

Pharmacotherapy for and alcohol



comorbid depression dependence

Evidence is mixed for antidepressants, alcohol dependence medications, or a combination

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With a lifetime prevalence of 30%, alcohol use disorders (AUDs)—which in DSM-IV-TR include alcohol abuse and alcohol dependence—are among the most common psychiatric disorders.¹ Depressive disorders, including major depressive disorder (MDD) and dysthymia, frequently co-occur with AUDs.²⁻⁴ This pattern of comorbidity adversely affects the prognosis, course, and treatment of both MDD and AUDs.⁵ High severity in 1 of these disorders is associated with high severity in the other.^{2,6} Alcohol dependence appears to prolong the course of depression^{7,8} and increases the risk of suicidal symptoms and behaviors.^{9,10} Patients with depression and AUDs are at increased risk of relapse to heavy drinking.^{7,11}

Whether the high comorbidity rate of depressive disorders and AUDs is a result of 1 disorder causing the other (ie, AUDs leading to depression or vice versa) or can be attributed to shared etiology is unknown. Clinicians need to consider this question when treating patients with this pattern of comorbidity because distinguishing primary depression from secondary depression influences treatment decisions.¹²

There is a great need for pharmacologic interventions that can concurrently treat both depression and AUDs. This article reviews the evidence for current treatments for dually diagnosed patients and highlights novel agents that are worthy of further study for this complex patient population.

Current treatment options

Pharmacotherapy for MDD and alcohol dependence is common when these conditions occur alone. FDA-approved medications for treating



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Findings regarding the efficacy of SSRIs in patients with comorbid depression and alcohol dependence have been mixed

Table 1

Serotonergic antidepressants for patients with AUDs and depression

Study	Sample	Results
Cornelius et al, 1997 ¹⁴	Outpatients with severe major depression and AD 1. Fluoxetine (20 to 40 mg/d; n = 25) 2. Placebo (n = 26)	Greater reductions in depressive symptoms and drinking in patients treated with fluoxetine compared with placebo
Roy, 1998 ¹⁵	Inpatients with current major depression and AD who were abstinent for ≥ 2 weeks 1. Sertraline (100 mg/d; n = 18) 2. Placebo (n = 18)	Greater reductions in depressive symptoms in patients treated with sertraline compared with placebo. Drinking outcomes were not emphasized because 35 of 36 patients reported continuous abstinence throughout the trial
Kranzler et al, 1995 ¹⁶	Outpatients with AD. Fourteen percent had current major depression. All received weekly individual or group CBT focused on relapse prevention and skills building 1. Fluoxetine (mean daily dose: 48 mg; n = 51) 2. Placebo (n = 50)	Significant decrease in alcohol consumption for both groups during the trial. No significant differences in alcohol consumption between groups. Among those with current depression, patients treated with fluoxetine experienced greater reduction in depressive symptoms vs placebo
Moak et al, 2003 ¹⁷	Currently depressed, actively drinking, alcohol-dependent outpatients. All received individual CBT 1. Sertraline (mean daily dose: 186 mg; n = 38) 2. Placebo (n = 44)	Sertraline had an advantage over placebo in reducing depressive symptoms in women but not in men. Sertraline reduced drinks per drinking day but not other drinking-related outcomes
Cornelius et al, 2009 ¹⁸	Adolescents (age 15 to 20) with AA or AD and MDD. All received intensive manual-based therapy (CBT for MDD and AUD, MET for AUD) almost weekly 1. Fluoxetine (20 mg/d; n = 24) 2. Placebo (n = 26)	All improved during the course of trial. No significant differences between fluoxetine and placebo groups in depression- or drinking-related outcomes
Roy-Byrne et al, 2000 ¹⁹	Actively drinking alcohol-dependent outpatients with history of ≥ 1 depressive episode. All received weekly group therapy for alcoholism 1. Nefazodone (mean daily dose: 460 mg; n = 32) 2. Placebo (n = 32)	Greater reduction in depressive symptoms but not in drinking-related outcomes in patients treated with nefazodone
Hernandez-Avila et al, 2004 ²⁰	Outpatients with AD and current major depression. All received supportive psychotherapy for 10 weeks 1. Nefazodone (mean daily dose: 413 mg; n = 21) 2. Placebo (n = 20)	Depressive and anxiety symptoms declined significantly over time, but no statistically significant differences in depressive or anxiety symptoms between nefazodone and placebo. Patients treated with nefazodone had significantly greater reductions in heavy drinking days and in total drinks compared with placebo-treated patients

