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SUBSTANCE ABUSE: ADDICTION & RECOVERY

## **Comorbid Depression and Alcohol Dependence**

### ***New Approaches to Dual Therapy Challenges and Progress***

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Patients who are seen in clinical practice commonly have multiple problems, yet efficacy data often reflect treatment of a single illness. Thus, it is useful to know how standard treatment approaches need to be modified for comorbid disorders. This article briefly describes prevalence, assessment, clinical features, and treatment of comorbid major depression and [alcohol \(Drug information on alcohol\) dependence](#).

Evidence from clinical treatment trials and changes made in the delivery of treatment from inpatient to outpatient settings bring into question the long-held view that patients with co-occurring depression and alcohol dependence must achieve abstinence from alcohol before treatment of depression can begin. Historically, there were good reasons for adhering to this view.

There are real concerns about medication interactions with alcohol in patients who were still drinking. Also, depressive symptoms can be brought on by excessive alcohol use, which makes it difficult to separate a substance-induced depression from an independent disorder of clinical depression. Traditionally, placing patients in 28-day inpatient settings, which helped patients abstain from alcohol, easily permitted an independent depressive disorder to be identified and treated. This practice is much less of an option in today's US health care environment, and this has challenged us to rethink our clinical management of these patients.

Both major depression and alcohol dependence carry a significant risk for the development of the other. Severity in one disorder is associated with severity in the other.<sup>1-4</sup> Moreover, alcohol dependence prolongs the course of depression, and persistent depression during abstinence from alcohol is a risk factor for relapse to heavy drinking.<sup>5-9</sup> Thus, logic dictates that both disorders be identified and managed concurrently and aggressively. Integrated psychosocial outpatient treatment programs and the ability to treat alcohol and depression simultaneously have reinforced the need to revisit the traditional management of comorbid major depression and alcohol dependence more formally.

#### **Prevalence**

Recent estimates of the co-occurrence of these disorders in the general population are derived from the National Epidemiologic Survey on Alcohol and Related Conditions, a large-scale, nationally representative survey using DSM-IV diagnostic criteria.<sup>10</sup> Data were collected on a sample of 43,093 adults (18 years and older) who were interviewed between 2001 and 2002 to determine lifetime and current (past 12 months) DSM-IV diagnoses. For those with a diagnosis of current alcohol dependence, the prevalence rate for an independent major depressive disorder was 20.5%. These alcohol-dependent individuals were 3.7 times more likely to have major depression than those without alcohol dependence. For those individuals with a current alcohol use disorder (abuse or dependence) who were seeking treatment, 40.7% had at least 1 current independent mood disorder.

#### What is already known about treating alcohol dependence and comorbid depression?

Prevalence rates of co-occurring psychiatric and substance dependence disorders are formidable, and numerous reports describe individuals with both major depression and alcohol dependence as clinically more severely ill and more difficult to keep well than those who either are depressed or are alcohol-dependent. Over the past quarter of a century, results from well-controlled trials have demonstrated that antidepressant medications can reduce depressive symptoms in some persons who suffer from both major depression and alcohol dependence. However, the majority of these trials demonstrated that these medications had virtually no effect on reducing excessive drinking.

#### What new information does this article add?

This article reports on a recently published controlled trial that indicated that the combination of a medication to treat alcohol dependence (eg, [naltrexone](#)([Drug information on naltrexone](#))) and an antidepressant (eg, [sertraline](#)([Drug information on sertraline](#))) might be the optimal course of treatment for patients with co-occurring depression and alcohol dependence.

#### What are the implications for psychiatric practice?

Combining a medication to treat alcohol dependence (eg, naltrexone) with an antidepressant (eg, sertraline) with some basic psychosocial support and advice for both disorders can provide an aggressive approach to treating patients with co-occurring depression and alcohol dependence.

### Diagnostic difficulties

Identifying the cause of the depression in individuals with alcohol dependence has been thought to be important for determining the course of the disorder and the optimal treatment approach. For example, if the depressive symptoms are clearly related to alcohol use, then an antidepressant may not have any therapeutic impact beyond what abstinence would achieve. In some cases, depressive symptoms will spontaneously remit with abstinence from alcohol. In such cases, antidepressant pharmacotherapy may be an unnecessary cost and may be burdensome to the patient. However, it is often difficult to distinguish a substance-induced depression from major depression in the presence of alcohol dependence because the clinical symptoms of a substance-induced depression can appear identical to those seen in major depression.

Prolonged abstinence from alcohol can be of great value in making a distinction. Indeed, Brown and Schuckit<sup>11</sup> demonstrated a significant drop in depressive symptoms for those with primary alcohol dependence who completed a 4-week inpatient program. Nonetheless, many patients have difficulty in abstaining from alcohol during outpatient treatment and eventually may drop out of treatment because of continued drinking and/or deepening depression. To this point, Greenfield and colleagues<sup>12</sup> demonstrated that untreated depression—whether primary or secondary—predicted worse drinking

outcomes. Finally, while depression may precede or be precipitated by alcohol dependence, implying causation, there may be common risk factors for depression and for alcohol dependence. These include stressful events, psychological trauma, and genetic vulnerability that lead to co-occurring expression, without one disorder causing the other.

