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Comorbid bipolar disorder and substance abuse: Evidence-based options

Medication selection may vary based on which substance patients abuse

Among DSM axis I diagnoses, bipolar disorder (BD) has the highest rates of comorbid substance use disorders (SUDs).[1-3] Approximately 60% of patients with bipolar I disorder have a lifetime diagnosis of an SUD.[1] Excluding tobacco, alcohol is the substance most often abused by BD patients, followed by cannabis, amphetamines, and cocaine.[1-3]

BD patients with comorbid SUD usually exhibit more severe clinical presentations and poorer outcomes than their counterparts without SUDs. Compared with patients with BD alone, those with BD and SUD comorbidity (BD-SUD) experience earlier onset of mood symptoms; higher rates of anxiety disorders, suicide attempts, accidents, hospitalizations, and rapid cycling; more depressive episodes; and lower treatment compliance.[4-9]

Several treatment options are available for patients with BD-SUD, including psychotherapy modalities, medications primarily used to treat BD, and medications primarily used to treat SUDs. Evidence-based support for these treatments remains limited, and no treatment of choice has emerged. This article reviews evidence on the longer-term treatment of BD-SUD, including general strategies and specific psychosocial and pharmacologic interventions. Short-term treatment strategies, such as pharmacotherapy for detoxification, are outside the scope of this review.

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General strategies

The causes of BD-SUD are complex. Evidence suggests that the presence of affective symptoms is associated

Comorbid BD and SUDs

Table 1

Lithium for BD patients with substance use disorders

Study	Intervention	Design	Substance use disorder	Results
Geller et al, 1998[13]	Lithium vs placebo	Double-blind, placebo-controlled	Alcohol and cannabis use disorders	Decreased positive drug screen results
Nunes et al, 1990[14]	Lithium	Open label	Cocaine abuse	Nonsignificant decrease in cocaine use

BD: bipolar disorder

Clinical Point

Treating only mood symptoms in the hope that doing so will control substance abuse may not be enough

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with an increased risk for substance misuse. This should be kept in mind when treating a patient with BD-SUD because controlling mood symptoms probably will help control substance abuse. However, evidence also shows that SUDs may be independent of mood episodes. Therefore, treating only mood symptoms in the hope that doing so will control substance abuse may not be enough.

Because the negative impact of SUDs on BD outcome is well documented, inform patients that limiting their use of alcohol and/or drugs is vital to control their mood disorder. Efforts to educate, stimulate, and support patients to moderate or stop their alcohol and/or drug use are likely to result in positive changes.[10] Therefore, treatment for BD-SUD should follow, in part, the same recommendations for treatment of SUDs in patients with no comorbid axis I disorders:

- identify the problem (ie, the existence of a comorbid SUD)
- share your concerns with your patient
- offer appropriate and specific treatments, such as detoxification and/or self-help and counseling programs.[10]

Because SUDs usually are chronic and relapsing conditions, periods of drug and/or alcohol use should be expected and not considered a sign of treatment failure. In addition, integrating treatment for both conditions probably is better than managing each separately. Therefore, targeting BD symptoms with mood-stabilizing medications and substance abuse with nonpharmacologic modalities such as drug counseling likely will bring about the best results.

Compared with BD patients without comorbid SUD, BD-SUD patients have a 7-fold increased risk of antidepressant-induced mania.[11] Therefore, antidepressants should be prescribed cautiously for patients with BD-SUD.

Integrated psychosocial therapy

BD-SUD patients may benefit from attending self-help programs such as Alcoholics Anonymous and Narcotics Anonymous, provided their mood is stable enough to allow them to participate. Other forms of psychotherapy for BD-SUD patients include standard group drug counseling and integrated group therapy that simultaneously addresses both conditions.

Integrated group therapy is based on the premise that changing maladaptive mood cognitions and behaviors will facilitate recovery from SUDs, and changing maladaptive substance use cognitions and behaviors will facilitate recovery from mood disorders.[12] In a recent randomized controlled trial, 62 BD-SUD patients were blindly assigned to integrated group therapy or standard group drug counseling and followed for 3 months.[12] Pharmacotherapy was prescribed as usual. Substance use decreased for both groups. However, compared with patients in the drug counseling group, those who participated in integrated group therapy spent fewer days using substances in general and alcohol in particular, fewer days using alcohol to intoxication, and had a shorter time from treatment initiation to the first abstinent month. There were no differences between groups in number of weeks in a mood episode.