AA: alcohol abuse; AD: alcohol dependence; AUDs: alcohol use disorders; CBT: cognitive-behavioral therapy; MDD: major depressive disorder; MET: motivational enhancement therapy



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depression include monoamine oxidase inhibitors, tricyclic antidepressants (TCAs), tetracyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), and serotonin-norepinephrine reuptake inhibitors.

SSRIs are the most widely used class of antidepressants. They gained FDA ap-

proval based on studies conducted in non-comorbid patients because patients with comorbid conditions usually are excluded from research studies.¹³ Few trials have evaluated patients with depression and AUDs; TCAs and SSRIs are best studied in these patients.

Table 2

Limited evidence supports TCAs for comorbid depression and AUDs

Study	Sample	Results
Mason et al, 1996 ²⁴	Outpatients with AD and secondary depression. Part of larger study including non-depressed patients with AD (N = 71) 1. Desipramine (mean daily dose 200 mg; n = 15) 2. Placebo (n = 13)	Greater reduction in depressive symptoms and drinking in desipramine-treated patients compared with placebo-treated patients
McGrath et al, 1996 ²⁵	Outpatients with AD or AA and major depression, dysthymia, or depressive disorder NOS 1. Imipramine (mean daily dose 260 mg; n = 36) 2. Placebo (n = 33)	Greater reduction in depressive symptoms for imipramine-treated patients compared with placebo-treated patients. Drinking-related outcomes were not directly affected by medication except improvements in mood led to reduced alcohol use
Altintoprak et al, 2008 ²⁶	Inpatients with AD and MDD 1. Mirtazapine (30 mg/d; n = 24) 2. Amitriptyline (100 mg/d; n = 20)	Drinking-related outcomes were not emphasized because all patients were required to abstain from drinking during the study. Both treatments reduced depressive symptoms; there were no significant differences between groups

AA: alcohol abuse; AD: alcohol dependence; AUDs: alcohol use disorders; MDD: major depressive disorder; NOS: not otherwise specified; TCAs: tricyclic antidepressants

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Compared with placebo, nefazodone was linked to greater reductions in depressive symptoms but did not reduce drinking

Serotonergic antidepressants

SSRIs are first-line medications for MDD because of their low abuse potential, favorable side effect profile, and relative safety in overdose.

Findings regarding the efficacy of SSRIs in patients with comorbid depression and AUDs have been mixed (Table 1).¹⁴⁻²⁰ Only fluoxetine and sertraline have been evaluated in double-blind, placebo-controlled trials; 4 studies were conducted with adults and 1 with adolescents. In a 12-week trial, Cornelius et al¹⁴ found that fluoxetine reduced depressive symptoms and alcohol use in 51 patients with MDD and alcohol dependence. Others researchers have reported that the SSRIs sertraline and fluoxetine reduced depressive symptoms but had few direct effects on drinking outcomes.^{15,16} A 2003 study¹⁷ compared sertraline, 200 mg/d maximum, with placebo for 12 weeks in 82 patients with MDD and alcohol dependence. Depressive symptoms and alcohol consumption decreased substantially over time for both groups. However, further analyses revealed that depression-related outcomes differed based on severity of depressive symptoms—patients with more severe depressive symptoms at baseline benefited the most from sertraline.

In a study of adolescents, Cornelius et al¹⁸ failed to find any differences between fluoxetine and placebo in any depression or drinking-related outcomes. This study compared the efficacy of fluoxetine, 20 mg/d, with placebo in 50 adolescents with MDD and AUDs who also received intensive, manual-based cognitive-behavioral therapy and motivational enhancement therapy. All patients improved during the trial, but there were no significant differences between fluoxetine- and placebo-treated adolescents.