DSM-IV-TR distinguishes between major and substance-induced depressive episodes and related disorders. For a depressive episode to be considered substance-induced, the depressed mood and/or diminished interest and pleasure must occur during (or within 1 month of) periods of intoxication or withdrawal and symptoms cannot be better explained by an independent mood disorder. A careful history can help make the differential diagnosis.

The following scenarios strongly suggest an independent mood disorder (eg, major depression):

- The mood disturbance precedes alcohol use
- The mood disturbance persists following prolonged abstinence (at least 1 month)
- Depressive symptoms occur in excess of those typically seen considering the quantity and frequency of alcohol consumption

Several large studies that carefully assessed DSM-IV criteria have shown that the prevalence of primary, independent depressive disorders (eg, major depression) are more common than substance-induced disorders in individuals with alcohol use disorders.<sup>10,13</sup> Furthermore, women who are alcohol-dependent and depressed are more likely to have an independent mood disorder than a substance-induced disorder.<sup>13</sup>

Today in the United States, alcohol dependence is almost always treated in an outpatient setting, where continued drinking and poor treatment attendance can be major obstacles to observing periods of abstinence. Clinicians are typically expected to decide how to treat depression in patients who are actively drinking, without benefit of observing that patient during an extended period of abstinence. Interview techniques that have been developed to help clinicians determine the origin of a patient's depression have demonstrated reliability and validity in academic settings.<sup>14-16</sup> However, little is known of the utility of these techniques in general practice.

Further studies are needed to elucidate a way to make accurate diagnoses of major depressive disorder and substance-induced depression in the presence of current alcohol dependence. It would be beneficial to know precisely under what conditions antidepressant therapy would yield optimal outcomes for treating comorbid depression and alcohol dependence.

### **Psychosocial treatment for major depression and alcohol dependence**

There have been 3 approaches to psychosocial interventions for treating comorbid disorders:

- Sequential: treating the primary disorder initially, followed by treating the other disorder
- Parallel: treating both disorders at the same time but in different settings
- Integrated: simultaneously treating both disorders

Although research and experience have been limited, integrated approaches have been shown to be superior to other approaches.<sup>17</sup> Hesse<sup>18</sup> identified only 5 randomized clinical trials that focused on the

treatment of comorbid substance abuse and depressive disorders: those trials showed that integrated treatment programs had statistically superior alcohol and drug outcomes compared with addiction treatment only. Measures of depression outcomes and treatment retention also appeared to favor integrated treatment programs, although these results did not reach statistical significance.)

## Pharmacotherapy

Research has been sparse on integrated psychosocial approaches and even less information is available on how to use pharmacotherapy for co-occurring major depression and alcohol dependence. Moreover, no evidence-based guide exists on how to integrate psychosocial and pharmacotherapy approaches in depressed alcohol-dependent patients. Major depression is generally responsive to pharmacological treatment, and antidepressants can be lifesaving for individuals at risk for suicide. However, studies that supported FDA approvals for these antidepressants typically excluded patients with comorbid alcohol dependence. Thus, the depression literature does not adequately address questions such as: Are antidepressants actually effective for reducing depressive symptoms in this patient population? Will antidepressants help reduce alcohol drinking, either directly or indirectly, by reducing depression? Would an antialcohol medication, singly or in combination with an antidepressant, reduce clinical symptoms for either or both disorders?

Historically, long-term drinkers were denied medications (except for detoxification) because of long-standing stigmas about alcohol-dependent patients taking any medications (“treating a drug with a drug”). Fortunately, this attitude is fading as scientists impart knowledge to professionals and the public about the possibilities of correcting the neurobiology of addiction by treating the addicted brain with certain medications. In addition, there are legitimate safety concerns about the potential interaction of medications with alcohol, or the potential for antidepressant overdose in depressed intoxicated patients.

Study (N)	Medication	Average daily dose (mg, times)	Depression	Drinking
Blazer <sup>18</sup> (20)	Desipramine	200 mg (2)	Med = placebo	Med = placebo
McIntosh <sup>19</sup> (26)	Imipramine	250 mg (2)	Med = placebo	Med = placebo
Conklin <sup>20</sup> (21)	Fluoxetine	20–40 mg (1/2)	Med = placebo	Med = placebo
Ray <sup>21</sup> (26)	Sertraline	100 mg (1)	Med = placebo	Med = placebo
Ray-Sanner <sup>22</sup> (24)	Nefopam	400 mg (2)	Med = placebo	Med = placebo
Palmer <sup>23</sup> (29)	Sertraline	150 mg (2)	Med = placebo	Med = placebo
Wise <sup>24</sup> (32)	Sertraline	100 mg (2)	Med = placebo	Med = placebo
Serlin <sup>25</sup> (31)	Nefopam	410 mg (2)	Med = placebo	Med = placebo
Kessler <sup>26</sup> (242)	Sertraline	50–150 mg (2)	Med = placebo	Med = placebo

