



# Depression and Bipolar Disorders in Patients With Alcohol Use Disorders

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This review details methods for meeting the challenges of diagnosing and treating mood disorders that coexist with substance use disorders.

**C**o-occurrence of depression and substance abuse often poses diagnostic and therapeutic challenges. This article reviews the prevalence, clinical considerations, and treatment of depression coexisting with alcohol use disorders (AUDs).

## PREVALENCE

Mood and substance use disorders (SUDs) are very common with an estimated lifetime prevalence in the U.S. of 17% for major depression, 4% for bipolar I and II disorders, 13% for alcohol abuse, and 5% for alcohol dependence.<sup>1</sup> Almost all of the associations between disorders of mood or anxiety and drug use were positive and statistically significant in the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), which included 43,093 noninstitutionalized patients.<sup>2</sup>

There is a reciprocal relationship between depression and alcoholism. Epidemiologic Catchment Area Survey results indicated that baseline symptoms of depression or alcohol abuse increased the risk of developing alcohol dependence or depression.<sup>3</sup> The risk of developing depression were elevated among people with increasing levels of alcohol-induced debility. Conversely, the presence of depressive symptoms increased the chance of developing alcohol dependence. The association between alcohol dependence and depression may be attributable to the depressive effects of ethanol; depression often remits with sobriety. Psychosocial consequences of problem drinking also may contribute to affective illnesses.

Alcohol dependence poses a major depression risk that contributes to higher rates of alcohol use. In people with

ethanol dependence, the prevalence of major depressive disorder (MDD) is 21%.<sup>4</sup> People who are alcohol dependent are 4 times more likely than are nondependents to have MDD. Forty-one percent of people who seek treatment for current alcohol abuse have a mood disorder.

The NESARC survey revealed strong associations between depression, substance use, and other psychopathologies.<sup>5</sup> Compared with MDD alone, SUD combined with MDD conferred high vulnerability to additional psychopathology, depressive episodes that were more severe and greater in number, and more suicide attempts.

## DEPRESSION CLINICAL CONSIDERATIONS

Depression linked to recent alcohol abuse may not respond well to an antidepressant drug beyond what is achieved with ethanol abstinence. In one study, depressive symptoms were assessed over the course of alcohol-related hospitalizations.<sup>6</sup> Depression was evident in 42% of patients 48 hours after admission, but only 6% remained clinically depressed by week 4 of hospitalization. Therefore, in the treatment of patients hospitalized for alcohol detoxification, it is common to observe them for 1 month before considering antidepressant medication. Mood likely will improve without pharmacotherapy.

However, delaying treatment for depression while a patient is hospitalized for alcohol detoxification presents some difficulties. Many patients do not remain sober during the first month after detoxification. One study found that 65% of patients imbibed alcohol within 2 weeks after discharge.<sup>7</sup> Furthermore, 50% relapsed into heavy drinking during the same period. More than 25% of patients who used alcohol and were diagnosed with substance-induced depression at baseline were reclassified with MDD the next year.<sup>8</sup>

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Careful clinical assessment is needed after alcohol detoxification. Depression that persists during ethanol abstinence predisposes a patient to relapse into heavy drinking. Therefore, failure to treat depression after alcohol detoxification poses considerable risk.<sup>9</sup> A study of the effect of depression on the return to drinking among patients with alcohol dependence found that depression at entry into inpatient treatment for alcohol dependence predicted a shorter time to first drink.<sup>9</sup> The prognosis for a drinking relapse was worse no matter whether the depression came first or was triggered by the alcohol. Depression does not predict drinking outcomes, but it is associated with a more rapid relapse to ethanol consumption.

Similarly, inpatients with premorbid or substance-induced depression were more likely to meet the criteria for drug dependence during outpatient follow-up.<sup>10</sup> In addition, patients who developed depression during the first 26 weeks after hospitalization were 3 times more likely than those without depression to relapse into drug dependence during follow-up.

Alcohol dependence may hasten the progression of depression. A study on the prognostic effect of alcoholism on the 10-year course of depression found a deleterious influence of current alcoholism after recovery from depression.<sup>11</sup> Patients with MDD were more likely to transition from being ill to improving if either they were forgoing alcohol or had never abused it. Another investigation verified that alcohol and drug dependence increased perceptions of affective symptomatology.<sup>12</sup>

Substance-induced depression also increases the risk for suicide. In 602 patients with substance dependence, depression was classified as occurring before dependence, during abstinence, or during substance use.<sup>13</sup> Depression increased the risk for suicide in 34% of patients who had already attempted suicide at least once. Compared with depression absent substance abuse, depression preceding substance use was associated with high vulnerability to additional psychopathology, depressive episodes that were more severe and greater in number, and more suicide attempts. Substance dependence predicted severity of suicidal intent, and abstinence predicted number of attempts.