Other serotonergic medications. Two studies have evaluated nefazodone, a serotonin (5-HT₂) antagonist, in dually diagnosed patients. In a 12-week trial, Roy-Byrne et al¹⁹ evaluated the efficacy of nefazodone (mean daily dose: 460 mg) vs placebo in 64 actively drinking alcohol-dependent patients who had ≥1 prior episode of depression; all participated in a weekly psychoeducation group on alcoholism. Nefazodone was associated with significantly greater reduction in depressive symptoms but no reductions in drinking compared with placebo. However, a 10-week study of nefazodone²⁰ (mean daily dose: 413 mg) vs placebo in 41 alcohol-



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TCA's may help reduce depressive symptoms in patients with AUDs but it is not clear if they also can reduce drinking

See this article at CurrentPsychiatry.com for a description of CRF₁ antagonists

Table 3

Can medications that target alcohol use also improve depression?

Study	Sample	Results
Petrakis et al, 2007 ²⁹	Outpatients with AD and an axis I disorder, including depression (secondary analysis of Petrakis et al, 2005 ³¹) 1. Naltrexone (50 mg/d; n = 34) 2. Disulfiram (250 mg/d; n = 43) 3. Naltrexone + disulfiram (n = 28) 4. Placebo (n = 34)	Generally, medication was more effective than no medication. No advantage of 1 medication over the other. There was no relationship between depression diagnosis and medication condition, which suggests that for patients with depression, there was no advantage to medication
Pettinati et al, 2010 ³⁰	Outpatients with AD and MDD 1. Sertraline (200 mg/d; n = 40) 2. Naltrexone (100 mg/d; n = 49) 3. Sertraline + naltrexone (n = 42) 4. Placebo (n = 39)	Greater proportion of patients in combined medication group abstained from alcohol and refrained from heavy alcohol use during the trial compared with those in sertraline-only or naltrexone-only groups. No significant differences among groups on depression-related outcomes

AD: alcohol dependence; MDD: major depressive disorder

dependent patients with current major depression found that those who received nefazodone significantly reduced heavy drinking days compared with the placebo group. There were no significant differences in depressive symptoms between groups.

Older studies of SSRIs conducted in patients with AUDs but not depression suggested that these medications may exacerbate AUDs in certain populations, specifically women and individuals with early onset AUD.²¹⁻²³ Use caution if you prescribe SSRIs to alcohol-dependent patients without comorbid depression. When prescribing SSRIs for those with comorbid AUDs, carefully monitor patients' drinking.

Conflicting evidence on TCAs

Although several studies suggest TCAs may help reduce depressive symptoms in patients with AUDs, results on their ability to reduce drinking are conflicting (Table 2, page 27).²⁴⁻²⁶ In 1 study, 6 months of desipramine (mean daily dose: 200 mg) reduced drinking in 28 alcohol-dependent individuals with secondary depression²⁴; in another, 12 weeks of imipramine plus weekly relapse prevention psychotherapy did not affect drinking-related outcomes in 69 actively drinking alcoholic outpatients with current depressive disorders.²⁵

Studies of TCAs largely were abandoned when SSRIs were introduced be-

cause SSRIs have a better safety profile. However, disappointing results with SSRIs have rekindled an interest in TCAs and other types of antidepressants.

Altintoprak et al²⁶ compared the efficacy of the antidepressant mirtazapine, 30 mg/d, with the TCA amitriptyline, 100 mg/d, in 44 patients with comorbid alcohol dependence and MDD. All patients were required to abstain from drinking alcohol during the study. Both medications resulted in steady reductions in depressive symptoms and alcohol cravings; however, researchers found no significant differences between the 2 treatment groups.

Analyses of combined studies

Pettinati²⁷ conducted a qualitative review of antidepressants for patients with depression and alcohol dependence that included 8 controlled clinical trials (2 on TCAs and 6 on serotonergic medications) conducted between 1994 and 2004. In this review, both TCAs and serotonergic medications were similarly effective in reducing depressive symptoms but not consistently effective in reducing drinking.