Pharmacotherapy options

For a table that summarizes the dosages and indications of the medications used

Table 2

Studies suggest anticonvulsants may reduce alcohol, cocaine use in BD patients

Study	Intervention	Design	Substance use disorder	Results
Salloum et al, 2005[16]	Divalproex sodium plus lithium vs placebo plus lithium	Double-blind, placebo-controlled	Alcohol dependence	Decreased number of drinking days and number of drinks per day and increased time of abstinence
Salloum et al, 2007[17]	Divalproex sodium	Open label	Cocaine dependence	Increased cocaine-abstinent days and decreased money spent on cocaine and cocaine use severity index
Brady et al,* 2002[18]	Carbamazepine vs placebo	Double-blind, placebo-controlled	Cocaine dependence	Decreased cocaine craving and cocaine use
Brown et al, 2006[19]	Lamotrigine	Open label	Cocaine dependence	Decreased cocaine craving and money spent on cocaine

*Sample included, but was not limited to, patients with BD
BD: bipolar disorder

to treat BD-SUD that are described below, visit this article at CurrentPsychiatry.com.

Lithium. Given its well-documented mood stabilizing effect, lithium would seem to be a reasonable option to treat BD-SUD patients, but scant evidence supports its role as an anti-alcohol or anti-drug medication (***Table 1***).[13,14] Lithium's efficacy was evaluated in a study of 25 adolescents suffering from mood disorders (mostly BD) and comorbid SUDs (mostly alcohol and cannabis) randomized to receive lithium or placebo for 6 weeks.[13] Lithium was well tolerated and improved psychiatric symptoms. At week 3, patients receiving lithium produced fewer positive results on randomly administered urine drug screens than those receiving placebo.

However, lithium seems to have little efficacy in reducing cocaine use in cocaine-dependent patients with bipolar spectrum disorders.[14] In an open-label study, 10 patients with a history of hypomania or cyclothymia received lithium monotherapy for 12 weeks. Although patients experienced improved mood symptoms and decreased cocaine use, the mean decrease was transitory and not statistically significant. Another factor that may limit lithium's use for BD-SUD patients is that these patients are more likely to comply with valproate treatment than with lithium.[15]

Anticonvulsants. In a double-blind, placebo-controlled study of 59 alcohol-dependent bipolar I disorder patients, lithium plus divalproex sodium was superior to lithium plus placebo in decreasing number of drinking days and number of drinks per day and in increasing periods of abstinence (***Table 2***).[16-19] Divalproex sodium was well tolerated and liver function improved in the divalproex sodium group compared with the placebo group, which probably was a benefit of decreased alcohol consumption. In addition, there was a strong association between mood symptoms and alcohol use, which suggests that maximizing mood symptom treatment may decrease alcohol use. However, the divalproex sodium and placebo groups did not differ in measures of mood symptoms, which implies that divalproex sodium might exhibit a positive effect on drinking regardless of its mood-stabilizing properties.

Divalproex sodium also has been used to treat BD comorbid with cocaine dependence. In a small open-label study, 15 patients receiving divalproex sodium plus counseling for mood and substance use disorders were followed for 6 weeks.[17] The 7 patients who completed the trial had significantly more cocaine-abstinent days, spent less money on cocaine, and experienced fewer manic and depressive symptoms. However, divalproex sodium's

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Clinical Point

In alcohol-dependent BD patients, lithium plus divalproex sodium increased abstinence

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Table 3

Evidence of efficacy for antipsychotics for BD patients with SUDs

Study	Intervention	Design	Substance use disorder	Results
Martinotti et al,* 2008[20]	Quetiapine	Open label	Alcohol dependence	Decreased alcohol consumption and alcohol craving
Brown et al, 2008[21]	Quetiapine vs placebo	Double-blind, placebo-controlled	Alcohol dependence	No difference between quetiapine and placebo in decreasing alcohol use and alcohol craving
Brown et al, 2002[22]	Quetiapine	Open label	Cocaine dependence	Decreased cocaine use and cocaine craving
Nejtek et al, 2008[23]	Risperidone vs quetiapine	Open label	Cocaine dependence and amphetamine dependence	Decreased drug use and drug craving
Brown et al, 2005[24]	Aripiprazole	Open label	Alcohol and cocaine dependence	Decreased alcohol and cocaine craving and money spent on alcohol

*Sample included, but was not limited to, patients with BD

BD: bipolar disorder; SUDs: substance use disorders

effect on cocaine use cannot be determined solely from this study because there was no placebo control group.