The advent of SSRIs, many of which are FDA-approved, mitigated many of the safety concerns about depressed alcohol-dependent patients taking antidepressants. If a patient drinks alcohol or feels suicidal, SSRIs are better tolerated and are generally thought to be safer than, for example, tricyclic antidepressants (TCAs). In addition, the frequency of adverse effects is relatively low and the severity of most adverse effects is mild or moderate. Investigators have been more willing to examine the

efficacy of SSRIs in alcohol-dependent patients, and clinicians have been more likely to prescribe SSRI medications than drugs in other classes for depression in alcohol-dependent patients because of the safety profile of these agents.

The **Table** summarizes the results of recent, well-controlled, double-blind, placebo-controlled studies of pharmacotherapies for comorbid depression and alcohol dependence. Typically, these trials have provided antidepressant medication and some form of weekly psychosocial treatment or counseling. (See also earlier reviews by Nunes and Levin<sup>19</sup> and Pettinati.<sup>20</sup>)

Six of the 9 studies (67%) that compared an antidepressant medication with placebo found a relationship between the medication and reductions in depressive symptoms, irrespective of type of antidepressant (eg, TCAs, SSRIs). Only 3 of the 9 studies (33%) found an advantage for the medication over placebo in reducing drinking in depressed alcohol-dependent patients. In the largest (N = 345) multicenter trial of sertraline (50 to 150 mg/d for 10 weeks), the drug provided no advantage over placebo in reducing depressive symptoms, nor did it reduce drinking, compared with placebo.<sup>21</sup> Because of this trial’s size, the results challenged those of all the other trials, indicating that antidepressants alleviate depression in depressed patients with alcohol dependence.

## New treatment strategy

We recently published the results of a double-blind, placebo-controlled, 14-week trial of 170 alcohol-dependent patients with major depressive disorder. Two FDA-approved medications were evaluated, one for depression (sertraline) and one for alcohol dependence (naltrexone).<sup>22</sup> An important aim of the study was to compare mood and drinking outcomes with the combined medications with those with placebo and with single-medication treatment. Patients received either 200 mg/d of sertraline, 100 mg/d of naltrexone, a combination of the two, or a double placebo for 14 weeks while receiving weekly cognitive-behavioral therapy.

The sertraline-naltrexone combination produced a higher alcohol abstinence rate (53.7%;  $P = .001$ ; odds ratio [OR] = 3.7) and a longer delay before relapse to heavy drinking (median delay, 98 days;  $P = .003$ ; Cohen  $d = .54$ ) than the other treatments: naltrexone (21.3% abstinent; delay, 29 days), sertraline (27.5% abstinent; delay, 23 days), or placebo (23.1% abstinent; delay, 26 days). A trend was also seen in the relief of depression symptoms in the medication combination group by the end of treatment (83.3% not depressed;  $P = .014$ ; OR = 3.6) compared with the single-medication or placebo group.

The patients treated with an SSRI and an opiate antagonist achieved greater abstinence from alcohol, delayed relapse to heavy drinking, and relief of depression symptoms by the end of treatment than did patients who received naltrexone or sertraline alone or placebo. As with other initial findings from clinical trials, the results await replication in other settings with different patient populations and with other antidepressants.

## Summary and future directions

Empirical data that support effective treatments for co-occurring depression and alcohol dependence are long overdue. Comorbid prevalence rates are formidable, and numerous reports describe patients with comorbid depression and alcohol dependence as clinically more severely ill and more difficult to keep well than patients who are either depressed or alcohol-dependent. Positive outcomes may depend on both the type and timing of the medication and psychosocial interventions needed to treat both disorders to symptom remission, as well as a solid doctor-patient relationship, attention to treatment compliance, and a commitment to treat both the alcohol dependence and the mood disorder.

While it seems logical to prescribe antidepressants for patients who are depressed, some alcohol-dependent patients—as well as some clinicians who treat them—are unwilling to use a medication. Fortunately, bias is fading as scientists learn more about treating the addicted brain with certain medications and correcting the neurobiology of addiction. Over the past 20 years, results from the majority of well-controlled trials have showed that antidepressants reduced depressive symptoms in patients with depression and alcohol dependence. However, in most of the trials, these medications had virtually no effect on reducing excessive drinking.

Recently published results of a controlled trial indicate that combining a medication to treat alcohol (naltrexone) with the antidepressant sertraline might be the optimal course of treatment for co-occurring depression and alcohol dependence.<sup>22</sup> While these findings require replication, they provide a practical recommendation to integrate or combine 2 medications—1 for treating alcohol dependence and 1 for treating depression. This combined pharmacotherapy, with some platform counseling that integrates support and advice for both disorders, can provide an aggressive approach to treating co-occurring depression and alcohol dependence.

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