Nunes and Levin²⁸ conducted a systematic, meta-analysis of the efficacy of antidepressants for patients with depression and alcohol and/or other substance use disorders that reviewed 8 placebo-controlled trials that included patients with depres-

sion and AUDs. Of these 8 trials, 2 used TCAs, 5 used serotonergic agents, and 1 used viloxazine, a bicyclic antidepressant morpholine derivative not available in the United States that acts as a selective norepinephrine reuptake inhibitor. Similar to Pettinati,²⁷ this review suggested that antidepressants can reduce depressive symptoms but not drinking. The authors also found evidence that the more the antidepressant reduced depressive symptoms, the more it reduced alcohol use. Studies published after these reviews have not substantially altered these findings.

Alcohol abuse medications

Four medications are FDA-approved for treating alcohol dependence:

- disulfiram
- naltrexone (in 2 formulations: oral and long-acting injectable)
- acamprosate.

After a few smaller studies suggested that naltrexone might reduce alcohol use

among dually diagnosed individuals, several larger studies were initiated (*Table 3*).²⁹⁻³¹ In a 12-week study, 254 outpatients with alcohol dependence plus an additional axis I disorder (including depression) were randomized to naltrexone, disulfiram, naltrexone plus disulfiram, or no medication.³¹ Overall, medication was more effective than no medication in consecutive abstinence, but researchers found no advantage for 1 medication over the other, and no advantage to the combination. In a secondary analysis that compared 139 patients with depression to those with other axis I diagnoses, medication offered no advantage over placebo in alcohol use outcomes.²⁹ There was a significant interaction among depression, medication group, and craving—depressed patients assigned to disulfiram reported lower cravings over time than depressed patients receiving naltrexone. In this study, most patients also received medication for their comorbid condition, but no standard medication was used.

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Depressed alcohol-dependent patients receiving disulfiram reported lower alcohol cravings than depressed patients receiving naltrexone



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Medications for treating depression or AUDs have, at best, only a modest effect in patients with both disorders

See this article at
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Related Resources

- Pettinati H. Antidepressant treatment of co-occurring depression and alcohol dependence. *Biol Psychiatry*. 2004;56(10):785-792.
- Nunes EV, Levin FR. Treatment of depression in patients with alcohol or other drug dependence: a meta-analysis. *JAMA*. 2004;291(15):1887-1896.

Drug Brand Names

Acamprosate • Campral	Ketamine • Ketalar
Amitriptyline • Elavil	Memantine • Namenda
Desipramine • Norpramin	Mirtazapine • Remeron
Disulfiram • Antabuse	Naltrexone • Revia, Vivitrol
Escitalopram • Lexapro	Nefazodone • Serzone
Fluoxetine • Prozac	Quetiapine • Seroquel
Imipramine • Tofranil	Sertraline • Zoloft

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In a double-blind, placebo-controlled study that compared sertraline, naltrexone, and sertraline plus naltrexone in 170 patients with comorbid alcohol dependence and MDD, a greater proportion of patients in the combined medication group abstained from alcohol or refrained from heavy alcohol use during the 14-week trial compared with those receiving sertraline or naltrexone alone.³⁰ Patients in the combined medication group also reported a longer time before relapse to any drinking. There were no significant differences between the 3 groups on depression-related outcomes, although the combined medication group reported fewer depressive symptoms in the last 3 weeks of treatment. This study suggests that when used together, combining medications to treat the underlying psychiatric disorder with medications to treat AUDs may be more effective than either medication alone.

Nevertheless, these studies suggest that medications for treating depression or

AUDs have, at best, only a modest effect in patients with both disorders.

Novel agents

Several novel medications have been evaluated as possible treatments for comorbid depression and AUDs because they target the underlying neurobiology of both disorders:

- agents that target the neurotransmitter glutamate, including the *N*-methyl-D-aspartate glutamate receptor antagonists memantine and ketamine
- dopaminergic agents such as quetiapine
- corticotropin-releasing factor (CRF) receptor 1 (CRF₁) antagonists.

Research has implicated glutamate system dysfunction in both AUDs and depression and suggested that memantine and ketamine may reduce depressive symptoms and alcohol craving. Muhonen et al³² compared memantine, 20 mg/d, to the SSRI escitalopram, 20 mg/d, in 80 outpatients with MDD and alcohol dependence. Although both medications reduced symptoms of depression and anxiety, there were no significant differences between treatments; the study did not evaluate alcohol-related outcomes.