Psychiatric hospitalizations often involve patients with a history of suicidal thinking or behavior and substance-induced depression. Clinicians can make reliable assessments of the degree to which a presenting psychiatric syndrome is substance-induced.<sup>14</sup> These patients require addiction treatment, including outpatient ad-

diction services capable of caring for suicidal persons. These individuals also are more likely to be homeless, unemployed, and uncooperative.<sup>15</sup>

Taking a psychiatric history and making a detailed inquiry into potential suicidal behavior, recent substance abuse, and current mood symptoms are warranted in persons with depression and/or SUD. Close follow-up is especially important for depressed patients likely to relapse into alcoholism soon after hospital discharge. Failure to recognize MDD or a bipolar disorder in such a patient may result in more relapses, recurrence of mood episodes, and elevated risk of completing suicide.<sup>16</sup>

### BIPOLAR CLINICAL CONSIDERATIONS

There is a lack of clarity regarding the effect of moderate-to-excessive alcohol use on the course of bipolar disorders. There is a negative effect on patients with alcohol-induced bipolar depression. In a study of group therapy patients with bipolar disorder co-occurring with substance dependence, data indicated that number of days of alcohol use predicted development of depression a month later.<sup>17</sup> These findings were associated with heavy alcohol consumption. In these patients, substantial drinking increased the risk of a depressive episode. In another study, comorbid SUDs were correlated with suboptimal treatment compliance.<sup>18</sup> The authors of a 1998 literature review concluded that comorbid SUD makes bipolar symptoms more severe.<sup>19</sup>

A number of studies have failed to confirm a negative effect of alcohol on bipolar depression.<sup>20</sup> There were no differences in 1-year course and outcome between bipolar patients with different alcohol use levels (abstinence, incidental use, moderate abuse, excessive consumption). Other investigators concluded that SUDs were not associated with slower recovery from depression but could contribute to a higher risk of switching to a manic, mixed, or hypomanic state.<sup>21</sup>

Substance use disorders are associated with increased suicidal behavior in people with a bipolar disorder. The risk of attempted suicide is about double for these patients relative to bipolar patients who do not abuse alcohol.<sup>22</sup> Of those who abuse drugs, 14% to 16% complete suicide.<sup>23</sup>

### PSYCHOTHERAPY

Reportedly, integrated cognitive behavioral therapy (CBT) provided better substance abuse outcomes compared with 12-step programs.<sup>24</sup> There also was less substance abuse within the year after CBT. Integrated

psychosocial treatment for patients with a mood disorder and substance abuse should involve simultaneous treatment of the 2 conditions. A sequential approach addresses the primary concern and subsequently treats the comorbid disorder, whereas a parallel approach manages both at the same time but in different surroundings. In both approaches, conflicting therapeutic ideologies are a potential difficulty. Given the multiple treatment locations and separate appointments, scheduling problems are an additional difficulty. Coexisting illnesses also are important to consider in the clinical treatment for bipolar patients. As with individual treatments, group therapies take either a sequential approach (more acute disorder treated first) or a parallel approach (disorders treated simultaneously but in separate settings).

Integrated group therapy (IGT) considers patients as having a single diagnosis, focuses on commonalities between relapse and recovery, and reviews the relationship between both conditions. One study compared IGT and treatment as usual in subjects with comorbid bipolar and AUD.<sup>25</sup> The IGT group evidenced fewer days of alcohol use. Other research compared IGT with group drug treatment and found that IGT subjects were more likely to remain abstinent.<sup>26</sup> This type of psychotherapy showed promise in a meta-analysis of integrated treatment in patients with depression and SUDs.<sup>26</sup>

Compared with placebo, sertraline/CBT combined treatment reduced alcohol consumption on drinking days.<sup>27</sup> This combination was effective in reducing depression, especially in females.

Acceptance and commitment therapy (ACT) combines mindfulness and behavioral change to increase psychological flexibility. The goal in ACT is for patients to become more accepting of their unpleasant feelings. In a study of alcohol abusers with affective disorders, those treated with ACT, compared with controls, had higher abstinence rates and lower depression scores.<sup>28</sup>

#### PHARMACOTHERAPY AND BIPOLAR DISORDER

Even when bipolar symptoms were resolved with use of mood-stabilizing medications, usually some alcohol use continued, though no association was found between bipolar disorder and AUDs.<sup>29</sup> With patients' illness severity and ethanol consumption rated weekly over 7 years, no temporal correlation was found between drinking alcohol and bipolar symptoms.

Similarly, in a study, relief of depressive bipolar symptoms did not result in less frequent alcohol relapse.<sup>30</sup> One hundred fifteen outpatients with bipolar disorder and

AUD were randomly assigned to either 12 weeks of quetiapine therapy or placebo. Patients in the quetiapine group experienced significant improvement in mood, but sobriety was not enhanced.

Two studies indicated trends of reduced drinking with use of prescribed alcohol-deterrent drugs. An investigation that compared naltrexone with placebo did not reach statistical significance, but naltrexone was reasonably effective in reducing alcohol consumption and craving.<sup>31</sup> A report on patients with bipolar disorder treated with acamprosate also did not identify any significant differences in alcohol drinking prognosis.<sup>32</sup> Nevertheless, acamprosate was well tolerated and seemed to confer some clinical benefit.