Despite its widespread use as a mood stabilizer and potential use in alcohol detoxification, carbamazepine scarcely has been studied in BD-SUD patients. A double-blind, placebo-controlled study of 139 cocaine-dependent patients with BD or other affective disorders found that patients taking carbamazepine for 12 weeks experienced modest reductions in positive urine drug screens and increased time to cocaine use.[18] They also reported less cocaine craving than patients taking placebo, and mood symptoms (mostly depressive) improved.

An open-label study used lamotrigine as adjunctive therapy or monotherapy for 62 cocaine-dependent BD patients followed for 36 weeks.[19] There was some decrease in cocaine craving, money spent on cocaine, and rate of depressive and manic symptoms, but no effect on cocaine use. A placebo-controlled trial is necessary to confirm these modest effects.

No studies have evaluated the potential role of topiramate in treating BD-SUD, despite its FDA-approved indication for alcoholism treatment. Topiramate's well-known safety and tolerability profile in BD patients make it an interesting option for those with co-occurring alcohol dependence.

Atypical antipsychotics. In an open-label study, 16 weeks of quetiapine monotherapy effectively decreased alcohol consumption, alcohol craving, and psychotic and affective symptoms in 28 alcoholics with a variety of psychiatric diagnoses, including BD, schizoaffective disorder, and borderline personality disorder (***Table 3***).[20-24] However, in a double-blind study of augmentation with quetiapine or placebo for 102 alcohol-dependent BD patients, no significant differences in alcohol use were found between groups.[21]

Quetiapine may be effective for treating BD patients with comorbid cocaine dependence. In an open-label study, 12 weeks of quetiapine augmentation in 17 cocaine-dependent BD patients was associated with decreased cocaine craving and improvement in depressive symptoms.[22] In another open-label study, 80 BD patients with comorbid cocaine or amphetamine dependence were randomly assigned to receive quetiapine or risperidone as adjunctive therapy or monotherapy for 20 weeks.[23] Both groups showed significantly

Clinical Point

In a placebo-controlled trial, carbamazepine modestly reduced positive drug screens in cocaine-dependent BD patients

Table 4

Naltrexone and disulfiram for BD patients with alcohol dependence

Study	Intervention	Design	Substance use disorder	Results
Brown et al, 2006[26]	Naltrexone	Open label	Alcohol dependence	Decreased alcohol use and craving
Brown et al, 2009[27]	Naltrexone vs placebo	Double-blind, placebo-controlled	Alcohol dependence	Nonsignificant decrease in alcohol consumption
Petrakis et al, 2005[28] and 2007[29]	Naltrexone alone vs disulfiram alone vs naltrexone plus disulfiram	Double-blind, randomized, placebo-controlled	Alcohol dependence	More time in abstinence and decreased craving for both compounds

BD: bipolar disorder

Clinical Point

Open-label studies suggest quetiapine may be effective for treating cocaine-dependent BD patients

decreased drug use and drug craving and improved mood. This study suggests that risperidone also may be an option for BD patients with comorbid cocaine or stimulant dependence.

A 20-week, open-label study of 20 BD-SUD patients found that switching patients from their previous antipsychotic to aripiprazole resulted in less cocaine craving, less alcohol craving, and less money spent on alcohol.[24]

Olanzapine has not been systematically studied in BD-SUD patients. Some case reports suggest that olanzapine may decrease cocaine craving and use in patients with schizoaffective disorder (bipolar type) and alcohol craving and use in BD patients with comorbid alcohol dependence.[25]

SUD medications. Little evidence guides using medications indicated for treating SUDs—such as naltrexone, acamprosate, and disulfiram—as treatment for BD patients (***Table 4***).[26-29] In an open-label trial of 34 BD patients with alcohol dependence, naltrexone was well tolerated and associated with decreased alcohol craving and use and modest improvement in manic and depressive symptoms.[26]

In a double-blind, placebo-controlled study, 50 alcohol-dependent BD patients treated with standard mood-stabilizing therapy and cognitive-behavioral therapy were randomized to receive add-on naltrexone, 50 mg/d, or placebo.[27] Patients receiving naltrexone showed decreased alcohol consumption, although no measures were statistically significant. Effect sizes of alcohol use decrease and alcohol craving were moderate to large compared with placebo, which suggests that naltrexone may be effective for treating alcoholism in these patients.