In a case study, a 55-year-old man with treatment-resistant major depression and co-occurring alcohol and benzodiazepine dependence who received a single dose of IV ketamine, 0.5 mg/kg over 50 minutes, experienced “significant improvements” in depressive symptoms that lasted throughout the 7-day follow-up.³³ This study did not report on ketamine’s effects on his alcohol use.

The atypical antipsychotic quetiapine acts as a serotonin (5-HT_{1A} and 5-HT₂) and dopamine (D₁ and D₂) antagonist, and reports suggest it reduces alcohol craving and affective symptoms in patients with AUDs.^{34,35} In a 16-week, open-label study, quetiapine decreased alcohol consumption, alcohol craving, and intensity of some psychiatric symptoms in 28 alcohol-dependent patients with bipolar disorder, schizoaffective disorder, or borderline personality disorder.³⁶

For a description of the role CRF₁ antagonists may play in treating patients

with concurrent MDD and AUDs, and a table summarizing studies of memantine and quetiapine, see this article at CurrentPsychiatry.com

Interpreting the evidence

The co-occurrence of MDD and AUDs is a common and difficult clinical problem. Although FDA-approved medications targeting depression and AUD are effective when these conditions occur alone, their efficacy when these conditions co-occur is still under investigation. Antidepressants have modest efficacy in reducing depressive symptoms but are less effective in reducing alcohol consumption, which suggests that their action on mood has little direct impact on alcohol consumption. Evidence for the efficacy of medications to treat alcohol consumption is less robust. Results from studies of using a combination of antidepressants and medications that directly target alcohol use have been conflicting and disappointing.

These findings underscore the importance of thorough evaluations. SSRIs are a first-line treatment for depression and as such probably should be the first choice for patients with comorbid AUDs. Drinking should be monitored closely and abstinence encouraged. Using medications that target AUDs is safe and modestly effective in patients with comorbid depression. Evidence suggests that treating both disorders simultaneously is more effective than treating either alone. Medications should be prescribed as part of a comprehensive treatment plan that also includes psychotherapy.

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Research on using a combination of antidepressants and medications that target alcohol use have been disappointing

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Bottom Line

Antidepressants and medications that target alcohol use are safe and modestly effective in concurrently treating depressive disorders and alcohol use disorders (AUDs). Further research is needed to evaluate other agents, such as the *N*-methyl-D-aspartate glutamate receptor antagonists memantine and ketamine and dopaminergic agents such as quetiapine, that may be more effective for patients with depression and AUDs.

Box

CRF₁ receptor antagonists for concurrent depression and AUDs: For which patients might they work best?

Corticotropin-releasing factor (CRF) has a well-established role in stress and has been implicated for treating anxiety and depressive disorders. Evidence also suggests that CRF receptor 1 (CRF₁) may be a treatment target for alcohol use disorders (AUDs). Acute alcohol withdrawal and prolonged alcohol use are associated with elevated levels of extrahypothalamic CRF and correlated anxiety. CRF antagonists can reduce the anxiogenic effects of alcohol

withdrawal and reduce some symptoms of alcohol dependence, including excessive alcohol self-administration and stress-induced relapse to alcohol use in rats with alcohol dependence, but not in those without dependence. Therefore, CRF₁ receptor antagonists may be especially helpful for individuals who use alcohol to reduce negative emotional states such as anxiety or dysphoria, including those with concurrent major depressive disorder and AUDs.

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Table

Other agents may play a role in treating depression with AUDs

Study	Sample	Results
Muhonen et al, 2008 ³²	Outpatients with MDD and AD 1. Memantine (20 mg/d; n = 40) 2. Escitalopram (20 mg/d; n = 40)	Both treatments reduced depressive and anxiety symptoms. No significant differences between groups. Study did not examine alcohol-related outcomes
Martinotti et al, 2008 ³³	Outpatients with comorbid AD and either bipolar disorder, schizoaffective disorder or borderline personality disorder. Open-label study 1. Quetiapine (300 to 800 mg/d; n = 28)	Quetiapine was associated with reduced alcohol consumption, alcohol craving, and intensity of psychiatric symptoms

AD: alcohol dependence; AUDs: alcohol use disorders; MDD: major depressive disorder