There is a paucity of research focused on patients with bipolar disorder and substance dependence.<sup>33</sup> In one trial, patients with bipolar disorder and a diagnosis of alcohol dependence were randomly assigned to receive either valproate or placebo.<sup>34</sup> Valproate therapy decreased the number of heavy consumption days and drinks per drinking day in these patients. In a study of 362 patients with bipolar disorder and alcohol dependence treated with lithium or valproic acid, there was no change in drinking days despite adding quetiapine to the regimen.<sup>35</sup>

#### PHARMACOTHERAPY AND DEPRESSION

Lithium is not effective for patients with MDD and AUD. Lithium treatment for depressed patients with alcohol dependence did not improve abstinence, alcohol-related hospitalizations, or severity of either condition.<sup>36</sup>

Aripiprazole is an antipsychotic that partially agonizes dopamine receptors. Dopamine implicates reward circuitry and has a role in AUDs. Aripiprazole was used as an adjunctive intervention in a randomized trial of 35 patients with comorbid alcohol dependence and depression.<sup>37</sup> There was less depression in both the aripiprazole plus escitalopram group and the escitalopram group. Imaging showed a change in activity in the left cingulate gyrus in the patients with comorbid alcohol dependence and MDD. The action of aripiprazole may be mediated through the anterior cingulate cortex.

Research on patients with alcohol dependence treated with fluoxetine found decreased Hamilton Depression Rating Scale (HDRS) scores but no change in alcohol consumption.<sup>38</sup>

Sertraline diminishes depressive symptoms in abstinent alcoholics. In one study, depressed, recently abstinent alcohol users were randomly assigned to receive sertraline 100 mg daily or placebo.<sup>39</sup> Significant

improvement was noted in HDRS and Beck Depression Inventory scores at 3- and 6-week intervals.

Citalopram was studied in patients randomly assigned to receive citalopram or placebo for alcohol abuse or dependence.<sup>40</sup> Patients in the citalopram group had more days of drinking and showed little change in frequency of alcohol consumption. There was no improvement in depression severity in the citalopram group relative to the placebo group. Citalopram also has been studied in combination with naltrexone.<sup>41</sup> Patients with depression and alcohol dependence were randomly assigned to receive either citalopram or placebo, as well as naltrexone. There were no significant differences in depression severity or drinking outcomes.

Treating depression with selective serotonin reuptake inhibitors (SSRIs) had variable results. Most SSRIs improve depression severity but largely have no effect on drinking outcomes.

### Antidepressants

A meta-analysis on the efficacy of antidepressant medications in treating patients with depression and substance abuse revealed that the antidepressants had a somewhat advantageous effect.<sup>42</sup> That finding was supported by the Sequenced Treatment Alternatives to Relieve Depression (STAR\*D) study.<sup>43</sup> About 33% of patients with citalopram-treated major depression endorsed concurrent SUD symptoms, 19% reported diagnosable alcohol use, 6% had other drug abuses, and 5% exhibited both alcohol and drug use. The groups did not differ in time needed to attain a better mood or in rate of response to citalopram.

Patients with citalopram-treated MDD and alcohol or drug abuse responded about as well as those without an SUD. However, those with alcohol and/or drug abuse had reduced rates of remission, and their remission was delayed, as compared with those without alcohol or drug abuse. There were more suicide attempts and psychiatric hospitalizations among the cohort with drug abuse.

Selective serotonin reuptake inhibitors have a reported safety advantage in treating patients with a history of excessive alcohol intake.<sup>44</sup> Another advantage is that SSRIs are seldom abused and seldom lower seizure thresholds significantly. Deleterious effects of alcohol on motor skills or cognition are not potentiated. Adverse effects are usually mild, and overdoses are rarely dangerous.

Antidepressant medication decreased depression and diminished the amount of drinking in patients with depression who use alcohol.<sup>45</sup> In controlled research of patients with comorbid depression and alcohol dependence,

fluoxetine reduced the severity of these conditions. Substantial reductions in depressive symptoms occurred during detoxification and washout in both groups. There was a strong relationship between depression and drinking among people with depression and AUD.

Desipramine can produce similar results, with positive antidepressant drug effects on depression and drinking. Therefore, pharmacotherapy is indicated for patients with depression who abuse ethanol. Research found that alcohol-dependent patients with depression responded to desipramine.<sup>46</sup> Desipramine yielded prolonged abstinence in patients with depression who were using alcohol but not in alcohol users without depression.

A study of imipramine use in actively drinking outpatients found decreased alcohol consumption only for those whose depression responded to treatment.<sup>47</sup> However, there was no influence on drinking outcome. Patients whose mood improved reported decreased alcohol consumption after imipramine therapy.

### CONCLUSION

People with co-occurring depression and alcohol dependence are optimally treated with pharmacotherapies that address each condition. One investigation randomly assigned alcohol-dependent patients with depression to 14 weeks of treatment with sertraline 200 mg/d, naltrexone 100 mg/d, a combination of the drugs, or placebo.<sup>48</sup> The combination treatment produced the best rate of abstinence before a heavy drinking relapse. Also, fewer patients tended to be depressed in the final weeks of treatment when prescribed the combined regimen. Pharmacotherapy is the best approach for both depression and AUDs. ●

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and adverse effects—before administering pharmacologic therapy to patients.

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