Two other studies evaluated naltrexone and disulfiram in patients with BD or other mood disorders.[28,29] Naltrexone was well tolerated, caused no serious adverse side effects, and was significantly more effective than placebo in decreasing drinking rates and increasing the number of abstinent days.[28,29] Disulfiram was as effective as naltrexone, but the combination of both offered no advantage over use of either drug separately.

There are reports of a new-onset manic episode associated with naltrexone use in a patient with opioid dependence, and a manic episode triggered by naltrexone in a patient with BD with comorbid alcohol dependence.[30,31] At both low and high doses, disulfiram is associated with induction of psychotic mania in alcoholic patients without a personal or family history of BD.[32,33]

We found no studies that evaluated treating BD patients who abused other substances, such as cannabis or opiates. We recommend that BD patients with these substance use disorders should be referred to treatment modalities that are condition-specific, such as psychotherapy for cannabis use disorders or methadone or naltrexone treatment for opiate dependence. More severe cases of comorbid SUD probably would benefit from a referral to or consultation with a SUD specialist.

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Related Resource

- Tolliver BK. Bipolar disorder and substance abuse: Overcome the challenges of 'dual diagnosis' patients. Current Psychiatry. 2010;9(8):32-38.

Drug Brand Names

Acamprosate • Campral
Aripiprazole • Abilify
Carbamazepine • Carbatrol, Equetro, others
Disulfiram • Antabuse
Divalproex sodium • Depakote, Depakote ER
Lamotrigine • Lamictal
Lithium • Eskalith, Lithobid
Methadone • Dolophine
Naltrexone • ReVia, Vivitrol
Quetiapine • Seroquel
Risperidone • Risperdal
Topiramate • Topamax
Valproate • Depacon

Disclosures

Dr. Nery held a temporary work contract as a clinical research physician with Eli Lilly and Company Brazil from May 2009 to November 2009.

Dr. Soares was partly supported by National Institute of Health grants MH 68766, MH 69774, and RR 20571. He receives grant/research support from Bristol-Myers Squibb, Cephalon, GlaxoSmithKline, and Sunovion.

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Clinical Point

In 2 trials, naltrexone and disulfiram reduced drinking in patients with mood disorders

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Clinical Point

In case reports, naltrexone triggered mania in BD patients who were alcohol- or cocaine-dependent

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Bottom Line

Evidence suggests that lithium and divalproex sodium are options for treating bipolar disorder (BD) patients with comorbid alcohol use disorders; naltrexone and disulfiram also may be reasonable. For cocaine-dependent BD patients, carbamazepine has a modest effect on cocaine use; divalproex sodium, lamotrigine, quetiapine, and risperidone may be considered. Psychosocial treatments for substance use disorders always should be part of the treatment plan.

Table

Medications used to treat substance use disorders in bipolar disorder patients*

Drug	Dosages	FDA-approved indication(s)
Acamprosate	1,998 mg/d	Maintenance of abstinence from alcohol in patients with alcohol dependence
Aripiprazole	15 to 45 mg/d	Acute manic or mixed episode of bipolar disorder; augmentation therapy for major depressive disorder
Carbamazepine	400 to 1,200 mg/d	Manic and mixed episodes associated with bipolar disorder
Disulfiram	250 to 500 mg/d	Enforced sobriety in abstinent alcohol-dependence patients
Divalproex sodium	Initial dose: 750 mg/d Maximum dose: 60 mg/kg/d†	Manic episodes associated with bipolar disorder
Lamotrigine	200 mg/d	Maintenance treatment of bipolar I disorder
Lithium	900 to 1,800 mg/d for acute episodes 900 mg to 1,200 mg/d for maintenance‡	Manic episodes associated with bipolar disorder; maintenance treatment of bipolar disorder
Naltrexone	50 mg/d 380 mg/month	Alcohol dependence
Quetiapine	300 mg/d for bipolar depression 400 to 800 mg/d for bipolar mania 400 to 800 mg/d for maintenance treatment of bipolar disorder	Depressive and acute manic episodes associated with bipolar I disorder; maintenance treatment of bipolar I disorder
Risperidone	1 to 6 mg/d	Acute manic or mixed episodes associated with bipolar I disorder

*None of the medications cited in this table or the text have been specifically approved by the FDA for treating alcohol/drug abuse/dependence co-occurring with bipolar disorder

†Dose should correspond to valproic acid therapeutic levels between 50 and 100 µg/mL

‡Dose should correspond to lithium therapeutic levels between 0.8 and 1.2 mEq/L for acute manic episode treatment and 0.6 and 1.0 mEq/L for maintenance treatment

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