated with the percentage of weeks with cannabis abuse symptoms. Additionally, the Cannabis First group exhibited more alcohol dependence than did the Bipolar First group.

Most patients experienced a period of abstinence from cannabis use immediately following hospitalization. Similar to the previous study of co-occurring alcohol use,[7] this finding suggests that aggressive drug abuse treatment immediately following a first hospitalization might decrease rates of recurrence and new cases of cannabis use disorder in bipolar illness.

Treatment of Substance Use Disorders in Bipolar Disorder

Rates of substance/alcohol use appear to be higher in bipolar disorder than in any other Axis I mental illness. In general, the presence of substance use disorders in bipolar disorder negatively impacts the course of bipolar illness, resulting in significantly more lifetime hospitalizations, increased risk of violence toward self and others (including heightened risk of suicide), poor treatment adherence, and poor response to mood stabilizers,[5] although relative ages of onset mediate these effects as noted. Nonetheless, few well-controlled studies have identified effective treatments for these patients. In fact, subjects with substance use disorders are frequently excluded from clinical trials of patients with bipolar disorder.[5]

A recent review suggested that the ideal pharmacotherapy for co-occurring substance use and bipolar disorders would treat the bipolar illness, relieve withdrawal symptoms, and prevent relapse of both the substance abuse and affective symptoms.[9] Additionally, the ideal medication would have low abuse liability, require infrequent dosing, be well tolerated, and have a favorable side effect profile.[9] To date, no such medication has been identified.

A summary of treatment options for substance use and bipolar disorders is presented in the table below. The number of pluses suggests the strength of evidence for effective treatment, whereas minuses suggest that the treatment may be ineffective and question marks suggest little information is available. As noted, there is no treatment that has been shown to be effective for both the treatment of bipolar disorder and any substance use disorder.

Treatment of Substance Use Disorder

Drug	BPD	SA
Lithium	+++	+/-
VPA	+++	+
CBZ	++	+/-
TPM	-/+	++
Antipsychotics	+++	-/?
Antidepressants	+/-	+/-
Naltrexone	-/?	++
Disulfiram	-	+
AA/Behavioral	+/-	++

Table courtesy of Dr. Strakowski

A combination of psychotherapeutic interventions and pharmacotherapies targeting both disorders may be necessary for effective treatment. For example, Weiss and colleagues recently demonstrated that an integrated group therapy coupled with standard pharmacotherapies significantly improved outcome in bipolar patients with co-occurring substance dependence than drug counseling alone.[10] The application of tools, such as mood charting, can provide a

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long-term means of evaluating an individual's response to drug therapy and, when coupled with measures of substance abuse (eg, the Addiction Severity Index), can lead to integrated effective treatments to improve outcome. Clearly, there is a dearth of research in these complicated patient populations, limiting recommendations at this time. The promise of studies like those of Weiss et al, coupled with observations that there may be specific times in the course of illness (eg, immediately following hospitalization) that may be more amenable to treatment interventions for both conditions suggest clinical approaches that warrant additional investigation.

Summary

The co-occurrence of substance use disorders in bipolar illness is common and has significant negative impact on disease prognosis. Although the factors underlying the association of substance use disorders and bipolar disorder remain to be elucidated, it is likely that more effective treatments will emerge with increased understanding of the causes of substance use disorder during the course of bipolar illness.

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